INTRAMOLECULAR ENE REACTIONS OF THIOALDEHYDES

A thesis presented in part fulfillment
of the requirement for the Degree of
Doctor of Philosophy

by

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Finally, I would like to thank my parents, for without their sacrifice, I would not have come to Britain to read my B.Sc. degree.

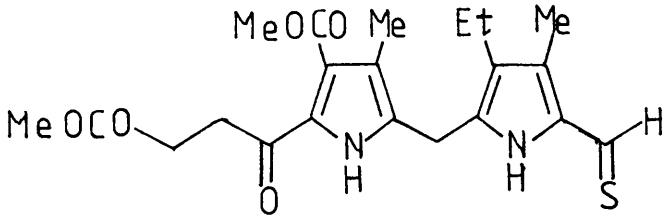
Summary

The intramolecular ene reactions of various alkenyl and cycloalkenyl thioxoacetates, ($RO_2C.CHS$) generated by thermal cleavage of various Diels-Alder adducts in solution (110°C) or by flash vacuum pyrolysis (FVP, 430-600°C), have been studied. Specifically, 3,3-dimethylallyl, *cis*-2-butenyl, *trans*-2-butenyl, 3-methyl-2-cyclohexenyl, 3-methyl-2-cyclopentenyl, and 4-methyl-3-pentenyl thioxoacetates were found to undergo Type I intramolecular ene reactions with C-C bond formation.

With cyclic or acyclic allylic thioxoacetates, selective attack occurred at '*cis*' CH groups. A Type II intramolecular ene reaction of 2-methyl-2-propenyl thioxoacetate which also resulted in C-C bond formation. 2-Propenyl, 3-butenyl, 4-pentenyl, and 5-hexenyl thioxoacetates underwent Type III ene reactions with C-S bond formation resulting, initially, in the formation of 7-, 8-, 9- and 10-membered rings.

Different approaches to the synthesis of thioxoacetate precursors, namely the cycloadducts of cyclopentadiene and alkenyl thioxoacetates, were explored. These approaches included generating the thioaldehydes from Bunte salts, trans-esterification of the adducts of methyl thioxoacetate, and esterification employing different condensing agents, *e.g. N,N'*-carbonyldi-imidazole, dicyclohexylcarbodiimide, diphenylphosphinoyl chloride, ethyl chloroformate, and oxalyl chloride.

CONTENTS



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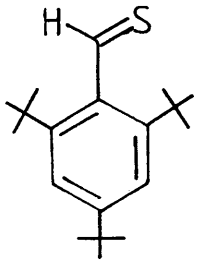

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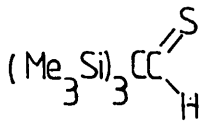

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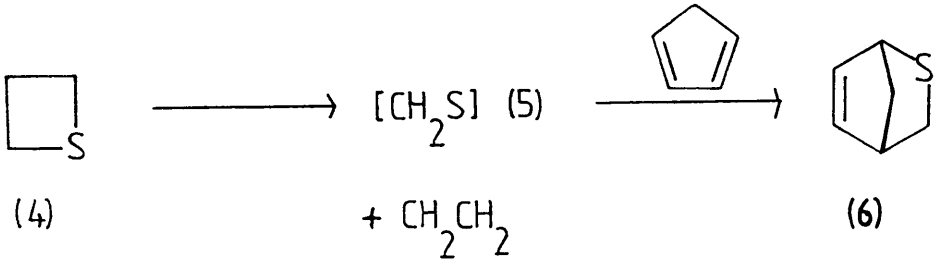
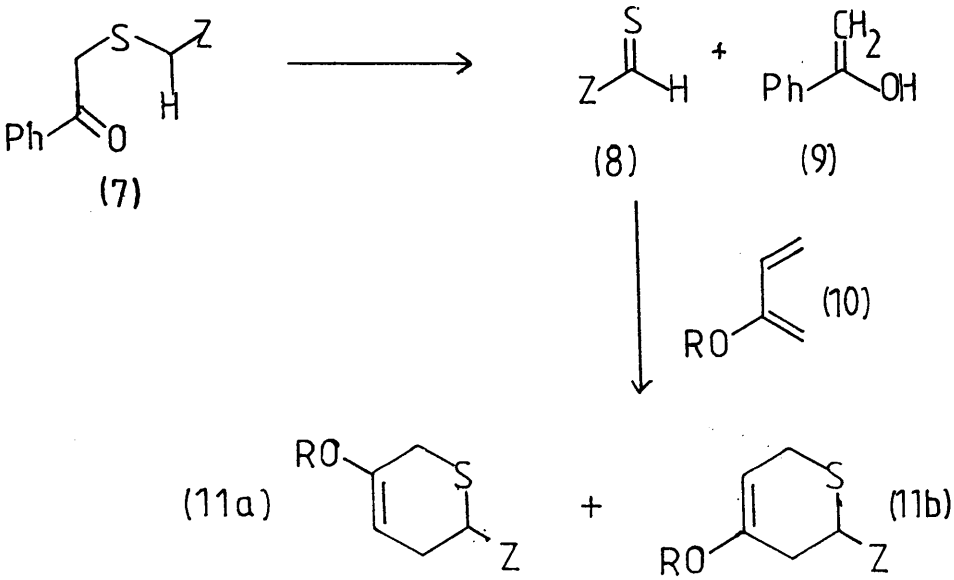


Scheme 1



Scheme 2

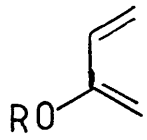
Chapter 1. Introduction

1.1. Pericyclic Reactions of Thioaldehydes

The pericyclic reactions of thioaldehydes had been entirely neglected until recently because thioaldehyde monomers were almost always too unstable to be isolated. Also, stable thioaldehydes, like those that are electronically stabilized, *e.g.* the pyrrole derivatives (1)[1], or sterically stabilized, *e.g.* tri-t-butylbenzenethial (2)[2] and tris(trimethylsilyl)ethanethial (3)[3], are of little use in synthesis because they are unreactive. Therefore, the synthetic applications of thioaldehydes depend upon good methods for their generation and trapping *in situ*, *e.g.* with conjugated dienes.

Photolysis of thietane (4) in the presnce of cyclopentadiene in the vapour phase at temperatures between 25 and 235°C was studied by Dice and Steer[4]. The product (6) clearly was derived from the Diels-Alder reaction of thioformaldehyde (5) and cyclopentadiene. The yield was found to increase with higher pressures of cyclopentadiene (Scheme 1).

In 1982, the Vedejs group, following an earlier observation by Woodward *et al.*, reported a mild, photochemical method for generating transient thioaldehydes[5]. The photolysis of phenacyl sulphides (7) afforded, by Norrish cleavage, the thioaldehydes (8) and the enol of acetophenone (9). These thioaldehydes, with an electron withdrawing group directly attached, were trapped successfully by a variety of dienes (10) to give the corresponding Diels-Alder adducts (11) (Scheme 2). The major adducts (11a) were found to be those with sulphur attached to the more electron-rich end of the diene. The same general selectivity pattern was



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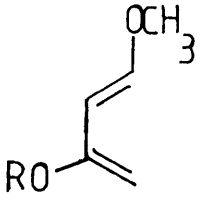

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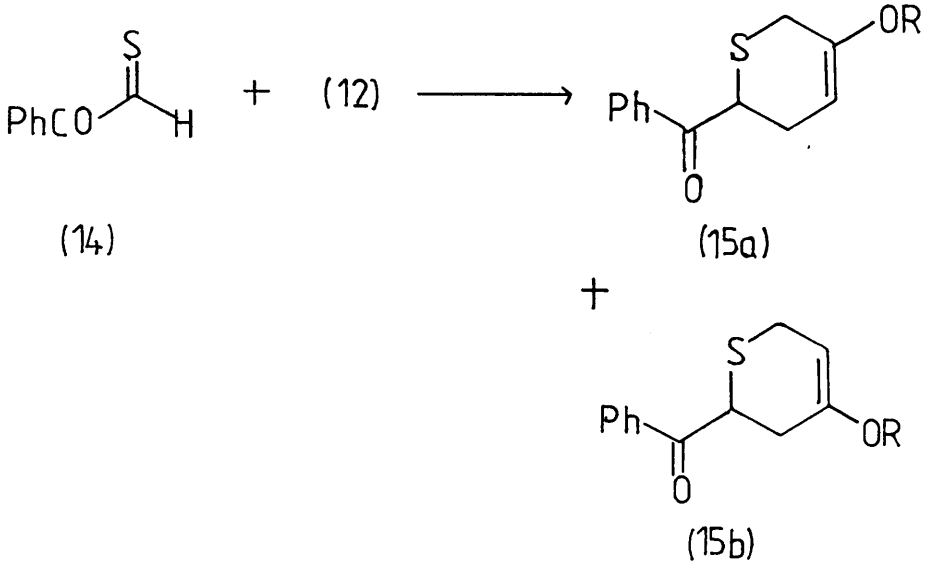
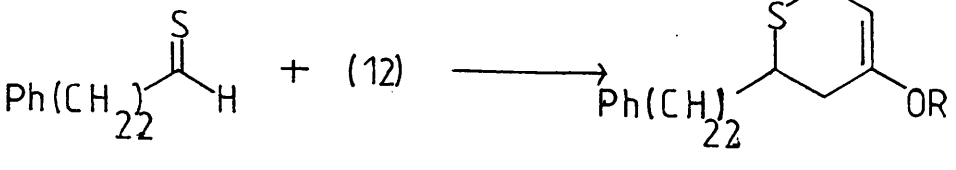


(14)

(15a)

(15b)

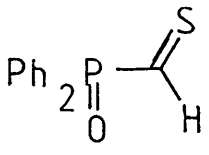


(16)

(17)

R = $SiMe_2Bu^t$

Scheme 3



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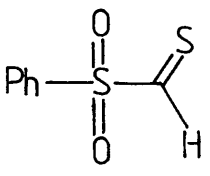
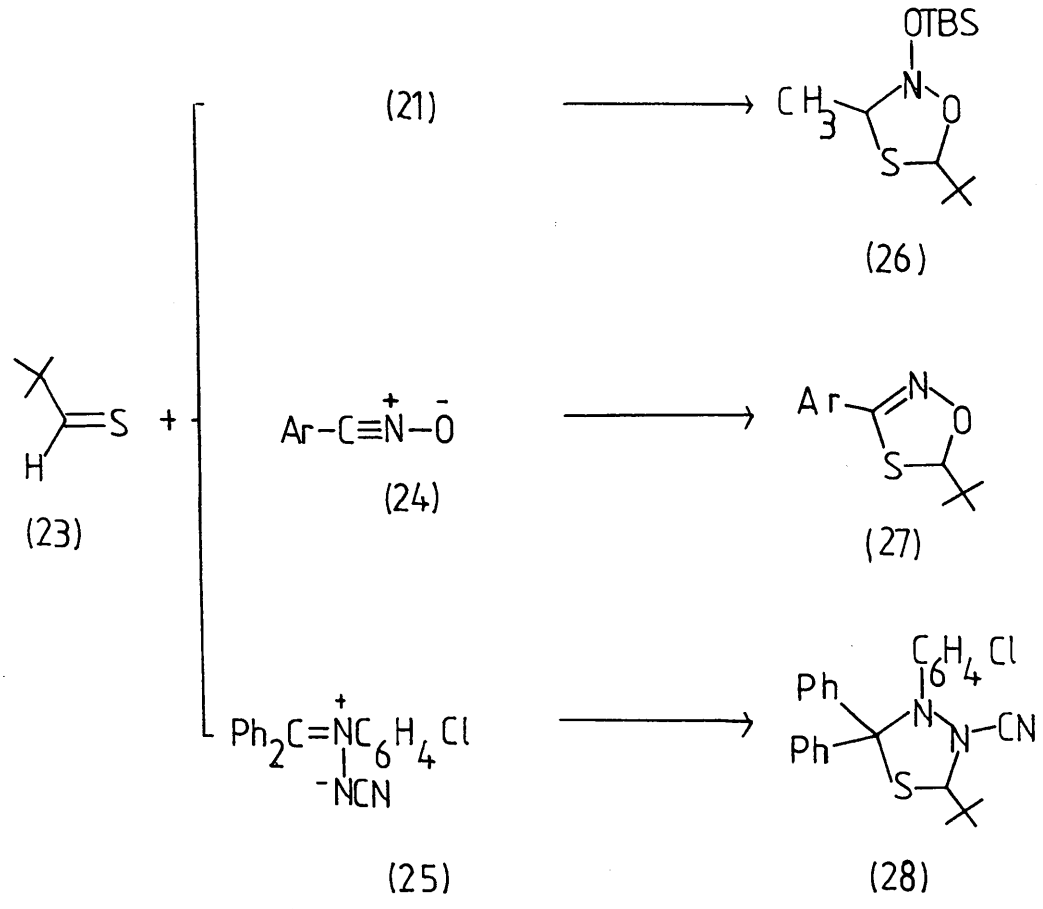
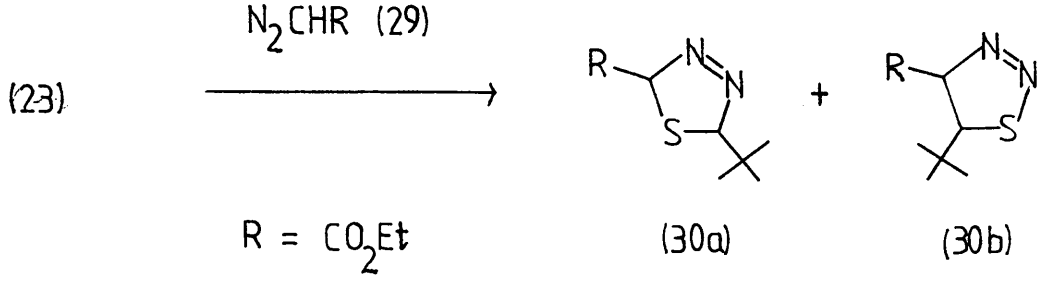


(19)

observed with dithioesters, but with greater selectivity. This was suggested to be due to the greater reactivity of thioaldehydes. However, they were unable to trap thiobenzaldehyde or thioacrolein with 2-ethoxybutadiene (10, R=Et). Later the same group reported successful trappings of thiobenzaldehyde and thioacrolein with 2-(tert-butyldimethylsiloxy)-1,3-butadiene (12) and with more effective Danishefsky diene (13)[7]. Recently, Vedejs *et al.* reported an extensive study on Diels-Alder reactions of the photo-chemically generated thioaldehydes[8], one class with electron-withdrawing groups, and the other class with electron-donating groups. It was found that the first class reacts efficiently with typical Diels-Alder dienes, especially with cisoid or donor-substituted derivatives, whereas the second class requires a large excess of the same dienes in order to react reasonably efficiently. The regioselectivity of the two series were found to be the reverse of each other. Thus, the thioaldehyde (14), having an electron-withdrawing group, PhCO, reacted with the diene (12) to give the cycloadduct (15a) as the major product (Scheme 3). In contrast, the thioaldehyde (16) lacking an electron-withdrawing group, gave exclusively the cycloadduct (17) of opposite regiochemistry. The difference in the regiochemistry of the adducts and in the rate of the Diels-Alder reactions could be rationalized by frontier MO considerations[7,8]. The photochemical route for generating thioaldehydes was extended to include examples such as Ph_2POCHS (18) and $PhSO_2CHS$ (19)[8]. They were also trapped by various dienes to give Diels-Alder adducts. As expected, since all these new types of thioaldehydes had electron-withdrawing groups, the regiochemistry of the major isomers corresponded to that of (15a) formed from the benzoyl derivative (14).

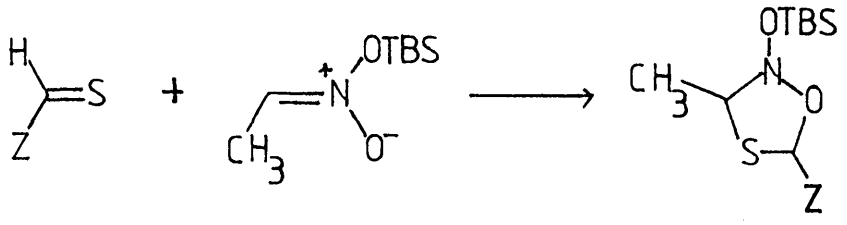


Scheme 5



Scheme 6

The thioaldehyde (20 a-b) were also reported to react readily with the highly reactive nitronate ester (21) to form 1,3-dipolar cycloadducts (22) (Scheme 4)[7]. Both the Danishefsky diene (13) and the 2-substituted-1,3-butadiene (12) were found to be less effective traps for thioaldehydes than the nitronate ester (21).



(20) (21) (22)

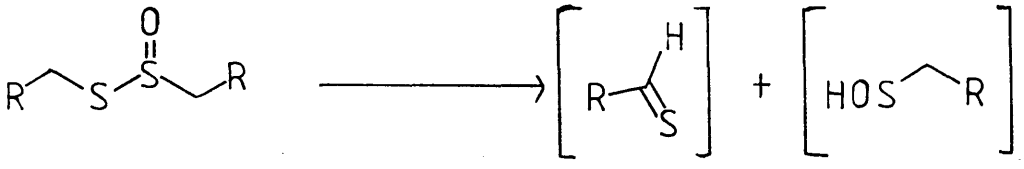
(a) Z = CH_2=CH

(b) Z = $PhCH_2CH_2$

TBS = $SiMe_2Bu^t$

Scheme 4

The preparation of reasonably stable solutions of thiopivaldehyde (23)[9] enabled the Vedejs group to study the reactivity of thioaldehydes as dipolarophiles. As expected, the thioaldehyde (23) reacted readily with representative 1,3-dipoles [the nitronate ester (21), the nitrile oxide (24), and the nitrile imine (25)], usually within minutes at room temperature, to give the corresponding [2+3] adducts (26-28) (Scheme 5). Only one regioisomer was obtained in each case. However, the reported [2+3] cycloaddition of thiopivaldehyde (23) with ethyl diazoacetate (29)[10] gave substantial amounts of the product (30b) of the more hindered cycloaddition (*ca.* 1:1 mixture of both regioisomers) (Scheme 6).



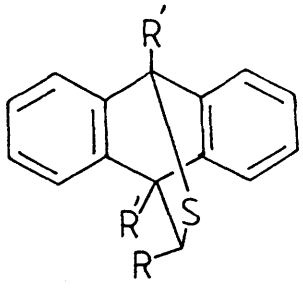
(31) (32) (33)

(a) R = Me

(b) R = Ph

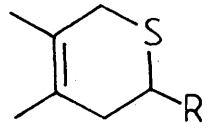
2 × (33) ⟶ (31) + H_2O

Scheme 7



(34) R' = H , (a) R = Me

(35) R' = Me , (b) R = Ph

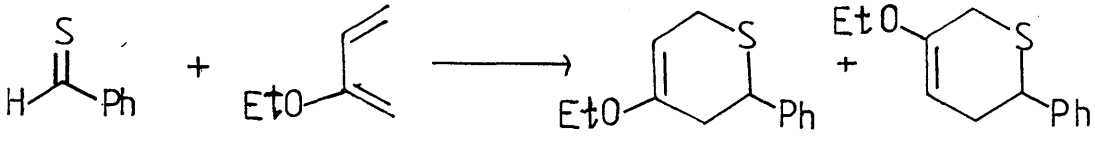


(36)

(a) R = Me

(b) R = Ph

Scheme 8

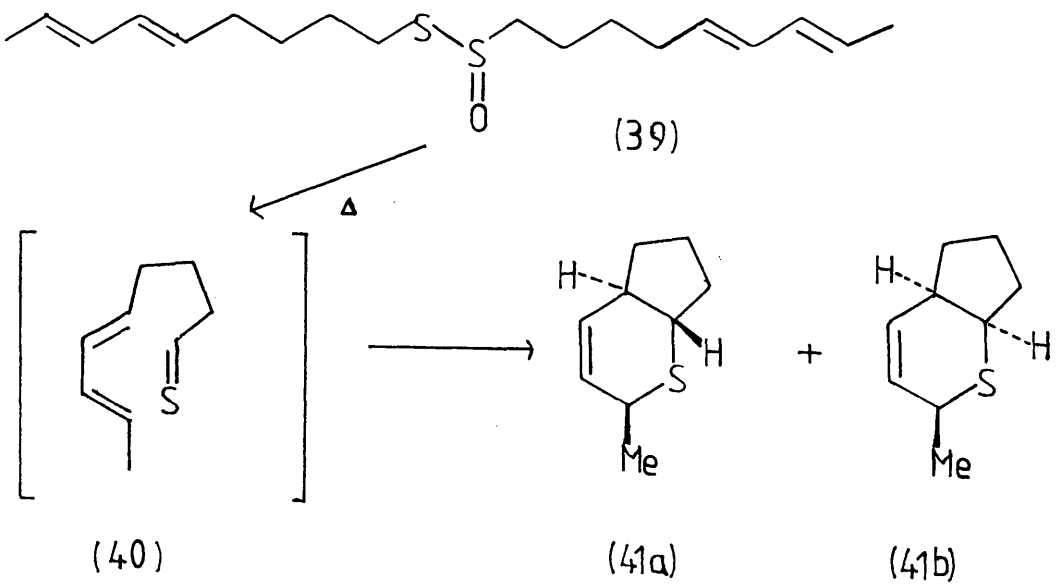


(32b) (37) (38a) (38b)

2.6 : 1

Scheme 9

Publication of photochemical method was closely followed by a report from Baldwin and Lopez[11] in which thioaldehydes were produced by the thermolysis of symmetrical alkyl thiosulphinates (31). This reaction, first discovered by Block and J. O'Conner[12], produced the thioaldehydes (32) and the sulphenic acids (33) as the initial products. The recombination of two molecules of the sulphenic acids (33) with elimination of water gave the starting thiosulphinates (31). Thus, eventually all the thiosulphinates were converted into the thioaldehydes (32) (Scheme 7). The thioaldehydes generated by this method were trapped efficiently by a variety of symmetrical 1,3-conjugated dienes such as anthracene, 9,10-dimethylanthracene and 2,3-dimethyl-1,3-butadiene to give the corresponding Diels-Alder adducts (34-36), apparently unaffected by the presence of the mol equivalent of water (Scheme 8). Both the anthracene adduct (34b) and the dimethylanthracene adduct (35b) were found to be an efficient and clean sources of thiobenzaldehyde (32b). Heating the adducts (34b) or (35b) with 2,3-dimethyl-1,3-butadiene in toluene gave the adduct (36b). Similarly, thiobenzaldehyde (32b) was trapped by the unsymmetrical 2-ethoxy-1,3-butadiene (37) to give the Diels-Alder adducts (38) (Scheme 9). As expected, the regioselectivity observed in this reaction of thiobenzaldehyde (32b) was less than when strongly electron-deficient thioaldehydes reacted with the same diene at room temperature[5]. This suggested that the latter thioaldehydes had a more effectively polarised thiocarbonyl group. The regioselectivity was also in the opposite sense, *i.e.* the isomer (38a) was the major product, suggesting that the phenyl group had acted as a non-electron-withdrawing group. Thiobenzaldehyde was successfully generated and trapped in this way with an acceptable yield, thus improving



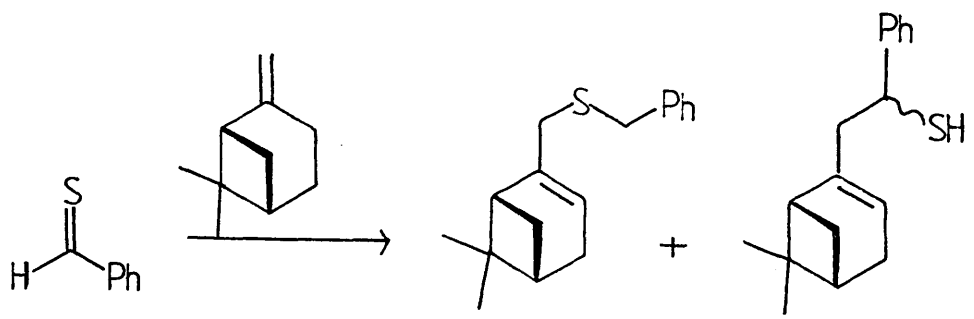
(39)

(40)

(41a)

(41b)

Scheme 10



(32b)

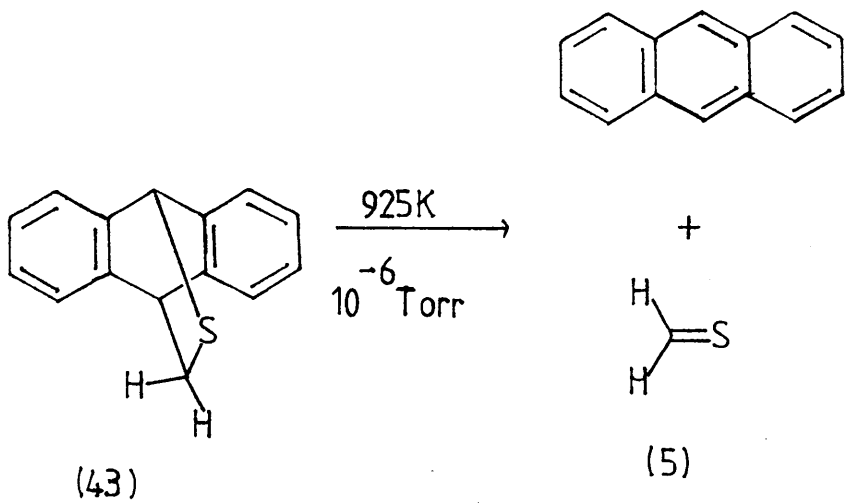
(42a)

(42b)

Scheme 11

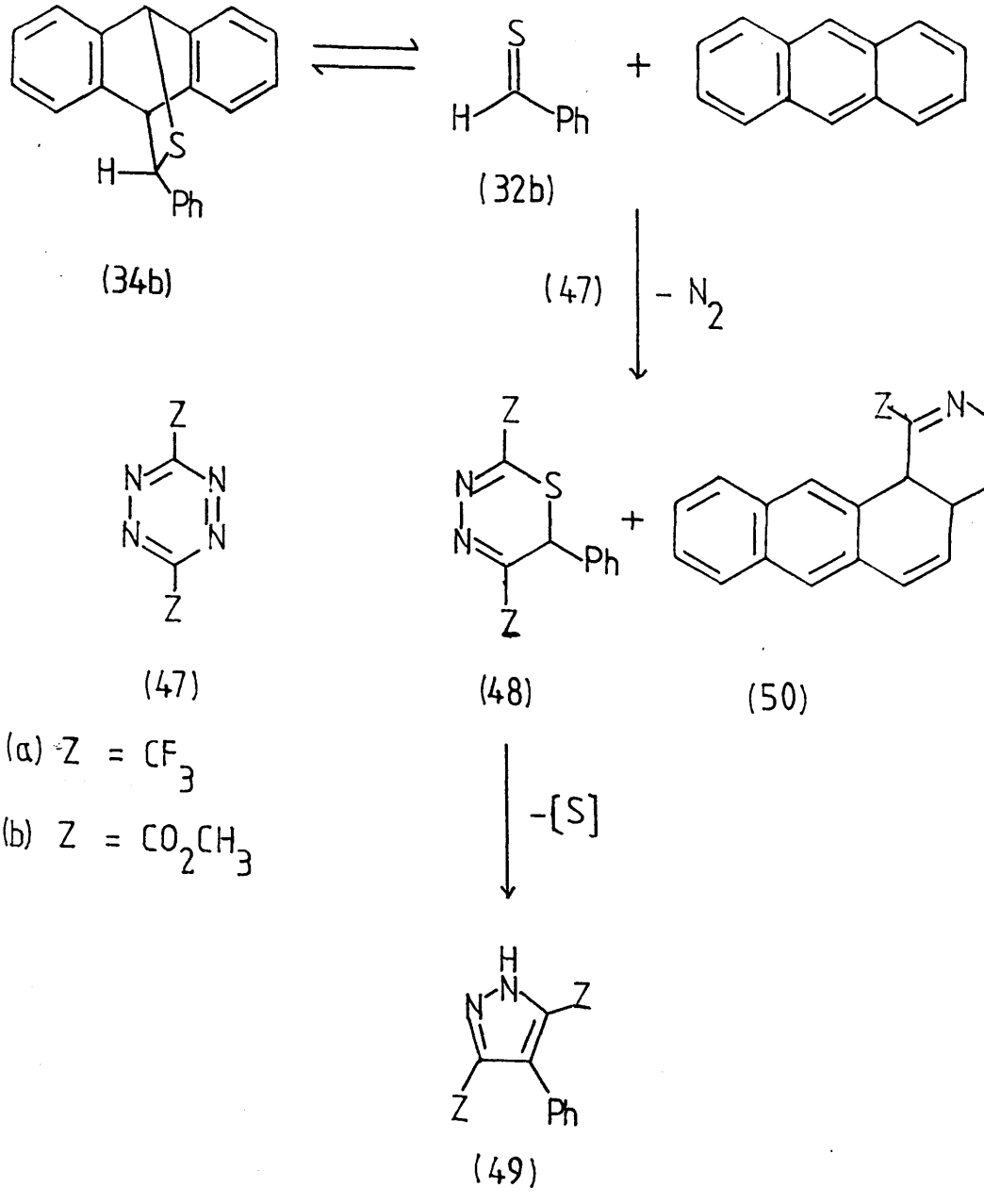
on the photochemical route[7]. The difference in temperatures may be crucial for improving the trapping efficiency of thiobenzaldehyde. The thermolysis of the thiosulphinate (39) gave, presumably, the transient thioaldehyde (40), which cyclised internally to give the Diels-Alder adducts (41a) and (41b) in a ratio of 1:1 (Scheme 10). This was the first reported example of an intramolecular Diels-Alder reaction of thioaldehydes. Thiobenzaldehyde (32b), generated by the thermolysis of the thiosulphinate (31b), gave a mixture of ene adducts (42a) and (42b) with β-pinene, in a ratio of 1:2 (Scheme 11).

Recently, flash vacuum pyrolysis of the anthracene adduct (43) was reported to afford methanethial (5) and anthracene *via* the retro Diels-Alder pathway[13] (Scheme 12).



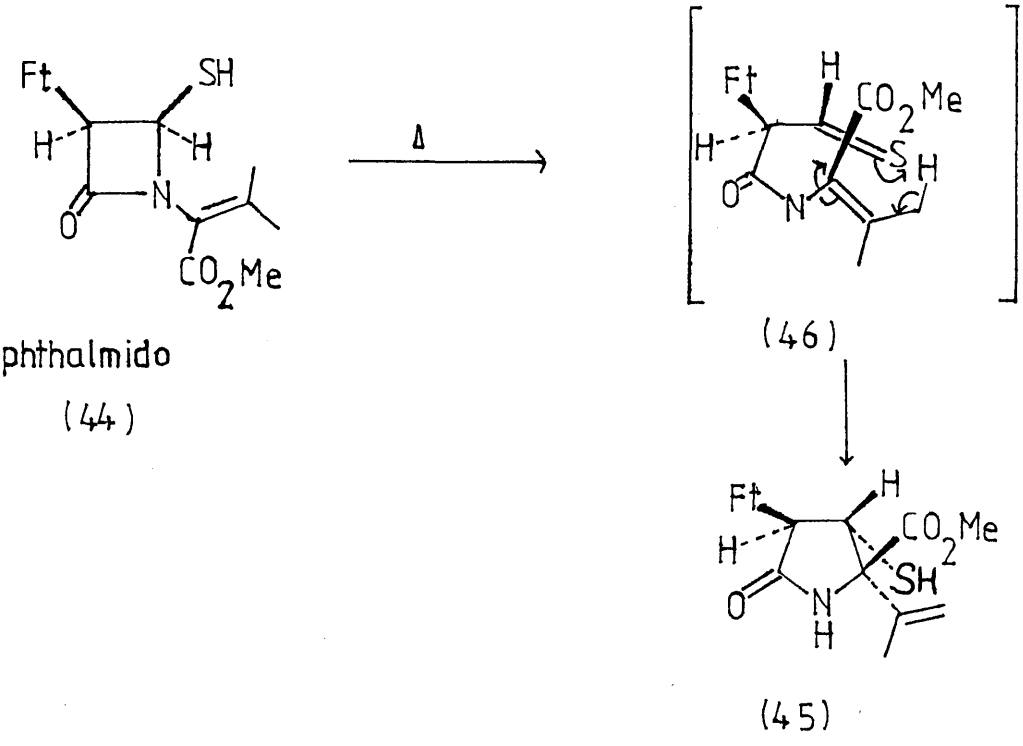
(43) (5)

Scheme 12



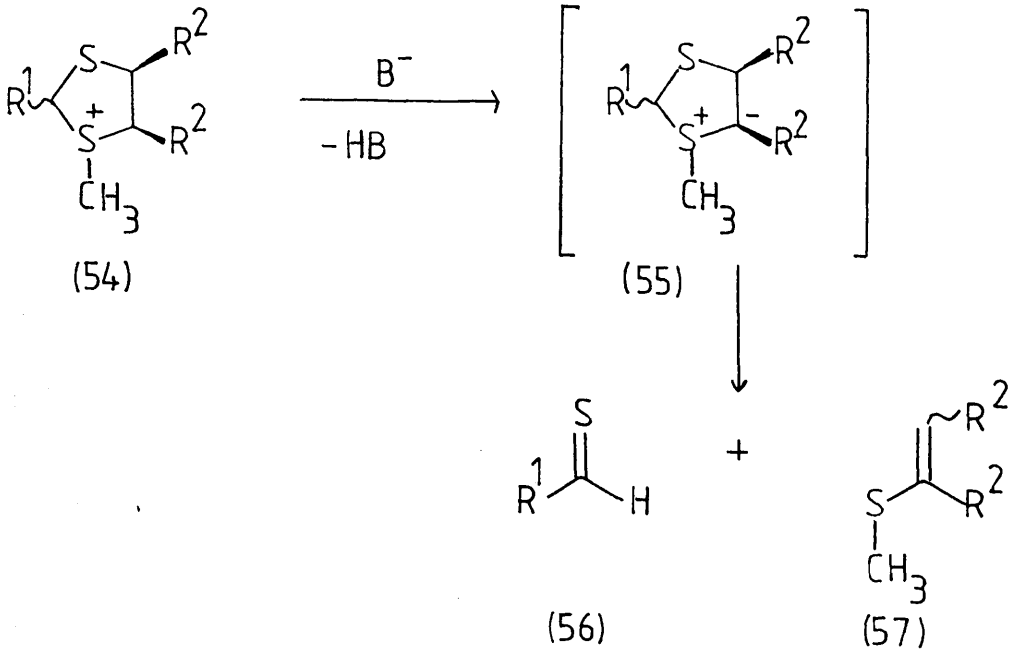
Scheme 14

In the pyrolysis of the 4-mercaptoazetidin-2-one (44), a new γ-lactam (45) was formed[14] (Scheme 13). Baldwin *et al.* suggested that the product was derived from the intramolcular ene reaction of the transient thioaldehyde (46), generated from the thermal opening of the β-lactam ring (44).

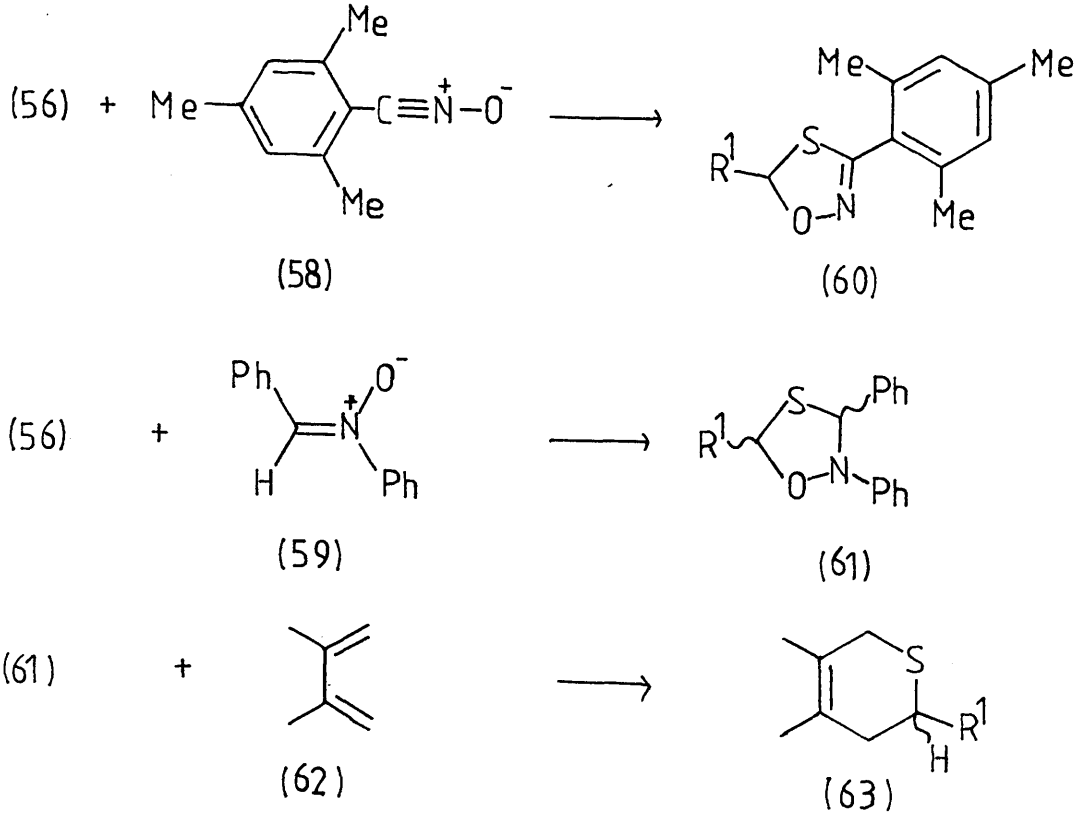


Scheme 13

Seitz *et al.* reported that thioaldehydes could also undergo "inverse" Diels-Alder reactions with tetrazines (47)[15]. Thus, thiobenzaldehyde (32b), generated in a retro Diels-Alder reaction from the cycloadduct (34b), was trapped by the tetrazines (47) with the extrusion of nitrogen to form the thiadiazines (48). Then the thiadiazines (48) underwent a ring contraction to form the 4-phenylpyrazoles (49) in moderate yields (Scheme 14). Interestingly, the tetrazines (47) also reacted with anthracene in a Diels-Alder manner to give the dihydronaphthophthalazines (50).

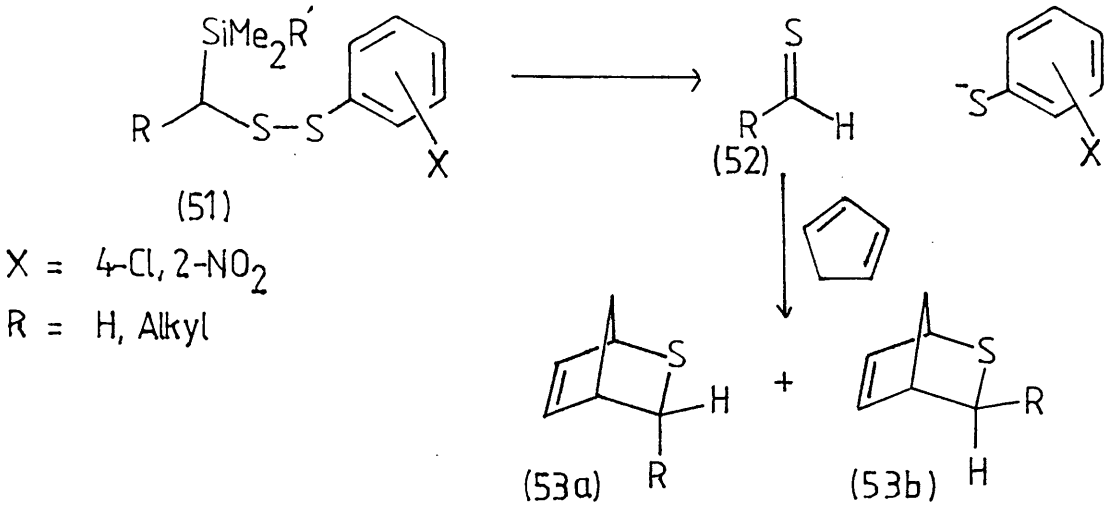


Scheme 16



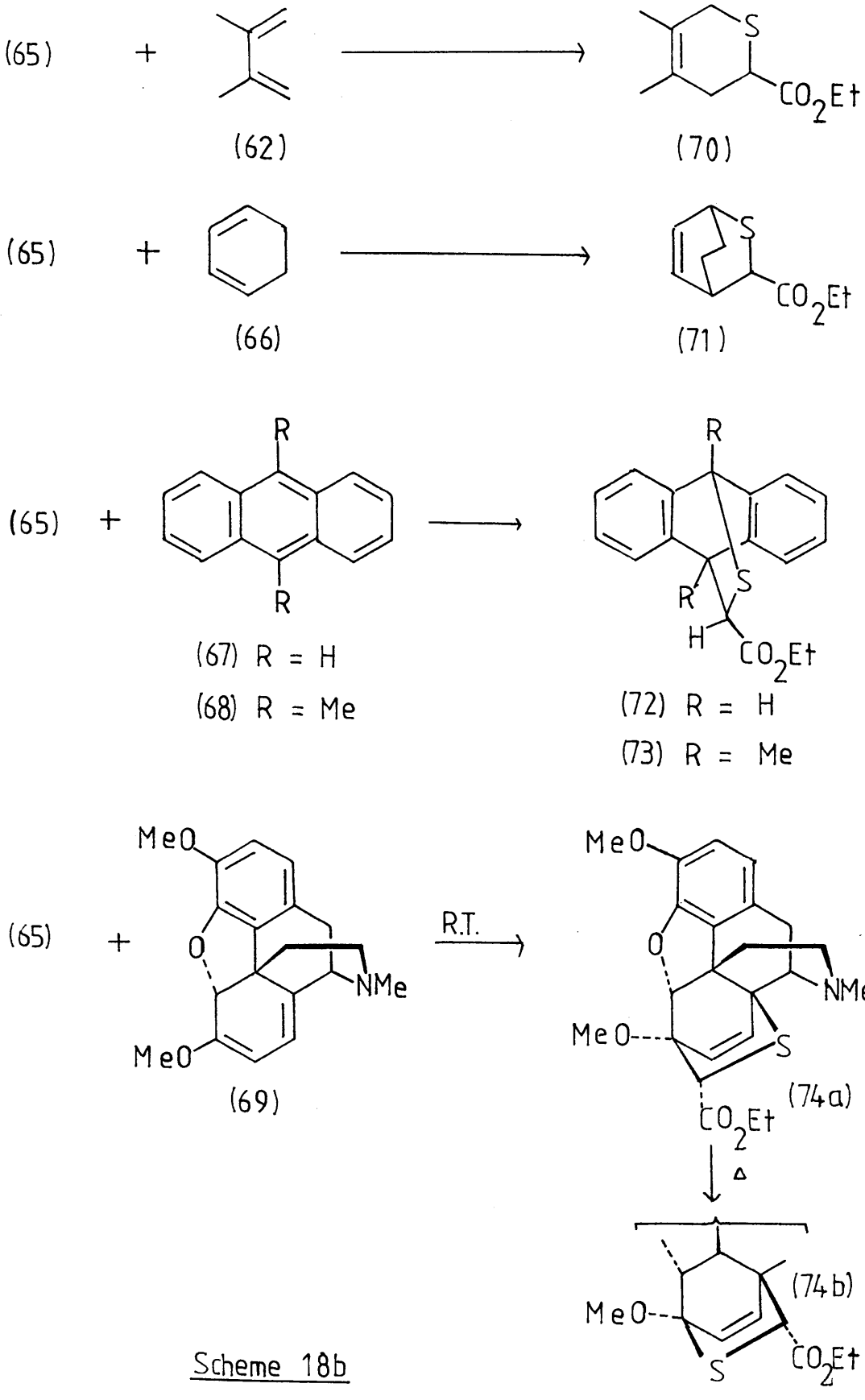
Scheme 17

An efficient method for the generation of thioaldehydes from α-silyldisulphides (51) was reported by Krafft and Mienke[16] (Scheme 15). Efficient trapping of the thioaldehydes (52) by cyclopentadiene resulted when the precursors (51) were cleaved by either caesium or tetrabutylammonium fluoride at 0-25°C. Mixtures of *exo*-(53b) and *endo*-adducts (53a) were obtained, with the *endo*-isomer (53a) predominating in all reactions.



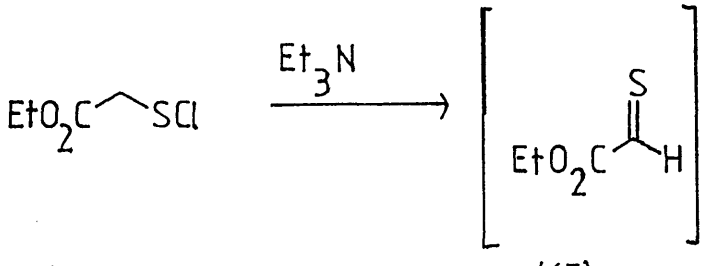
Scheme 15

Another convenient method for the generation of thioaldehydes under mild conditions was reported by Schaumann and Ruhter[17]. Deprotonation of the thioaldehyde precursor sulfonium salts (54) with sodium hydride or lithium diisopropylamide gave the ylides (55), which underwent spontaneous fragmentation to give the vinyl sulphides (57) and the thioaldehydes (56) (Scheme 16). The thioaldehydes (56) were trapped efficiently with mesitonitrile oxide (58) and with benzylidenaniline *N*-oxide (59) as the [2+3] adducts (60) and (61), respectively. When the [2+3] adduct (61) was heated in toluene with 2,3-dimethyl-1,3-butadiene (62), the thioaldehyde (56) generated was trapped as its Diels-Alder adduct (63) (Scheme 17).


(65)
(62)
(70)
(65)
(66)
(71)
(65)
(67) R = H
(68) R = Me
(72) R = H
(73) R = Me
(65)
MeO
NMe
(69)
R.T.
(74a)
(74b)

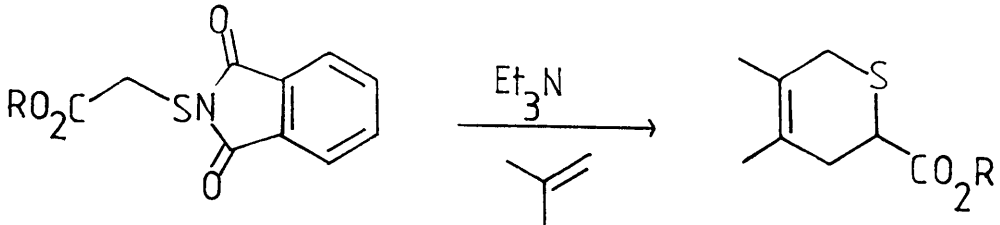
Scheme 18b

Shortly after Baldwin's thermolysis method[11] of generating thioaldehydes, Kirby *et al.* reported the formation of ethyl thioxoacetate (65) from the sulphenyl chloride (64) by elimination of hydrogen chloride with triethylamine (Scheme 18a). The thioaldehyde (65) was trapped, *in situ* by cycloaddition to various conjugated dienes, such as 2,3-dimethyl-1,3-butadiene (62), 1,3-cyclohexadiene (66), anthracene (67), 9,10-dimethyl-anthracene (68), and the alkaloid thebaine (69) to give their corresponding adducts (70-74)[18] (Scheme 18b). When the thebaine adduct (74a), prepared at room temperature, was heated under reflux in toluene for 8h, clean conversion into the isomer (74b) was observed, indicating that the isomer (74a) has been formed under kinetic control. Also, the anthracene and 9,10-dimethylanthracene adducts (72) and (73), were found to be clean sources of ethyl thioxoacetate (65). A clean transfer of the thioxoacetate (65) from the anthracene and 9,10-dimethyl-anthracene adducts to either thebaine (69) or 1,3-cyclohexa-diene (66) was observed.



(64) (65)

Scheme 18a



(75)

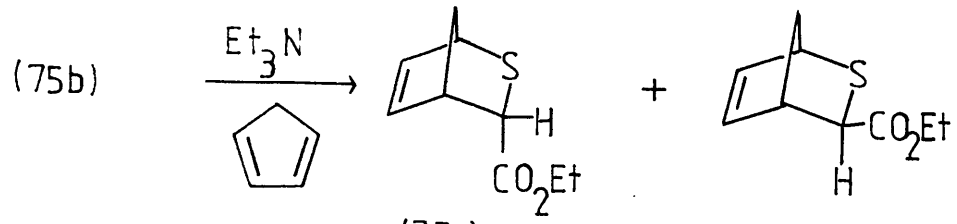
(a) R = Me

(b) R = Et

(62)

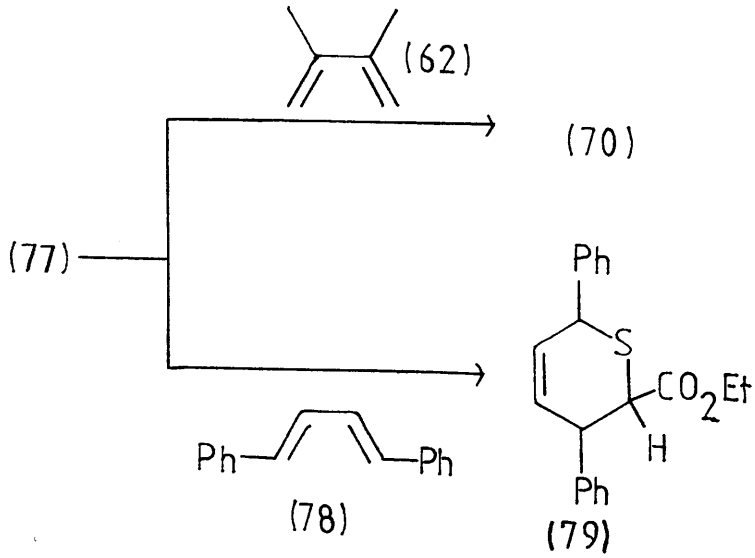
(76) R = Me

(70) R = Et



(77a)

(77b)

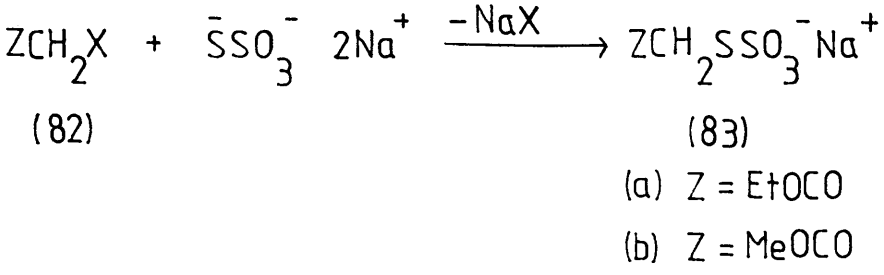


(78)

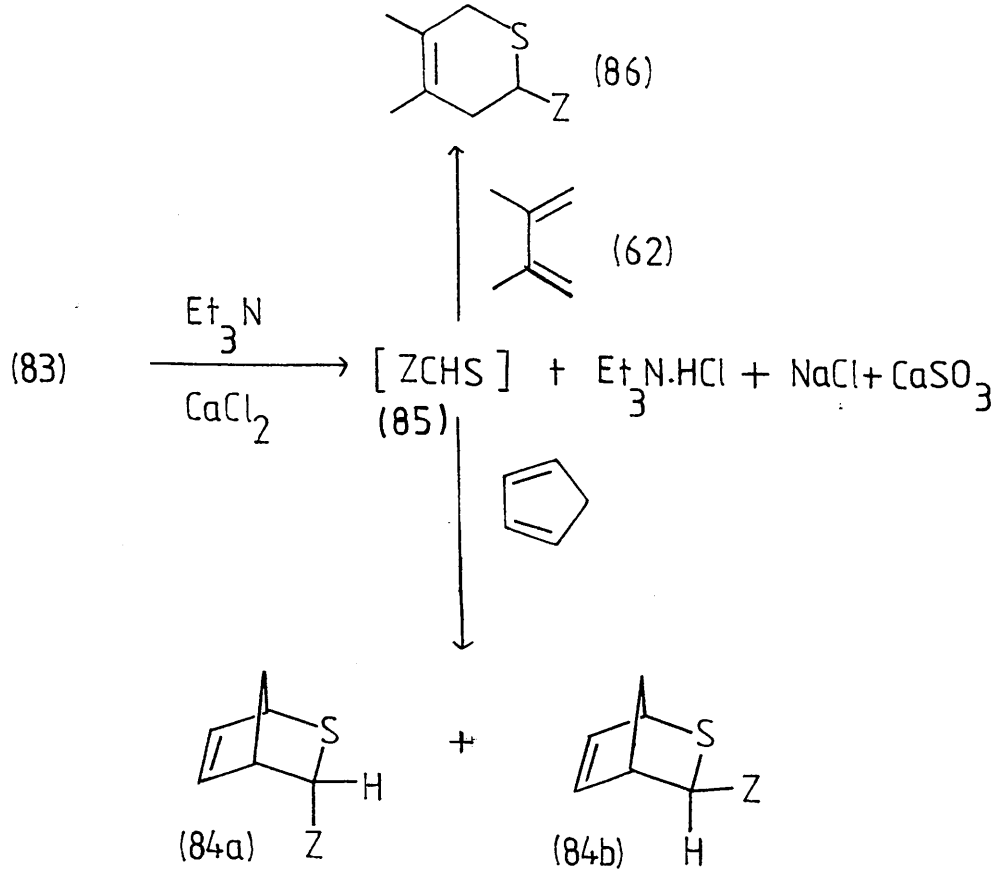
(79)

However, the sulphenyl chloride elimination route (Scheme 18) had its limitations. If the diene reacted with the sulphenyl chloride before elimination, as in the case of 1,3-cyclohexadiene (66), yields of adducts would be low. An alternate route employing *N*-(alkoxycarbonylmethylthio)phthalimides (75) was reported later by the same group[19]. The *N*-thiophthalimides (75a, R=Me) and (75b, R=Et) were treated with triethylamine in the presence of 2,3-dimethyl-1,3-butadiene (62) to afford the corresponding adducts (76) and (70) in excellent yields. The *exo*-(77b) and *endo*-adducts (77a) were produced almost quantitatively, in the ratio 3:7, at room temperature with cyclopentadiene as the diene. Heating the kinetically determined mixture of (77a) (70%) and (77b) (30%), or each isomer separately, in toluene under reflux for 7h gave, clearly, a mixture of *exo*-(77b) (70%) and *endo*-isomers (77a) (30%). This suggested the cyclopentadiene adducts (77) might, by thermal dissociation, be used preparatively as a 'clean' source of ethyl thioxoacetate (65) since the only by-product, cyclopentadiene, could be readily removed by evaporation. The value of employing cyclopentadiene adducts (77) as a source of thioxoacetate (65) was demonstrated by the successful transfer of the thioxoacetate (65) from the cyclopentadiene adducts to form the 2,3-dimethyl-1,3-butadiene adduct (70) and the *trans,trans*-1,4-diphenyl-1,3-butadiene adduct (79). In the latter transfer experiment, a slow stream of argon was used to remove cyclopentadiene, liberated in the reaction, and thus prevent recapture of the thioaldehyde; otherwise formation of the adduct (79) was inconveniently slow.

Scheme 20

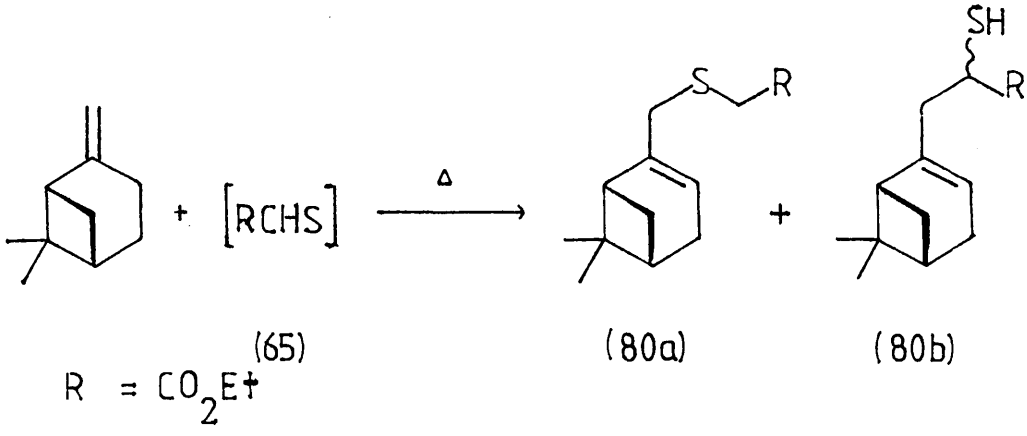


Scheme 21



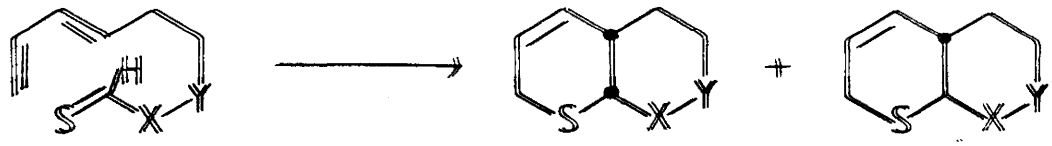
Scheme 22

Ethyl thioxoacetate (65), generated from the thermolysis of the anthracene adduct (72) in boiling toluene, reacted with (-)-β-pinene to afford two ene products (80a) (78%) and (80b) (21%)[20] (Scheme 19).



Scheme 19

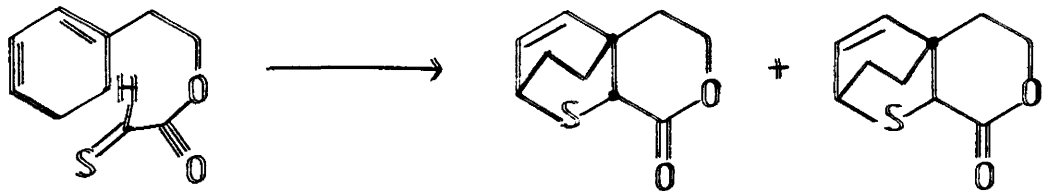
It was realized that a general series of thioaldehyde precursors (81) was possible where X is a good leaving group and Z is an electron-withdrawing group able to render the methylene protons acidic enough for mild, base-induced elimination (Scheme 20). Thus, the new series of precursors (81, X=SO_3Na) was studied[21]. These precursors are known as 'Bunte Salts', readily available from the treatment of simple alkyl halides (82) with sodium thiosulphate (Scheme 21). These thiosulphate *S*-esters were first described by the German chemist Hans Bunte[22]. Treatment of the Bunte salt (83) with triethylamine in the presence of cyclopentadiene and calcium chloride dihydrate gave high yields of a mixture of the *exo*-(84b) and *endo*-adducts (84a), the *endo*-isomers being the major isomer (Scheme 22). Similarly, the thioaldehyde (85) were also trapped by the less reactive 2,3-dimethyl-1,3-butadiene (62) to give reasonable yields of the desired adduct (86) (Scheme 22).



(90) X=Y=CH_2 ⟶ (94)

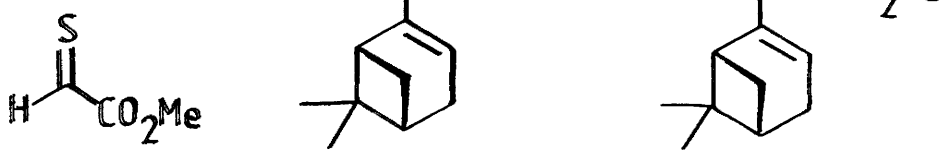
(91) Y=CH_2, X=C(O) ⟶ (95)

(92) Y=O, X=C(O) ⟶ (96)



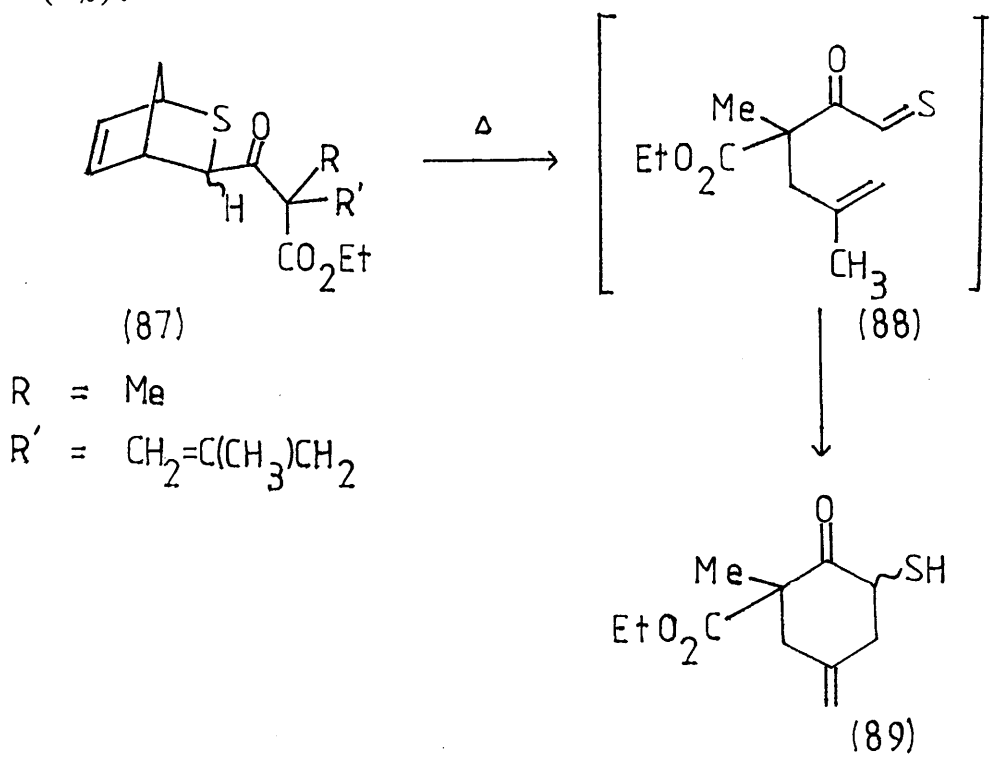
(93) (97)

Scheme 24

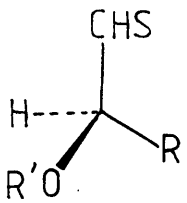


(98) (99) (100)

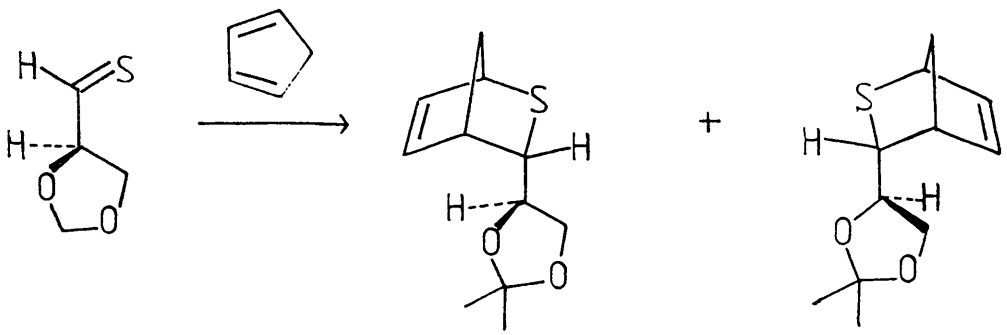
Recently, Vedejs *et al.* reported both intramolecular Diels-Alder reactions and ene reactions of thioaldehydes[23]. When the thioaldehyde precursor (87) was thermolysed in toluene in a sealed tube at 140°C for 2h, a mixture of diastereomeric thiols (89) resulted *via* an intramolecular ene reaction of thioaldehyde (88) (Scheme 23). The thioaldehyde (90-93), generated by photolysis of the corresponding phenacyl sulphides [*c.f.*(7)], underwent intramolecular Diels-Alder reactions to afford the cycloadducts (94-97) (Scheme 24). Methyl thioxoacetate (98), generated photochemically from its phenacyl sulphide (7, Z=CO_2Me), at 20°C, reacted with β-pinene to give the allyl sulphide (99) in 75% yield, and the isomeric thiol (100) was not formed. In contrast, pyrolysis of the cyclopentadiene adducts of methyl thioxoacetate (84, Z=$MeCO_2$) at 100°C in the presence of β-pinene for 20h afforded the sulphide (99) (74%) and the thiol (100) (2%).



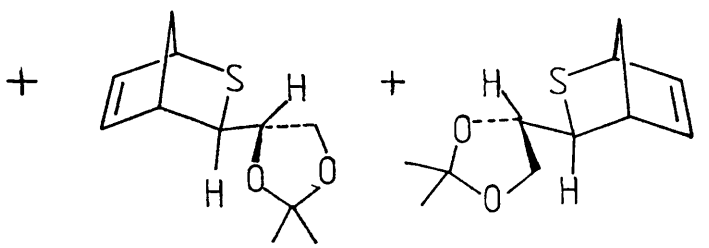
Scheme 23



(101)



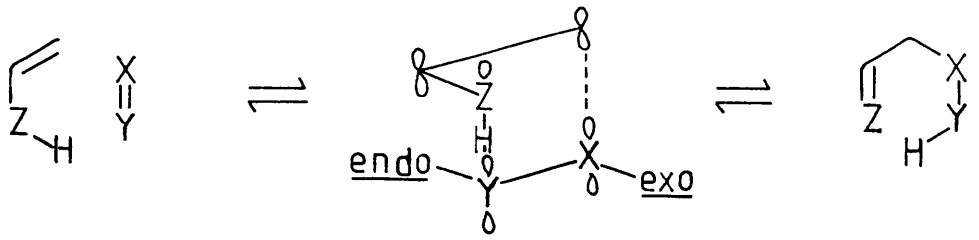
(102) (103a) (82%) (103b) (2.5%)



(103c) (15%) (103d) (0.5%)

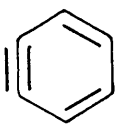
Scheme 25

Very recently, Vedejs *et al.* reported the Diels-Alder reactions of chiral α-oxygen substituted thioaldehydes (101) and it was shown that the reaction proceeded with selectivity for one face of the thioformyl group[24]. The highest face selectivity was obtained with the acetonide of thioglyceraldehyde (102) (Scheme 25).



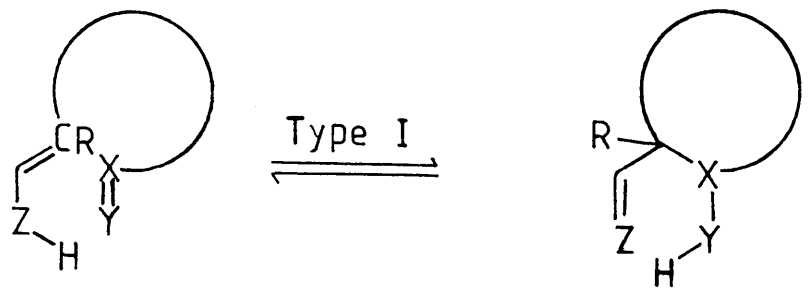
(A)

X=Y = >C=C< , >C=O , >C=S , O=O ,

-N=O , -N=N- ,  .

Z = CR_2 , O.

Scheme 26

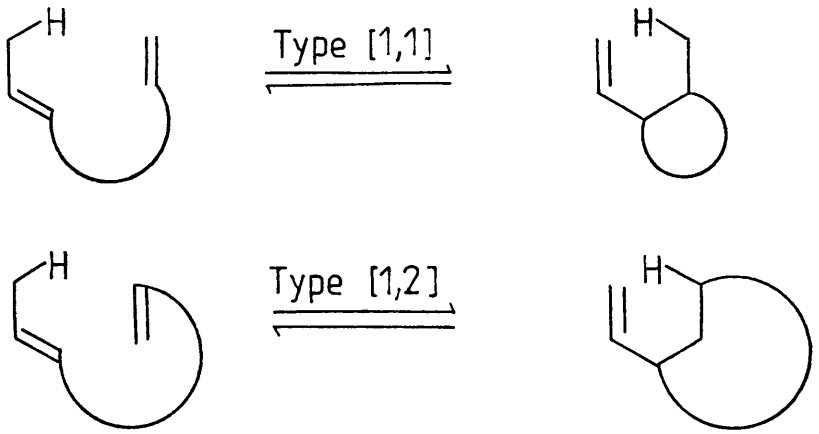


Scheme 27

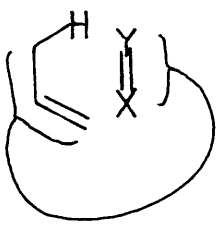
1.2. The Intramolecular Ene Reaction

Although ene reactions have been known for over 40 years, it is only until recently that the synthetic value has been recognised and studied. The ene reaction is the addition of a compound with multiple bond, the enophile, to an olefin containing an allylic hydrogen, the ene, and involves an allylic shift of one double bond, transfer of the allylic hydrogen to the enophile and bonding between unsaturated termini (Scheme 26). Experimental evidence[25] and orbital symmetry considerations[26] are consistent with a concerted pathway involving a supra-suprafacial, *endo*- or *exo*-oriented interaction (Scheme 26). However, recent calculations[26] concerning ene process suggest that in the transition state (A) the C-X bond is more developed than the H-Y bond (Scheme 26). The ene reaction has been reviewed by different authors; Hoffmann on the mechanistic and preparative aspects[27], Oppolzer and Snieckus[28] and Taber[29] on intramolecular ene reactions, and Snider[30] on Lewis acid catalysed ene reactions.

The intramolecular ene reaction has obvious entropic advantage over the intermolecular reaction and exhibits preparatively useful regio- and stereo-selectivity. Three different modes of thermally induced cyclizations (and cycloreversions) were defined by Oppolzer and Snieckus[28] (Scheme 27) In a Type I ene reaction the enophile is attached to the olefinic terminal of the 3-carbon ene unit by an appropriate bridge. In a Type II process, attachment is to the central atom of the ene unit, and in a Type III process attachment is to the allylic terminal of the ene unit. However, Snider and Phillips suggested there were in principle six types of intramolecular ene reactions[31], since the new bond formed can be attached at



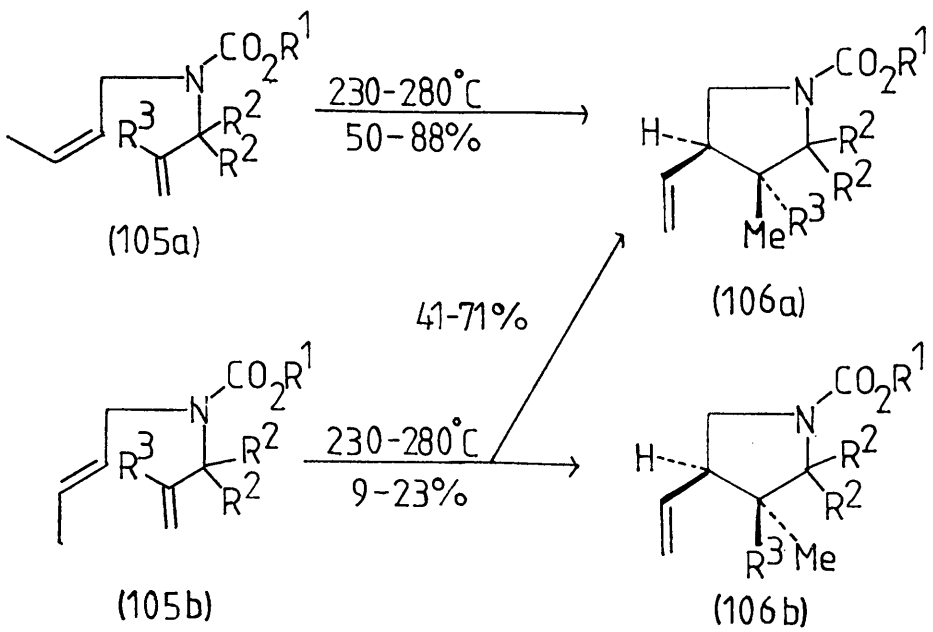
Scheme 28



X=Y = $-C\equiv C-$, $\diagdown C=C \diagup$, $\diagdown C=O$, $\diagdown C=S$,

$-N=O$, $-N=N-$

(104)



Scheme 29

either two positions on the enophile (Scheme 28). Using this terminology, Oppolzer's Type I becomes [1,1] or [1,2], Type II becomes [2,1] or [2,2] and Type III becomes [3,1] or [3,2].

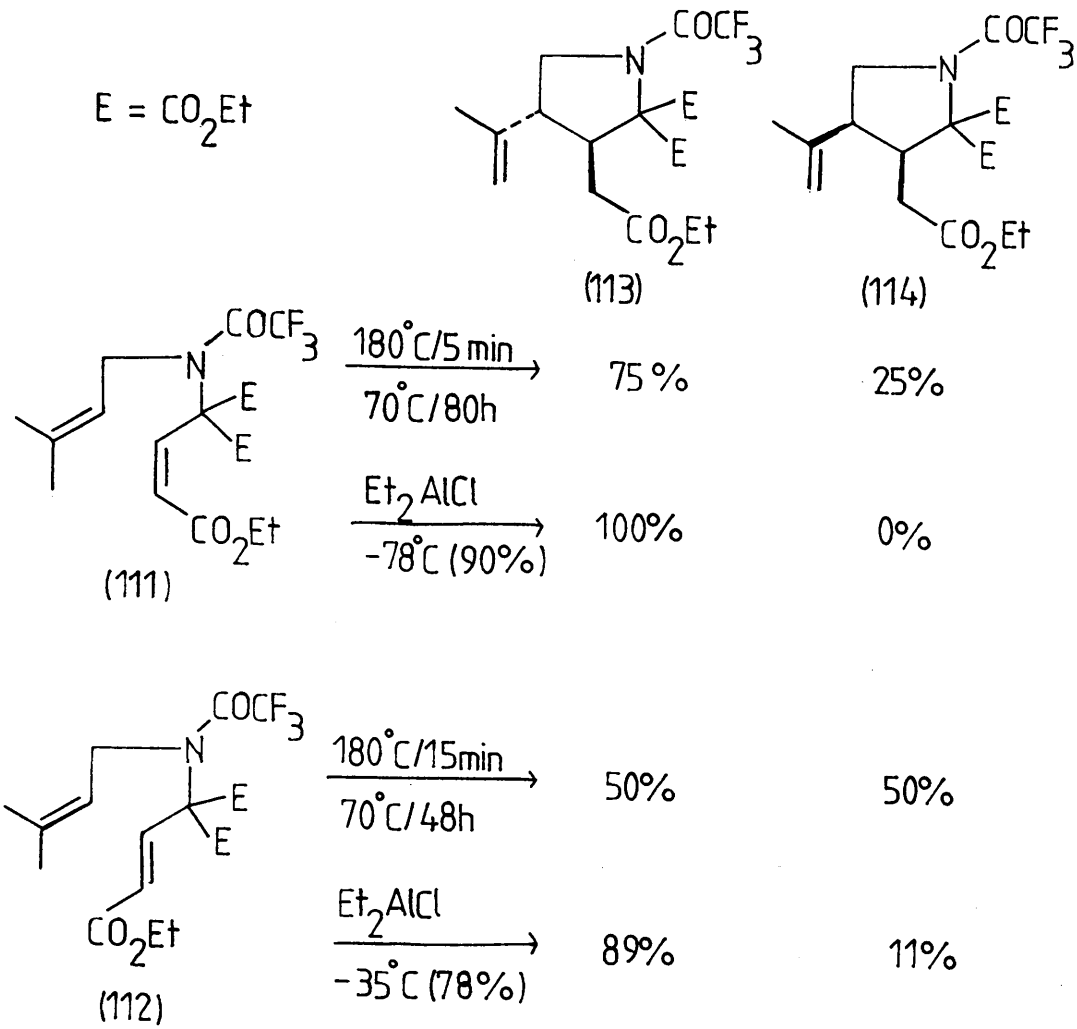
Since the ene unit in our study involved an olefin with an allylic carbon containing a hydrogen, the following discussion would be limited to the intramolecular ene reaction of this particular type of ene (104).

1.2.1. Olefinic and Acetylenic Enophiles

The intramolecular ene reactions involving olefinic or acetylenic enophiles have been comprehensively reviewed by Oppolzer and Snieckus[28], and Taber[29].

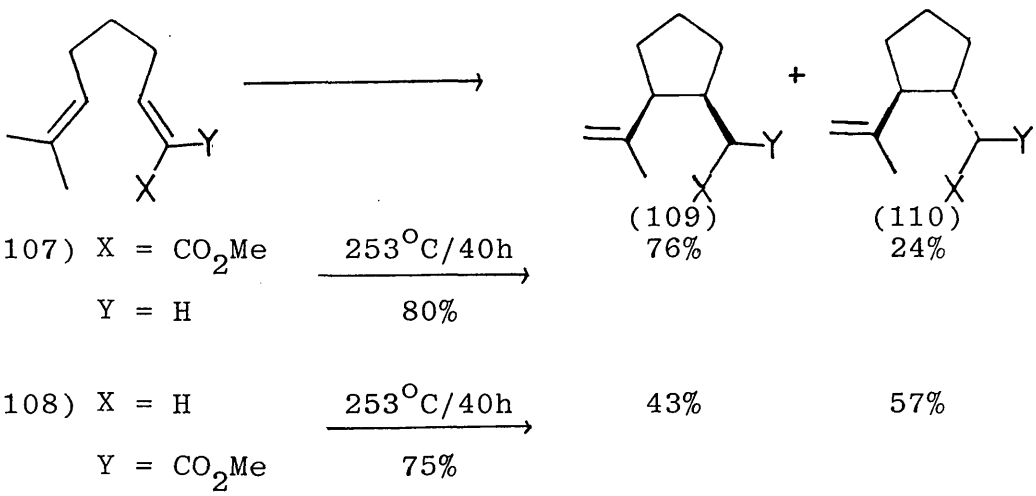
The majority of intramolecular ene reactions are concerned with the thermolysis of 1,6-dienes. The first systematic investigation of the influence of ene geometry on the stereochemistry of intramolecular ene products dealt with the regioselective thermal cyclization of the *N*-allyl-*N*-(2-butenyl)amides (105a) and (105b)[32] (Scheme 29). The *cis*-dienes (105a) reacted under kinetic control with 100% stereoselectivity to afford (106a), whereas the *trans*-dienes (105b) furnished at the same temperature in addition to (106a) minor amounts of the *trans*-isomer (106b). From these studies, it appeared that not only the stereochemical outcome but also the rate of intramolecular ene reaction of 1,6-dienes may be largely independent of the ene-geometry.

In a recent study of stereochemical control in Type I intramolecular ene reactions of the 1,6-dienes (107) and (108)[33] (Scheme 30). Ghosh and Sarker showed that the rate of intra-

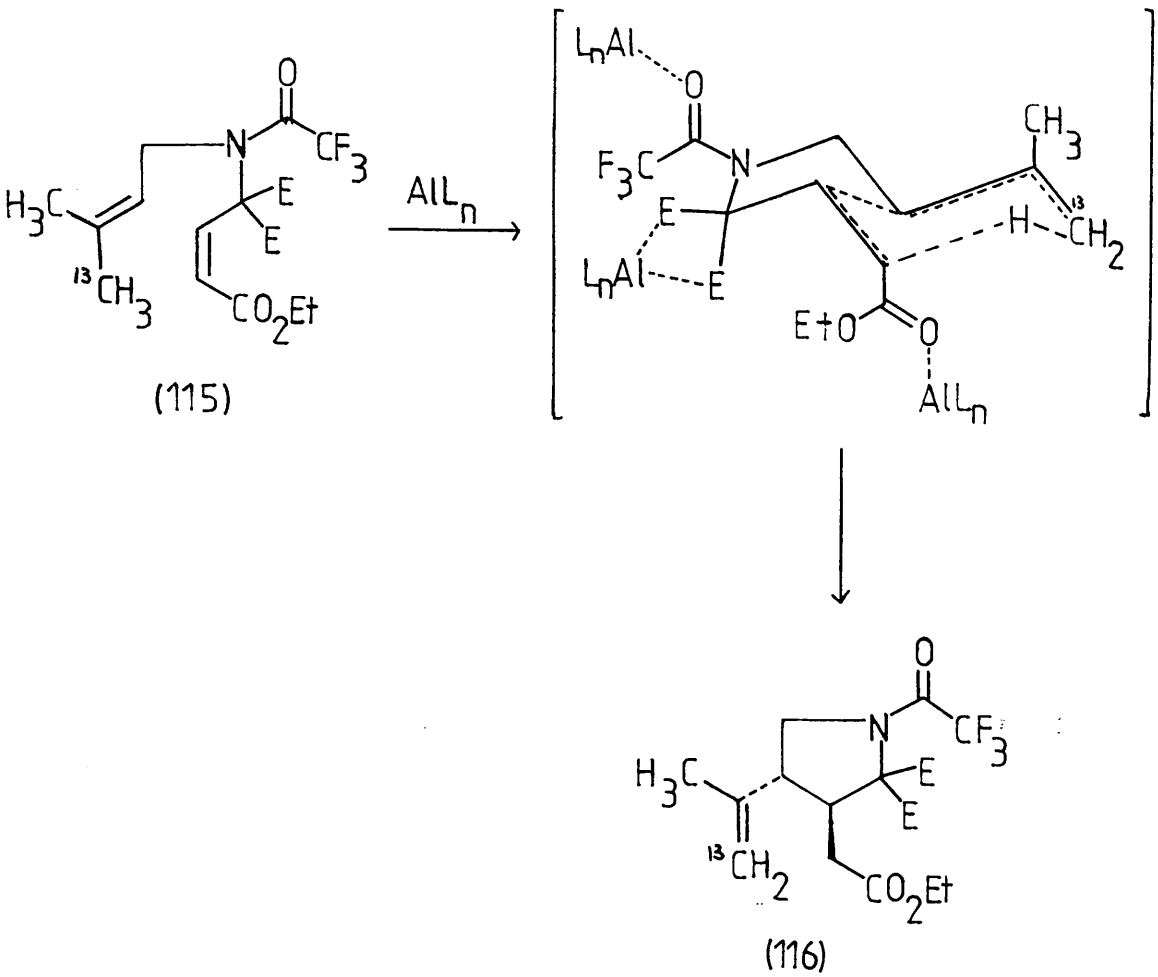

E = CO2Et
COCF3
N
E
E
CO2Et
(113)
(114)
(111)
(112)
180°C/5 min
70°C/80h
75 %
25%
Et2AlCl
-78°C (90%)
100%
0%
180°C/15min
70°C/48h
50%
50%
Et2AlCl
-35°C (78%)
89%
11%

Scheme 31

molecular ene reaction of 1,6-dienes appeared to be largely independent of the enophile geometry. In contrast, the enophiles substitution pattern had a direct effect on the stereochemical outcome in these reactions. Thus, while the *E*-diene (107), gave largely the *cis*-product (109), the *Z*-diene (108) gave a small excess of the *trans*-isomer (110). In addition, in an early study of the diastereoselectivity of intramolecular ene reactions of the bisethoxycarbonylsubstituted enoates (111) and (112)[34], Oppolzer and Robiani reported a 50% diastereoselectivity in favour of the *trans*-product (113) from the thermolysis of (*Z*)-enoate (111), while a 50:50 mixture of *trans*-(113) and *cis*-products (114) was obtained from the thermolysis of (*E*)-enoate (112). Cyclization of (111) and (112) in the presence of diethylaluminium chloride, which acted as a mild Lewis acid and HCl scavenger, resulted in an enormous rate acceleration and improved diastereoselectivity (Scheme 31).



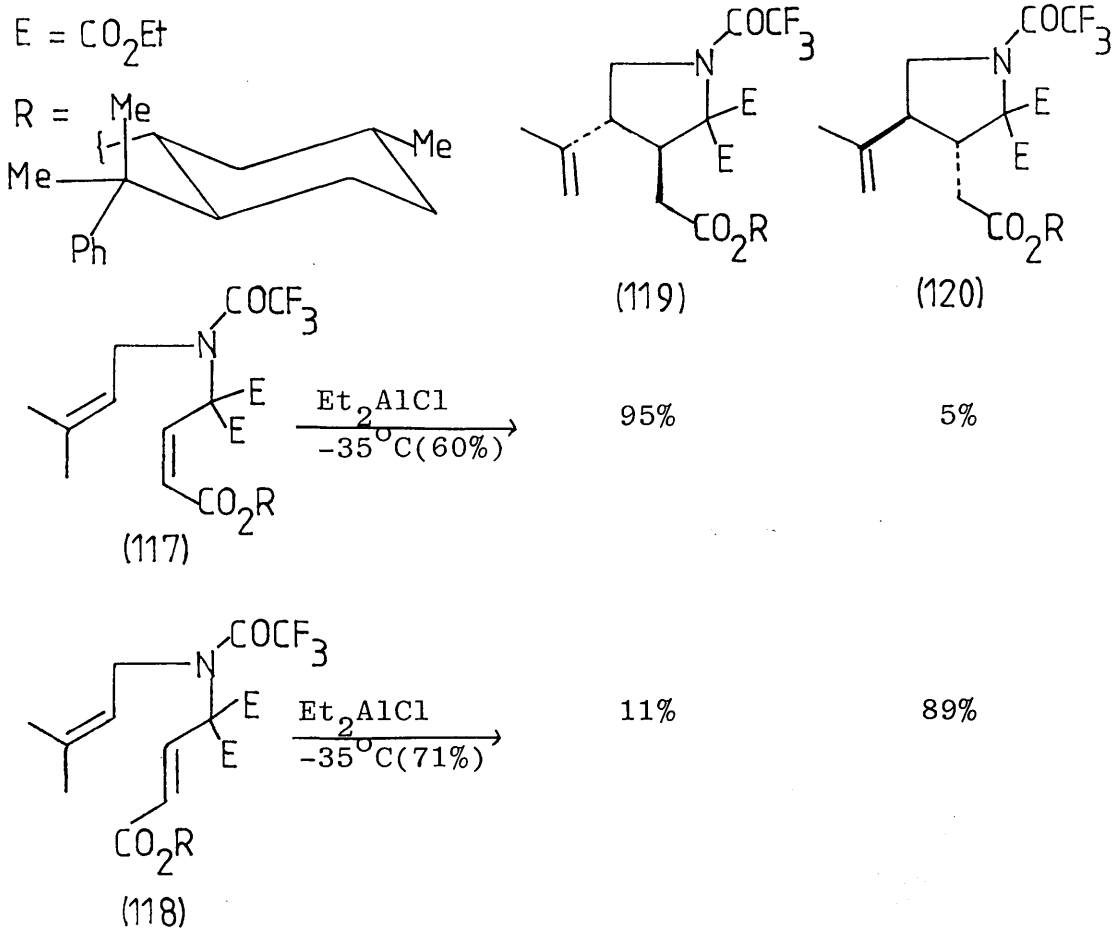
Scheme 30



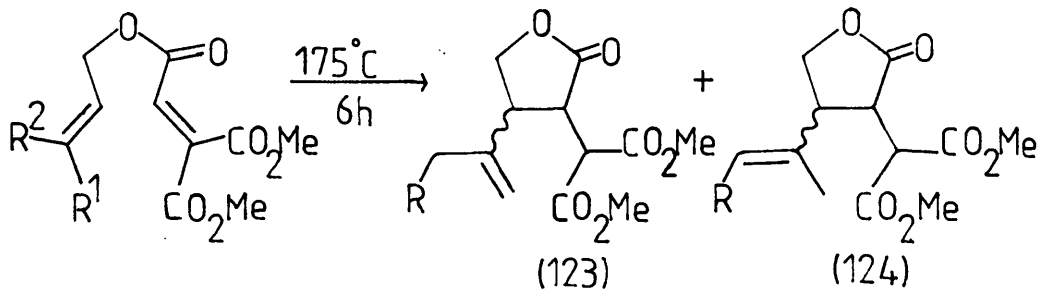
Scheme 32

Oppolzer and Mirza later reported the treatment of the 1,6-dienoate (115), labelled with ^{13}C selectively (83%) in the *trans*-methyl group, with Et_2AlCl at -78°C[35]. The ene product (116) was enriched with ^{13}C (83%) only in the olefinic methylene group, showing that H-transfer occurred exclusively from the *trans*-methyl group of the dienoate (115). This is consistent with a concerted ene process (Scheme 32).

Intramolecular ene reactions can also proceed with high asymmetric induction[36]. A Lewis acid-mediated intramolecular ene reaction of the chiral 8-phenylmenthyl (*Z*)-dienoate (117) yielded the pyrrolidines (119) and (120) in a ratio of 95:5. Similar cyclization of the chiral (*E*)-dienoate (118) resulted in a 11:89 mixture of (119) and (120) (Scheme 33).



Scheme 33

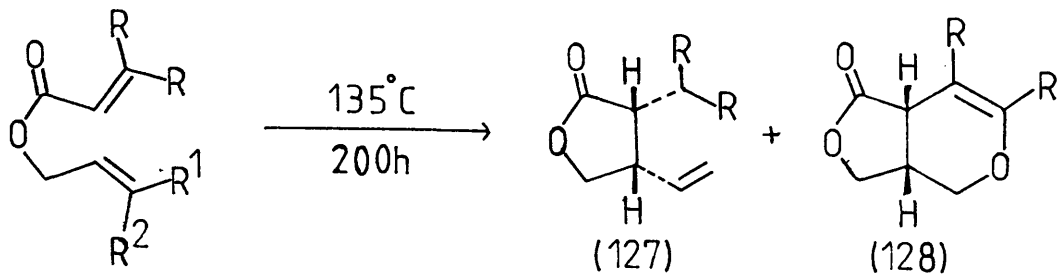


(121) R^1 = Me, R^2 = RCH_2 — 3 : 2

(122) R^1 = RCH_2, R^2 = Me — 2 : 3

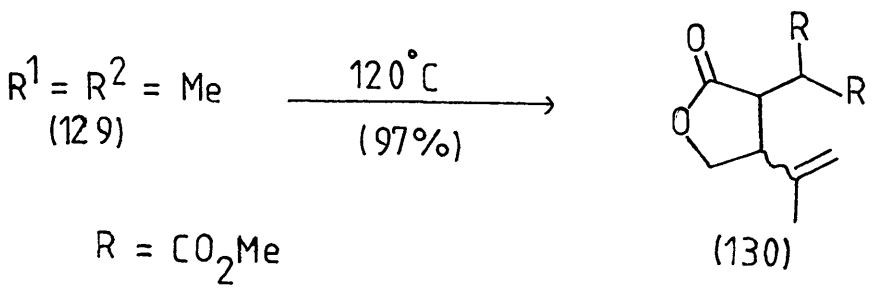
R = $(CH_3)_2C{=}CHCH_2$

Scheme 34



(125) R^1 = Me, R^2 = H — 1 : 1

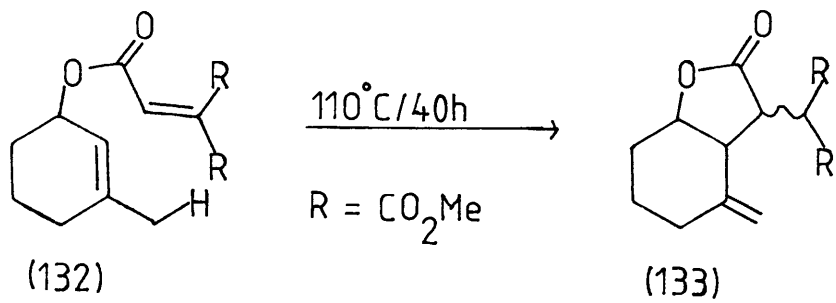
(126) R^1 = H , R^2 = Me — 9 : 1

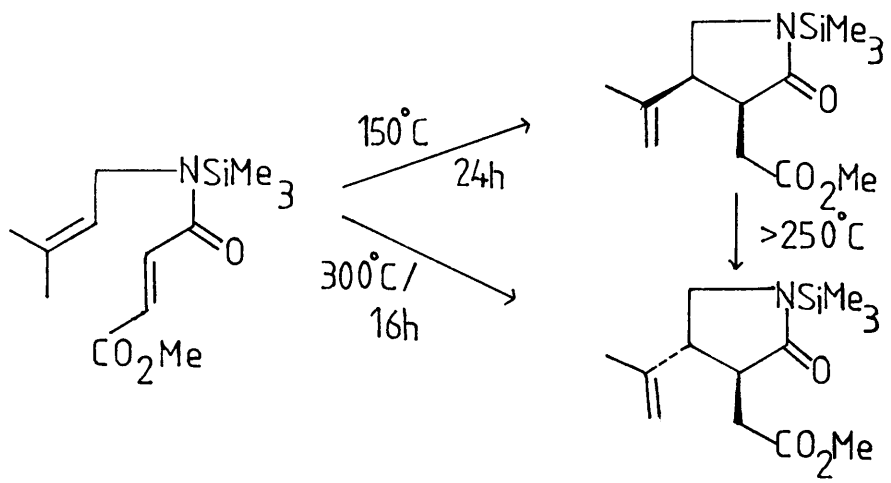


R = CO_2Me

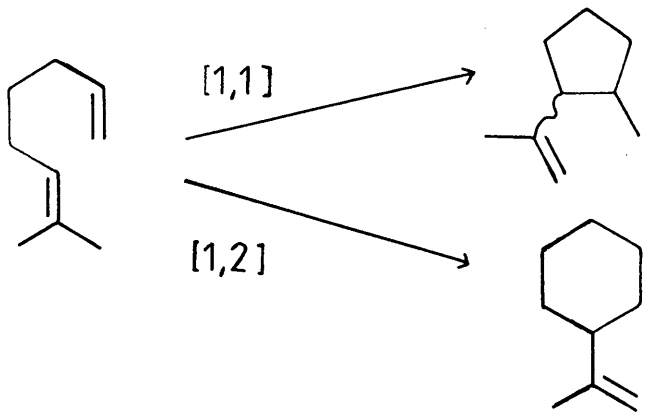
Scheme 35

From the thermolysis of neryl triester (121) and geranyl triester (122)[37], *ca.* 3:2 and *ca.* 2:3 mixtures of (123) and (124). were obtained, respectively, after chromatography. This suggested a *ca.* 1.5:1 proference for abstraction of hydrogen from the carbon *trans* to the ester (Scheme 34). Thermolysis of the *trans*-(125) and *cis*-crotyl triester (126) separately afforded mixtures of the *cis*-substituted ene adduct (127) and the Diels-Alder adduct (128) (Scheme 35). A 1:1 mixture of *cis*- and *trans*-lactones (130) were obtained as the ene adducts from the thermolysis of more reactive 3-methyl-2-butenyl ester (129). Moreover, the cyclic 1,6-diene (132) underwent an intramolecular ene reaction to afford the *exo*-methylene lactone (133) as a mixture of diastereomers. At elevated temperatures, certain ene adducts can be equilibrated[28] (Scheme 36).

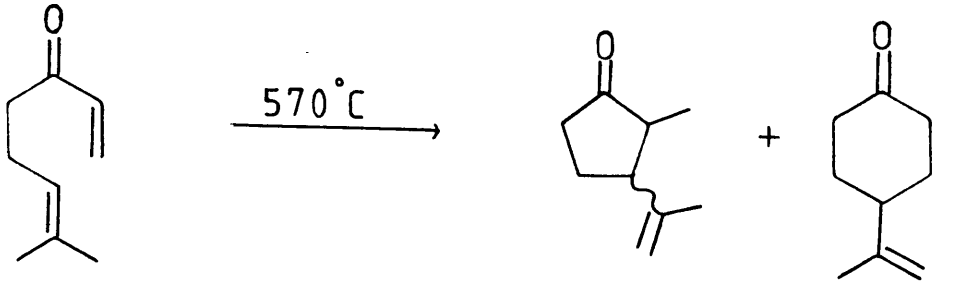




Scheme 36



Scheme 37

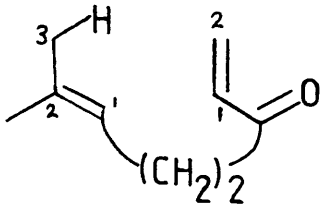


(134)

(135)
(53%)

(136)
(18%)

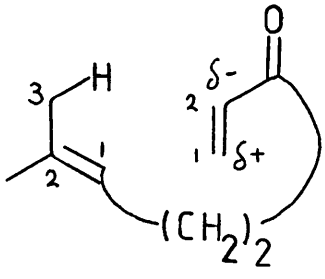
Scheme 38



(135a)

↓

(135)

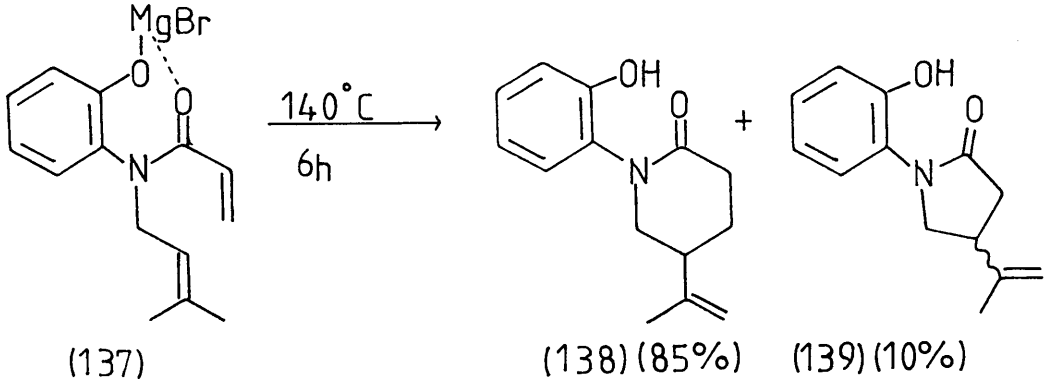


(136a)

↓

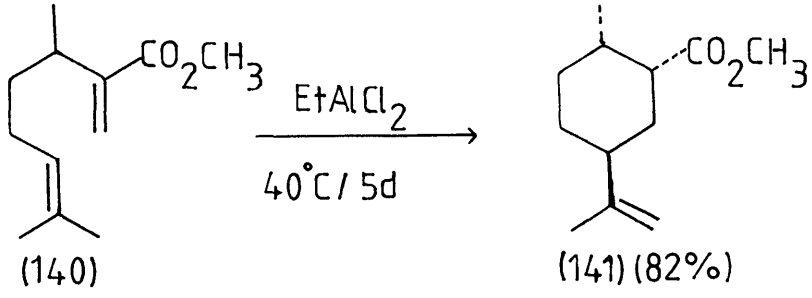
(136)

Although most intramolecular ene reactions of 1,6-dienes give 5 membered rings *via* Type [1,1] instead of 6-membered rings *via* Type [1,2] cyclisations (Scheme 37), the electronically favoured [see (136a)] [1,2]-adduct (136) was obtained as a minor component (18%) of a mixture with the geometrically favoured [see (135a)] [1,1]-adducts (135)(53%) from the thermal ene reaction of the ketone (134) [38] (Scheme 38). Both [1,2]-(138) and [1,1]-adducts (139) were obtained from butylmagnesium bromide-catalysed intramolecular ene reaction of acrylamides (137) at 140°C[39] (Scheme 39). More recently, Snider *et al.* reported the formation of the trisubstituted cyclohexane (141) as the only product derived from the $EtAlCl_2$-catalysed [1,2]-reaction of the octenoate (140)[31] (Scheme 40).



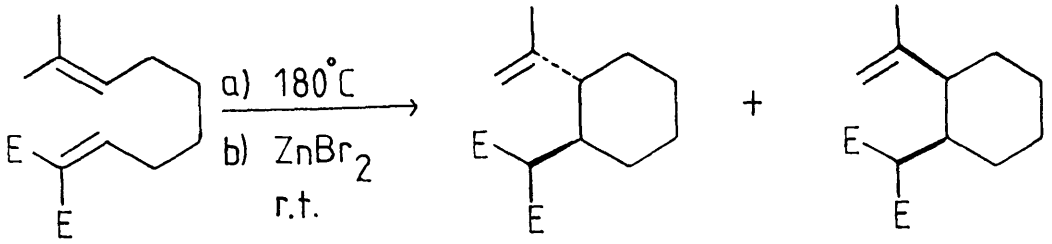
(137) (138) (85%) (139) (10%)

Scheme 39



(140) (141) (82%)

Scheme 40



(142)	yield/ %	(143a)		(143b)
a)	73 ;	99	:	1
b)	88 ;	>99	:	1

Scheme 41

(144) (145)

(a) R = H;	210°C, 62h	100%
(b) R = CO_2CH_3;	135°C, 24h	>95%
(c) R = CH_3;	≥225°C, 48h	15%

(146) (147)

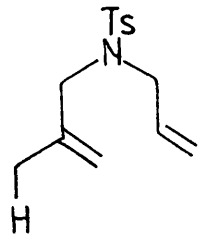
(a) R = CO_2CH_3;	225°C, 62h	85%
(b) R = H;	≥235°C, 48h	17%

Scheme 42

Usually, 1,7-dienes undergo intramolecular ene reactions less readily than the corresponding 1,6-dienes. Thus, higher temperatures are required to bring about the process and low yields are obtained. However, recently Tietze and Beifuss[40] showed that the thermal or Lewis acid-catalysed intramolecular ene reaction of the 2,8-decadienoate (142) gave two diastereoisomeric malonates(143), with diastereomeric excess >98%, favouring the trans-isomer (143a) (Scheme 41).

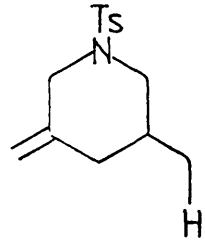
In contrast to olefins, acetylenes generally participate in intramolecular ene reactions as enophiles under considerably milder conditions, perhaps because orbital overlap is easier to achieve with the cylindrically symmetrical acetylenic π-bond. Ene reactions of 1,6-(144) and 1,7-enynes (146) have been investigated[41] (Scheme 42). Pyrolysis of the terminal 1,6-enyne (144a) at 210°C for 62h and the carbomethoxy-1,6-enyne (144b) at 135°C for 24h gave, with complete conversions, their corresponding ene adducts (145) in over 95% yield. In contrast pyrolysis of the enyne (144c), a methyl acetylene, at 225°C for 48h gave only 15% conversion to (145c). At higher temperatures or longer reaction times, a variety of unidentified products were formed. A similar trend of reactivity was observed in the ene reactions of 1,7-enynes. Pyrolysis of the ester (146a) at 225°C for 62h gave the ene adduct (147a) in 85% yield, but the terminal 1,7-enyne (140a) at 235°C for 48h underwent only 17% conversion to the ene adduct (147b).

It has been shown[42] that the sulphoxide (148) containing an allenic enophile unit cyclizes quantitatively to the functionalized cyclopentene derivative (149). The reaction

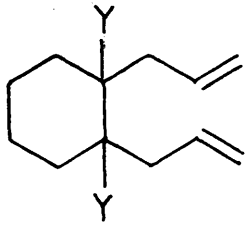


Type II

280°C / 7h

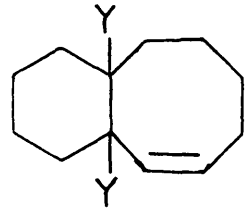


(152) (153) (40 %)

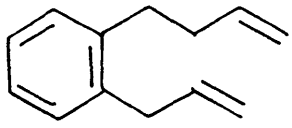


Type III

300°C / 90h



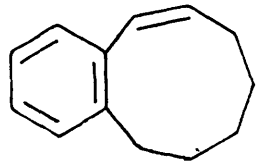
(154) Y : $OSiMe_3$ (155)



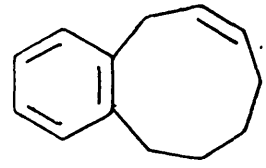
Type III

350°C

1d



+

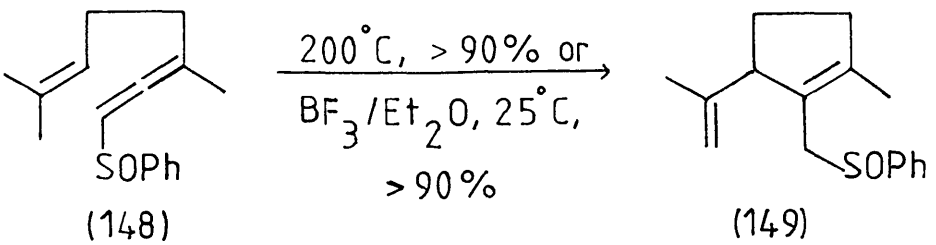


(156) (157) (158)

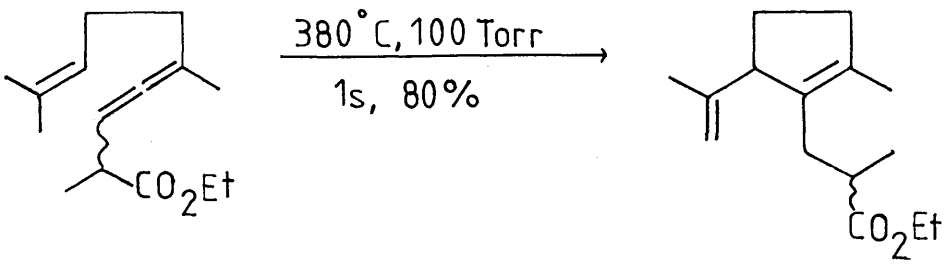
is catalysed by Lewis acids. Similarly an industrial process carried out on a scale of several 100Kg, involves efficient thermolysis of the allene (150) to give the cyclopentene derivatives (151)[43].

The Type II process of dienes has received relatively little attention. This reaction occurs less readily than the corresponding Type I process, as seen by low conversion of (152) into (153)[28].

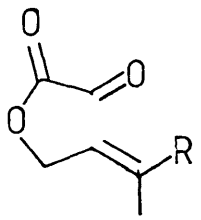
Thermolysis of a stereoisomeric mixture of 1,7-dienes (154) afforded the cycloctene (155) as major product[45] *via* the rarely observed Type III process. Similarly, Lambert and Napoli reported the cyclisation of 1,8-nonadiene (156) to form an equal mixture of (157) and (158) *via* the Type III process[45].



(148) (149)



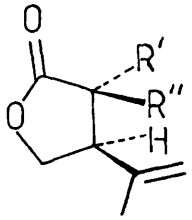
(150) (151)



(159)

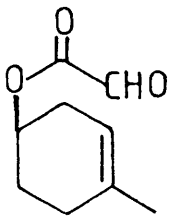
(a) R = CH_3 — 90°C / 60h → (a) R'' = OH, R' = H; (b) R'' = H, R' = OH (30%)

(b) R = H — 150°C // →



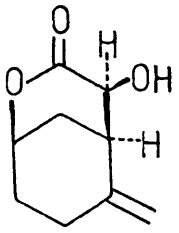
(160)

Scheme 43



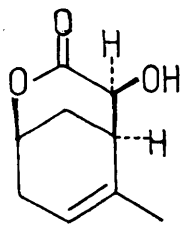
(161)

$SnCl_4$, 25°C (64%) →



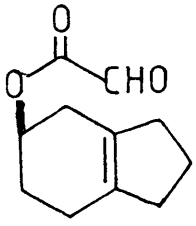
(162)

+



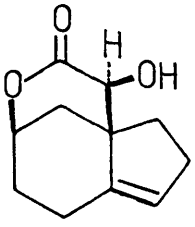
(163)

2 : 1



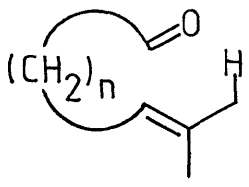
(164)

$SnCl_4$, 25°C (85%) →

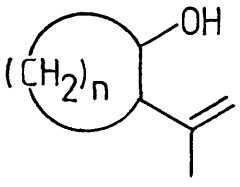


(165)

Scheme 44



Type I →



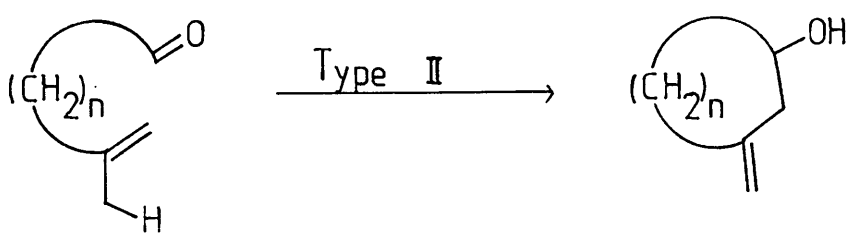
Scheme 45

1.2.2. Heteroenophiles

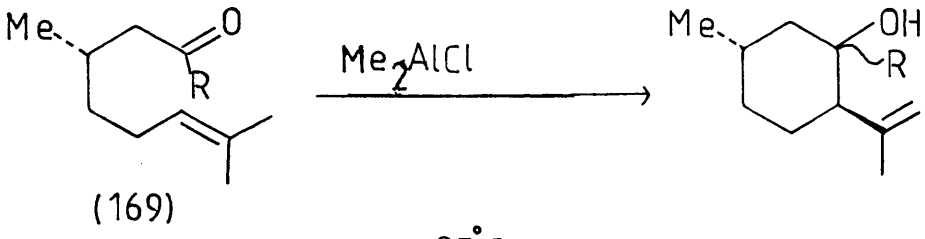
Different research groups have been studying the synthetic scope of ene reactions involving heteroenophiles. This is because of the enhanced rates of these reactions and their potential in preparing heterocycles.

Both Snider's and Lindner's group have studied the intramolecular ene reaction of glyoxylate esters. Snider and Straten reported that the prenyl glyoxylate (159a) reacted slowly at 90°C, giving a 30% yield of a 1:1 mixture of *cis*-(160a) and *trans*-(160b) ene adducts after 60h. However, the *trans*-crotyl glyoxylate (159b) decomposed at 150°C without undergoing the desired ene reaction[46] (Scheme 43). Later, Lindner and his co-workers showed that treatment of the glyoxylate ester (161) with stannic chloride produced a 64% yield of the bicyclic hydroxylactones (162) and (163) in a ratio of 2:1[47]. Furthermore, treatment of the ester (164) with stannic chloride afforded a single compound, the tricyclic hydroxylactone (165) (Scheme 44).

Intramolecular ene reactions of unsaturated carbonyl compounds have also been studied. They can be classified into Type I (Scheme 45, n = 3,4) and Type II (Scheme 46, n = 3,4) processes. Generally, these reactions can be catalysed by Lewis acids[30], thus extending their scope.



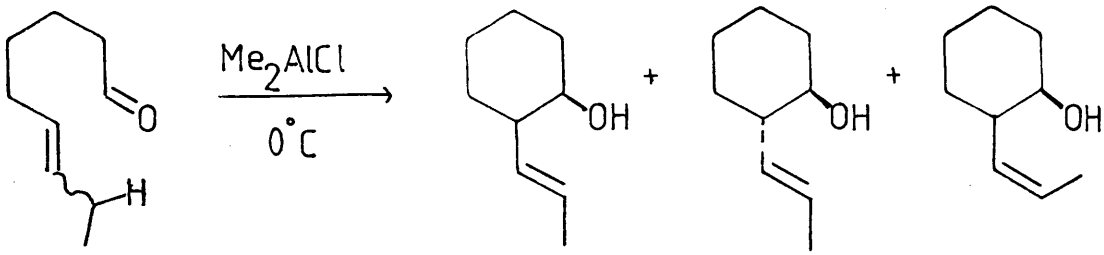
Scheme 46



(169)

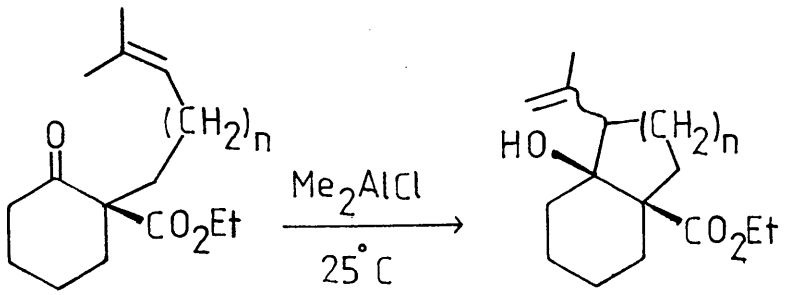
(a) R = Me $\xrightarrow{25^\circ C}$ (170) R = Me

(b) R = H $\xrightarrow{0^\circ C}$ (171) R = H



(172)	(173a)	(173b)	(173c)
(a) Z-	75%	0%	0%
(b) E-	12%	54%	10%

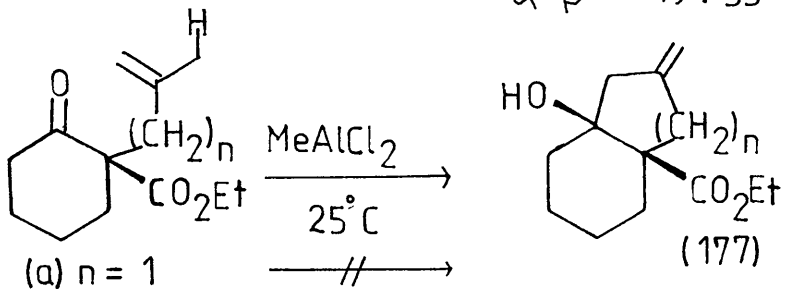
Scheme 48



(174) (a) n = 1 ⟶ //

(b) n = 2 ⟶ (176b) (52%)

α : β = 19 : 33



(177)

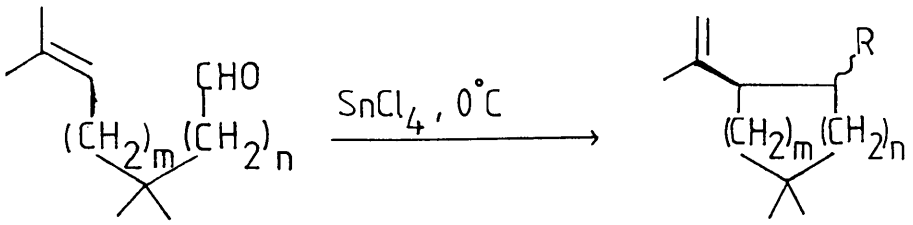
(175) (a) n = 1 ⟶ //

(b) n = 2 ⟶ (67%)

(c) n = 3 ⟶ (low yield)

Scheme 49

$SnCl_4$-catalysed cyclization of the aldehyde (166b) afforded the diastereoisomeric alcohols (168a) and (168b) in the ratio 92:8, while the aldehyde (166a) reacted much more slowly to give the diastereomeric alcohols (167a) and (167b) in a 20:80 ratio. Furthermore, the higher homologue (166c) failed to cyclise (Scheme 47)[48].



(166) (a) R = α-OH; (b) R = β-OH

(a) m = 1, n = 1 ⟶ (167) a:b, 1:4

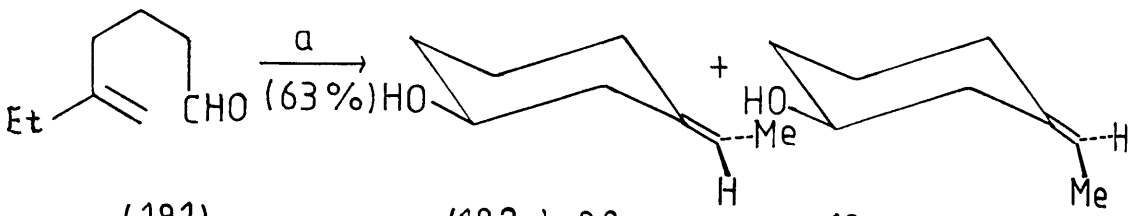
(b) m = 2, n = 1 ⟶ (168) a:b, 92:8

(c) m = 2, n = 2 ⟶ //

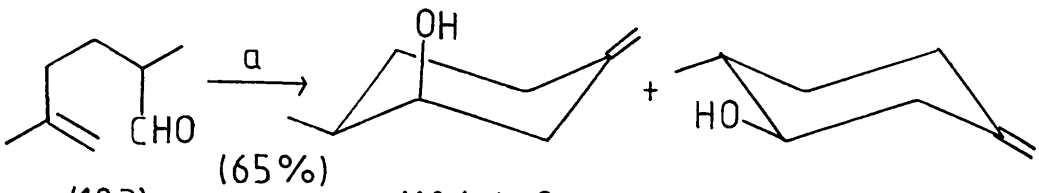
Scheme 47

With Me_2AlCl as the Lewis acid, both the unsaturated ketone (169a) and aldehyde (169b) were cyclised to give mixtures of the corresponding cyclohexanols (170) and (171), respectively[49]. Furthermore, the (*Z*)-1,6-enone (172a) underwent a Me_2AlCl-catalysed ene reaction to afford only the *cis*-substituted adduct (173a), while the (*E*)-isomer (172b) gave a mixture of *cis*- and *trans*-isomers (173) (Scheme 48). The reactions of the (*E*)-isomer (172b) and (*Z*)-isomer (172a) are both slower than that of (169b) as expected.

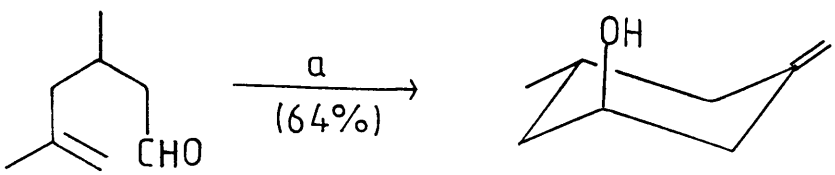
The keto group in the β-keto esters (174b) and (175b) has been shown to act as an enophile in the Lewis acid-catalysed ene reactions to afford the cyclohexanols (176b) and (177b) respectively *via* either a Type I or Type II process (Scheme 49)[50]. The cycloheptanol (177c) was formed in low yield from (175c) *via* a Type II process.



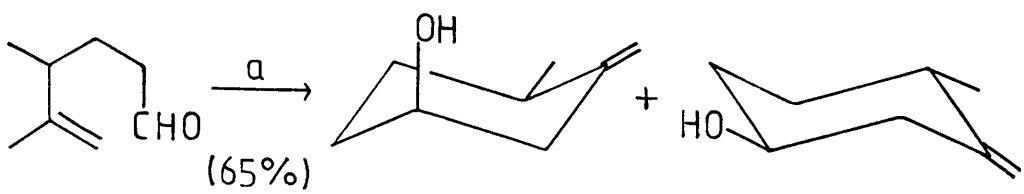
(181) (182a) 88 : 12 (182b)



(183) (186a) 90 : 10 (186b)



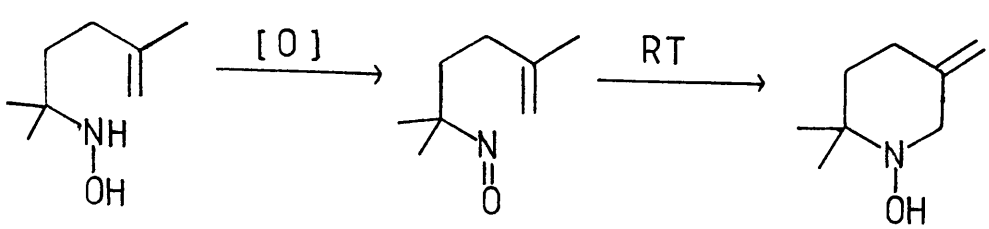
(184) (187)



(185) (188a) 96 : 4 (188b)

a : Me_2AlCl, -78°C

Scheme 51

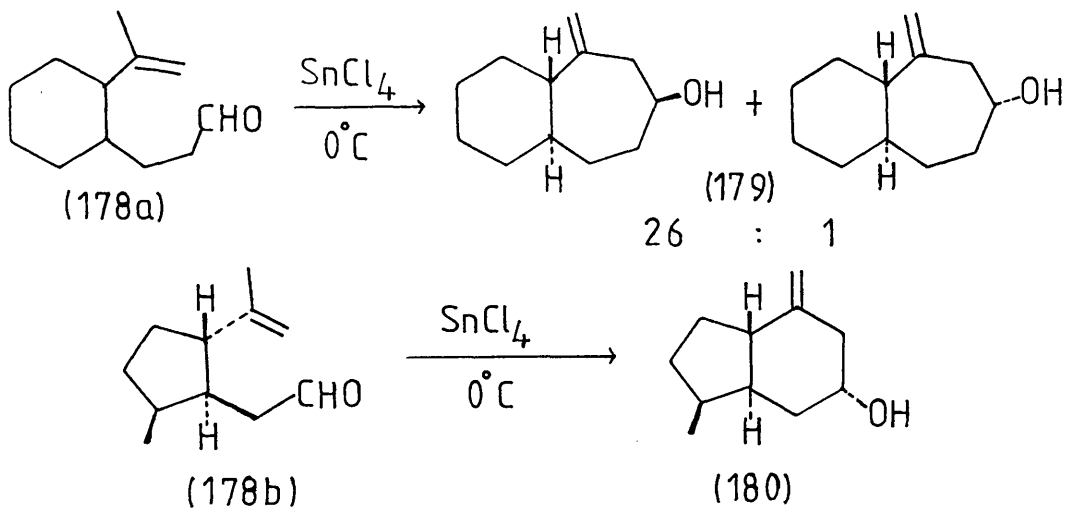


(189) (190) (191)

Scheme 52

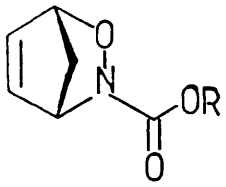
Anderson and his co-workers reported the stannic chloride-catalysed Type II ene reaction of unsaturated aldehydes[51] (Scheme 50). The 1,6-enal (178a) and 1,5-enal (178b) afforded the diastereoisomeric cycloheptanols (179) and α-hydroxy-cyclohexane (180), respectively. But attempts to make cyclo-pentanols failed.

Recently, Snider *et al.* investigayed the stereochemical outcome in Lewis acid-catalysed Type II ene reactions of γ,ε-unsaturated aldehyde[52]. The ene reaction of the aldehyde (181) gave the (*E*)-adduct (182a) with 85-90% selectivity depending on the Lewis acid used. Aldehydes (183-185) reacted with 90-100% selectivity to give isomer with an equatorial methyl group and an axial hydroxyl group (186a), (187) and (188a) (Scheme 51).

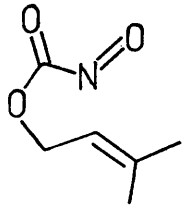


Scheme 50

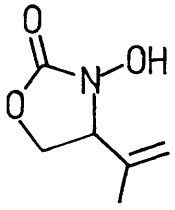
Motherwell and Roberts were the first to report the intra-molecular Type II ene reaction of an unactivated nitroso compound[53] (Scheme 52). The unsaturated nitroso compound (190), which was formed by oxidation of the hydroxylamine (189), rearranged rapidly at room temperature, to give a new hydroxyl-



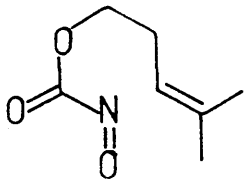
(195)



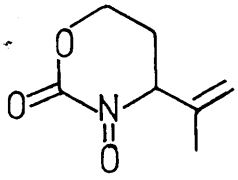
97%



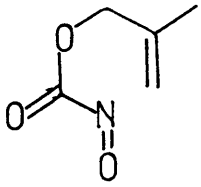
(196a) (197a)



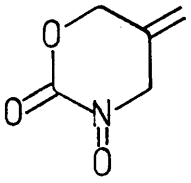
72%



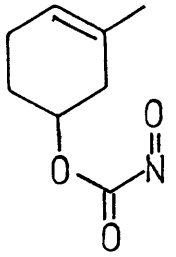
(196b) (197b)



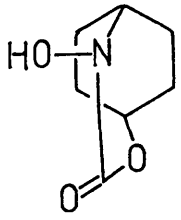
36%



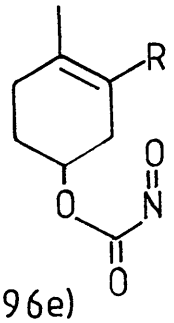
(196c) (197c)

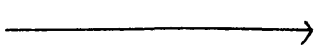


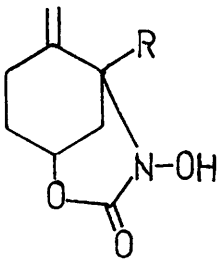
58%



(196d) (197d)





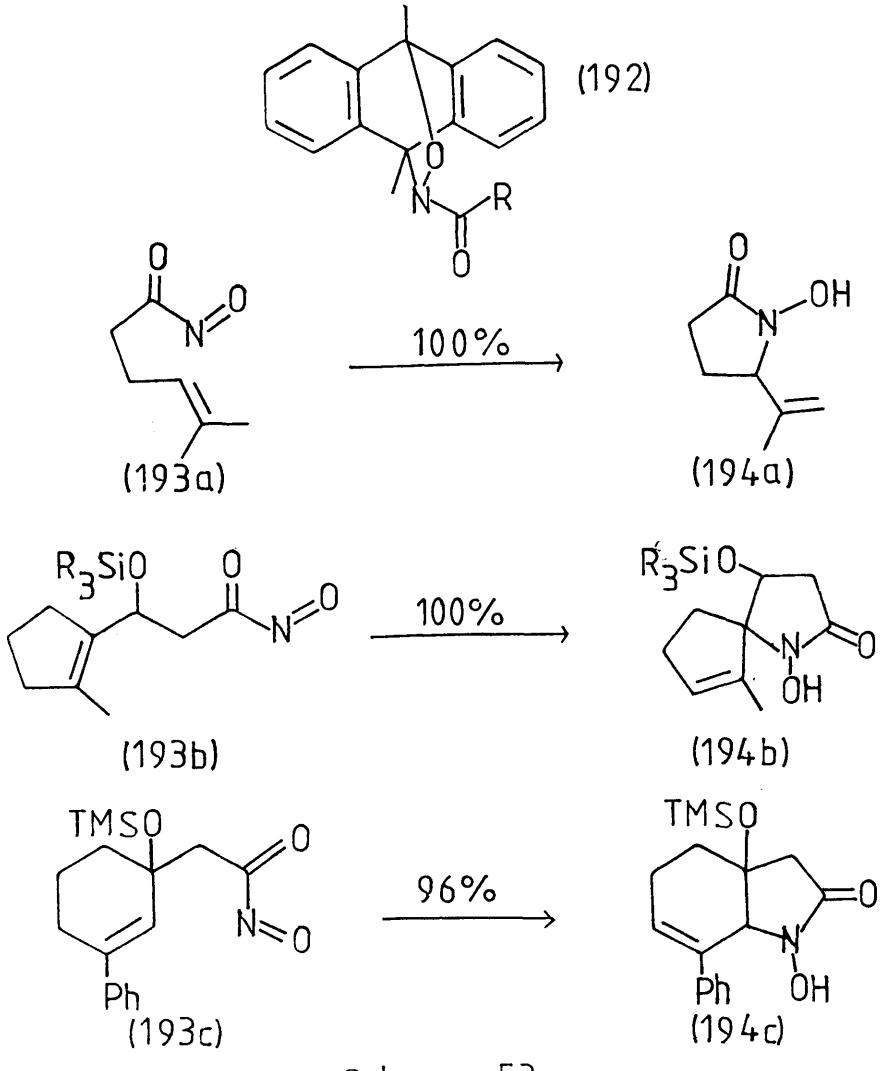


(196e) R = H (197e) R = H

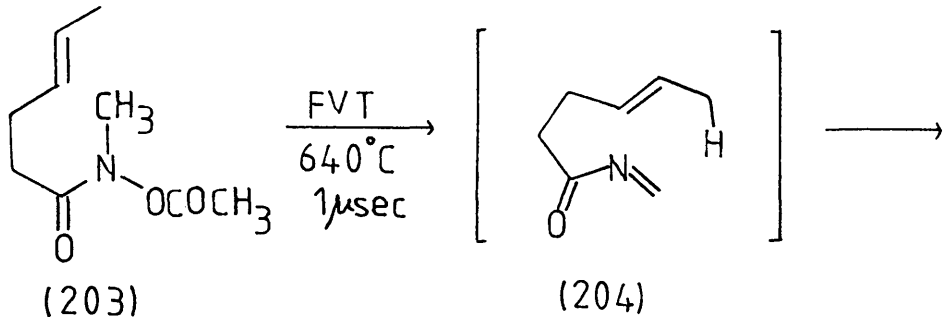
(196f) (197f) R = Me (39%)

Scheme 54

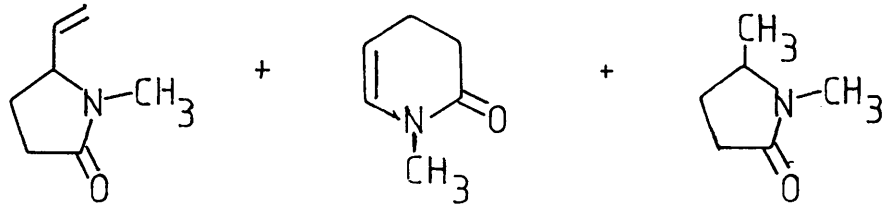
amine (191). In addition, two classes of activated nitroso compounds, the acylnitroso compounds and the nitrosoformate esters, have been reported to participate as enophiles in intramolecular ene reactions. The acylnitroso compounds (193a-c) derived from the thermolysis of dimethylanthracene adducts (192) at 80°C, gave various nitrogen-containing rings, including monocyclic (194a), spirocyclic (194b), and fused bicyclic systems (194c)[54] (Scheme 53). The *C*-nitrosoformate esters (196a-f) released from the thermolysis of their corresponding cyclopentadiene adducts (195), underwent either Type I or Type II processes to afford 5-(197a), 6-(197b,c,e,f) or 7-membered (197d) heterocyclic rings[55] (Scheme 54).



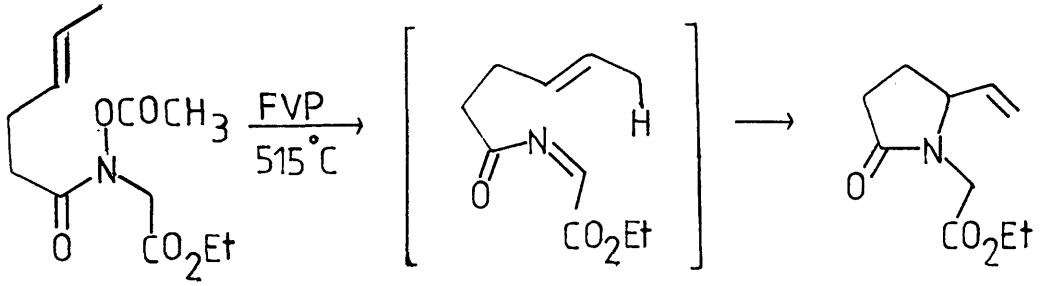
Scheme 53



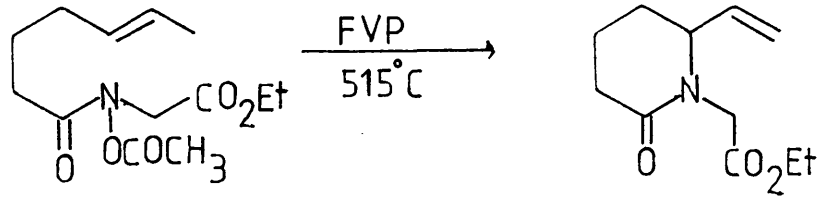
(203) (204)



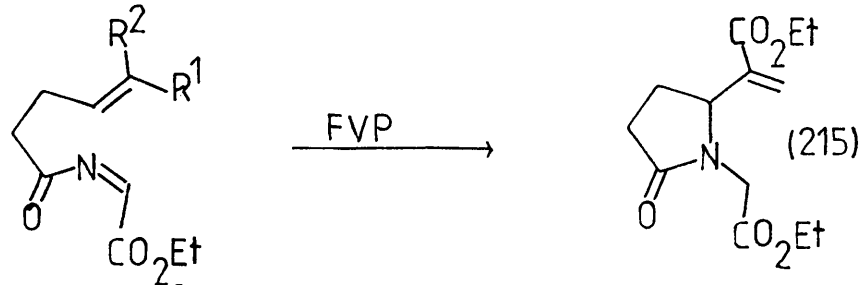
(205)(40%) (206)(15%) (207)(15%)



(208) (209) (210)(53%)



(211) (212)(7%)

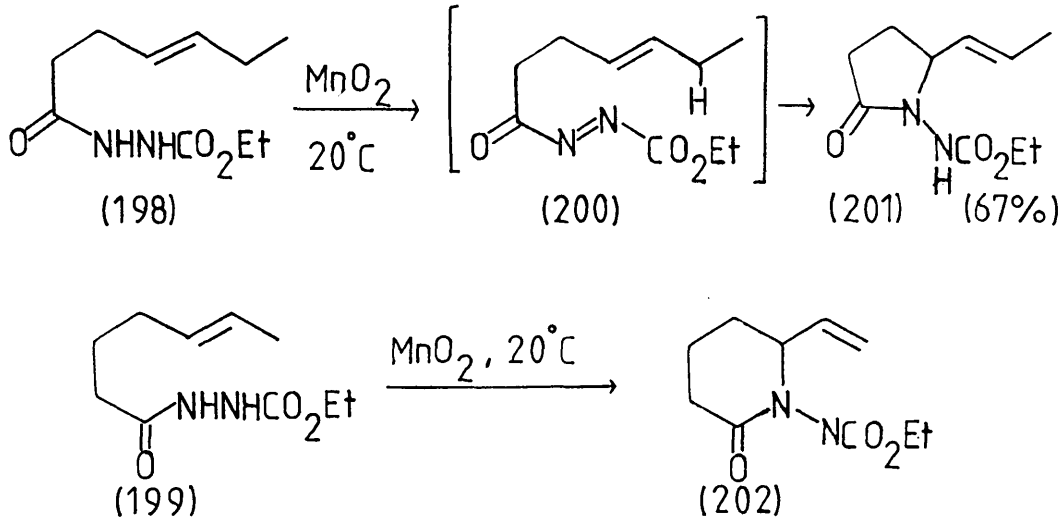


(213) $R^1 = CH_3$, $R^2 = CO_2Et$ (<25%)

(214) $R^1 = CO_2Et$, $R^2 = CH_3$ (100%)

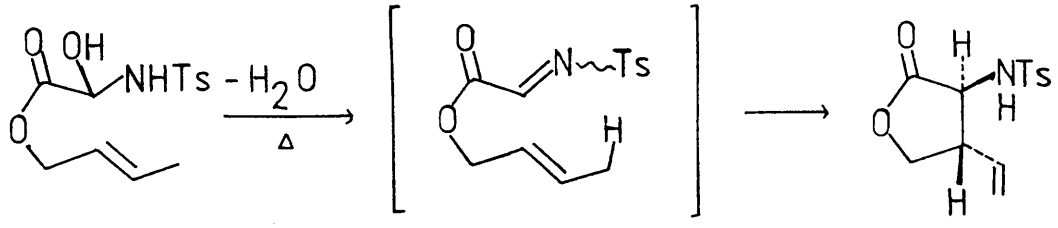
Scheme 56

N-Acylazo compounds also undergo rapid intramolecular ene reactions. Thus, the *N*-acylazocarboxylic esters having γ,δ-(200) or δ,ε-unsaturation, generated by MnO_2 oxidation of the corresponding hydrazones (198) and (199), underwent Type I reaction at room temperature to give 5-(201) or 6-membered lactam derivatives (202)[56] (Scheme 55).

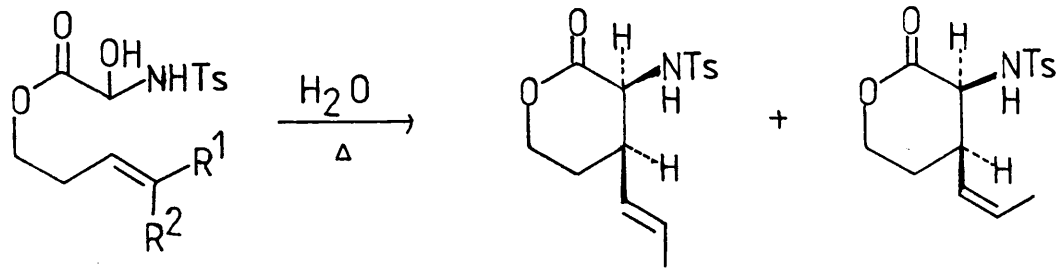


Scheme 55

Recently two classes of imines were reported to undergo intramolecular ene reactions. Fowler's group reported the ene reaction of *N*-acylimines produced by the flash vacuum thermolysis of hydroxamic acid derivatives, to afford nitrogen heterocycles (Scheme 56)[57]. Evaporation of the hydroxamic acid drivative (203) through a hot tube gave the ene adduct (205) (40%) as the major product. Two additional products (206) (15%) and (207) (15%) were also isolated; the pathway for their formation is unknown. The ene reaction was accelerated by carbonyl substituents on the carbon of the *N*-acylimine (208). The thermal elimination of carbon dioxide and methanol, as well as the ene reaction, occurred at a temperature approximately 150-200°C lower than that required



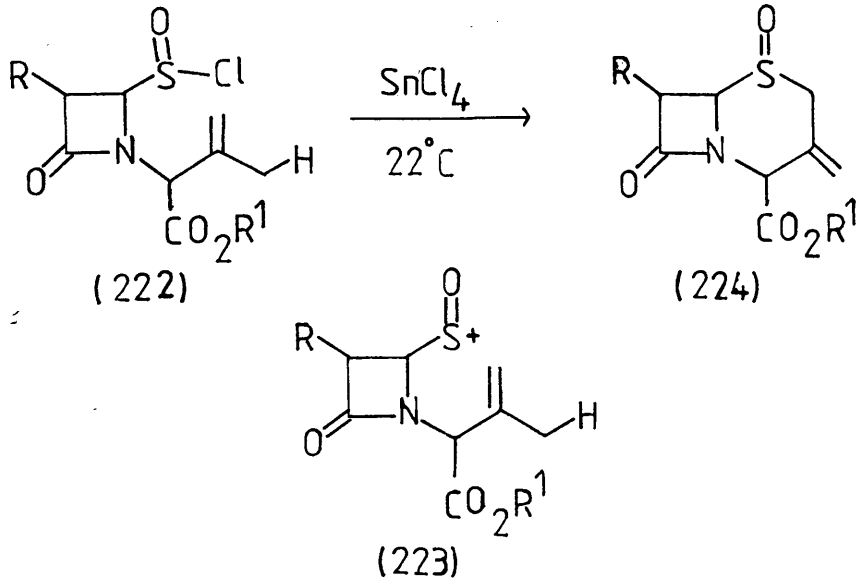
(216) (217) (218)



(219) (220) (221)

(a) R^1 = Et, R^2 = H	9	:	1
(b) R^1 = H, R^2 = Et	9	:	1

Scheme 57



(222) (223) (224)

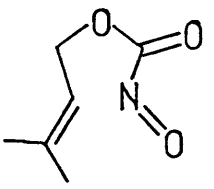
Scheme 58

for (203), and produced the pyrrolidine (210) in a 53% yield after chromatography. However, evaporation of the hydroxamic acid derivative (211) through the pyrolysis tube gave the piperidine (212) as the major product in only 7% yield. Furthermore, the *Z*-isomer (214) gave the ene product (215) in quantitative yield. In contrast, the *E*-isomer (213) gave a considerably more complex product mixture. N.m.r. analysis showed that the mixture contained less than 25% of the ene proudct (215).

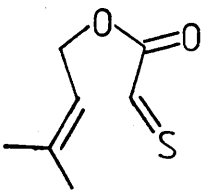
The *N*-sulphonylimines (217) also underwent intramolecular ene reaction. The α-hydrosulphonamide (216), containing a catalytic amount of anhydrous aluminium chloride left from its preparation, was heated in *o*-dichlorobenzene to afford a single ene product (218)[58]. Similarly, both the (*E*)-isomer (219a) and (*Z*)-isomer (219b) afforded ene adducts (220) and (221) in a 9:1 ratio (Scheme 57).

A Type II intramolecular ene reaction involving a sulphinium cation(223) as enophile was suggested for the ring closure of the sulphinyl chloride (222) with a Lewis acid[59] (Scheme 58).

At the start of our work, there was no published study of intramolecular ene reactions involving thioaldehyde as enophiles. But shortly after the preliminary publication[60] on our work, Vedejs *et al.* also reported his work in this area[23], which has already been discussed in the previous section.



(196a)



(229)

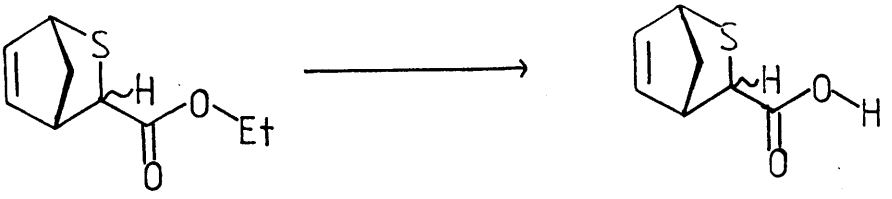
Chapter 2 Discussion

We planned to study the intramolecular ene reactions of allylic and homoallylic thioxoacetates. On the commencement of our work in this area, no examples of such reaction had been reported, although a few examples of the intermolecular ene reaction of thioaldehydes were known[11,20,23].

Thioaldehydes are generally unstable and, in order to avoid bimolecular decompostion of thioaldehydes, it was decided to generate unsaturated thioxoacetates by the retro-Diels-Alder cleavage of appropriate cycloadducts. It was hoped that they could be generated at a rate slow enough to avoid biomolecular decomposition but fast enough to minimize thermal decomposition of the ene product. Since cyclopentadiene is readily available, and forms cycloadducts in good yield, it was the preferred, ancillary diene. Cycloadducts of anthracene and 9,10-dimethylanthracene were also suitable but the former does not form cycloadducts of thioaldehydes as efficiently as cyclopentadiene and the latter is not so readily available. Also, both these aromatic compounds must be separated chromatographically from the desired ene products.

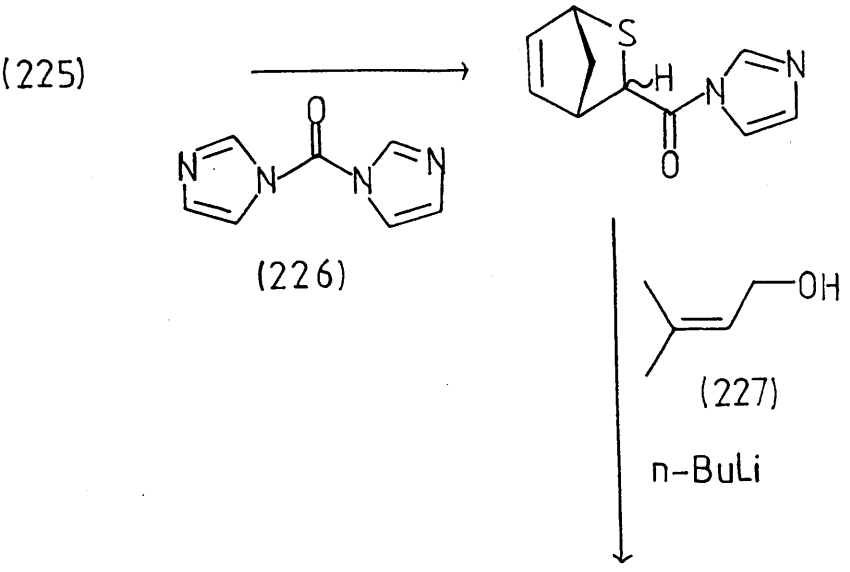
3,3-Dimethylallyl alcohol is readily available and its *C*-nitrosoformate derivative (196a) was found[55] to undergo an intramolecular ene reaction faster than other esters tested. Therefore, we decided to start with the analogue of this nitrosoformate (196a), 3,3-dimethylallyl thioxoacetate (229).

The cycloadduct of cyclopentadiene and 3,3-dimethylallyl thioxoacetate (228) was prepared from the carboxylic acid (225), which was readily available from the hydrolysis of its corres-



(77) (a) Endo
(b) Exo

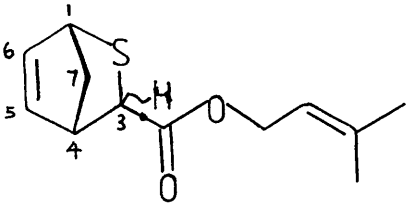
(225)



(226)

(227)

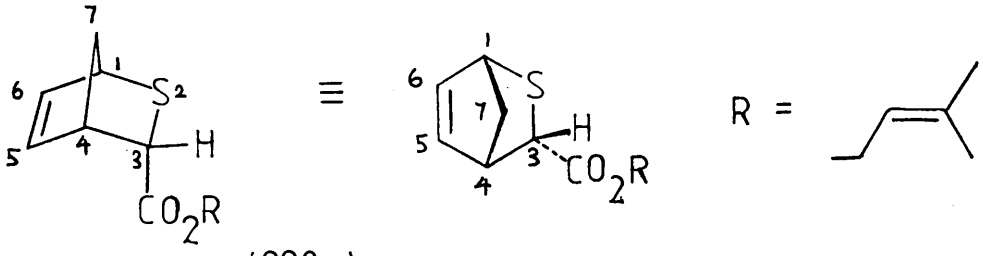
n-BuLi



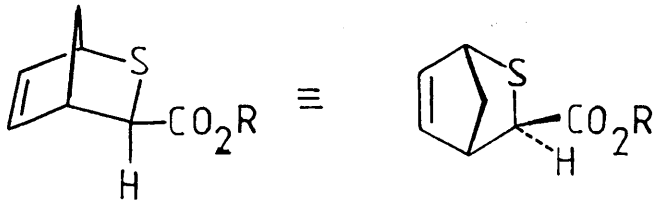
(228) (a) Endo
(b) Exo

Scheme 59

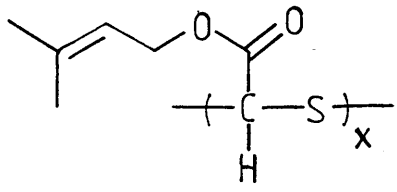
ponding ethyl ester (77)[21]. The acid (225) was treated in dichloromethane at room temperature with *N,N'*-carbonyldi-imidazole (226), followed by 3,3-dimethylallyl alcohol (227) in dichloromethane containing a catalytic amount of alkoxide generated with n-butyl-lithium (Scheme 59). The mixture was diluted with dichloromethane and washed with aqueous base to afford a yellow oily product. Chromatography of the mixture gave the *endo*-(228a) and *exo* - esters (228b) separately as colourless oils with a total yield of 91%. The ^{1}H n.m.r. spectrum of the *endo*-isomer (228a) showed two double doublets at δ 5.86 (*J* 3.0 and 5.5 Hz) and δ 6.47 (*J* 3.0 and 6.0 Hz) which were attributed to the olefinic protons, 5- and 6-H, of the cyclopentene ring. The olefinic proton of the allyl group gave a triplet of multiplets, δ 5.32 (*J* 7.0 Hz), and a broad doublet, δ 4.56 (*J* 7.0 Hz), was assigned to the allylic methylene group. The bridgehead methine protons, 1- and 4-H, gave two broad singlets, δ 3.76 and δ 4.08. A doublet δ 4.41 (*J* 4.0 Hz) for 3-H established the *endo* configuration; *exo* isomers generally show singlets for the corresponding protons. Two broad singlets at δ 1.68 and δ 1.72 were assigned to the two vinylic methyl groups and the 7-methylene protons gave multiplets at δ 1.62. The i.r. spectrum confirmed the formation of an ester with a carbonyl stretching band at 1734 cm^{-1}. Mass spectrometry confirmed the molecular formula $C_{12}H_{16}O_2S$. The ^{1}H n.m.r. spectrum of the *exo*-isomer (228b) showed a singlet at δ 3.29 for 3-H. The 7-methylene protons gave an AB quartet, at δ 1.63 and δ 1.93 (*J* 9.5 Hz). The i.r. spectrum showed a carbonyl stretching band at 1736 cm^{-1}. Combustion analysis and accurate mass measurement on the colourless oily mixture of *exo*-isomer established the formula $C_{12}H_{16}O_2S$, expected for



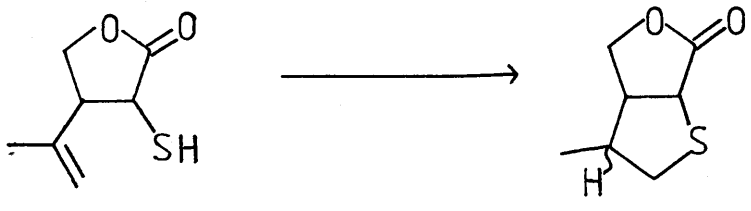
(228a)



(228b)



(230)

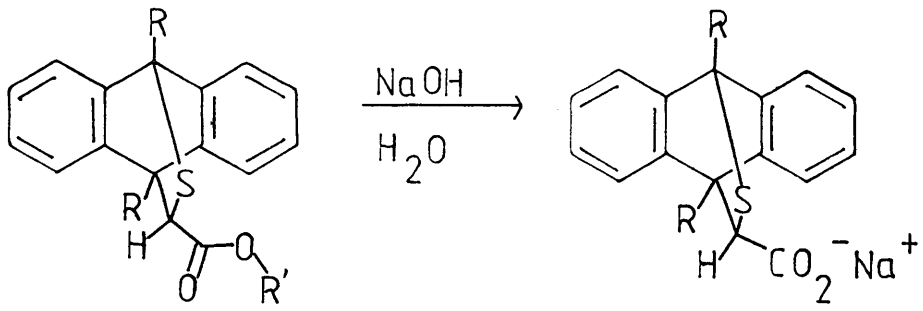


(231) (232)

the adduct (228b).

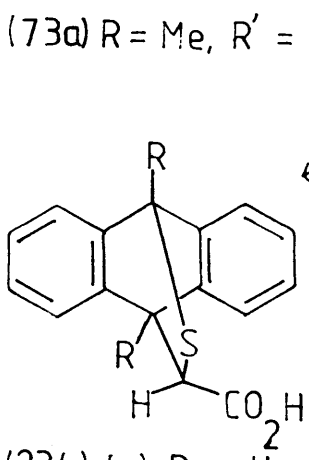
The esterification could be carried out in the absence of alkoxide by raising the temperature[61]. Thus, esterification of the acid (225) with 3,3-dimethylallyl alcohol was effected with *N,N'*-carbonyldi-imidazole in tetrahydrofuran with heating under reflux for 31h. A mixture of the *endo*-(228a) and *exo*-esters (228b) was then obtained in 62% yield after chromatography. The ^{1}H n.m.r. spectrum of the product agreed well with that of a sample of ester (228) prepared earlier.

The *exo*-cyclopentadiene adduct (228b) was then heated in boiling toluene under nitrogen and the course of the reaction was followed by t.l.c. After 2.5h, a spot corresponded to the *endo*-adduct (228a) appeared and, although the reaction was judged by t.l.c. to be incomplete after 34.2h, the reaction was stopped in fear of thermal decomposition of the ene product. Evaporation of the solvent gave a brown oil. In the ^{1}H n.m.r. spectrum broad signals at δ 1.71, 3.40, 4.64 and 5.36 suggested the presence of a 3,3-dimethylallyl ester, possibly the thial 'polymer' (230), and there were no signals for the starting material. A band at 1729 cm^{-1} in the i.r. spectrum suggested the presence of an ester. Chromatography of the brown oil gave the 'thial polymer' as the major component, with a minor component, whose ^{1}H n.m.r. spectrum was later shown to be identical to that of a bicyclic lactone (232). The bicyclic lactone (232) was thought to be derived from the cyclisation of the thioaldehyde ene product (231). Therefore, it seemed that the ene poduct (232) had been formed but, because the overall reaction was too slow (see later), the ene product had decomposed during the extended period of heating, perhaps by reversal to the thioaldehyde and thence to the polymer (230).

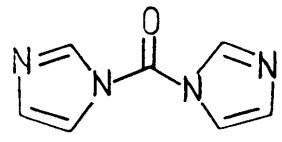


(72) R = H, R' = Et
(73a) R = Me, R' = Me

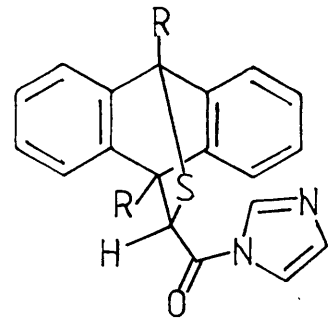
(235) R = H

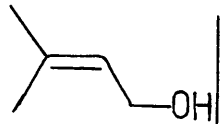


(234) (a) R = H
(b) R = Me

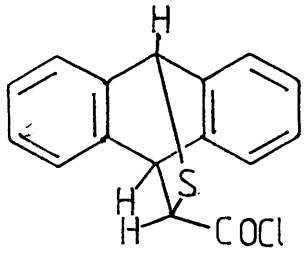


(226)

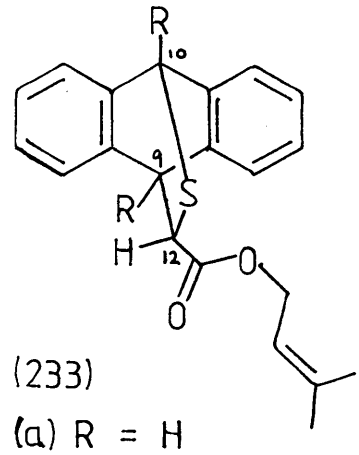




(227)



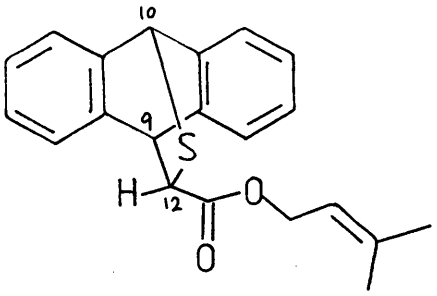
(235)



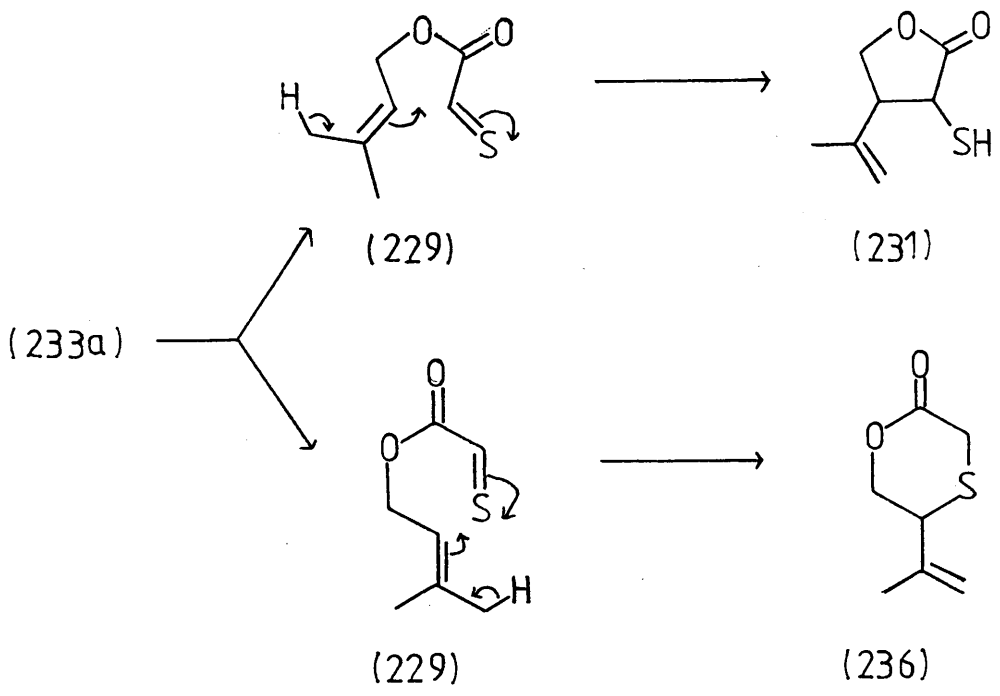
(233)
(a) R = H
(b) R = Me

Scheme 60

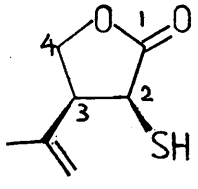
Anthracene adducts of thioxoacetate esters were known to dissociate faster than cyclopentadiene adducts. Therefore, the 3,3-dimethylallyl thioxoacetate adduct (233a) was prepared from the carboxylic acid (234a), which was readily available from the hydrolysis of its corresponding ethyl ester (72)[20]. In the preparation of the carboxylic acid (234a), in order to facilitate purification, the ethyl ester (72), contaminated with anthracene, was hydrolysed with sodium hydroxide to form the sodium salt of the acid (235). The aqueous alkaline solution was washed with dichloromethane to remove anthracene, acidification and extraction of the solution afforded essentially pure acid (234a). On treatment of the carboxylic acid (234a) in tetrahydrofuran (THF) at room temperature with *N*,*N*'-carbonyl-diimidazole (226) followed by 3,3-dimethylallyl alcohol (227) in THF containing a catalytic amount of alkoxide generated with n-butyl-lithium, the carboxylic ester (233a) was formed (Scheme 60). The mixture was diluted with ether and washed with aqueous sodium hydroxide to afford the pure ester (233a) as a yellow oil in 86% yield. Comparison of the ^{1}H n.m.r. spectrum with those of the ethyl ester (72) and the dimethylallyl esters (228) confirmed the structure (233a). The i.r. spectrum showed a carbonyl stretching band at 1735 cm^{-1}, as expected. Accurate mass measurement confirmed the formula $C_{21}H_{20}O_2S$. The carboxylic ester (223a) was also prepared from the acid chloride (235). The acid chloride (235) was prepared by treatment of the carboxylic acid (234a) in benzene with freshly distilled thionyl chloride under reflux. Evaporation of the solution gave the acid chloride (235) as a brownish green oil. The i.r. spectrum showed two carbonyl stretching bands, at 1812 and 1795 cm^{-1}. Without purification, the acid chloride (235) in anhydrous



(233a)



Scheme 61

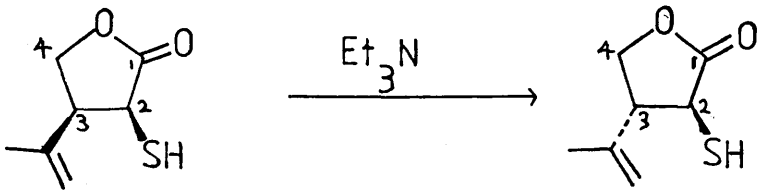


(231a)

diethyl ether was treated with 3,3-dimethylallyl alcohol (227) and triethylamine to give the ester (233a) and anthracene in the ratio of 9:1 (measured by ^{1}H n.m.r. spectroscopy). Anthracene was thought to be formed from the decomposition of the acid (234a). Chromatography afforded the pure ester (233a) in 50% yield.

The anthracene adduct (233a) was heated in boiling toluene (32mM) under nitrogen, and the course of the reaction was followed by t.l.c.. There were two possible ene products from the thioxoacetate (229); one a thiol (231) and the other a sulphide (236) (Scheme 61). On t.l.c. plates, thiols usually appeared as white spots immediately after the plates had been exposed to iodine vapour. However, with longer exposure, the spots develop the normal yellow colour. This phenomenon was employed as a test for the presence of thiols throughout the course of our study. After 4h, the reaction was judged to be complete, as no spot corresponding to the adduct remained and a new, white spot was observed at lower R_f. Evaporation of the solvent afforded a mixture of a yellow oil with white crystals. The i.r. spectrum confirmed the formation of a five-membered lactone, with a carbonyl stretching band at 1780 cm^{-1}. ^{1}H N.m.r. spectroscopy revealed complete conversion of the adduct (233a) into a mixture of anthracene and the thiol (231a).

Resonances at δ 8.32, 7.96 and 7.41 were attributed to anthracene. Two broad singlets at δ 4.74 and 5.04 were assigned to two olefinic protons. The methylene group attached to oxygen gave a doublet, δ 4.40 (J 8.0 Hz), and a double doublet, δ 3.83, (J 5.0Hz and 7.5 Hz), was assigned to 2-H. A broad quartet (J 8.0 Hz) was attributed to 3-H. The mercapto proton gave a



(231a) (231b)

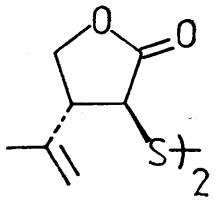
doublet at δ 1.89 (*J* 4.5 Hz, exchangeable with D_2O) and the vinyl methyl group gave a singlet at δ 1.76. The *cis*-stereochemistry (231a) was demonstrated by treatment of the thiol with triethylamine in dichloromethane at room temperature to give, essentially quantitatively, the *trans*-thiol (231b). The ^1H n.m.r. spectrum of the *trans*-thiol (231b) showed triplets at δ 4.08 and 4.51 (*J* 9Hz), attributed to the methylene group attached to oxygen. The mercapto proton gave a doublet at δ 2.27 (*J* 4.7 Hz). The i.r. spectrum showed a carbonyl stretching band at 1783 cm^{-1}. Confirmation of the *cis*-stereochemistry of the thiol (231a) came from ^1H n.m.r. data and from n.O.e. experiments. The vicinal coupling constants, $J_{2,3}$, for the *cis*-(231a) and *trans*-thiol (231b) were 7.5 and 9.5 Hz, respectively. These values are typical for 2,3-disubstituted butyrolactones[62].

Table 1. N.O.e. enhancements (%) for the thiols (231)

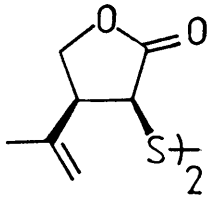
	cis-Thiol (231a)		*trans*-Thiol (231b)	
2-H	4.78	irr.[a]	0	irr.
3-H	irr.	4.67	irr	0

[a] proton irradiated

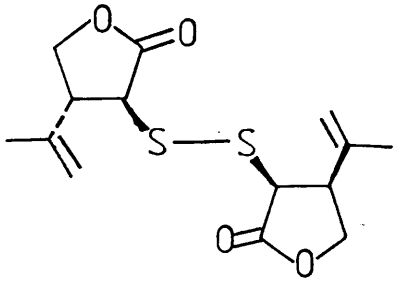
The n.O.e. experiments (Table 1) showed that there was a close spatial relationship between 2-H and 3-H in the thiol (231a), implying a *cis*-relationship, but not in the thiol (231b), which must be the *trans*-isomer. The high diastereselectivity of the cyclisation of (229) to (231a), with the formation of the less stable epimer, indicated a concerted ene reaction.



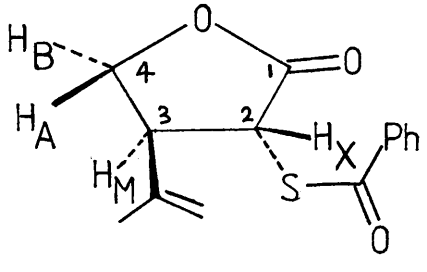
(237a)



(237c)



(237b)



(238)

Attempted purification using preparative SiO_2 plates and column (SiO_2) chromatography resulted in the partial epimerization and oxidation of the *cis*-thiol (231a) to form a mixture of disulphides. In principle,there are 6 possible diastereoisomers [4 racemic and 2 *meso*; representative structures are (237a), (237b), and (237c), in order of decreasing probable percentage]. Reduction of the mixture of disulphides (judged to have a *cis:trans* ratio of their component 'halves' of *ca.* 1:3, by ^1H n.m.r. spectroscopy) with sodium dithionite and sodium bicarbonate in aqueous tetrahydrofuran under nitrogen gave a mixture of the thiols (231a) and (231b) (*ca.* 1:4 as judged by ^1H n.m.r. spectroscopy). Purification of the *cis*-thiol (231a) was achieved on a Chromatotron (SiO_2) under nitrogen. However, partial epimerization of the *cis*-thiol (231a) had occurred on the SiO_2 plate to give a mixture of thiols (231) (*cis:trans*, 9:1, by ^1H n.m.r. spectroscopy) as a colourless oil. Mass spectroscopy with accurate mass measurement showed the oil had the expected molecular formula $C_7H_{10}O_2S$.

The *cis*-thiol (231a) was further characterised by treatment, without prior chromatography, with benzoyl chloride and triethylamine in chloroform to give the corresponding *trans*-thiol benzoate (238) as a brown oil. This afforded a white solid, m.p. 120-120°C, on crystallization from dichloromethane and light petroleum (b.p. 40-60°C). Microanalysis confirmed the composition $C_{14}H_{14}O_3S$. The *trans*-stereochemistry of the thiol benzoate (239) was assigned on the basis of ^1H n.m.r. data ($J_{2,3}$ = 11.0 Hz[62]) (Table 2) and n.O.e. experiments (Table 3). The small enhancement of the signal for H_M upon irradiation of H_X suggested a *trans*-relationship. In fact, this

small enhancement value might be due to the partial irradiation of H_A

Table 2

	H_M	H_B	H_X	H_A
δ(p.p.m.)	3.31	4.16	4.45	4.52
J (Hz)	brq, 10	t, 9.0	d, 11.0	t, 8.0

Table 3 N.O.e. enhancements (%) for *trans*-thiol benzoate

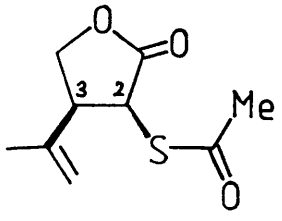
H_M	H_B	H_X	H_A
irr.[a]	Nil	4.24[c]	4.24[c]
0.47	irr.[a]	15.06[c]	15.06[c]
0.77	1.29	irr.[b]	irr.part.[b]
6.40	13.48	irr.part[b]	irr.[b]

a: proton irradiated

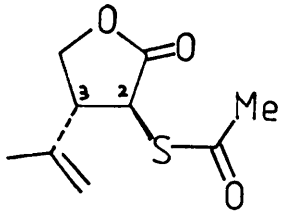
b: since the chemical shifts of H_A and H_X are too close, irradiation of H_A would result in partial irradiation of H_X and *vice versa*

c: since the chemical shifts of H_A and H_X are too close, the enhancement values shown are the sum of the enhancement values of H_A and H_X.

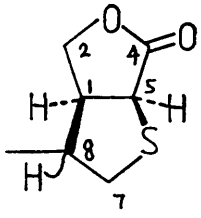
A mixture of disulphides: [(±)-(237c) and the related *meso*-diastereoisomer] was prepared by treatment of *cis*-thiol (231a) with potassium iodide and iodine in ethanol. The methine proton adjacent to sulphur gave in the ^1H n.m.r. spectrum a doublet at δ 4.02 (*J* 8.0 Hz) for one diastereomer, and a doublet at δ 4.20 (*J* 8.0 Hz) for the other diastereomer. Chromatography of these *cis*-disulphides afforded a mixture of disulphides [(±)-(237a) and the related *meso*-diastereoisomer]



(239a)



(239b)

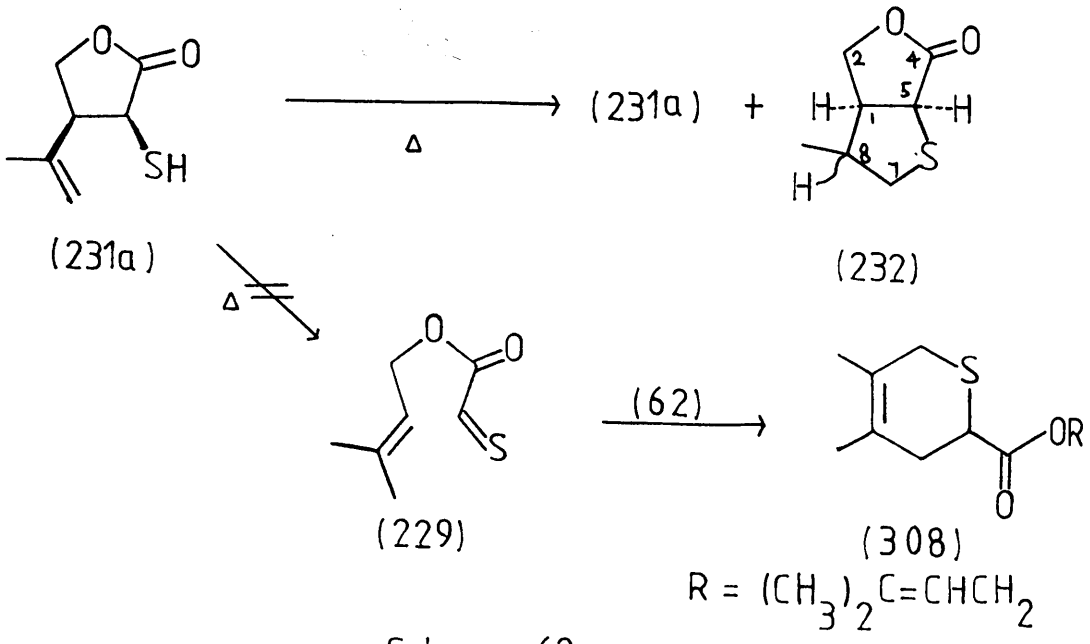


(232)

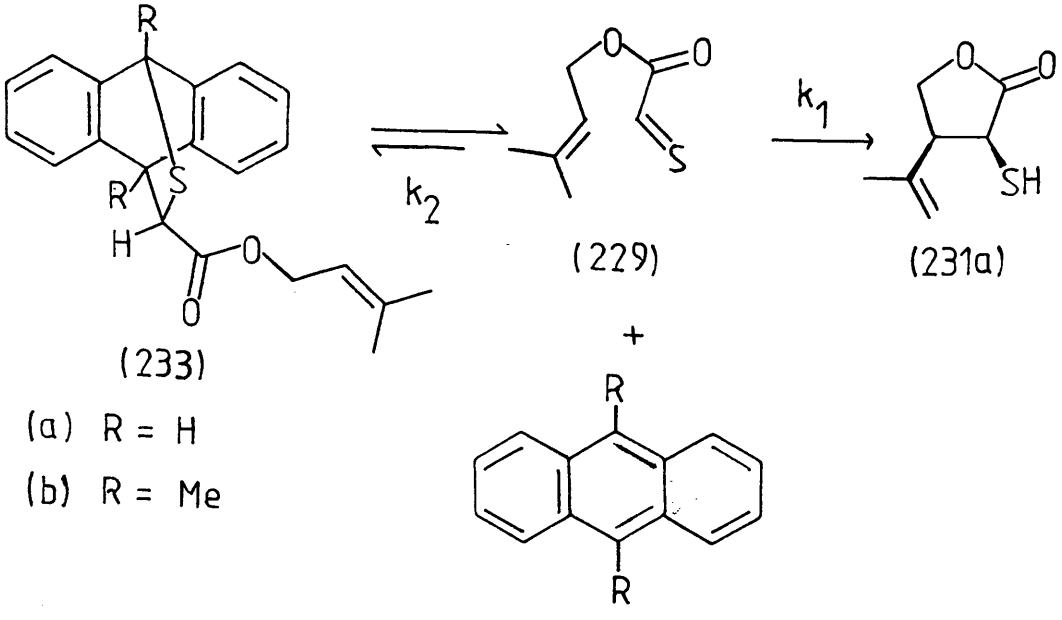
as a yellow oil. Again, the methine proton adjacent to sulphur gave doublets at δ 3.78 (*J* 9.5 Hz) one diastereomer and at δ 3.87 (*J* 9.5 Hz) for the other diastereomer. Mass spectrometry, with accurate mass measurement, confirmed the formula $C_{14}H_{18}O_4S_2$ for these *trans*-disulphides.

The *trans*-thiol acetate (239b) was also prepared as a yellow oil, by treatment of the *cis*-thiol (231a) with acetic anhydride and triethylamine in chloroform. The i.r. spectrum showed two carbonyl stretching bands at 1785 and 1705 cm^{-1}. Accurate mass measurement confirmed the formula $C_9H_{12}O_3S$. In the ^1H n.m.r. spectrum, a singlet at δ 2.40 was attributed to the thiol acetate group. The *trans*-stereochemistry was assigned on the basis of the vicinal coupling constant, $J_{2,3}$= 10.4 Hz[62], which was larger than that of the *cis*-isomer (239a), prepared as follows. It was thought that the epimerization of the *cis*-isomer was catalysed by both base and acid. In order to prepare a sample of the *cis*-thiol acetate (239a) under neutral conditions, the *cis*-thiol (231a) was treated with acetic anhydride, generated *in situ* from acetic acid and dicyclohexylcarbodiimide. The ^1H n.m.r. spectrum of the resulting *cis*-thiol acetate gave a vicinal coupling constant, $J_{2,3}$ = 8.0Hz. Attempted purification of *cis*-thioacetate on a Chromatotron (SiO_2) under nitrogen resulted in the epimerization to form the *trans*-thiol acetate (239b).

Furthermore, the *cis*-thiol (231a) was heated in boiling benzene with azobisisobutyronitrile (AIB), a mixture of diastereoisomeric bicyclic lactones (232) was obtained as a yellow oil, which was identical to a minor product from the thermolysis of the *exo*-cyclopentadiene adduct of 3,3-dimethylallyl thioxoacetate. In the ^1H n.m.r. spectrum, doublets at δ1.09 (*J* 6.8 Hz)



Scheme 62



Scheme 63

and 1.13 (J 6.7 Hz) were assigned to the methyl groups of a pair of diastereoisomers. The i.r. spectrum, ν_{max} 1780 cm^{-1}, confirmed the presence of a five-membered lactone. Accurate mass measurement confirmed the formula $C_7H_{10}O_2S$. An attempt to demonstrate the retro-ene reaction of the ene product (231a) by heating the *cis*-thiol in toluene under nitrogen with 2,3-dimethylbutadiene (14 mol equiv.) for 41h gave a mixture of the thiol (231a) and the cyclized product (232) (*ca.* 1:2, by ^1H n.m.r. spectroscopy) (Scheme 62).

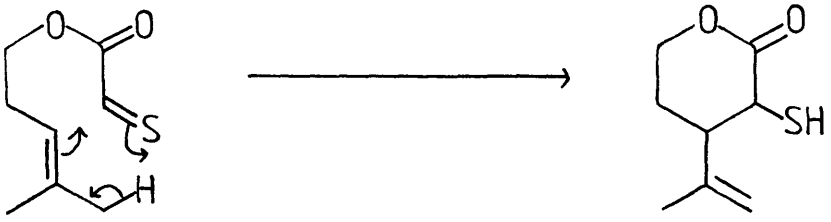
The effect of the initial concentration of the anthracene adduct (233a) on the rate of formation of the ene product was studied by carrying out thermolysis experiments using two different concentrations of the adduct. The adducts were heated under reflux in toluene at different initial concentrations (32 and 94 mM) under nitrogen for 1h; the extent of reaction in each case [63 and 36% thiol (231a), respectively] was determined by ^1H n.m.r. spectroscopy. Thus, the conversion of the adduct (233a) into the thiol (231a) was slower for the more concentrated solution. It appears that anthracene, liberated in the reaction, retards the first-order (k_1) formation of the ene product by second-order (k_2) recapture of the thioaldehyde (229) (Scheme 63). This conclusion is in agreement with the observation made by Kirby *et al.*[55].

The adduct (233b) of 9,10-dimethylanthracene (DMA) and 3,3-dimethylallyl thioxoacetate was then prepared by the usual method from the carboxylic acid (234b) (Scheme 60). However, a mixture of the adduct (233b) and dimethylanthracene (*ca.* 6%, by ^1H n.m.r. spectroscopy) resulted; presumably the dimethylanthracene was derived from the decomposition of either the acid (234b) or the ester (233b). Chromatography afforded the

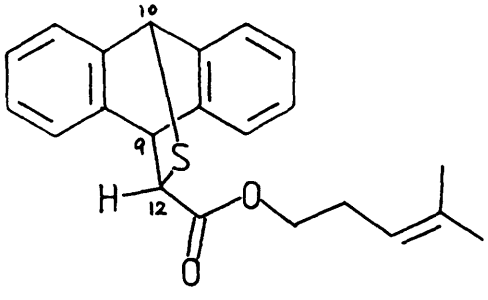
pure ester (233b) as a yellow oil in 69% yield. In the ^1H n.m.r. spectrum, two broad singlets at δ 2.14 and 2.27 were attributed to the two methyl groups of the dimethylanthracene part of the adduct. The methylene protons adjacent to oxygen gave a broad doublet at δ 4.47 (*J* 6.0 Hz). The i.r. spectrum ν_{max} 1746 cm^{-1}, confirmed the formation of an ester. Accurate mass measurement confirmed the formula $C_{23}H_{24}O_2S$. Thermolysis of the dimethylanthracene adduct (233b) in refluxing toluene under nitrogen gave the same *cis*-thiol (231a) as from the corresponding anthracene adduct (233a). The rates of decomposition of the dimethylanthracene (DMA) adduct and anthracene adduct was carried out by heating the adducts in boiling toluene with same initial concentrations (32mM) (Table 4). The extent of decomposition was judged by ^1H n.m.r. spectroscopy. The results indicated a faster dissociation rate of the DMA adduct (233b), which resulted in a bigger conversion to the thiol (231a) than was observed for the anthracene adduct (233a) in the first hour. However, the trapping efficiency of DMA was also better than that of anthracene. Therefore, as the concentration of DMA built up, the decomposition of the DMA adduct was relatively retarded, and a greater decomposition of the anthracene adduct was observed after 3h.

Table 4. Thermal decomposition of the cycloadducts (233a) and (233b)

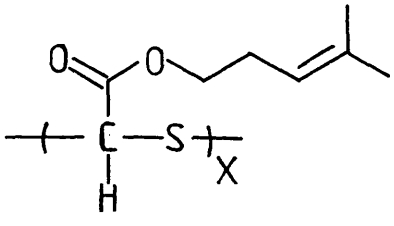
		Thiol (231a) (%)	
	Time/h	1	3
Starting adducts	(233a)	60	95
	(233b)	79	86



(240) (241)

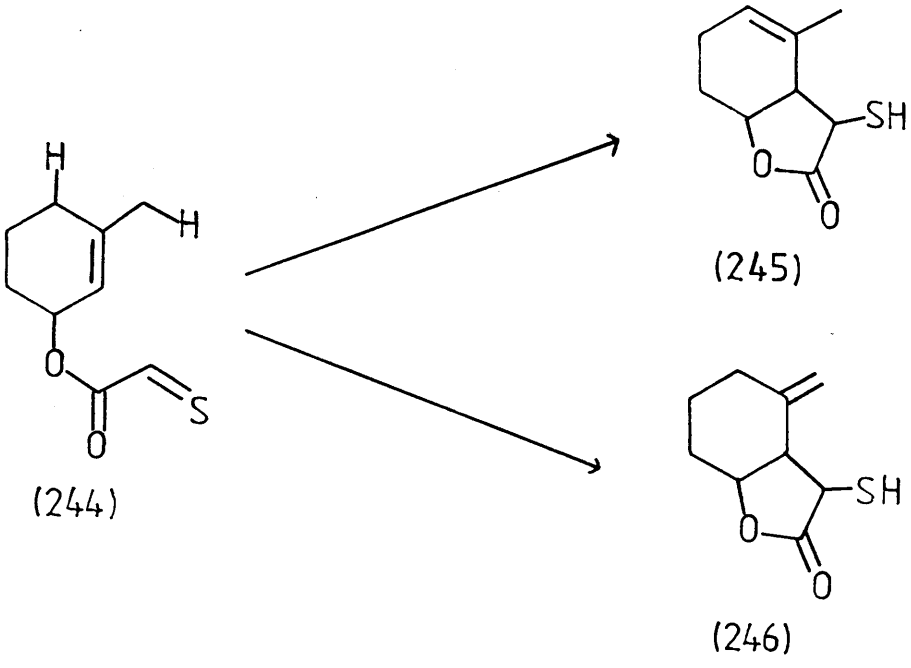


(242)

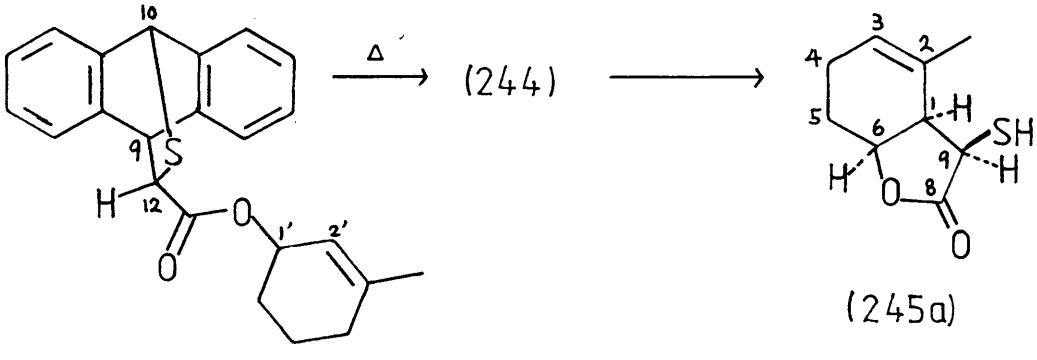


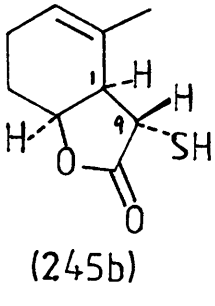
(243)

The homoallylic analogue of 3,3-dimethylallyl thioxoacetate (229), 4-methyl-3-pentenyl thioxoacetate (240), was the next compound studied. It was expected that this thioxoacetate (240) would undergo a Type I intramolecular ene reaction to form the six-membered lactone ring (241). Ethyl 4-methyl-3-pentenoate was made by the literature method[63] and was reduced with lithium aluminium hydride ($LiAlH_4$) in anhydrous diethyl ether to give 4-methyl-3-penten-1-ol. The 4-methyl-3-pentenyl ester (242) was prepared by the usual method from the anthracene carboxylic acid (234a). The ^1H n.m.r. spectrum showed a doublet at δ 5.03 (*J* 2.5 Hz) for 9-H. The methylene group adjacent to oxygen gave a triplet at δ 3.95 (*J* 7.5 Hz). The adduct (242) was heated in boiling toluene (32mM) under nigrogen for 17.5h. Evaporation of the solvent afforded a yellow oil. The ^1H n.m.r. spectrum of the product mixture showed that *ca.* 50% of the adduct (242) had decomposed. T.l.c. showed two major spots, due to the starting adduct and anthracene, and several others, one giving a positive test (white spot in iodine vapour) for a thiol. However, the ^1H n.m.r. spectrum showed no sign of thiol. The yellow oil was then heated in boiling toluene for a total of 38.5h. The n.m.r. spectrum of the crude product showed *ca.* 60% decomposition of the cycloadduct (242). Again, there was no sign of any ene product. It was thought that the thioxoacetate (240) might not be reactive enough at this temperature. So the mixture was heated in boiling xylene under nitrogen for 5.5h. The ^1H n.m.r. spectrum then showed no sign of the cycloadduct (242). However, signals at δ 1.67 (br d, *J* 6.0 Hz), 2.34 and 4.12 (2 x m), 3.58 (s), and 5.11 (br d, *J* 4 Hz) suggested that 'thioaldehyde polymers' (243) might have formed. It was thought the rate of intramolecular ene reaction of thioxo-


H
H
O
S
O
(244)
SH
O
O
(245)
SH
O
O
(246)

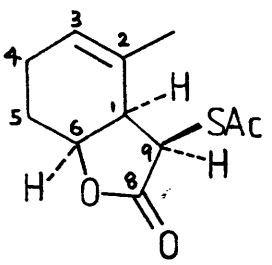
Scheme 64


10
9
S
H
12
O
O
1'
2'
(247)
Δ
(244)
3
2
4
5
1
H
6
SH
9
H
H
O
8
O
(245a)

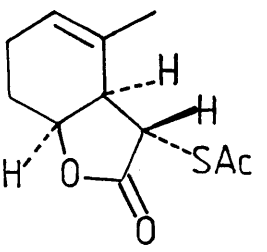

1
H
H
9
H
O
SH
O
(245b)

acetate (240) was much slower than the recapture rate by the anthracene (*cf.* Scheme 63); on prolonged heating, the intermediate thial (240) polymerized. An efficient synthesis of the thiol (241) will be described later.

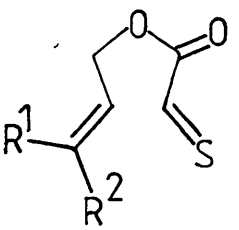
It was believed that unsaturated alicyclic thioxoacetates would show interesting regiospecificity in their intramolecular ene reactions, from which deductions about the geometrical requirements of the transition states of these reactions could be made. 3-Methyl-2-cyclohexenyl thioxoacetate (244) can, in theory, give two possible regioisomeric ene products (245) and (246) (Scheme 64). The carboxylic ester (247) was prepared from its acid (234a) and the readily available 3-methyl-2-cyclohexen-1-ol by the usual method. The ^{1}H n.m.r. spectrum of the resulting yellow oil showed a multiplet at δ 5.24-5.46 for 1'-H and a doublet at δ 4.08 (*J* 3.0 Hz) for 12-H. The i.r. spectrum, ν_{max} 1728 cm^{-1}, confirmed the formation of an ester. The adduct (247) was heated in boiling toluene (32 mM) for 7h under nitrogen to afford a clean conversion to the bicyclic thiol (245a); no isomer of (245a) was detected by ^{1}H n.m.r. spectroscopy. In the ^{1}H n.m.r. spectrum, a multiplet at δ 5.77 was attributed to the olefinic proton. The methyl group gave a broad singlet at δ 1.77 and the thiol proton, exchangeable with D_2O, a doublet at δ 2.22 (*J* 4.0 Hz). In the i.r. spectrum a band at 1778 cm^{-1} confirmed the formation of a five-membered lactone. Chromatography on a Chromatotron (SiO_2) under nitrogen gave a yellow oil, which crystallised from dichloromethane and light petroleum to afford the bicyclic lactone (245a), m.p. 58-61°C. Microanalysis and mass spectrometry establish the molecular formula $C_9H_{12}O_2S$. The 1,9-*cis* configuration of (245a) was established by epimerization



(248a)



(248b)



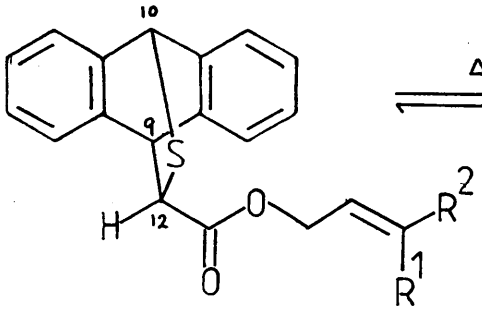
(249)

(a) R^1 = H , R^2 = Me

(b) R^1 = Me, R^2 = H

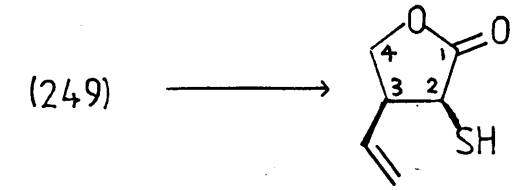
with triethylamine in dichloromethane, essentially complete inversion of configuration at C(9) occurred. The ^{1}H n.m.r. spectrum of the 1,9-*trans*-thiol (245b) a doublet at δ 2.42 *J* 4.5 Hz) for the mercapto proton. The ene product (245a) was further characterized by convertion to the thiol acetate (248a) The *cis*-thiol (245a) in dichloromethane was treated with a preformed mixture of acetic acid and dicyclohexylcarbodiimide for 24h to afford the pure thiol acetate (248a) as a yellow oil after chromatography on a Chromatotron (SiO_2). The 1,9- *cis* configuration in (248a) was confirmed by comparison with the 1,9-*trans*-thiol acetate (248b) from the 1,9-*trans*-thiol (245b). The 1,9-*trans*-thiol (245b), prepared from the *cis*-thiol by epimerization with triethylamine in dichloromethane, was treated with acetyl chloride and triethylamine for 1h to afford the 1,9-*trans*-thiol acetate (248b) as a yellow oil. Accurate mass measurements showed that both compounds had the formula $C_{11}H_{14}O_2S$.

The regio-outcome of the cyclization of 3-methyl-2-cyclohexenyl thioxoacetate (244) prompted us to study the ene reaction of *trans*-2-butenyl thioxoacetate (249a) and *cis*-2-butenyl thioxoacetate (249b). *Trans*-2-buten-1-ol was made by the literature method from the reduction of *trans*-crotonaldehyde with lithium aluminium hydride ($LiAlH_4$)[64]. In the literature, *cis*-2-buten-1-ol was prepared from the partial hydrogenation of 2-butyn-1-ol in methanol using palladium on barium sulphate as catalyst[64]. However, we had difficulty in distilling-off methanol without loss of the product, so dry diethyl ether was used as the solvent. After hydrogenation, a mixture of *cis*- and *trans*-2-buten-1-ol [*ca.* 3:1, by ^{1}H n.m.r. spectroscopy using $Eu(fod)_3$ as shift reagent] was obtained. It was thought that the isomerization



(250)

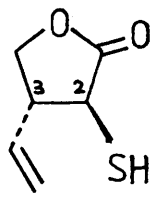
(249)



(251a)

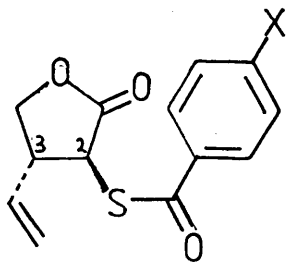
(a) R^1 = H , R^2 = Me

(b) R^1 = Me, R^2 = H



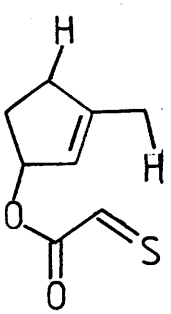
(251b)

might be caused by the catalyst and that certain amines might decrease the activity of the catalyst. Thus, catalytic hydrogenation of 2-butyn-1-ol was carried out in diethyl ether with palladium on barium sulphate and isoquinoline. Filtration and fractional distillation gave the *cis*-2-buten-1-ol as a colourless liquid. The *trans*-(250a) and *cis*-adducts (250b) were prepared in the usual way from the carboxylic acid (234a) and the corresponding alcohols. Both adducts were obtained initially as yellow oils, but the *cis*-adduct (250b) crystallised from ether gave as white crystals, m.p. 97-98^{o}C. Heating the anthracene adduct (250b) of *cis*-2-butenyl thioxoacetate in boiling toluene (32mM) for the 10h under nitrogen proceeded with *ca.* 50% decomposition (by ^{1}H n.m.r. spectroscopy) of the starting material and formation of the *cis*-thiol (251a). Prolonged heating of the adduct for longer than 10h resulted in extensive decomposition of the product. As discussed before, the decomposition of the adduct was faster for less concentrated solution. Therefore, the *cis*-adduct (250b) was heated in boiling toluene (11mM) for 8h under nitrogen. ^{1}H n.m.r. spectrum showed a complete conversion of the adduct (250b) to give anthracene and the *cis*-thiol (251a), with no sign of the epimer. In the ^{1}H n.m.r. spectrum of the thiol (251a), signals at δ 5.79 (ddd, J 7.5, 10.0 and 17.5 Hz), 5.29 (br d, J 10.0 Hz), and 5.20 (br d, J 17.5 Hz), were assigned to the three olefinic protons of the ethenyl side chain. The mercapto proton, exchangeable with D_2O, gave a doublet at δ 1.91 (J 5.5 Hz). The i.r. spectrum confirmed the presence of a five-membered lactone ring, ν_{max} 1772 cm^{-1}. Chromatography of the *cis*-thiol (251a) on a Chromatotron (SiO_2) under nitrogen resulted in partial epimerization to afford a mixture of the *cis*-(251a) and trans-

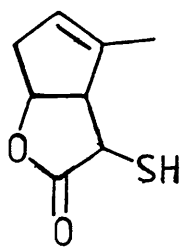


(252) X = H

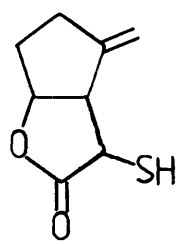
(253) X = NO_2



(254)

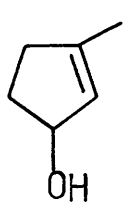


(255)



(256)

Scheme 65

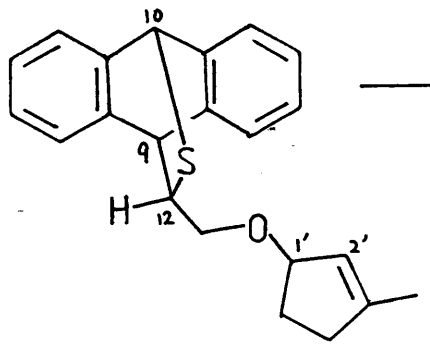


(257)

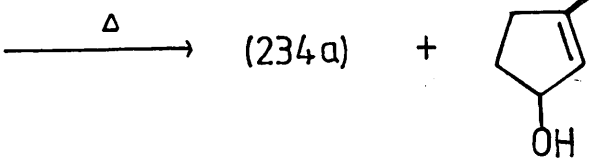
thiols (251b) (*ca.* 1:1, by ^{1}H n.m.r. spectroscopy) as a colourless oil. Accurate mass measurement confirmed the formula $C_6H_8O_2S$. Attempts to epimerize either the *cis*-thiol (251a) or a mixture of the *cis*-and *trans*-thiols (251a) and (251b) resulted in decomposition of the thiols to intractable products. The *cis*-stereochemistry of the ene product (251a) was assigned on the basis of n.m.r. chemical shifts and coupling constants[62]. The mercapto protons in the *cis*- and *trans*-thiols gave doublets at δ 1.91 (*J* 5.5 Hz) and 2.32 (*J* 5.0 Hz), respectively. The stereochemically significant vicinal coupling constants for the *cis* and *trans*-thiols were $J_{2,3}$ = 8.0 and 10.0 Hz, respectively. These values were also comparable with those obtained for the *cis*-(231a) and *trans*-thiols (231b). The ene product (251a) was further characterized by treatment with benzoyl chloride and *p*-nitrobenzoyl chloride in the presence of triethylamine to afford the thiol benzoate (252) and thiol *p*-nitrobenzoate (253), respectively. Both were obtained as yellow oils. Accurate mass measurements confirmed the formula $C_{13}H_{12}O_3S$ and $C_{13}H_{11}NO_5S$, respectively.

The *trans*-adduct (250a) was much more resistant to thermolysis than its *cis* isomer. Thus, heating in boiling toluene (11 mM) for 8h under nitrogen caused (^{1}H n.m.r. control) only *ca.* 20% decomposition; there was no sign of any ene product. Further heating resulted in further decomposition of the adduct (250a) with no detectable formation of ene product.

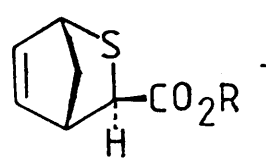
3-Methyl-2-cyclopentenyl thioxoacetate (254) was also thought to be an interesting compound to examine. Again the regioisomers (255) and (256) were possible ene products *via* a Type I process (Scheme 65). 3-Methyl-2-cyclopenten-1-ol (257) was prepared by reduction of 3-methyl-2-cyclopenten-1-one with



(258)

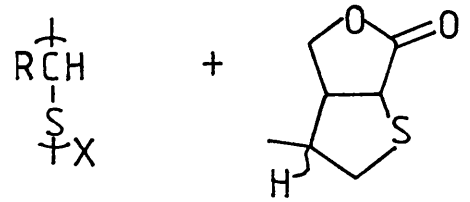


(234a) + (257)

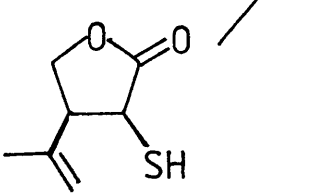


R : $CH_2CH{=}CMe_2$

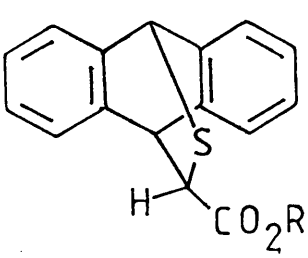
(228b)



(230) + (232)



(231a)



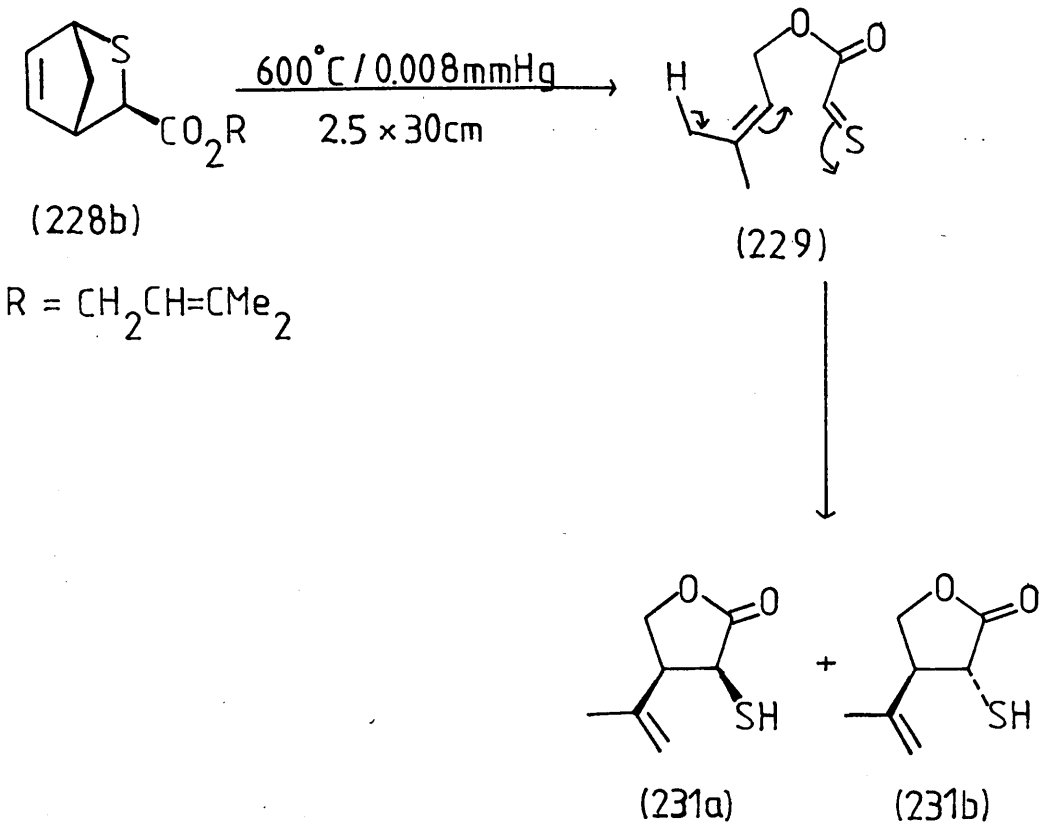
(233a)

R : $CH_2CH{=}CMe_2$

lithium aluminium hydride. The anthracene adduct (258) of 3-methyl-2-cyclopentenyl thioxoacetate was prepared in the usual way from the carboxylic acid (234a) and 3-methyl-2-cyclopenten-1-ol (257). However, upon chromatography on SiO_2 plates, the ester (258) was hydrolysed to form its carboxylic acid (234a) and alcohol (257). It was thought that this problem might be overcome if a Chromatotron (SiO_2) were employed, since no drying of the plate was required and the ester (258) would have no prolonged contact with the silica. Indeed, the ester (258) was purified successfully on a Chromatotron (SiO_2) under nitrogen.

The ^1H n.m.r. of the product showed significant signals at δ 4.07 (d, *J* 3.0 Hz, 12-H) and 1.74 (s, Me) confirming the ester structure (258). Furthermore, the i.r. spectrum showed an ester band at 1730 cm^{-1}. The adduct (258) was heated in boiling toluene (32mM) for 7h under nitrogen. The ^1H n.m.r. spectrum of the crude product showed that the adduct (258) had decomposed to the corresponding carboxylic acid (234a) and alcohol (257). I.r. bands at 1712 and 3500-2400 cm^{-1} confirmed the presence of a carboxylic acid. This thermolysis reaction was not studied further. Another study of the ene reaction of the thioaldehyde (254) will be described later.

In our preliminary thermolysis study of the *exo*-adduct (228b) of cyclopentadiene and 3,3-dimethylallyl thioxoacetate, 'thioaldehyde polymers' (230) (major product) and the bicyclic lactone (232) (minor product) were formed. Later, the thermolysis of the corresponding anthracene adduct (233a) gave a clean conversion to the expected ene product (231a). So it was thought that, in the thermolysis of cyclopentadiene adduct (228b), the ene product (231a) might have formed first, but on prolonged heating (34.2h in boiling toluene), had either decomposed



(228b)

R = $CH_2CH{=}CMe_2$

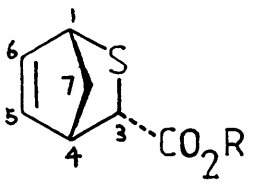
(229)

(231a) (231b)

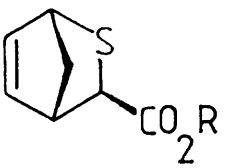
Scheme 66

or cyclised to form the bicyclic lactone (232), Since cyclopentadiene adducts have certain advantages, discussed earlier, as precursors of thioaldehyde, the thermolysis of the adducts (228a-b) was studied further in the hope of improving the yield of the ene products. A mixture of the *endo*-(228a) and *exo*-cyclopentadiene adducts (228b) were heated in toluene at 110°C (11mM) for 15h under nitrogen to afford a mixture of starting adducts (228) and ene product (231a) (*ca.* 2:1; by ^{1}H n.m.r. spectroscopy). A greater conversion (63% was obtained in xylene, in the presence of a small amount of the radical inhibitor 2,6-di-tert-butyl-*p*-cresol, under otherwise identical conditions but with nitrogen passing through the solution to expel cyclopentadiene as it was formed. However, it was clear that thermolysis of cyclopentadiene adducts was still inconveniently slow for preparative purposes. Flash vacuum pyrolysis (FVP) was chosen as an alternative procedure, since unimolecular dissociation and ene cyclisation could occur consecutively without competition from the bimolecular recapture of thioaldehyde by cyclopentadiene or other dienes. In fact, flash vacuum pyrolysis of the adduct (43) of anthracene and methanethial had been shown to afford methanethial (5) and anthracene[13]. The procedure thereby serves as a convenient source of methanethial (5). At this point of our work, Dr. I. Gosney, (University of Edinburgh) kindly lent his apparatus[65] for a preliminary flash vacuum pyrolysis study.

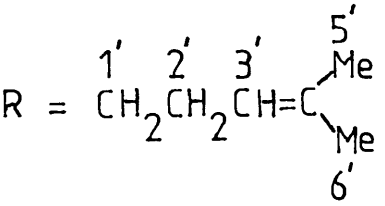
The *exo*-3,3-dimethylallyl ester (228b) was evaporated slowly at 80°C and 0.008 mmHg through a silica tube at 600°C; the products were collected in a trap cooled in liquid nitrogen then were dissolved in dichloromethane at room temperature. Evaporation of the solvent and cyclopentadiene gave the pure thiols



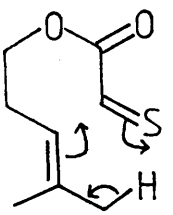
(259a)



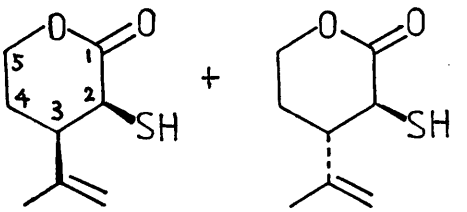
(259b)



(259b) $\xrightarrow[2.5\times30\text{cm}]{600^{\circ}C\,/\,0.008\text{mmHg}}$



(240)

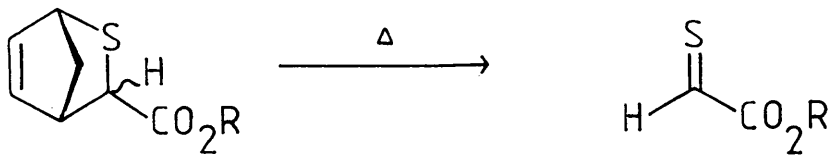


(241a) (241b)

Scheme 67

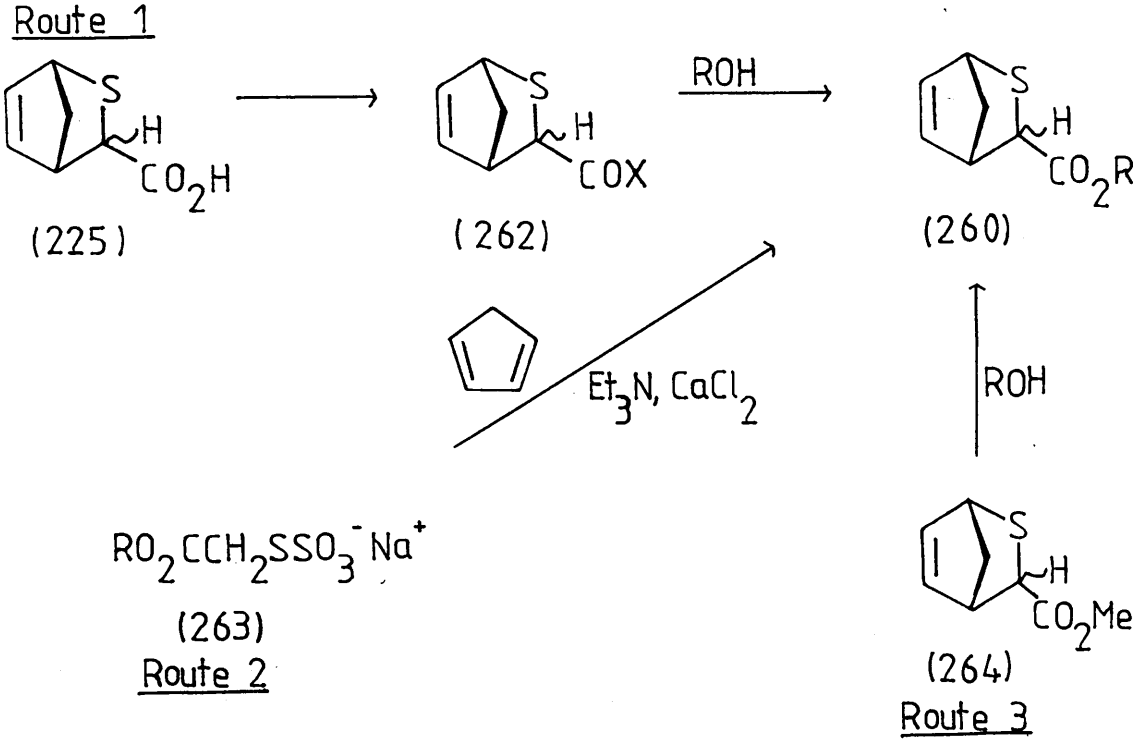
(231a-b) (95%) as a mixture of the *cis*- and *trans*-isomers (*ca.* 1:3, by ^{1}H n.m.r. spectroscopy). Presumably, partial epimerization of the *cis*-thiol (231a) had occurred in the hot tube (Scheme 66).

Then the adduct (259) of cyclopentadiene and 4-methyl-3-pentenyl thioxoacetate was prepared from carboxylic acid (225) and 4-methyl-3-penten-1-ol in the usual way. Chromatography of the crude esters (259) gave the *endo*-(259a) and *exo*-isomers (259b) separately as colourless oils. ^{1}H n.m.r. spectrum of the *endo*-ester (259a) double doublets at δ 5.86 and 6.45 (*J*, 3.0 and 5.5 Hz) arising from the olefinic protons of the cyclopentene ring, and a doublet at δ 4.40 (*J* 4.5 Hz) from 3-H. The i.r. spectrum showed the band at 1730 cm^{-1}, expected for an ester, and the molecular formula was confirmed by accurate mass measurement. In the ^{1}H n.m.r. of the *exo*-ester (259b) a broad singlet at δ 3.27 was observed for 3-H. The 1'-methylene protons gave a triplet at δ 4.10 (*J* 7.0 Hz). Both i.r. spectroscopy and accurate mass measurement confirmed the ester structure (259b) with a band at 1732 cm^{-1} and a molecular formula $C_{13}H_{18}O_2S$. Evaporation of the *exo*-homoallylic ester (259b) at 100°C, and pyrolysis as before, afforded the δ-lactone (241) (62%) as a yellow oil, again as a mixture of the *cis*-(241a) and *trans*-isomer (241b) (*ca.* 1:9) (Scheme 67). The ^{1}H n.m.r. spectrum showed doublets at δ 1.99 (*J* 4.5 Hz) and 2.52 (*J* 3.5 Hz), which both disappeared after D_2O exchange, assigned to the mercapto protons in the *cis*-(241a) and trans-isomer (241b), respectively. The i.r. spectrum showed the expected band at 1730 cm^{-1}. The molecular formula of the δ-lactone was confirmed by accurate mass measurement.



(260) (261)

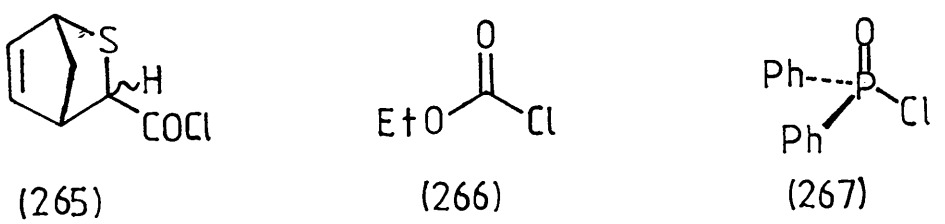
Scheme 68



(225) (262) (260) (263) (264)

Route 1 Route 2 Route 3

Scheme 69



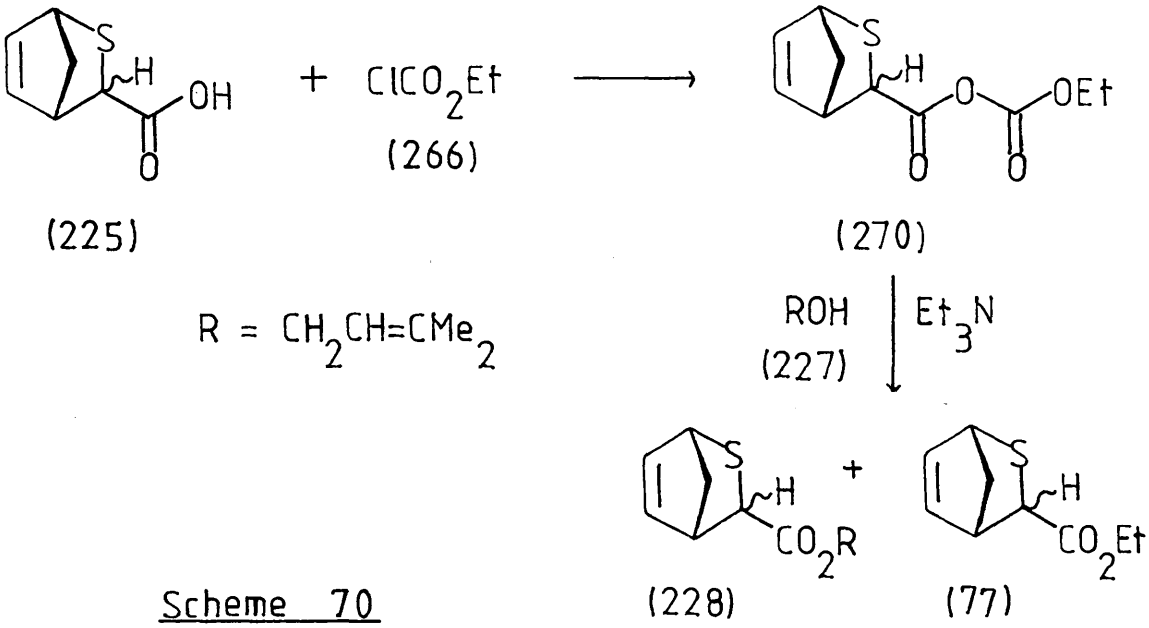
(265) (266) (267)

(268) (269)

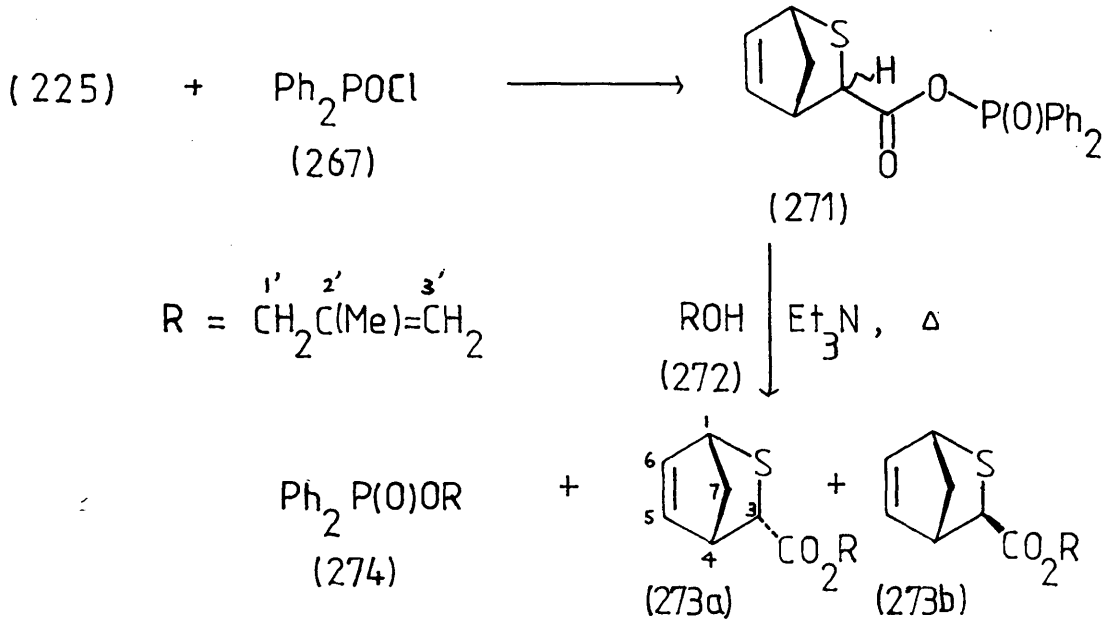
Once, cyclopentadiene adducts (260) had been shown to provide a good source of thioxoacetates (261) (Scheme 68) other routes to the adducts (260) were investigated. Three possible synthetic routes to the target cyclopentadiene adducts (260) were considered (Scheme 69).

Although *N,N'*-carbonyldi-imidazole gave high yields in the esterification of the acid (225), this reagent is expensive and is usually contaminated with imidazole and therefore must be assayed before use. Other condensing agents were therefore tested. Following a general procedure of ester synthesis[66], the carboxylic acid (225), 3,3-dimethylallyl alcohol (227) and *p*-toluenesulphonic acid in pyridine were treated with dicyclohexylcarbodiimide to afford the ester (228) in 54% yield after chromatography. This yield was clearly not acceptable for our purposes. It was thought that conversion of the carboxylic acid (225) into its corresponding acid chloride (265) followed by treatment with the appropriate alcohol and triethylamine could afford the target ester (260). However, an attampt to prepare the acid chloride (265) from the acid (225) by treatment with oxalyl chloride in benzene resulted in the decomposition of the starting acid. The i.r. spectrum of the reaction mixture showed no carbonyl bands attributable to the carboxylic acid (225) or its acid chloride (265).

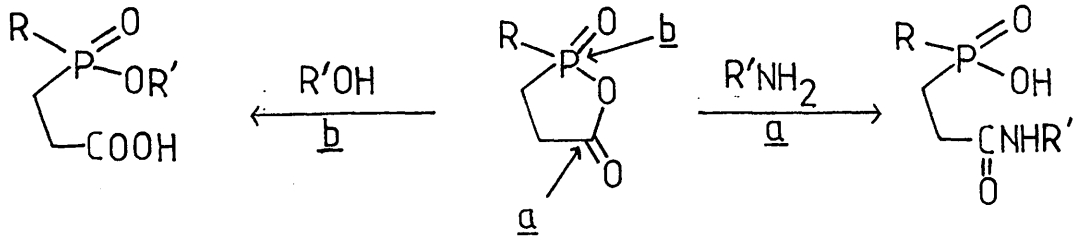
Ethyl chloroformate (266)[67] and diphenylphosphinoyl chloride (267)[68] have been commonly used in peptide chemistry for the formation of amide. The mixed anhydrides (268) and (269) were formed as intermediates. Therefore, the carboxylic acid (225) was treated with triethylamine and ethyl chloroformate (266) in dichloromethane. The mixed anhydride (270) was isolated as a yellow oil in 95% yield. In the ^{1}H n.m.r. spectrum, two quartets at δ 4.33 and 4.36 (J 7.0 Hz) were attributed to the



Scheme 70



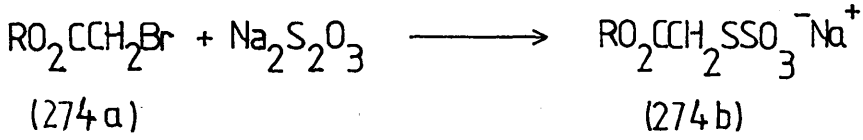
Scheme 71



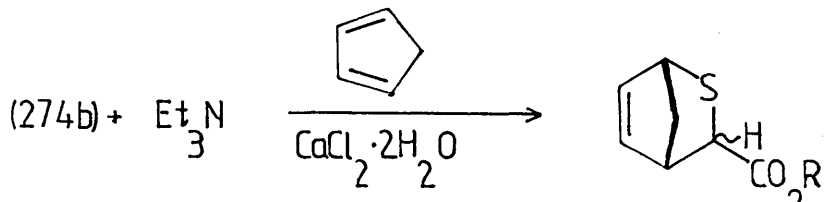
Scheme 72

ethoxy methylene protons in the *endo*-(270a) and *exo*-isomers (270b) respectively. The i.r. spectroscopy confirmed the formation of a mixed anhydride with bands at 1817 and 1733 cm^{-1}. Treatment of the mixed anhydride (270) in dichloromethane with 3,3-dimethylallyl alcohol (227) and triethylamine gave a mixture of the 3,3-dimethylallyl ester (228) and the ethyl ester (77) (*ca.* 3:1, by ^1H n.m.r. spectroscopy) (Scheme 70). Presumably, ethanol liberated during formation of the required ester (228) attacked the mixed anhydride in competition with the alcohol (227).

The diphenylphosphinic mixed anhydrides (271) were formed by treatment of the carboxylic acid (225) in dichloromethane with diphenylphosphinoyl chloride (267) at -20°C using *N*-methylmorpholine as the base. The anhydrides (271) formed, in dichloromethane, were heated under reflux for 14h with 2-methyl-2-propen-1-ol (272) in the presence of triethylamine. The ^1H n.m.r. spectrum of the product showed a mixture of carboxylic ester (273) and diphenylphosphinate (274) (*ca.* 16:1) (Scheme 71). Chromatography gave separately the pure *endo*-(273a) and *exo*-esters (273b) as colourless oils in a total yield of 70%. The diphenylphosphinate (274) might be formed by the attack of the alcohol (272) at phosphorus. With the cyclic carboxylic-phosphinic anhydrides the regiospecificity of attack depends on the nature of the nucleophile; in aminolysis, the attack follows path *a*, whereas in alcoholysis it occurs by attack at phosphorus, path *b* (Scheme 72)[69]. In the ^1H n.m.r. spectrum of the *endo*-ester (273a), the 3-H gave a doublet at δ 4.48 (*J* 2.5 Hz) and the 1'-methylene group a singlet at δ 4.50. The i.r. spectrum showed a carbonyl stretching band at 1740 cm^{-1}. Both microanalysis and accurate mass measurement confirmed the



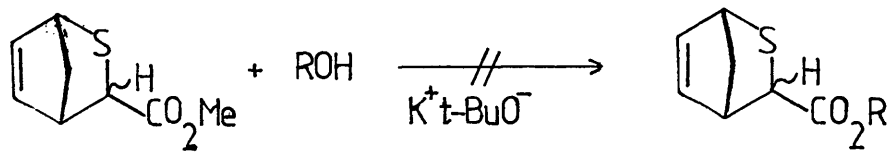
(274a) (274b)



(228)

R = $Me_2C{=}CHCH_2$

Scheme 73



(264) (227) (228)

R = $Me_2C{=}CHCH_2$

Scheme 74

formula $C_{11}H_{19}O_2S$. The ^1H n.m.r. spectrum of the *exo*-isomer (273b) gave broad singlets at δ 3.34 for 3-H and 4.58 for 1'-CH_2. A carbonyl stretching band at 1738 cm^{-1} was seen in the i.r. spectrum. Accurate mass measurement confirmed the molecular formula. 2-Methyl-2-propenyl diphenylphosphinate (274) was isolated as a yellow solid. Accurate mass measurement established the formula $C_{16}H_{17}O_2P$. In the ^1H n.m.r. spectrum, a doublet at δ 4.42 (*J* 7.5 Hz) was attributed to the methylene protons adjacent to oxygen. A stretching band (P-OR) at 1048 cm^{-1} in the infra-red spectrum confirmed the formation of a phosphinic ester.

Although esterification using diphenylphosphinoyl chloride gave satisfactory results, *N,N'*-carbonyldiimidazole gave better yields and a product that was easier to purify.

Normally in the preparation of cyclopentadiene adducts (84) *via* the Bunte salt method (Scheme 22)[21], either methanol or ethanol is used as the solvent. However, it was thought that in the case of our target adducts (260) (Scheme 69), neither ethanol nor methanol could be used as solvents because transesterification would occur. Therefore, a new solvent system had to be used. Several experiments using acetone and water in different ratios as solvents were carried out to prepare the ethyl ester adduct (77). A best yield of 76% was obtained by using a water-acetone mixture (*ca.* 1:7) as solvent. Treatment of dimethylallyl bromoacetate (274a), obtained *via* a literature method[46], with sodium thiosulphate in acetone-water (*ca.* 1:1) at room temperature gave the crystalline Bunte salt (274b). Microanalysis confirmed the formula $C_7H_{11}O_5NaS_2$, expected for the structure (274b). The i.r. spectrum showed characteristic stretching bands at 1210, 1055 and 670 cm^{-1}. Treatment of the

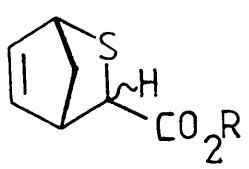
Bunte salt (274b) in acetone-water (*ca.* 7:1) with triethylamine in the presence of cyclopentadiene and calcium chloride dihydrate gave the adduct (228) (Scheme 73) in 75% yield as a light yellow mobile oil after usual work-up. ^{1}H N.m.r. spectroscopy showed that the *endo*-(228a) and *exo*-adducts (228b) were the only products.

An attempt to prepare the target esters (260) by ester interchange technique was unsuccessful. Molecular sieves (5A) were employed to shift the equilibrium by selective adsorption of the alcohol of low molecular weight[70]. Thus, heating a mixture of methyl ester (264), 3,3-dimethylallyl alcohol (227) and potassium t-butoxide in boiling benzene in the presence of 5A molecular sieves for 3.5h gave a yellow oily product (Scheme 74). ^{1}H N.m.r. spectroscopy suggested that the cyclopentadiene adduct had decomposed. However, a singlet at δ 3.77 and a stretching band at 1736 cm^{-1} in the i.r. spectrum indicated that the product had a methyl ester group.

After all these investigations into other possible routes to prepare the target esters (260), the procedure employing *N,N'*-carbonyldiimidazole (226), with a catalytic amount of n-butyl lithium in the alcoholysis step (Scheme 59), seemed to be the most efficient. This is particularly true when the alcohol employed is expensive.

The success in the preliminary flash vacuum pyrolysis study prompted us to exploit this technique more widely. Dr. Gosney kindly provided details in the construction of our apparatus. A description of the FVP apparatus and general procedure are included in the Experimental Section.

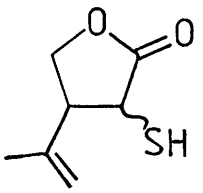
In a repeated experiment, the adduct (228) of cyclopentadiene and 3,3-dimethylallyl thioxoacetate was evaporated slowly



(228)

600°C/0.004mmHg

s.t.

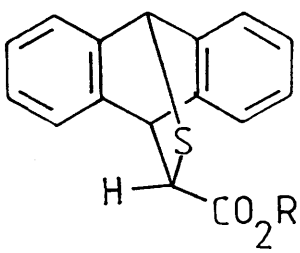


(231)

R = $CH_2CH{=}CMe_2$

s.t. = silica tube, 2.5×55cm (Schemes 75-92)

Scheme 75



(233a)

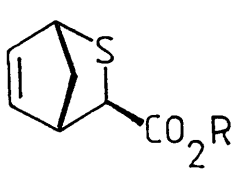
600°C/2×10^{-5} mmHg

s.t.

(231)

R = $CH_2CH{=}CMe_2$

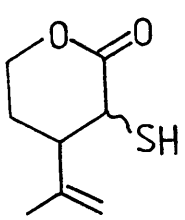
Scheme 76



(259b)

500°C/0.003mmHg

s.t.



(241)

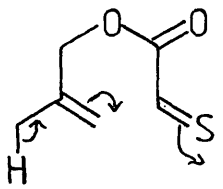
R = $(CH_2)_2CH{=}CMe_2$

Scheme 77

at 80°C and 0.004 mmHg through a silica tube at 600°C; the products were collected in a trap cooled in liquid nitrogen, then were dissolved in dichloromethane at room temperature. Evaporation of the solvent and cyclopentadiene gave, as before, the pure thiol (231) (100%) as a mixture of the *cis*-(231a) and trans-isomer (231b) (*ca.* 1:2) (Scheme 75). Similarly, evaporation of the corresponding anthracene adduct (233a), which was deposited on Celite to increase the rate of volatilization at 180°C and 2 x 10^{-5} mmHg, and pyrolysis as before, gave the same thiol (231) (80%), as a mixture of the *cis*- and *trans*-isomer (*ca.* 2:3), with traces of impurities (Scheme 76).

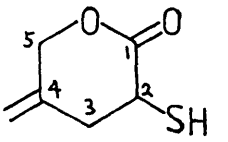
Pyrolysis of the *exo*-homoallylic ester (259b) was also repeated; thus slow evaporation at 100°C and 0.003 mmHg through a silica tube at 500°C gave the oily δ-lactone (241) (99%), as a mixture of *cis*- and *trans*-isomers (*ca.* 2:3) containing only traces of impurities (Scheme 77).

It was thought that the simplest allylic thioxoacetate that could possibly demonstrate a Type II intramolecular ene reaction was 2-methyl-2-propenyl thioxoacetate (275) (Scheme 78). The corresponding adduct (273b) was prepared from its carboxylic acid (225) using diphenylphosphinoyl chloride (267) as condensing agent as discussed before (Scheme 71). Evaporation of the *exo*-adduct (273b) at 80°C and 0.003 mmHg through a hot silica tube at 600°C gave the δ-lactone (276) (52%) and some impurities. In the ^{1}H n.m.r. spectrum a doublet at δ 2.42, *J* 6.0 Hz, (exchangeable with D_2O) was assigned to the mercapto proton. The methine proton, 2-H, gave a double triplet at δ 3.92, *J* 5.5 and 7.5 Hz. Attempted purification of this product on the Chromatotron (SiO_2) under nitrogen resulted in decomposition, possibly *via* the hydrolysis of the lactone. Pyrolysis of the *exo*-adduct (273b)

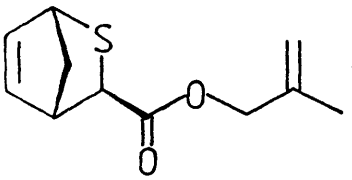


(275)

Type II



(276)



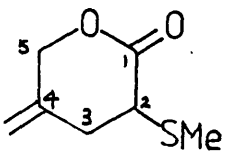
(273b)

430°C/0.003mmHg
s.t.

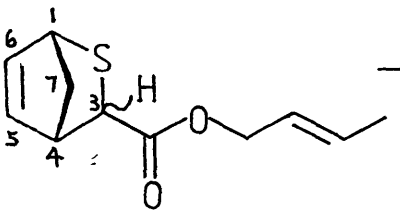
(276)

Scheme 78

(276) + MeI



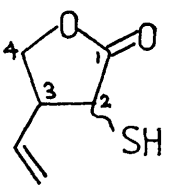
(277)



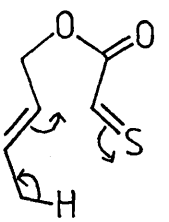
(278)

(a) Endo
(b) Exo

600°C/0.004mmHg
s.t.



(251)
(a) Cis
(b) Trans



(249a)

Scheme 79

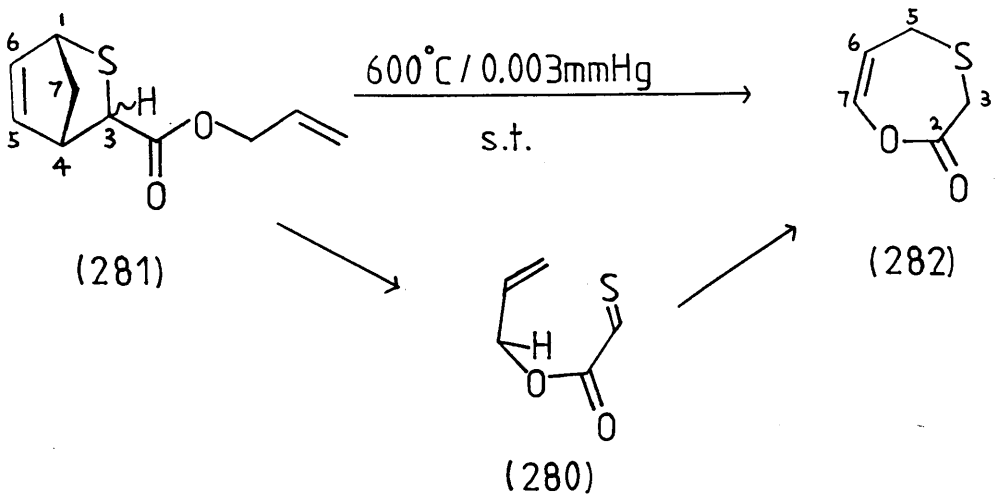
at lower temperature, 430°C, gave a relatively cleaner (as judged by ^{1}H n.m.r. spectroscopy) conversion (73%) to the δ-lactone (276) (Scheme 78). Treatment of the thiol (276) with methyl iodide in anhydrous acetone saturated with potassium carbonate gave its methyl sulphide (277) (30% from the cycloadduct) as a yellow oil. The ^{1}H n.m.r. spectrum showed a singlet at δ 2.24 for methylthio group. Accurate mass measurement confirmed the formula $C_7H_{10}O_2S$ for this methyl sulphide (277).

Although, as described earlier, the adduct (250a) of anthracene and *trans*-2-butenyl thioxoacetate gave no ene product on thermolysis in solution, inspection of models suggested that an intramolecular ene reaction of this thioxoacetate (249a) was feasible (Scheme 79). Therefore, a mixture of the corresponding cyclopentadiene adducts (278) was prepared from the acids (225) and *trans*-2-buten-1-ol using *N,N'*-carbonyldiimidazole as condensing agent. Chromatography gave two separate isomers, the *endo*-(278a) and *exo*-adducts (278b). The ^{1}H n.m.r. spectra of the two isomers showed, as expected, signals at δ 4.42 (d, *J* 4.0 Hz) and δ 3.28 (s) for 3-H in the *endo*- and *exo*-isomers, respectively. The i.r. spectra confirmed the structure for an ester with a stretching band at 1732 cm^{-1} for the *endo*-ester (278a) and at 1730 cm^{-1} for the *exo*-ester (278b). Accurate mass measurements verified the molecular formular of the two isomers. The cycloadducts (278) was evaporated slowly at 80°C and 0.004 mmHg through a silica tube at 600°C to give the pure thiol (251) (100%), as a mixture of the *cis*-(251a) and *trans*-isomers (251b) (*ca.* 1:1, by ^{1}H n.m.r. spectroscopy)

The adducts (279) of cyclopentadiene and 3-methyl-2-cyclopentenyl thioxoacetate were also prepared from the acid (225) and 3-methyl-2-cyclopenten-1-ol (257) using the usual method.

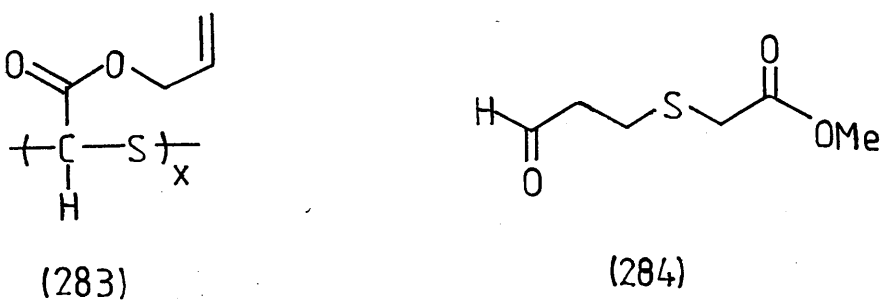
Purification of the esters (279) was achieved on a Chromatotron (SiO_2) under nitrogen to afford a mixture of *endo*- and *exo*-isomers (279). In the ^1H n.m.r. spectrum of the mixture a broad singlet at δ 1.82 was attributed to the methyl group in both isomers. Signals for 3-H were observed at δ 3.27 (s) for the *exo*-isomer and at δ 4.40 (d, *J* 4.5 Hz) for the *endo*-isomer. An i.r. band was observed at 1726 cm^{-1}, and mass spectrometry confirmed the formula of the esters (279). Evaporation of the adducts (279) at 80°C and 0.0004 mmHg through a silica tube at 620°C (Scheme 80) gave a yellow oily product (54%). The i.r. spectrum showed a strong band at 1760 cm^{-1}, suggesting that a five-membered lactone ring had been formed. Many spots were seen on t.l.c., of which one showed a positive thiol test. As discussed before, the thioaldehyde (254) could, in theory, give two structural isomers (255) and (256) *via* an intramolecular ene reaction (Scheme 65). But we expected the isomer (255) with an endocyclic double bond to be the product, because we had evidence for selective attack at the 'cis' methyl group of dimethylallylic thioxoacetates. No attempt was made to purify the product because of lack of material. In the ^1H n.m.r. spectrum a doublet at δ 2.19 (*J* 6.0 Hz, exchangeable with D_2O) was attributed to the thiol proton. Signals at δ 3.96 (dd, *J* 9.0 and 6.0 Hz, 4-H) and 5.19 (dt, *J* 4.0 and 7.0 Hz, 1-H) supported the structures (255) or (256).

It was thought that the parent allyl thioxoacetate (280) might possibly undergo a Type III reaction (Scheme 81), although Type III ene reactions are rarely observed. The corresponding cyclopentadiene adducts (281) were prepared from the acids (225) and allyl alcohol using *N,N'*-carbonyldiimidazole. Chromatography gave separate *endo*-(281a) and *exo*-isomers (281b). As

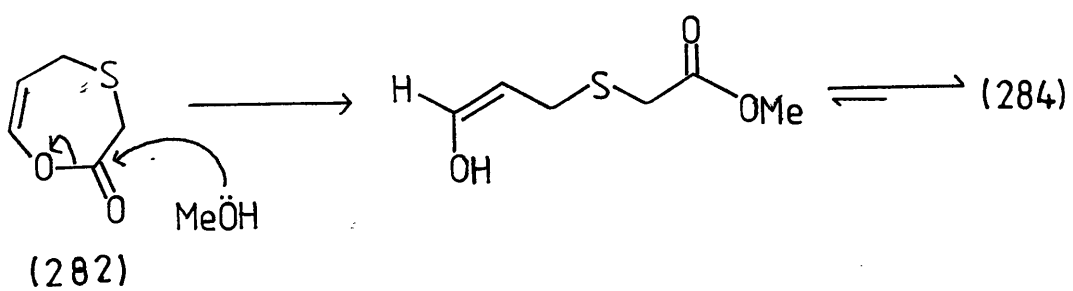


(281) (280) (282)

Scheme 82



(283) (284)



(282) (284)

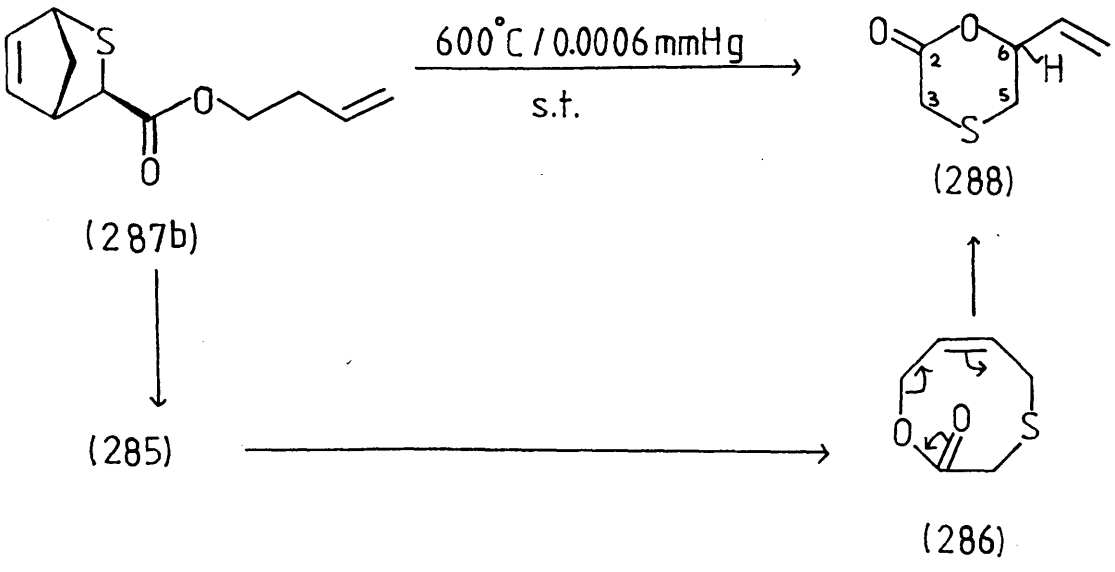
Scheme 83

usual, the separate isomers gave n.m.r. signals for 3-H at δ 4.47 (d, *J* 3.5 Hz) and 3.34 (s), for (281a) and (281b), respectively. The methylene groups attached to oxygen gave doublets at δ 4.60 (*J* 5.8 Hz) in the *endo*-isomer and at δ 4.67 (*J* 5.0 Hz) in the *exo*-isomer. The i.r. spectra showed bands at 1734 cm^{-1} for the *exo*-ester (281b) and at 1735 cm^{-1} for the *endo*-ester (281a). Microanalysis and mass spectroscopy confirmed the molecular formula of the mixture of esters (281). Evaporation of the adducts (281) at 100°C and 0.003 mmHg through a silica tube at 600°C gave the vinyl ester (282) as a yellow oil in 36% yield after chromatography (Scheme 82). The i.r. spectrum confirmed the structure as vinyl ester structure with stretching bands at 1760 and 1642 cm^{-1}. In the ^1H n.m.r. spectrum of the yellow oil, diagnostic signals were observed at δ 6.58 (d, *J* 6.0 Hz, 7-H), 5.65 (dt, *J* 6.0 and 8.0 Hz, 6-H), 3.42 (s, 3-CH_2), and 3.39 (d, *J* 8.0 Hz, 5-CH_2). Accurate mass measurement showed that the yellow oil had the formula $C_5H_6O_2S$. A white solid was also isolated from the reaction mixture; its i.r. spectrum showed a strong band at 1735 cm^{-1}, suggesting the compound might be a 'thioaldehyde polymer' (283). Further characterization of the ene product, a vinyl ester (282), was achieved by the methanolysis. Treatment in methanol with silica gave the methyl ester (284) as a yellow oil (Scheme 83). Accurate mass measurement confirmed the molecular formula. The ^1H n.m.r. spectrum showed singlets at δ 3.27 and 3.77 arising from the methylene group adjacent to the ester group and the methyl group, respectively. The aldehyde proton, gave a triplet at δ 9.76 (*J* 1.5 Hz). The i.r. spectrum showed a band at 1732 cm^{-1}.

The homologue of the allyl thioxoacetate (280), 3-butenyl thioxoacetate (285), was the next compound studied. It was

(285) (286)

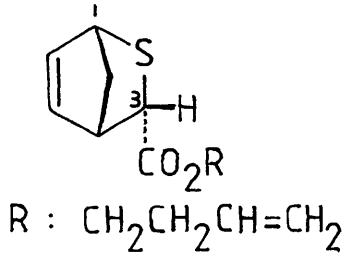
Scheme 84



(287b) (288)

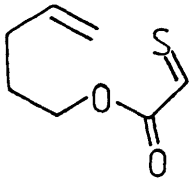
(285) (286)

Scheme 85



R : $CH_2CH_2CH=CH_2$

(287a)

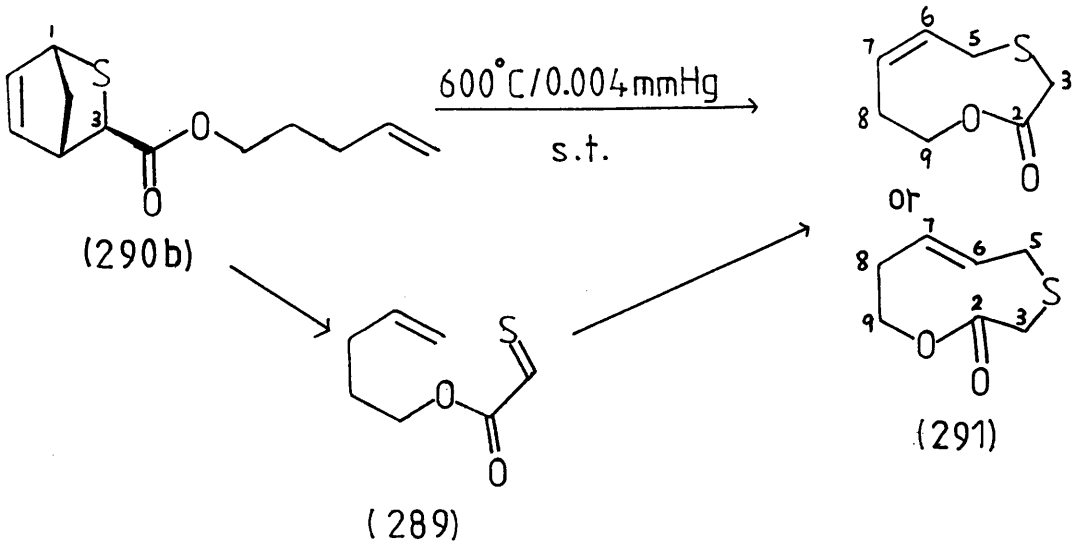


(289)

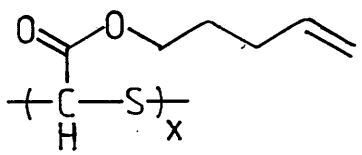
expected that the thioxoacetate (285) might undergo a Type III process to form the eight-membered lactone (286) (Scheme 84). The corresponding cyclopentadiene cycloadducts (287) were prepared by the usual method. Chromatography gave two separate isomers, the *endo*-(287a) and *exo*-esters (287b). Infra-red spectra confirmed their structures with bands at 1735 cm^{-1} for the *endo*-ester (287a) and at 1732 cm^{-1} for the *exo*-ester (287b). Accurate mass measurements showed both isomers had the formula $C_{11}H_{15}O_2S$. Evaporation of the adduct (287b) at 80°C and 6 x 10^{-4} mmHg through a silica tube at 600°C gave the six-membered lactone (288) as a yellow oil in 34% yield after chromatography (Scheme 85). The i.r. spectrum showed a stretching band at 1738 cm^{-1} and mass spectrometry established the formula $C_6H_8O_2S$. In the ^1H n.m.r. spectrum, signals at δ 5.38 (br d, J 10.0 Hz), 5.48 (br d, J 17.0 Hz), and 5.97 (ddd, J 5.5, 10.0 and 17.0 Hz) were attributed to the ethenyl side chain, Signals at δ 5.03 (dt, J 5.0 and 10.0 Hz, 6-H), 3.25 and 3.60 (Abq, J 14.4 Hz, 3-CH_2) confirmed the remainder of the structure. It was thought that the eight-membered lactone (288) was formed first, then underwent a [3,3] sigmatropic rearrangement to give the six-membered lactone (288).

In view of the ease of formation of medium size lactone rings using the FVP technique, we extended our study to other thioxoacetates. Our aim was to develop the FVP technique in the preparation of medium and large lactone rings.

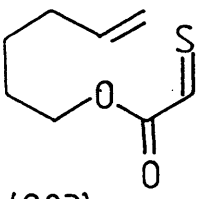
The next higher homologue studied was 4-pentenyl thioxoacetate (289). The corresonding cyclopentadiene adduct (290) was prepared using the usual method. The *endo*-(290a) and *exo*-esters (290b) were obtained separately as colourless liquids after chromatography. The ^1H n.m.r. spectra of separate isomers



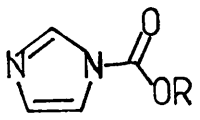
Scheme 86



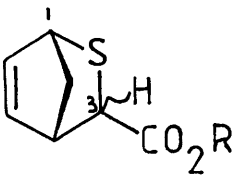
(292)



(293)



(294)

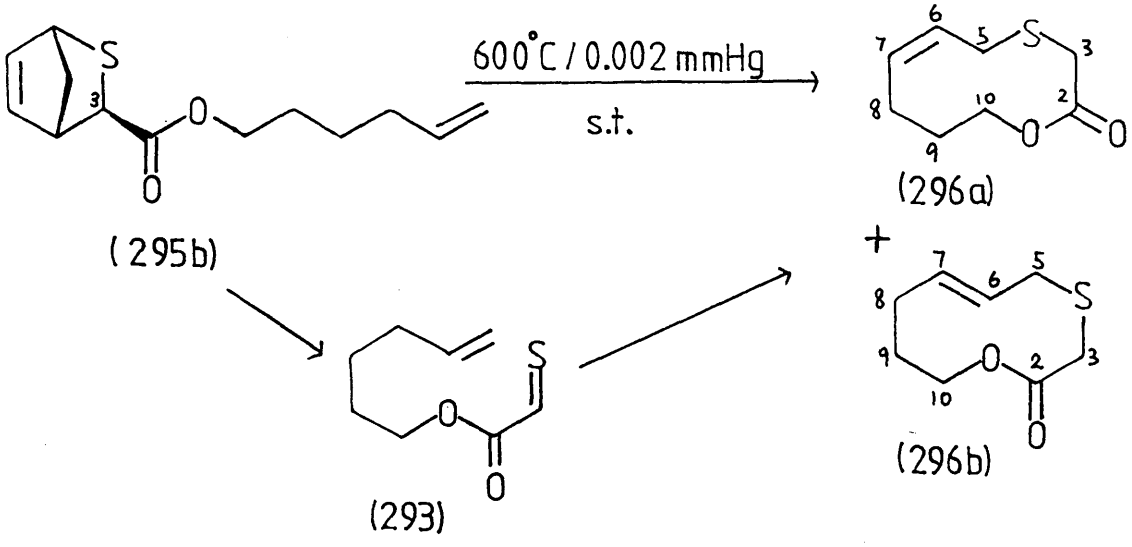


(295)

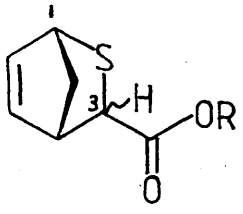
R = $(CH_2)_4CH{=}CH_2$

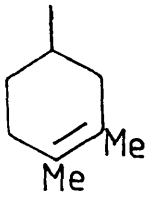
were consistent with the structures (290a) and (290b). Accurate mass measurement verified the formula of the mixture of esters (290) and the i.r. spectra showed the expected bands at 1732 and 1735 cm^{-1} for the *endo*- and *exo*-isomers, respectively. The adduct (290b) was slowly evaporated at 100°C and 0.004 mmHg though a silica tube at 600°C. The products consisted of a yellow oil mixed with a white solid. Chromatography separated the nine-membered lactone (291) as a yellow oil in 33% yield from the'thioaldehyde polymers' (292) (Scheme 86). In the ^1H n.m.r. of the lactone (291), signals were assigned as follows: δ 5.36-5.86 (m, 6- and 7-H), 4.22 (t, *J* 5.0Hz, 9-CH_2), 3.36 (d, *J* 7.4 Hz, 5-CH_2), and 3.23 (s, 3-CH_2). Since the coupling constant between two olefinic protons could not be measured, the stereochemistry of the double bond was not established. Accurate mass measurement confirmed the formula of the lactone (291). In the ^1H n.m.r. of the 'thial polymers' a broad singlet at δ 3.50 was attributed to the thioformyl proton. Other broad resonances at δ 1.70, 2.33, 4.35, 5.35 and 5.84 resembled those in the ^1H n.m.r. spectrum of the ester (290) derived from 4-penten-1-ol. The i.r. spectrum confirmed the presence of an ester group with a band at 1730 cm^{-1}.

Then attention was paid to the next higher homologue, 5-hexenyl thioxoacetate (293). Again the corresponding adducts (295) were prepared from the carboxylic acids (225) and 5-hexen-1-ol using *N,N'*-carbonyldiimidazole (226). However, the product was a mixture of the carboxylic ester (295), and the imidazole-*N*-carboxylate (294), as shown from the ^1H n.m.r. spectrum. The imidazole-*N*-carboxylate might be derived from the n-butyl-lithium-catalysed reaction between the alcohol and excess *N,N'*-carbonyl-diimidazole. The *endo*-(295a) and *exo*-esters (295b) were



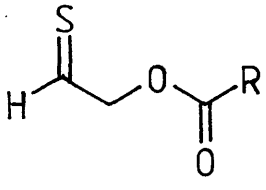
Scheme 87



(297) R = 

(298) R = $(CH_2)_2C(Me)CH_2$

(299) R = $CH_2CH{=}CHPh$



(300)

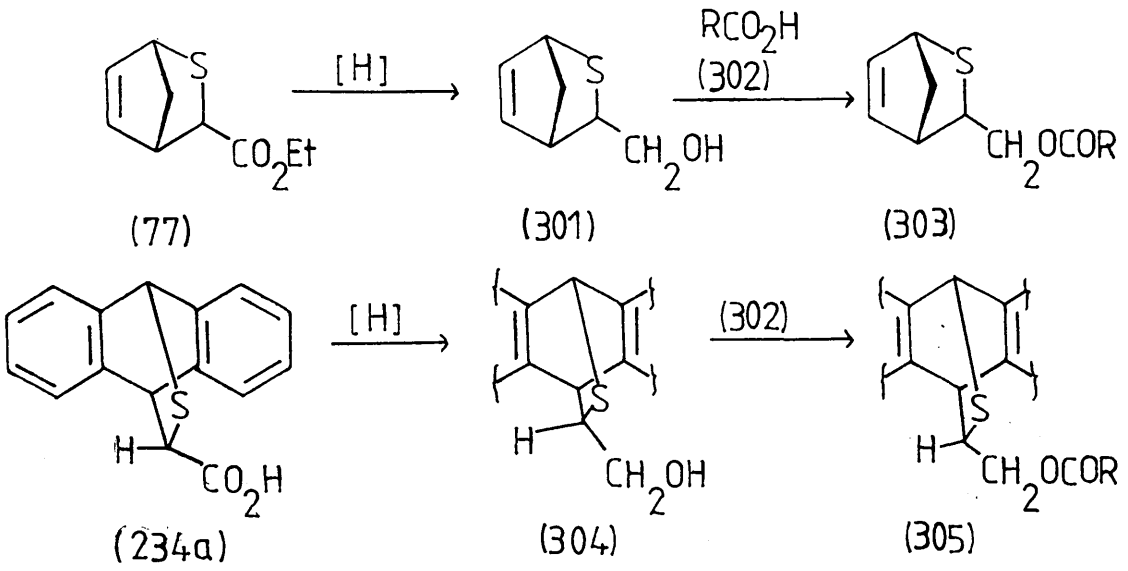
ene

?

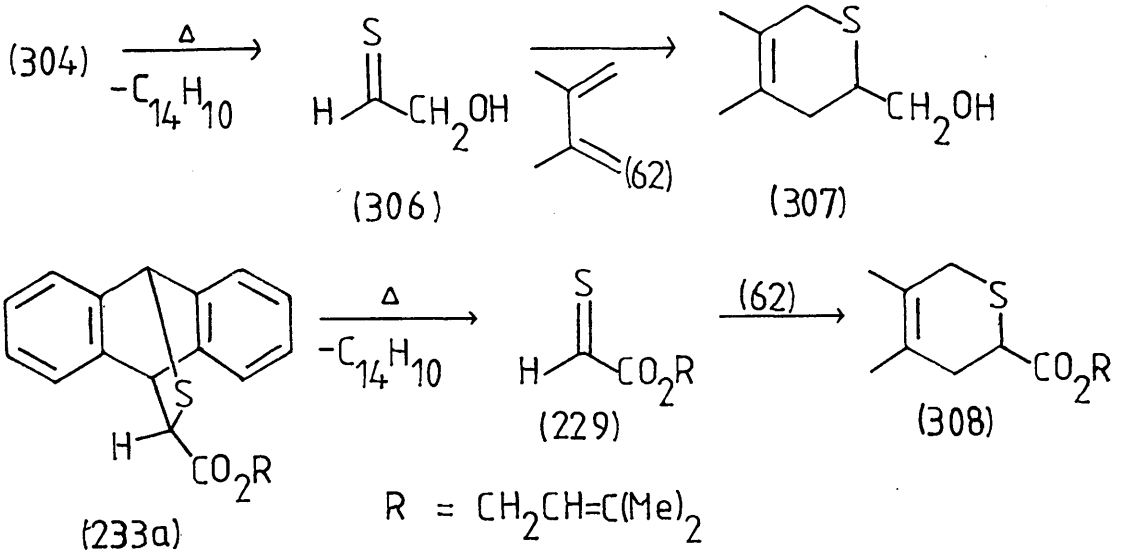
obtained as separate isomers after chromatography. Accurate mass measurement verified the formula of the esters (295). The i.r. spectra of the *endo*- and *exo*-esters showed bands at 1733 and 1734 cm^{-1}, respectively. The ^1H n.m.r. spectra of separate isomers were consistent with the structures (295a) and (296b). Evaporation of the *exo*-adduct (295b) at 100°C and 0.002 mmHg through a silica tube at 600°C gave a yellow oil (83%) (Scheme 87). Chromatography on SiO_2 plates afforded a yellow oil (21%), which appeared as one spot on t.l.c.. However, the complexity of the ^1H n.m.r. spectrum suggested that there was more than one isomer in the yellow oil; presumably the *cis*-(296a) and *trans*-isomers (296b) were present. Signals at δ 3.24 (s, 3-CH_2) and 4.26 (t, *J* 6.0 Hz, 10-CH_2) supported the structures (296). Chromatography on SiO_2 impregnated with $AgNO_3$[71] afforded two compounds. However, not enough material was obtained for ^1H n.m.r. spectroscopy. The i.r. spectra of the separate compounds showed bands at 1739 cm^{-1} for more polar compound and 1733 cm^{-1} for less polar compound. Mass spectroscopy established the formula $C_8H_{12}O_2S$ for both compounds.

Other adducts (297-299) were prepared from the acids (225) and the appropriate alcohol using the normal procedure. However, there was not enough time to proceed with the pyrolysis on these adducts.

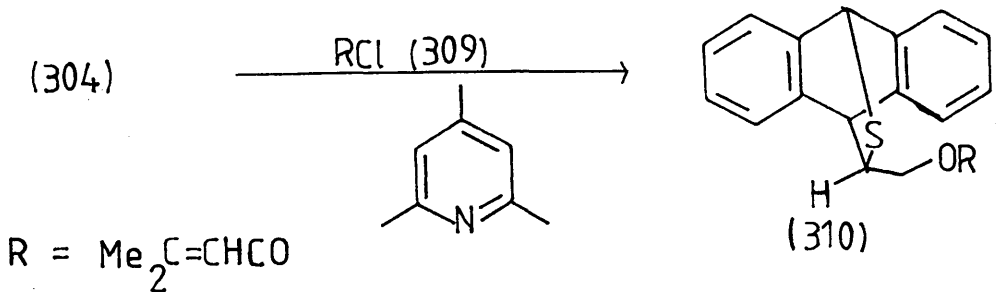
It was thought that thioaldehydes with an α-methylene group (300) might also undergo intramolecular ene reactions to give different lactones. The electronic properties of the thial Π-bond in (300) would be different from our 'classical' thioaldehydes with an α-carbonyl group. Again, their corresponding anthracene and cyclopentadiene adducts could be a source of the thioaldehydes (300). Thus, esterification of the alcohol adducts



Scheme 88

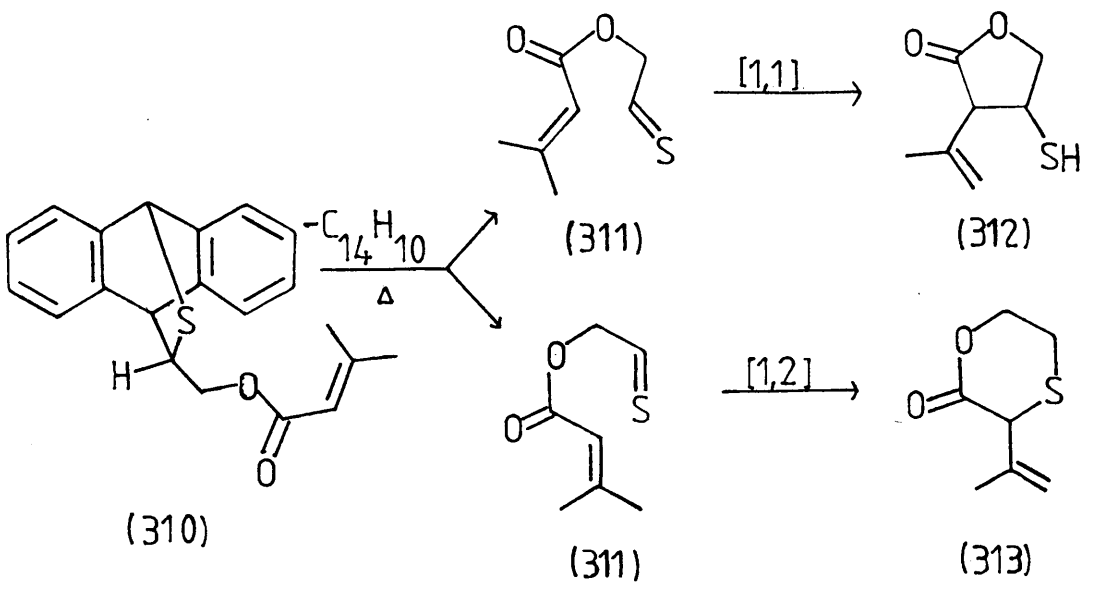


Scheme 89

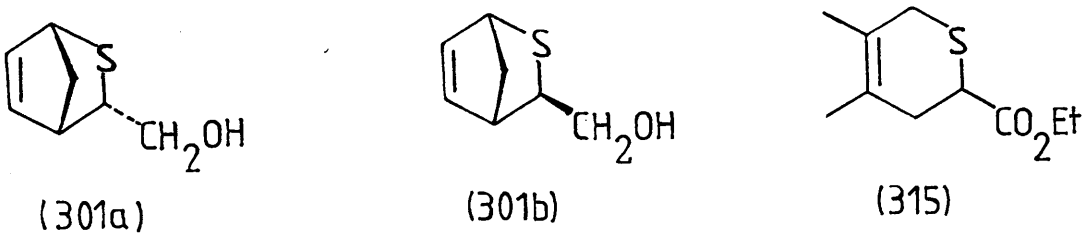


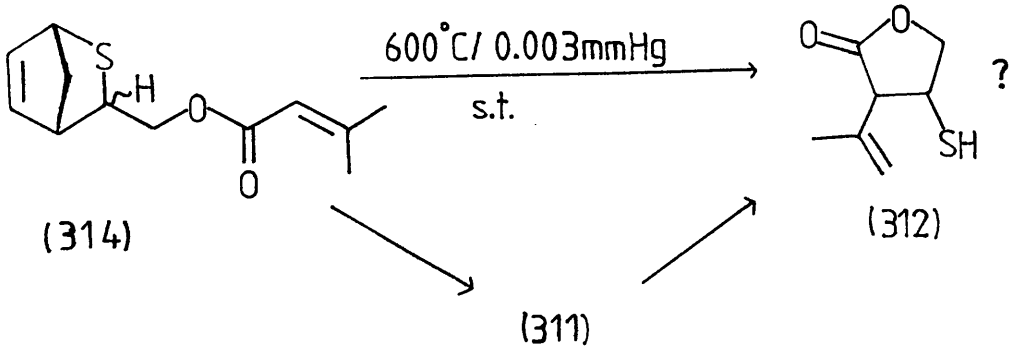
Scheme 90

(301) or (304), derived by reduction of the corresponding ester (77) or acid (234a), with an appropriate acid (302) would give the required precursor (Scheme 88). Reduction of the acid (234a) with lithium aluminium hydride ($LiAlH_4$) in tetrahydrofuran gave the alcohol (304). Accurate mass measurement confirmed the formula of the alcohol (304). Heating the alcohol (304) in boiling toluene with 2,3-dimethyl-1,3-butadiene (62) (10 mol. equivalent) for 4.5h and 29.5h caused *ca.* 16 and *ca.* 40% transfer, respectively, of the thioaldehyde (306) to 2,3-dimethyl-1,3-butadiene to give the cycloadduct (307). In comparison, thioxoacetate (229) was completely transferred from the corresponding anthracene adduct (233a) in boiling toluene to 2,3-dimethyl-1,3-butadiene in 2.45h (Scheme 89). Treatment of the alcohol (304) and 2,4,6-trimethylpyridine in anhydrous diethyl ether with 3,3-dimethylacryloyl chloride (309) gave the conjugated ester (310) (Scheme 90). In the ^1H n.m.r. spectrum, two broad singlets at δ 1.90 and 2.16 were attributed to the two methyl groups. The olefinic proton of the side chain gave a broad singlet at δ 5.77. The i.r. spectrum confirmed the presence of a conjugated ester group with bands at 1711 and 1644 cm^{-1}. Accurate mass measurement verified the formula of the conjugated ester (310). Thermolysis of the conjugated ester adduct (310) would give the thioaldehyde (311) which might undergo ene reactions to give two possible products (312) and (313) *via* a [1,1]-process and a [1,2]-process respectively (Scheme 91). Heating the adduct (310) in boiling toluene under nitrogen for 4h caused *ca.* 14% decomposition (by ^1H n.m.r. spectroscopy). However, there was no sign of any ene product in the ^1H n.m.r. spectrum. In view of this slow decomposition, the experiment was abandoned.



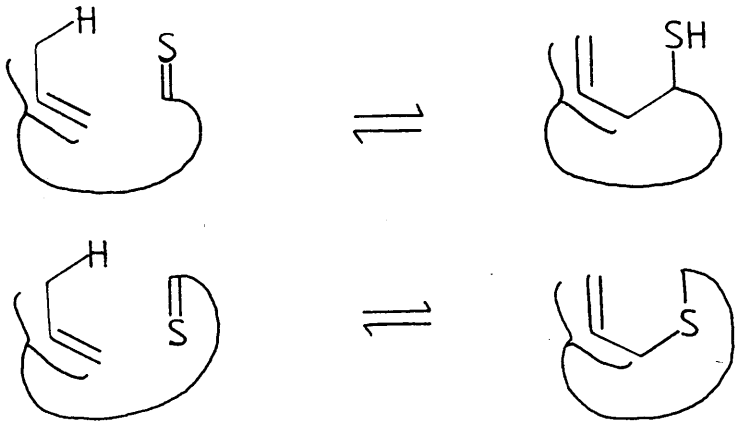
Scheme 91



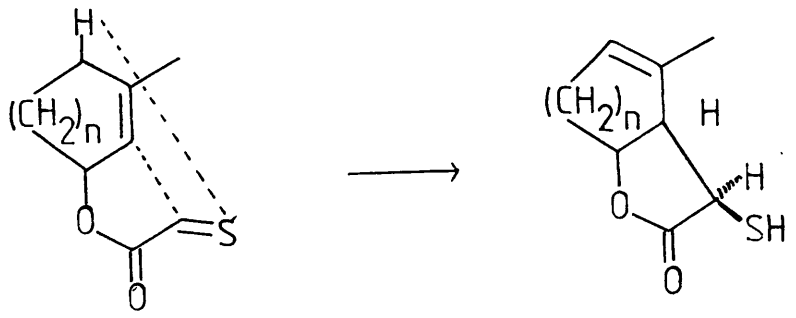


Scheme 92

The alcohols (301) were also prepared by reduction of the ethyl esters (77) in anhydrous diethyl ether with $LiAlH_4$. The alcohol (301) was characterized as a mixture of *endo*-(301a) and *exo*-isomers (301b). Both microanaylsis and mass spectroscopy showed that the alcohol had the formula $C_7H_{10}O_2S$. Separate *endo*- and *exo*-isomers were also prepared by reduction of the corresponding *endo*-(77a) and *exo*-ethyl esters (77b). Treatment of the alcohols (301) in pyridine with 3,3-dimethylacryloyl chloride (309) for 24h gave a mixture of the *endo*-(314a) and *exo*-isomers (314b). The i.r. spectrum confirmed the presence of a conjugated ester group with bands at 1711 and 1648 cm^{-1}. Accurate mass measurement verified the formula of the conjugated esters (314). Evaporation of these adducts (314) at 100°C and 0.003 mmHg through a silica tube at 600°C gave a yellow oil(45%). (Scheme 92) There were many spots on t.l.c., of which one showed positive thiol test. The ^1H n.m.r. spectrum of the yellow oil was very complicated. The i.r. spectrum suggested a five-membered lactone ring had formed by a strong band at 1772 cm^{-1}. Attempted purification of the yellow oil on a Chromatotron (SiO_2) under nitrogen gave intractable products. Because of the shortage of time, only this preliminary study of the ene reaction of thioaldehyde (311) could be carried out. However, it was quite clear that the reactivity of the thial π-bond had been enhanced by the adjacent carbonyl group in the thioxoacetate esters.

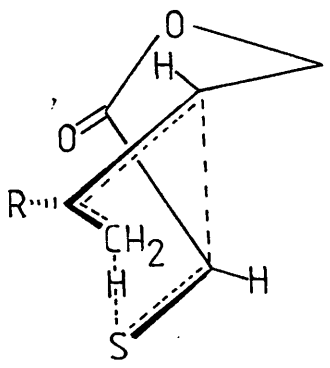


Scheme 93

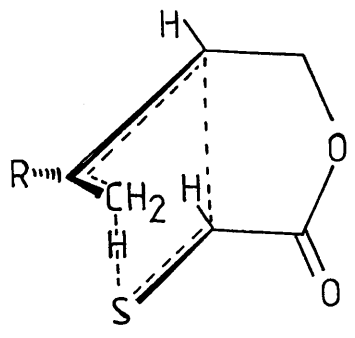


(315)

Scheme 94



Endo



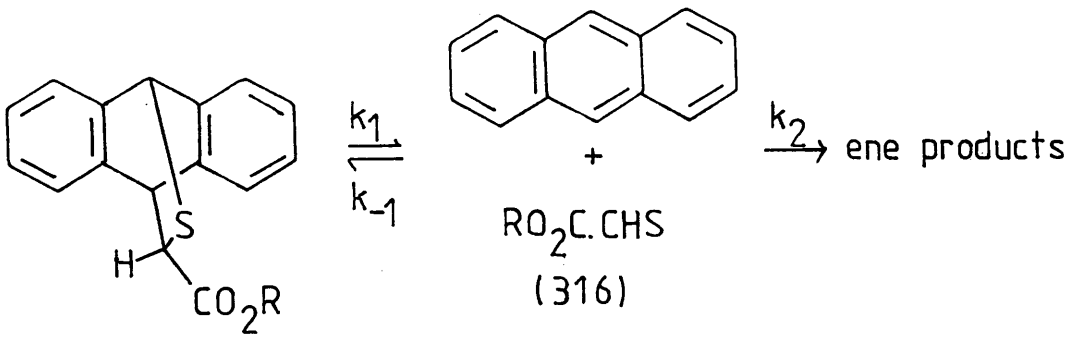
Exo

Scheme 95

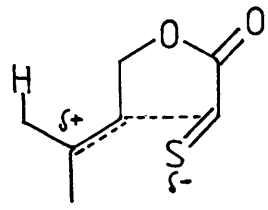
Conclusion

From the eleven examples of the intramolecular ene reactions of the thioxoacetates (229, 240, 244, 249a-b, 254, 275, 280, 285, 289, and 293) which we have studied, various conclusions can be drawn. Firstly, although there is an inherent regiochemical preference of α-oxo thioaldehydes to form C-S bonds[20,23] (Scheme 93), this can be easily overcome by conformational factors. Thus, C-C bond formation was observed in the ene reactions of thioaldehydes (229, 240, 244, 249a-b, 254, and 275) which underwent Type I or II ene reactions. In constrast, Type III ene reactions of the thioaldehydes (280, 285, 289, and 293) proceeded, as expected from both conformational factors and the inherent regiochemical preference to form C-S bonds, exclusively with C-S bond formation. Further, in Type I ene reactions of cyclic or acyclic allylic thioxoacetates, selective attack occurs at '*cis*' CH groups (315).

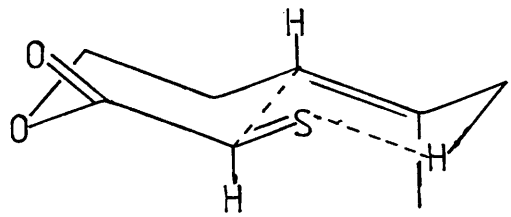
When the thioxoacetates (229, 244, and 249b) underwent Type I ene reactions to form 5-membered lactones (231a, 245a, and 251a), the products all had *cis* hydrogens at the new chiral centres connecting the original ene and thial units. (Scheme 94) This stereochemical result is in agreement with conclusions drawn from molecular models[72]. Thus, a concerted cyclisation *via* an *exo* transition state, rather than the more strained *endo* transition state, would lead to the observed, *cis* stereochemistry (Scheme 95).



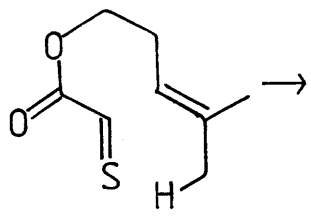
Scheme 96



(317)

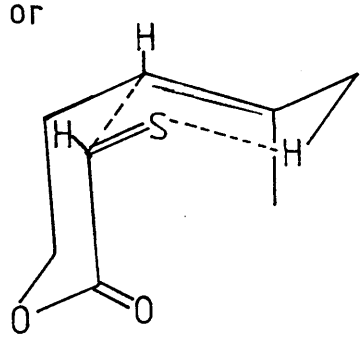


(318a)

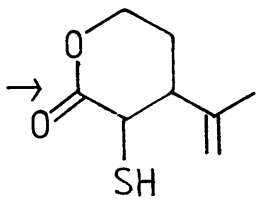


(240)

or



(318b)



(241)

Scheme 97

If the dissociation (rate constant k_1) and recombination rates (k_{-1}) of anthracene adducts (Scheme 96) are all about the same for various thioxoacetates (316), then the overall rates for the formation of anthracene are a measure of the relative rates of the ene reaction steps (k_2). Dimethylallyl thioxoacetate (229) reacts faster than *cis*-monomethylallyl thioxoacetate (249b). This may be due to the fact that, in the transition state, the C-C bond is more developed than the S-H bond[26]. As a result, a partial positive charge is developed at the central carbon of the ene unit (317). Therefore, an additional methyl group helps to stabilize the positive charge.

Although the cyclisation of 4-methyl-3-pentenyl thioxoacetate (240) may proceed *via* a *trans*-(318a) or *cis*-fused decalin transition state (318b) to give the 6-membered lactone (241) (Scheme 97), a *trans*-decalin transition state should be favoured because of the 1,3-diaxial interaction in the *cis*-decalin transition state. However, we are unable to compare this prediction with experiment because, in our generation of 6-membered lactone (241) by FVP (Scheme 67), epimerization of the ene products (241) might occur in the hot tube (*c.f.* Scheme 66).

Although Type III intramolecular ene reactions are rarely observed, moderate yields were obtained from the Type III ene reactions of 2-propenyl, 3-butenyl, 4-pentenyl, and 5-hexenyl thioxoacetates (280, 285, 289, and 293) to give medium size lactone rings (281, 288, 291 and 296). It is thought that three factors are contributing to the readiness of Type III ene reactions of thioxoacetates. They are (1) the reactivity of the thial π-bond which is enhanced by the α-oxo group, (2) the inherent preference to form C-S bond, and (3) the size of the

sulphur atom which helps to relieve the strain in the transition state. This unexpected ease of formation of medium size lactone rings might be employed for the synthesis of medium and large rings as an alternative to cyclisation of the corresponding hydroxy acids.

Chapter 3. Experimental

General Procedures

Melting points were recorded on a Kofler hot-stage apparatus and were corrected.

Infra-red spectra were recorded on either a Perkin-Elmer 580 or 257 spectrometer by Mrs. F. Lawrie and her staff. All solid samples were prepared by dispersion in potassium bromide discs.

Proton n.m.r. spectra were recorded on a Perkin-Elmer R32 (90MHz) spectrometer, unless otherwise stated. 200 MHz spectra were recorded on a Bruker WP 200SY instrument in the pulsed Fourier Transform (F.T.) made by Dr. D.S. Rycroft and 60MHz spectra were recorded on a Varian T-60A spectrometer. Unless otherwise stated, deuteriochloroform was used as the solvent with tetramethylsilane as internal standard. All proton chemical shifts are quoted to the nearest 0.01 p.p.m..

Low resolution mass spectra were recorded in the E.I. mode at 70eV on an A.E.I.M.S. 12 instrument, and high resolution spectra on an A.E.I.M.S. 9 instrument coupled to a GEC-905 Computer for data collection and processing, by Mr. A. Richie and his staff. Microanalysis was performed by Ms. Harkness and her staff.

Analytic t.l.c. was carried out on a precoated Merck Kieselgel GF_{254} plates of thickness 0.25mm. Spots were viewed under an ultra-violet lamp (254nm) and developed by iodine vapour. Column chromatography was carried out on Merck silica HF_{254} or 60H under reduced pressure according to the method of Harwood[73]. Preparative thin-layer chromatography was carried

out on 20cm x 20cm glass plates coated with a 0.5mm layer of Merck GF_{254} silica with detection of compounds by U.V. light. Cetrifugal thin-layer chromatography was carried out on a Chromatotron under nitrogen. The rotor was coated with a 2mm layer of silica PF_{254} (Merck) and compounds were detected by U.V. light.

All solvents and reagents were of analytical grade unless otherwise stated. 'Light petroleum' refers to the fraction b.p. 60-80^{o}C. 'Ether' refers to diethyl ether. Organic solvents were generally evaporated on a Büchi rotary evaporator under water-pump vacuum with slight heating.

Preparation of Sodium S-(Ethoxycarbonylmethyl) Thiosulphate (83a) (Bunte salt).[74]

Ethyl bromoacetate (8.37g, 0.05mol) in ethanol (25ml) and sodium thiosulphate pentahydrate (12.65g, 0.05ml) in water (25ml) were refluxed together for 0.75h. The solvents were then evaporated under reduced pressure with heating to give a white solid mass. The 'Bunte salt' was extracted with hot ethanol (75ml). The hot extract was filtered and the filtrate was set aside to cool. The 'Bunte salt' separated as white crystals which were filtered off and dried (3.40g, 0.015mol, 30.6%); ν_{max} (KBr) 1718, 1218, 1052, and 653 cm^{-1}. The i.r. spectrum was essentially the same as that of a sample prepared by A. Sclare.[75]

Improved Preparation of Sodium S-(Ethoxycarbonylmethyl) Thiosulphate (83a) (Bunte salt).

Ethyl bromoacetate (8.00g, 0.049mol) in acetone (25ml) and sodium thiosulphate pentahydrate (12.13g, 0.049mol) in water (25ml) were shaken together for 3 min at room temperature. A homogenous solution was resulted and completion of the reaction was confirmed by analytical t.l.c.. The solvents were evaporated under reduced pressure with heating to give a white solid residue. The 'Bunte Salt' was extracted with hot ethanol (75ml). The hot extract was filtered and the filtrate was set aside to cool. The 'Bunte salt' separated as white crystals which were filtered off and dried (9.18g, 0.041mol, 84%). The i.r. spectrum agreed well with that of a sample prepared earlier.[75]

Preparation of Ethyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (77)[21]

A literature method was followed[21]. Freshly distilled cyclopentadiene (0.64g, 9.7mmol) was added to a suspension of the 'Bunte salt' (83a) (2.07g, 9.3mmol) and calcium chloride dihydrate (1.40g, 9.5mmol) in ethanol (23ml). Then triethylamine (0.95g, 9.4mmol) was added dropwise to the mixture with stirring at room temperature. A white precipitate was formed upon the addition of triethylamine. Stirring was continued for 24h at room temperature. Then the reaction mixture was acidified with 5% hydrochloric acid (25ml) to form a clear yellow solution. The mixture was then extracted with chloroform (3 x 25ml). The combined organic extracts were washed successively with 5% hydrochloric acid (20ml), water (20ml) aqueous sodium carbonate (0.6M, 20ml), and water (3 x 20ml), and were then dried ($MgSO_4$) and evaporated to give a light yellow oil (1.40g). The ^1H n.m.r. spectrum of the crude product revealed the presence of the cycloadducts (77) (*endo:exo*, 7:3) and traces of the disulphide. The crude product (0.29g) was distilled (Kugelrohr) to afford the pure adducts (59% yield from the Bunte salt), with unchanged *endo:exo* ratio, as a colourless mobile liquid (0.21g), b.p. 80-90^oC (0.02mbar) (lit.[21] b.p. 95^oC/0.02mbar). Again, the crude product (1.00g) was chromatographed using preparative silica plates to afford two pure isomers, ethyl 2-thiabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylate (77a) as a colourless oil (0.61g); δ 1.22 (t, J 7.0 Hz, CH_3) 1.62 (m, 7-H_2), 3.74 (br.s, 4-H), 4.07 (br.s, 1-H), 4.22 (q, J 7.0 Hz, OCH_2), 4.41 (d, J 4.0 Hz, 3-H), and 5.88 (dd, J 3.0 and 5.5 Hz, 5-H), 6.46 (dd, J 3.0 and 5.8 Hz, 6-H), and ethyl 2-thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (77b)

as a colourless oil (0.26g); δ 1.26 (t, *J* 7.2 Hz, CH_3), 1.64 and 1.91 (ABq, *J* 10.0 Hz, 7-H_2), 3.28 (s, 3-H), 3.52 (br.s, 4-H), 4.09 (br.s, 1-H), 4.21 (q, *J* 7.0 Hz, OCH_2), 5.93 (dd, *J* 3.0 and 5.5 Hz, 5-H), and 6.37 (dd, *J* 3.0 and 5.5 Hz, 6-H). The pure cycloadducts were obtained in a combined yield of 87% from the Bunte salt.

Hydrolysis of the *endo*-ester (77a).

1.03M Sodium hydroxide (8ml) was added to a solution of the foregoing *endo*-ester (77a) (0.33g, 1.8mmol) in tetrahydrofuran (2ml) and the mixture was stirred at room temperature for 1h. Then the mixture was concentrated under reduced pressure with heating. The resulting aqueous solution was washed with dichloromethane (3 x 10ml), then acidified with 5% hydrochloric acid (10ml) and extracted with dichloromethane (3 x 10ml). The organic extracts were washed with brine (10ml), dried ($MgSO_4$), and evaporated to give the pure 2-thiabicyclo[2.2.1]hept-5-ene-3-*endo*-carboxylic acid (225a) (0.18g, 1.2mmol, 64%), m.p. 91-93°C (from hexane); ν_{max} (KBr) 1700 and 1690 cm^{-1}; δ 1.46-1.83 (m, 7-H_2), 3.80 (br.s, 4-H), 4.12 (br.s, 1-H), 4.45 (d, *J* 4.0 Hz, 3-H), 5.89 (dd, *J* 3.0 and 6.0 Hz, 5-H), 6.50 (dd, *J* 3.5 and 6.0 Hz, 6-H), and 9.30 (br.s, CO_2H, exch. with D_2O).

Hydrolysis of the *exo*-ester (77b)

The *exo*-ester (77b) (0.22g, 1.2mmol) was hydrolysed as described for the *endo*-isomer to give 2-thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylic acid (225b) (0.16g, 1.0mmol, 85%), m.p. 101-103°C (from hexane); ν_{max} (KBr) 1704 cm^{-1}; δ 1.65 and 1.90 (ABq, *J* 9.5 Hz, 7-H_2), 3.32 (s, 3-H), 3.37 (br.s, 4-H), 4.14 (br.s, 1-H), 5.94 (dd, *J* 3.5 and 5.5 Hz, 5-H), 6.38 (dd, *J* 2.5

and 5.5 Hz, 6-H), and 11.12 (br.s, CO_2H, exch. with D_2O).

Hydrolysis of a mixture of the *endo*- and *exo*-esters (77a) and (77b)

A mixture of the *endo*- and *exo*-esters (77a) and (77b) (*endo:exo*, 7:3) (0.19g, 1.2mmol) was hydrolysed as described for the *endo*-isomer to give their corresponding carboxylic acids (0.13g, 0.86mmol, 70%), m.p. 78-80°C (from hexane), with the *endo:exo* ratio unchanged.

Preparation of 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylic acid (234a)

Ethyl mercaptoacetate (1.32g, 11mmol) was added dropwise with stirring to a suspension of *N*-chlorosuccinimide (1.76g, 13.2mmol) in benzene (20ml) at room temperature. A yellow colour signifying the formation of the sulphenyl chloride, developed after a while. After 2.5h, the solution of the sulphenyl chloride was added dropwise, by a glass syringe, with stirring to anthracene (9.80g, 55mmol) and distilled dried (KOH) triethylamine (1.33, 13.2mmol) in chloroform (140ml) with heating under reflux. 30 min after the last addition of sulphenyl chloride solution, the mixture was cooled and excess anthracene was filtered off. The filtrate was then washed with dilute hydrochloric acid (10ml), then water (2 x 20ml), dried ($MgSO_4$) and evaporated under reduced pressure with heating. The residue was then dissolved in tetrahydrofuran (THF) (15ml) and aqueous sodium hydroxide (1.0M, 15ml) with stirring at room temperature. After 7h the THF was evaporated under reduced pressure with heating. The aqueous solution was washed with dichloromethane (5 x 30ml), then acidified with 5% hydrochloric

acid (15ml) and extracted with dichloromethane (5 x 20ml). The organic extracts were then washed with brine (10ml), dried ($MgSO_4$), and evaporated. The residue of substantially pure acid (234a) (2.24g, 8.35mmol, 76% from ethyl mercaptoacetate) was chromatographed on a silica (60H for t.l.c.) column, eluted with chloroform-light petroleum (2:8) then chloroform, and crystallized from dichloromethane to give the *carboxylic acid* (234a) (1.33g, 4.46mmol, 45% yield from ethyl mercaptoacetate), m.p. 177-178^{o} (from dichloromethane) (Found: C, 71.75; H, 4.54; S, 12.14. $C_{16}H_{12}O_2S$ requires C, 71.61; H, 4.51; S, 11.95%) (Found: *m/z* 168.0557. $C_{16}H_{12}O_2S$ requires M^+, 168.0558); ν_{max} (KBr) 1710 cm^{-1}; δ 4.16 (d, *J* 3.0 Hz, SC<u>H</u>CO_2H), 5.17 (d, *J* 3.0 Hz, 9-H), 5.28 (s, 10-H), 7.10-7.52 (m, Ar-H), and 7.83 (br.s, COOH, exch. with D_2O).

<u>Preparation of 3-Methyl-2-butenyl 9,10-Dihydro-10,9-thiaethano-anthracene-12-carboxylate (233a)</u>

<u>Method 1</u>

The carboxylic acid (234a) (0.63g, 2.3mmol) in tetrahydrofuran (THF) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.40g, 2.5mmol) at room temperature, and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-buten-1-ol (227) (0.20g, 2.3mmol) and n-butyl lithium (0.30mmol) in THF (1ml) were added. Stirring was continued for 8 h. THF was then evaporated under reduced pressure with heating. The residue was shaken with water and was followed by extraction with ether (4x20ml). The combined ethereal layers were washed with aqueous sodium hydroxide (1.0M, 10ml), water (2 x 10ml) and dried (Na_2SO_4) and evaporated to afford pure 3-*methyl*-2-*butenyl* 9,10-*dihydro*-10,9-*thiaethanoanthra*-

cene-12-*carboxylate* (233a) as a yellow oil (0.67g, 2.0mmol, 86%) (Found: *m/z* 336.1192. $C_{21}H_{20}O_2S$ requires M^+, 336.1184); ν_{max} (liquid film) 1735 and 1677 cm^{-1}; δ 1.64 and 1.72 (2 x br.s, 2 x CH_3), 4.11 (d, *J* 2.0 Hz, 12-H), 4.52 (m, OCH_2), 5.07 (d, *J* 2.0 Hz, 9-H), 5.11 (s, 10-H), 5.27 (br.t, *J* 7.0 Hz, C=CH) and 7.03-7.55 (8H, m, Ar-H).

Method 2

The carboxylic acid (233a) (0.22g, 0.84 mmol) and freshly distilled thionyl chloride (0.21g, 1.8mmol) in anhydrous benzene (5ml) were heated under reflux in an atmosphere of nitrogen for 7.5 h. Then excess thionyl chloride and solvent were removed under reduced pressure with heating to give a greenish brown oil (0.29g); ν_{max} ($CHCl_3$) 1812 and 1795 cm^{-1}. The residue in anhydrous diethyl ether (12ml) was added dropwise to a mixture of 3-methyl-2-buten-1-ol (227) (73mg, 0.85 mmol) and triethylamine (86mg, 0.85mmol) in anhydrous diethyl ether (2ml), with stirring at 0^oC. Stirring was continued for 1h at room temperature.and the reaction mixture was diluted with diethyl ether (20ml), washed with dilute hydrochloric acid (10ml), aqueous sodium hydroxide (1M, 10ml) and water (2 x 10ml) and dried ($MgSO_4$) and evaporated. The residue, judged from ^1H n.m.r. spectroscopy, contained *ca.* 10% anthracene. Chromatography on a silica column (60H, for t.l.c.), eluted with chloroform-light petroleum (2:8) gave pure ester (233a) (0.14g, 0.42 mmol, 50%). The ^1H n.m.r. spectrum agreed well with that of a sample of the ester prepared before.

Thermolysis of 3-Methyl-2-butenyl 9,10-Dihydro-10,9-thiaethano-anthracene-12-carboxylate (233a)

The anthracene adduct (233a) (0.37g, 1.1 mmol) was heated under reflux in anhydrous toluene (34ml) under a nitrogen atmosphere. The reaction was followed by t.l.c. (eluted with chloroform) and was judged to be complete after 4 h. Evaporation of solvent under reduced pressure yielded cis-3-*isopropenyl*-2-*mercaptobutan*-4-*olide* (231a) and anthracene; ν_{max} ($CHCl_3$) 1780 cm^{-1}. The crude product was chromatographed on a Chromatotron (SiO_2; ethyl acetate-light petroleum, 3:7) under nitrogen to give the pure 3-*isopropenyl*-2-*mercaptobutan*-4-*olide* (231) (0.12g, 0.78 mmol, 71%) as a mixture of *cis*-(231a) and *trans*-isomers (231b) (*ca.* 9:1) (Found *m/z* 158.0409. $C_7H_{10}O_2S$ requires M^+ 158.0401); δ 1.76 (br.s, CH_3), 1.89 (d, *J* 4.5 Hz, *cis*-SH, exch. with D_2O), 2.27 (d, *J* 4.7 Hz, *trans*-SH, exch. with D_2O), 3.00 (br.q, *J* 8 Hz, *trans*-3-H), 3.30 (br.q, *J* 8 Hz, *cis*-3-H), 3.67 (dd, *J* 9.5 and 4.8 Hz, *trans*-2-H), 3.87 (dd, *J* 7.1 and 4.1 Hz, *cis*-2-H), 4.08 and 4.51 (2 x t, *J* 9.Hz, *trans*-4-CH_2), 4.40 (d, *J* 7.3 Hz, *cis*-4-CH_2), 4.74 and 5.05 (2 x br.s *cis*-vinyl-H), and 4.94 and 5.00 (2 x br.s, *trans*-vinyl-H).

Epimerization of *cis*-thiol (231a)

The *cis*-thiol (231a), prepared from the thermolysis of the adduct (233a) (0.10g, 0.31mmol), in dichloromethene (10ml), was stirred with triethylamine (0.063g, 0.61mmol) at room temperature for 3h. The mixture was then diluted with dichloromethane (20ml) and washed with hydrochloric acid (0.05M, 10ml), water (2 x 10ml), dried (Na_2SO_4) and evaporated to dryness to give trans-3-*isopropenyl*-2-*mercaptobutan*-4-*olide* (231b); ν_{max} ($CHCl_3$) 1783 cm^{-1}.

Oxidation of *cis*-3-Isopropenyl-2-mercaptobutan-4-olide (231a)

The *cis*-thiol (231a), prepared from the thermolysis of the adduct (233a) (0.37g, 1.1mmol), in ethanol (10ml) was mixed with an ethanolic solution of potassium iodide and iodine (1.007M, 1.5ml) for 5 min. The reaction mixture was diluted with ether (20ml), washed with aqueous sodium thiosulphate (0.37M, 6ml), water (2 x 20ml) and dried (Na_2SO_4). Solvents were evaporated under reduced pressure to give a mixture of *cis*-disulphides [(±)-(237c) and the related *meso*-diastereoisomer]. ν_{max} ($CHCl_3$) 1777 cm^{-1}; δ 1.76 (br.s, CH_3), 3.22-3.60 (m, 3-H), 4.02 (d, *J* 8.0 Hz, 2-H-one diastereoisomer), 4.20 (d, *J* 8.0 Hz, 2-H-one diastereoisomer), 4.39 (d, *J* 7.0 Hz, OCH_2) and 4.77 and 5.00 (2 x br.s, $C=CH_2$). The crude product was chromatographed on preparative t.l.c. plates to afford a mixture of *trans*-disulphides [(±)-(237a) and the related *meso*-diastereoisomer], (0.15g, 0.48mmol, 87% from the adduct (233a)) (Found *m/z* 314.0641. $C_{14}H_{18}O_4S_2$ requires M^+ 314.0647); ν_{max} ($CHCl_3$) 1780 cm^{-1}; δ 1.77 (br.s, CH_3), 3.39 (br.q, *J* 9 Hz, 3-H), 3.78 (d, *J* 9.5 Hz, 2-H-one diastereoisomer), 3.87 (d, *J* 9.5 Hz, 2-H-one diastereoisomer), 4.07 (t, *J* 8.0 Hz, OCH), 4.47 (t, *J* 8.0 Hz, OCH) and 4.97 (br.s, $C=CH_2$).

Reduction of a mixture of disulphides (237)

A mixture of disulphides (227) [(237a):(237b), *ca.* 3:1] (0.20g) tetrahydrofuran-water mixture (1:1; 12ml) were stirred for 6 h with sodium bicarbonate (0.23g, 2.7 mmol) and sodium dithionite (0.20g, 1.0mmol) at room temperature under nitrogen. Then the reaction mixture was diluted with diethyl ether (30ml) washed with water (2 x 10ml), dried (Na_2SO_4) and evaporated under reduced pressure with slight heating to give a mixture of

cis-(231a) and *trans*-butan-4-olide (231b) (*ca.* 1:4).

Preparation of *tran*-3-Isopropenyl-2-(S-benzoylthio)butan-4-olide (238)

The *cis*-thiol (231a), prepared from the thermolysis of the adduct (233a) (0.26g, 0.76mmol), in chloroform (5ml) was stirred for 45 min with triethylamine (0.11g, 1.1mmol) and benzoyl chloride (0.11g, 0.80mmol). Then the reaction mixture was diluted with chloroform (20ml), washed with water (10ml), aqueous sodium bicarbonate (0.05M, 20ml), water (2 x 10ml), dried (Na_2SO_4) and evaporated under reduced pressure with heating. The crude product was chromatographed on preparative SiO_2 plates to afford trans-3-*isopropenyl*-2-*(S-benzoylthio)-butan*-4-*olide* (238) (0.10g, 0.39mmol, 52% from adduct (233a), m.p. 120-122^{o} (from dichloromethane and petroleum ether 40-60^{o}C) (Found: C, 63.94; H, 5.27; S, 12.30. $C_{14}H_{14}O_3S$ requires C, 64.10; H, 5.38; S, 12.22%); ν_{max} 1785 and 1666 cm^{-1}; δ 1.81 (br.s, CH_3), 3.31 (br.q, *J* 10 Hz, 3-H), 4.16 (t, *J* 9.0 Hz, OCH), 4.45 (d, *J* 11.0Hz, 2-H), 4.52 (t, *J* 8.0 Hz, OCH'), 4.93 (br.s, $C=CH_2$), 7.30-7.70 (m, *o*- and *p*-Ar-H) and 7.84-8.01 (m, *m*-Ar-H).

Preparation of *trans*-3-Isopropenyl-2-(S-acetylthio)butan-4-oldie (239b)

The *cis*-thiol (231a), prepared from the thermolysis of the adduct (233a) (0.21g, 0.63mmol), in chloroform (5ml) was stirred for 10h with triethylamine (0.082g, 0.81mmol) and acetic anhydride (0.076mmol) at room temperature. The reaction mixture was diluted with chloroform (30ml), washed with water (10ml), aqueous sodium bicarbonate (0.05M, 10ml), water (10ml), hydrochloric acid (0.05M, 10ml) and water (2 x 10ml) and dried

(Na_2SO_4) and evaporated under reduced pressure with heating to give a yellow oil. The crude product was chromatographed on preparative SiO_2 plates to give trans-3-*isopropenyl*-2-*(S-acetylthio)butan*-4-*olide* (239b) (0.058g, 0.29mol, 46% from adduct (233a) (Found: *m/z* 200.0509. $C_9H_{12}O_3S$ requires M^+ 200.0507); ν_{max} ($CHCl_3$) 1785 and 1705 cm^{-1}; δ 1.80 (br.s, $CH_2=CC\underline{H}_3$), 2.40 (s, $COCH_3$), 3.23 (br.q, *J* 9Hz), 4.13 (t, *J* 9.6 Hz, OCH), 4.28 (d, *J* 10.4 Hz), 4.49 (t, *J* 8.8 Hz, OCH') and 4.90-5.03 (m, $C=CH_2$).

Preparation of *cis*-3-Isopropenyl-2-(S-acetylthio)butan-4-olide (239a)

Acetic acid (0.017g, 0.28mmol) in dichloromethane (3ml) was stirred with dicyclohexylcarbodiimide for 1h at room temperature. Then the *cis*-thiol (231a), prepared from the thermolysis of the adduct (233a) (0.095g, 0.28mmol), in dichloromethane (5ml) was added to the reaction mixture and stirring was continued for 24h. The reaction mixture was filtered and solvents were removed under reduced pressure with heating to afford cis-3-*isopropenyl*-2-*(S-acetylthio)butan*-4-*olide* (239a) and traces of dicyclohexylurea as a yellow oil. ν_{max} ($CHCl_3$) 1780 and 1702 cm^{-1}; δ 1.63 (s, $CH_2 = CC\underline{H}_3$), 2.35 (s, $COCH_3$), 3.35 (ddd, *J* 3.0, 6.0 and 8.0 Hz, 3-H), 4.24 (dd, *J* 3.0 and 9.0 Hz, OCH), 4,49 (dd, *J* 6.0 and 9.0 Hz, OCH'), 4.66 (d, *J* 8.0 Hz, 2-H) and 4.74 and 4.90 (2 x br.s, $C = CH_2$). The crude product was chromatographed on a Chromatotron (SiO_2; ethyl acetate-light petroleum, 3:7) under nitrogen to give the *trans*-isomer (239b) (0.032g, 43%). ^1H n.m.r. of the purified product was essentially the same as that of the *trans*-isomer (239b) prepared earlier.

Preparation of 8-Methyl-3-oxa-4-oxo-6-thiabicyclo[3.3.0]octane (232)

The *cis*-thiol (231a), prepared from the thermolysis of the adduct (233a) (0.16g, 0.49mmol) was heated under reflux in anhydrous benzene (15ml) under nitrogen. Then azobisisobutyronitrile (AIBN) (9.2mg, 0.068mmol, 0.15mol. equiv.) was added into the reaction mixture. Heating under reflux was continued for 10h. Evaporation of solvent and the cyclization was shown to be 84% complete, judged from ^{1}H n.m.r. spectroscopy, to give a mixture of bicyclic lactone (232) and starting *cis*-thiol (231a). The crude mixture was chromatographed on preparative SiO_2 plates to afford a mixture of diastereoisomeric 8-*methyl*-3-*oxa*-4-*oxo*-6-*thiabicyclo*[3.3.0.]*octane* (232) (*ca.* 2:5, 0.044g, 0.28mmol, 57%) as a yellow oil (Found *m/z* 158.0398. $C_7H_{10}O_2S$ requires M^+ (58.0401); ν_{max} (liquid film) 1780 cm^{-1}; δ (200 MHz) 1.09 (d, *J* 6.8 Hz, major - CH_3), 1.13 (d, *J* 6.7 Hz, minor - CH_3), 2.26-2.47 (m, minor-8-H), 2.53-2.79 (m, major-8-H), 2.70 (dd, *J* 6.3 and 11.1 Hz, minor-7-H), 2.79-2.97 (m, minor-1-H), 2.82 (t, *J* 10.6 Hz, major-7-H), 2.95 (dd, *J* 10.5 and 6.8 Hz, major-7-H'), 3.14 (dd, *J* 5.7 and 11.0 Hz, minor-7-H'), 3.92 (d, *J* 7.7 Hz, 5-H), 4.03 (dd, *J* 9.5 and 14.2 Hz, minor-2-H), 4.05 (dd, *J* 8.5 and 18.0 Hz, major-2-H), 4.29 (dd, *J* 8.8 and 9.5 Hz, major-2-H'), 4.40 (dd, *J* 7.5 and 9.5 Hz, minor-2-H').

Thermal conversion of the Anthracene Adduct (233a) into the 2,3-Dimethyl-1,3-butadiene Adduct (308)

2,3-Dimethyl-1,3-butadiene (0.63g; 0.77mmol) was added to the anthracene adduct (233a) (0.26g, 0.76mmol) in anhydrous toluene (10ml) and the mixture was heated under reflux for 2.45h. The solution was evaporated to dryness and ^{1}H n.m.r.

spectrum of the crude mixture showed a complete transfer. The mixture was chromatographed on preparative SiO_2 plates to give 3-*methyl*-2-*butenyl* 3,6-*dihydro*-4,5-*methyl*-2H-*thiin*-2-*carboxylate* (308) (0.14g, 0.57mmol, 75%) as a colourless oil, b.p. 100-110°C (0.1-0.15mmHg, Kugelrohr) (Found: *m/z* 248.1205. $C_{13}H_{20}O_2S$ require M^+, 248.1184); ν_{max} (liquid film) 1732 cm^{-1}; δ 1.45-1.77 (m, $C=C(CH_3)_2$), 1.60 (br.s, 4- and 5-CH_3), 2.24-2.47 (br.d, *J* 5.8 Hz, 3-CH_2), 2.98 (br.s, 6-CH_2), 3.52 (t, *J* 6.5 Hz, 2-H), 4.54 (d, *J* 7.5 Hz, OCH_2), 5.28 (br.t, *J* 7.0 Hz, C=CH).

Attempted Study of the Retro-ene Reaction of 3-isopropenyl-2-mercaptobutan-4-olide (231a).

The *cis*-thiol (231a), obtained from the thermolysis of the adduct (233a) (0.083g, 0.25mmol), in anhydrous toluene (2.9ml) was heated under reflux with 2,3-dimethyl-1,3-butadiene (0.28g, 3.4mmol 13.6 mol. equiv) under nitrogen for 41h. Solvent and excess butadiene were removed under reduced pressure with heating. ^1H n.m.r. spectrum of the crude mixture showed a mixture of starting *cis*-thiol (231a) and the cyclised product (232) (*ca.* 3:7). The mixture was then chromatographed on preparative SiO_2 plates to afford 8-methyl-3-oxa-4-oxo-6-thiabicyclo[3.3.0]octane (232). The ^1H n.m.r. spectrum agreed well with that of a sample of bicyclic lactone prepared earlier.

Preparation of 4-Methyl-3-pentenenitrile

Prenyl bromide (1.94g, 0.013mol), sodium cyanide (1.95g, 0.04mol, 3mol equiv), and cetyltrimethylammonium bromide (0.075g) were stirred in a benzene:water (1:1) (3.8ml) mixture. After 3 days stirring at room temperature, the reaction mixture was poured into water (150ml) and extracted with ether (3 x 150ml).

The combined ethereal layers were washed with brine (3 x 100ml), and were dried ($MgSO_4$) and evaporated. The crude product (0.88g) was distilled to afford 4-methyl-3-pentenenitrile as a colourless liquid (0.65g, 6.8mmol, 53%), b.p. 71-73°C (19 mmHg) [lit.[63] 60-65°C (21 mmHg)]; ν_{max} (KBr) 2224, 1675 cm^{-1}; δ 1.67 (br.s, CH_3), 1.74 (br.s, CH_3), 3.03 (br.d, J 7.0 Hz, CH_2), and 5.18 (br.t, J 7.0 Hz, C=CH).

Preparation of 4-Methyl-3-pentenoic Acid

4-Methyl-3-pentenenitrile (0.64g, 6.7mmol) and sodium hydroxide (0.29g, 7.2mmol) in water (9.6ml) were refluxed for 5h and left to stand at room temperature for 11h. The reaction mixture was washed with ether (2 x 10ml), then acidified with 5% hydrochloric acid (10ml) and extracted with ether (4 x 25ml). The combined ethereal layers were washed with brine (30ml), dried ($MgSO_4$), and evaporated. The crude product (0.70g) was distilled to afford the carboxylic acid (0.62g, 5.4mmol, 81%), b.p. 116-118°C (15 mmHg) [lit.[63] 97-101°C (10 mmHg)]; ν_{max} (liquid film) 1708 cm^{-1}; δ 1.62 (br.s, CH_3), 1.71 (br.s, CH_3), 3.05 (br.d, J 6.8 Hz, CH_2), 5.29 (br.t, J 6.8 Hz, C=CH), and 9.10-9.90 (br.s, CO_2H).

Preparation of Ethyl 4-Methyl-3-pentenoate

4-Methyl-3-pentenoic acid (0.57g, 5.0mmol) was added to a solution of ethanolic hydrogen chloride prepared from acetyl chloride (0.82g) and dried (Mg) ethanol (11ml). The reaction mixture was kept for 1d at room temperature and protected from moistur by a guard tube containing silica gel. The reaction mixture was evaporated under reduced pressure with slight heating and the residual liquid was diluted with ether (50ml), washed successively

with aqueous sodium bicarbonate (0.25M, 25ml) and water (2 x 15ml), and was dried ($MgSO_4$), and evaporated. The crude product (0.56g) was distilled to afford pure ethyl 4-methyl-3-pentenoate (0.43g, 3.0mmol, 60%), b.p. 70-72°C (13mmHg) [lit[77] 58-59°C (11 mmHg)]; ν_{max} (liquid film) 1749 cm^{-1}; δ 1.24 (t, *J* 8.0 Hz, $CH_2\underline{CH}_3$), 1.63 (br.s, $C=CCH_3$), 1.72 (br.s, $C=CCH_3$), 3.01 (br.d, *J* 8.0 Hz, $C=CCH_2$), 4.14 (q, *J* 7.0 Hz, $O\underline{CH}_2CH_3$), and 5.31 (br.t, *J* 7.0 Hz, C=CH).

Preparation of 4-Methyl-3-penten-1-ol

Ethyl 4-methyl-3-pentenoate (0.38g, 2.7mmol) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.10g) in dry (Na) ether (10ml) in an ice-bath under nitrogen. After the last addition of the ester, the reaction mixture was allowed to warm up to room temperature and stirring was continued for 0.5h. Ice-water (10ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was extracted with ether (4 x 20ml). The combined etheral layers were washed with brine (10ml), and were dried (Na_2SO_4), and evaporated to afford a yellow liquid (0.31g). The residual liquid was distilled to afford 4-methyl-3-penten-1-ol as a colourless liquid (0.20g, 2.0mmol, 74%), b.p. 70°C (10mmHg) [lit.[77] 157-158°C (771 mmHg)]; ν_{max} (liquid film) 1672 cm^{-1}; δ 1.52 (br.s, OH), 1.63 (br.s, CH_3), 1.70 (br.s, CH_3), 2.25 (br.q, *J* 7.0 Hz, $C=CCH_2$), 3.61 (br.t, *J* 6.0 Hz, OCH_2), and 5.02 (br.t, *J* 8.0 Hz, C=CH).

Preparation of 4-Methyl-3-pentenyl 9,10-Dihydro-10,9-thiaethano-anthracene-12-carboxylate (242)

The carboxylic acid (239a) (0.22g, 0.82mmol) in tetrahydrofuran (THF) was stirred for 3h with *N,N'*-carbonyldiimi-

dazole (226) (0.17g, 1.0mmol) at room temperature, and the reaction mixture was kept dry by a guard tube containing silica gel. Then 4-methyl-3-penten-1-ol (0.07g, 0.73mmol) and n-butyl lithium (0.1mmol) in THF (2ml) were added. Stirring was continued for 8h. THF was then evaporated from the reaction mixture under reduced pressure with heating. The residue was shaken with 10ml water and followed by extraction with ether (4 x 20ml). The combined ethereal layers were washed with aqueous sodium hydroxide (1M, 10ml), water (2 x 10ml), dried (Na_2SO_4), and evaporated to dryness to afford pure *4-methyl-3-pentenyl* 9,10-*dihydro*-10,9-*thiaethanoanthracene*-12-*carboxylate* (242), as a yellow oil (0.26g, 0.74mmol, 100% from alcohol); δ 1.57 and 1.68 (2 x br.s, 2 x CH_3), 2.19 (br.q, *J* 7.Hz, $CH\underline{CH}_2$) 3.95 (t, *J* 7.5 Hz, $O\underline{CH}_2$), 4.09 (d, *J* 2.5 Hz, 12-H), 4.89-5.24 (m, C=CH), 5.03 (d, *J* 2.5 Hz, 9-H), 5.07 (s, 10-H) and 6.90-7.60 (8H, m, Ar-H).

Thermolysis of 4-Methyl-3-pentenyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylate (242)

The anthracene adduct (242) (0.19g, 0.53mmol) was heated under reflux in anhydrous toluene (17ml) under nitrogen for 17.5h. Then solvent was evaporated under reduced pressure and ^1H n.m.r. spectrum of the crude product showed the extent of decomposition was *ca.* 50%.

Preparation of 3-Methyl-2-cyclohexenyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylate (247)

The carboxylic acid (234a) (0.29g, 1.1mmol) in dichloromethane (CH_2Cl_2) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.18g, 1.1mmol) at room temperature, and the

reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-cyclohexen-1-ol (0.12g, 1.1mmol) and n-butyl lithium (0.15mmol) in dichloromethane (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (40ml), washed with aqueous sodium carbonate (0.5M, 10ml), water (3 x 20ml), dried (Na_2SO_4) and evaporated to afford pure 3-*methyl*-2-*cyclohexeneyl* 9,10-*dihydro*-10,9-*thiaethanoanthracene*-12-*carboxylate* (247) as a yellow oil (0.35g, 0.98mmol, 89%); ν_{max} ($CHCl_3$) 1728 cm^{-1}; δ 1.66 (br.s, CH_3), 1.40-2.02 (6H, m, $OCH(C\underline{H}_2)_3$), 4.08 (d, *J* 3.0 Hz, 12-H), 5.00-5.25 (m, C=CH), 5.02 (d, *J* 3.0 Hz, 9-H), 5.07 (s, 10-H), 5.24-5.46 (m, OCH) and 6.99-7.50 (8H, m, Ar-H).

Thermolysis of 3-Methyl-2-cyclohexeneyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylate (247)

The anthracene adduct (247) (0.27g, 0.76mmol) was heated under reflux in anhydrous toluene (24ml) under nitrogen. The reaction was followed by t.l.c. (eluted with chloroform) and was judged to be complete after 7h. Evaporation of solvent gave the crude mixture as a yellow oil with white solid. The crude mixture was chromatographed on a Chromatotron (SiO_2; ethyl acetate-light petroleum, 3:7) under nitrogen to give the pure (1R*, 6S*, 9S*)-9-*mercapto*-2-*methyl*-7-*oxa*-8-*oxobicyclo*[4.3.0]*non*-2-*ene* (245a) as a yellow oil (0.083g, 0.45mmol, 59%) crystallization from dichloromethane and petroleum ether (40-60°C) afforded yellow crystals (0.027g, 19%) m.p. 58-61°C (Found: C, 58,66; H, 6.82; S, 17.19. $C_9H_{12}O_2S$ requires, C, 58.7; H, 6.57; S, 17.4%) (Found: *m/z* 184.0550. $C_9H_{12}O_2S$ requires M^+, 184.0558); ν_{max} ($CHCl_3$) 1778 cm^{-1}; δ 1.60-2.30 (4H, m, $OCH(C\underline{H}_2)_2$), 1.77 (br.s, CH_3), 2.22 (d, *J* 4.0 Hz, SH, exch. with D_2O), 3.18 (br.t,

J 8.5 Hz, 1-H), 3.88 (dd, *J* 9.0 and 4.0 Hz, 9-H), 4.50-4.86 (m, 6-H), and 5.77 (m, 3-H).

Epimerization of (1R*, 6S*, 9S*)-9-Mercapto-2-methyl-7-oxa-8-oxobicyclo-[4.3.0.]non-2-ene (245a)

The thiol(245a) (0.036g, 0.2mmol) in dichloromethane (5ml) was stirred at room temperature with triethylamine (0.021g, 0.21mmol) under nitrogen for 3h. Then the mixture was diluted with dichloromethane (20ml) and the solution was washed with hydrochloric acid (0.05M, 10ml), water (2 x 10ml), dried (Na_2SO_4) and evaporated to dryness to give (1R*, 6S*, 9R*)-9 *mercapto* -2-*methyl*-7-*oxa*-8-*oxobicyclo*[4.3.0]*non*-2-*ene* (245b); ν_{max} ($CHCl_3$) 1765 cm^{-1}; δ 1.72 (br.s, CH_3), 1.55-2.25 (4H, m, $OCH(C\underline{H}_2)_2$), 2.42 (d, *J* 4.5 Hz, 5H), 2.55-2.75 (m, 1-H), 3.55 (t, *J* 4.5 Hz, 9-H), 4.82-5.05 (m, 6-H), and 5.63 (m, 3-H).

Preparation of (1R*, 6S*, 9S*)-9-(S-Acetylthio)-2-methyl-7-oxa-8-oxobicyclo[4.3.0]non-2-ene (248a).

Acetic acid (0.045g, 0.75mmol) in dichloromethane (3ml) was stirred with dicyclohexylcarbodiimide (241) for 1h at room temperature. Then the (1R*, 6S*, 9S*)-thiol, prepared from the thermolysis of the adduct (247) (0.26g, 0.72mmol), in dichloromethane (5ml) was added into the solution. Stirring was continued for 24h. The reaction mixture was filtered and evaporated to dryness. The residue was then chromatographed on a Chromatotron (SiO_2; ethyl acetate-light petroleum, 3:7) under nitrogen to give pure (1R*, 6S*, 9S*)-9-(S-*Acetylthio*)-2-*methyl*-7-*oxa*-8-*oxobicyclo*[4.3.0]*non*-2-*ene* (248a) as a yellow oil (0.076g, 0.34mmol, 47%) (Found *m/z* 226.0664. $C_{11}H_{14}O_3S$ requires M^+, 226.0663); ν_{max} ($CHCl_3$) 1774 and 1703 cm^{-1}; δ 1.63

(br.s $C=CCH_3$), 1.14-2.30 (4H, m, $OCH(C\underline{H}_2)_2$), 2.42 (s, $COCH_3$), 3.32 (br.t, *J* 8 Hz, 1-H), 4.59-4.92 (m, 6-H), 4.75 (d, *J* 9.5 Hz, 9-H), and 5.69 (br.s, C=CH).

Preparation of ($1R^*$, $6S^*$, $9R^*$)-9-(S-Acetylthio)-2-Methyl-7-oxa-8-oxobicyclo[4.3.0]non-2-ene (248b)

The ($1\underline{R}^*$, $6\underline{S}^*$, $9\underline{R}^*$)-thiol (245b) (0.036g, 0.20mmol) in dichloromethane (10ml) was stirred for 1h with triethylamine (0.022g, 0.22mmol) and acetyl chloride (0.026, 0.20mmol) at room temperature. Then the reaction mixture was diluted with dichloromethane (20ml), washed with water (10ml), hydrochloric acid (0.05M, 10ml), water (10ml), aqueous sodium bicarbonate (0.05M, 10ml) and water (2 x 10ml) and dried (Na_2SO_4). The solution was evaporated to dryness to afford pure ($1R^*$, $6S^*$, $9R^*$)-9-(S-*Acetylthio*)-2-*methyl*-7-*oxa*-8-*oxobicyclo*[4.3.0]*non*-2-*ene* (248b) as a yellow oil (0.034g, 0.15mmol, 75%). (Found: *m/z* 226.0662. $C_{11}H_{14}O_3S$ requires M^+, 226.0663); ν_{max} 1776 and 1702 cm^{-1}; δ 1.50-2.28 (4H, m, $OCH(C\underline{H}_2)_2$), 1.80 (br.s, $C=CCH_3$), 2.42 (s, $COCH_3$), 2.85 (br.t, *J* 6 Hz, 1-H), 4.16 (d, *J* 5.5 Hz, 9-H), 4.62-5.08 (m, 6-H), and 5.66 (br.s, C=CH).

Preparation of *cis*-2-Buten-1-ol

2-Butyn-1-ol (0.71g, 0.01mol), isoquinoline (0.23g, 1.7 mmol), and palladium on barium sulphate (0.23g) in dried (Na) ether (8.2ml) were stirred at room temperature in an atmosphere of hydrogen. When hydrogen (0.24l, 1 mol equiv.) had been taken up (after stirring for 8 h 28 min), the mixture was diluted with ether (20ml), and was filtered through Celite (0.7g). The filtrate was washed successively with 0.7M hydrochloric acid (15ml), brine (2 x 20ml), and was dried

(Na_2SO_4). Ether was removed from the ethereal solution by distillation and the residual liquid was distilled to afford *cis*-2-buten-1-ol as a colourless liquid (0.43g, 6mmol, 60%), b.p. 74°C (60mmHg) [lit.[64] 63-64°C (60mmHg)]; ν_{max} 1675 cm^{-1}; δ 1.65 (br.d, *J* 5.0 Hz, CH_3), 1.82 (s, OH), 4.19 (d, *J* 6.0 Hz, OCH_2), and 5.52-5.76 (m, HC=CH).

Preparation of *cis*-2-Butenyl 9,10-Dihydro-10,9-thiaethano-anthracene-12-carboxylate (250b)

The carboxylic acid (234a) (0.57g, 2.1mmol) in dichloromethane (CH_2Cl_2) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.34g, 2.1mmol) at room temperature, and the reaction mixture was kept dry by a guard tube containing silica gel. Then *cis*-2-buten-1-ol (0.34g, 2.1mmol) and n-butyl lithium (0.18mmol) in CH_2Cl_2 (2ml) was added. Stirring was continued for 8h. The reaction mixture was diluted with dichloromethane (40ml), washed with aqueous sodium carbonate (0.5M, 20ml), water (3 x 20ml), dried (Na_2SO_4) and evaporated to afford pure cis-2-*butenyl* 9,10-*dihydro*-10,9-*thiaethano-anthracene*-12-*carboxylate* (250b) as a yellow oil (0.54g, 1.7 mmol, 88%) which on crystallization from dichloromethane gave white crystals m.p. 97-98°C (Found: C, 74.42; H, 5.75; S, 10.22. $C_{20}H_{18}O_2S$ requires C, 74.50; H, 5.63; S, 9.95%) Found: *m/z* 322.1046. $C_{20}H_{18}O_2S$ requires M^+, 322.1028); ν_{max} (KBr) 1728 cm^{-1}; δ 1.61 (d, *J* 6.0 Hz, CH_3), 4.09 (d, *J* 2.5 Hz, 12-H), 4.56 (m, OCH_2), 5.03 (d, *J* 2.5 Hz, 9-H), 5.07 (s, 10-H), 5.21-5.90 (2H, m, HC=CH), and 7.00-7.50 (8H, m, Ar-H).

Thermolysis of *cis*-2-Butenyl 9,10-Dihydro-10,9-thiaethano-anthracene-12-carboxylate (250b)

The anthracene cycloadduct (250b) (0.11g, 0.34mmol) was heated under reflux in anhydrous toluene (52ml) under nitrogen for 8h. Evaporation of solvent under reduced pressure gave cis-3-*ethenyl*-2-*mercaptobutan*-4-*olide* (251a) and anthracene. The crude product was then chromatographed on a Chromatotron (SiO_2; ethyl acetate-light petroleum, 3:7) under nitrogen to give the pure 3-*ethenyl*-2-*mercaptobutan*-4-*olide* (251) (0.022g, 0.15mmol, 44%), as a mixture of *cis*-(251a) and *trans*-isomers (256b) (*ca.* 1:1) (Found: *m/z* 144.0250. $C_6H_8O_2S$ requires M^+, 144.0245); ν_{max} 1772 cm^{-1}; δ (251a, *cis*-epimer) 1.91 (d, *J* 5.5 Hz, SH, exch. with D_2O), 3.32 (br. quintet, *J* 7.5 Hz, 3-H), 3.80 (dd, *J* 7.5 and 5.0 Hz, 2-H), 4.29 (dd, *J* 7.0 and 5.0 Hz, 4-CH_2), 5.20 (br.d, *J* 17.5 Hz, CH=C<u>H</u>H), 5.29 (br.d, *J* 10.0Hz CH=CH<u>H</u>) and 5.79 (ddd, *J* 17.5, 10.0 and 7.5 Hz, C<u>H</u>=CH_2); δ (251b, trans-epimer) 2.23 (d, *J* 5.0 Hz, SH), 2.74-3.20 (m, 3-H), 3.54 (dd, *J* 10.0 Hz, and 5.0 Hz, 2-H), 4.49 (dd, *J* 9.5 and 8.0 Hz, 4-CH_2), and 5.10-6.08 (m, vinyl-H).

Attempted epimerization of *cis*-thiol (251a)

The *cis*-thiol, prepared from the thermolysis of the adduct (250b) (0.12g, 0.37mmol), in dichloromethane (10ml) was stirred with triethylamine (0.065g, 0.64mmol) at room temperature for 3h. The mixture was then diluted with dichloromethane (20ml). washed with hydrochloric acid (0.05M, 10ml), water (2 x 10ml), dried (Na_2SO_4) and evaporated to dryness to give a yellow oil. ^1H n.m.r. spectrum suggested the lactone had decomposed.

Preparation of *trans*-3-Ethenyl-2-(S-benzoylthio)butan-4-olide (252)

The *cis*-thiol (251a), prepared from the thermolysis of the adduct (250b) (0.11g, 0.34mmol), in dichloromethane (5ml) was stirred for 1h with triethylamine (0.039g, 0.38mmol) and benzoyl chloride (0.049g, 0.35mmol). Then the reaction mixture was diluted with dichloromethane (30ml), washed with water (10ml), hydrochloric acid (0.05M, 10ml), water (10ml) aqueous sodium bicarbonate (0.05M, 10ml) and water (2 x 10ml) and dried (Na_2SO_4) and evaporated to dryness. The crude product was chromatographed on preparative SiO_2 plates to afford trans-3-*ethenyl*-2-(S-*benzoylthio*)*butan*-4-*olide* (252) (0.041g, 0.17 mmol, 50%) (Found *m/z* 248.0519. $C_{13}H_{12}O_2S$ requires M^+ 248.0507); ν_{max} ($CHCl_3$) 1786 and 1672 cm^{-1}; δ 3.28 (br. quintet, *J* 9Hz, 3-H). 4.10 (t, *J* 9.0 Hz, OCH), 4.30 (d, *J* 10.5 Hz, 2-H), 4.56 (t, *J* 8.5 Hz, OCH'), 5.22 (br.d, *J* 9.5 Hz, CH=C<u>H</u>H), 5.24 (br.d, *J* 17.5 Hz, CH=CH<u>H</u>), 5.82 (ddd, *J* 7.5, 9.5 and 17.5 Hz, C<u>H</u>=CH_2), 7.32-7.72 (m, *o*- and *p*-Ar-H) and 7.87-8.10 (m, *m*-Ar-H).

Preparation of *trans*-3-Ethenyl-2-(S-p-nitrobenzoylthio)butan-4-olide (253)

The *cis*-thiol (251a), prepared from the thermolysis of the adduct (250b) (0.17g, 0.53mmol), in dichloromethane (6ml) was stirred for 1h with triethylamine (0.058g, 0.57mmol) and *p*-nitrobenzoyl chloride (0.099g, 0.53mmol). Then the reaction mixture was diluted with dichloromethane (30ml), washed with water (10ml), hydrochloric acid (0.05M, 10ml), water (10ml) aqueous sodium bicarbonate (0.05M, 10ml) and water (2 x 10ml) and dried (Na_2SO_4) and evaporated to dryness. The crude product

was chromatographed on preparative SiO_2 plates to afford trans-3-*ethenyl*-2-*(S-p-nitrobenzoylthio)butan*-4-*olide* (253) as a yellow oil (0.058g, 0.20mmol, 38%) (Found: *m/z* 293.0361. $C_{13}H_{11}NO_5S$ requires M^+ 293.0358); ν_{max} ($CHCl_3$) 1786 and 1678 cm^{-1}; δ 3.32 (br.quintet, *J* 10 Hz, 2-H), 4.59 (t, *J* 9.0 Hz, OCH'), 5.26 (br.d, *J* 17.5 Hz, CH=CHH), 5.27 (br.d, *J* 10.0 Hz, CH=CHH), 5.82 (ddd, *J* 8.0, 10.0 and 17.5 Hz, CH=CH_2), and 7.98-8.42 (4H, m, Ar-H).

Preparation of *trans*-2-Butenyl 9,10-Dihydro-10,9-thiaethano-anthracene-12-carboxylate (250a).

The carboxylic acid (234a) (0.80g, 3.0mmol) in dichloromethane (CH_2Cl_2) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.50g, 3.1mmol) at room temperature, and the reaction mixture was kept dry by a guard tube containing silica gel. Then *trans*-2-buten-1-ol (0.20g, 2.7mmol) and n-butyl lithium (0.36mmol) in dichloromethane (2ml) were added. Stirring was continued for 8h. The reaction mixture was diluted with dihclormethane (40ml) and washed with aqueous sodium carbonate (0.5M, 20ml), water (3 x 20ml), dried (Na_2SO_4) and evaporated to dryness to afford pure trans-2-*butenyl* 9,10-*dihydro*-10,9-*thiaethanoanthracene*-12-*carboxylate* (250a) as a yellow oil. (0.76g, 2.4mmol, 87%) (Found: *m/z* 332.1026. $C_{20}H_{18}O_2S$ requires M^+ 322.1027); ν_{max} ($CHCl_3$) 1735 cm^{-1}; δ 1.62 (d, *J* 6.0 Hz, CH_3), 4.10 (d, *J* 2.5 Hz, 12-H), 4.35-4.52 (m, OCH_2), 5.05 (d, *J* 2.5 Hz, 9-H), 5.07 (s, 10-H), 5.22-5.90 (2H, m, CH=CH), and 7.00-7.55 (8H, m, Ar-H).

Thermolysis of *trans*-2-Butenyl 9,10-Dihydro-10,9-thiaethano anthracene-12-carboxylate (250a).

The anthracene adduct (250a) (0.11g, 0.33mmol) was heated under reflux for 8h in anhydrous toluene (31ml) under nitrogen. The reaction mixture was evaporated to dryness and ^1H n.m.r. spectrum of the crude mixture showed the extent of decomposition was *ca.* 20%.

Preparation of 3-Methyl-2-cyclopentenyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylate (258)

The carboxylic acid (234a) (0.66g, 2.5mmol) in dichloromethane (8ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.40g, 2.5mmol) at room temperature, and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-cyclopenten-1-ol (257) (0.23g, 2.3mmol) and n-butyl lithium (0.30mmol) in dichloromethane (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (4.0ml) and washed with aqueous sodium carbonate (0.5M, 20ml), water (2 x 20ml), dried (Na_2SO_4) and evaporated to dryness to give a brown oil. The crude product was then chromatographed on a Chromatotron (SiO_2; chloroform-light petroleum, 4:6) under nitrogen to give 3-*methyl*-2-*cyclopentenyl* 9,10-*dihydro*-10,9-*thiaethanoanthracene*-12-*carboxylate* (258) as a yellow oil (0.41g, 61%); ν_{max} ($CHCl_3$) 1730 cm^{-1}; δ 1.69 (br.s, CH_3), 1.49-2.52 (4H, m, $(CH_2)_2$), 4.07 (d, *J* 2.5 Hz, 12-H), 5.02 (d, *J* 2.5 Hz, 9-H), 5.07 (s, 10-H), 5.20-5.68 (m, C=CHCH) and 6.90-7.50 (8H, m, Ar-H).

Thermolysis of 3-Methyl-2-cyclopentenyl 9,10-Dihydro-10,9-thia-ethanoanthracene-12-carboxylate (258)

The anthracene adduct (258) (0.21g, 0.59mmol) was heated under reflux in anhydrous toluene (18ml) under nitrogen for 7h. Then the reaction mixture was evaporated to dryness under reduced pressure with heating. ^{1}H n.m.r. spectrum of the crude mixture suggested the adduct (258) had decomposed to the carboxylic acid (234a). Infra-red spectrum of the crude product showed stretching bands at 1712 and 3500-2400 cm^{-1}.

Preparation of 9,10-Dihydro-9,10-dimethyl-10,9-thiaethano-anthracene-12-carboxylic acid (234b)

Methyl mercaptoacetate (0.65g, 6.1mmol) was added dropwise with stirring to a suspension of *N*-chlorosuccinimide (0.98g, 7.3mmol) in dichloromethane (10ml) at room temperature. A yellow colour, signifying the formation of sulphenyl chloride, developed after a while. After 2h, the solution of the sulphenyl chloride was added dropwise, by a glass syringe, with stirring to dimethylanthracene (1.27g, 6.2mmol) and distilled dried (KOH) triethylamine (0.74g, 7.3 mmol) in dichloromethane (32ml) with heating under reflux. 30 Min after the last addition of sulphenyl chloride solution, the mixture was cooled and washed with dilute hydrochloric acid (2 x 10ml), water (3 x 25ml) and dried ($MgSO_4$) and evaporated to dryness. The residue was then dissolved in tetrahydrofuran (THF) (20ml) and aqueous sodium hydroxide (1.3M, 20ml) with stirring at room temperature. After 14h the solution was washed with dichloromethane (4 x 75ml), then acidified with 5% hydrochloric acid (15ml) and extracted with ether (4 x 50ml). The combined ethereal layers were washed with brine (20ml), dried ($MgSO_4$) and evaporated. The residue of substantially pure acid (234b) (1.10g, 3.7mmol 60%) was crystallised from ether as *carboxylic acid* hemiethereate (0.85g, 2.5mmol 41%) m.p. 171-173^{o} (Found: C, 73.01; H, 5.52; S, 11.3. $C_{18}H_{16}O_2S$ requires C, 72,94; H, 5.44; S, 10.93%) (Found: *m/z* 296.0853. $C_{18}H_{16}O_2S$ requires M^+ 296.0871); ν_{max} (KBr) 1712 cm^{-1}; δ 2.10 and 2.40 (2 x br.s, 2 x CH_3), 3.78 (s, 12-H), 7.07-7.47 (8H, m, Ar-H), and 9.27-9.57 (br.s, COOH),

Preparation of 3-Methyl-2-butenyl 9,10-Dihydro-9,10-dimethyl-10,9-thiaethanoanthracene-12-carboxylate (233b)

The carboxylic acid hemietherate (234b) (0.28g, 0.84mmol) in dichloromethane (CH_2Cl_2) (5ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.14g, 0.86mmol) at room temperature, and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-buten-1-ol (227) (0.07g, 0.81mmol) and n-butyl lithium (0.08mmol) in CH_2Cl_2 (2ml) were added. Stirring was continued for 7h. The reaction mixture was diluted with dichloromethane (20ml), washed with aqueous sodium carbonate (0.5M, 10ml), water (2 x 20ml) and dried (Na_2SO_4) and evaporated to dryness. ^1H n.m.r. spectrum of the crude product revealed that it was a mixture of the adduct (233b) and dimethylanthracene (*ca.* 6%). The crude product was chromatographed on SiO_2 plates to give pure 3-*methyl*-2-*butenyl* 9,10-*dihydro*-9,10-*dimethyl*-10,9-*thiaethanoanthracene*-12-*carboxylate* (233b) as a yellow oil (0.20g, 0.56mmol, 69%) (Found: *m/z* 364.1521. $C_{23}H_{24}O_2S$ requires M^+ 364.1497); ν_{max} ($CHCl_3$) 1746 cm^{-1}; 1.62 and 1.71 (2 x br.s, $C=C(CH_3)_2$) 2.14 and 2.27 (2 x br.s, 2 x CH_3), 3.83 (s, 12-H), 4.47 (br.d, *J* 6.0 Hz, OCH_2), 5.24 (br.t, *J* 6.0 Hz, C=CH) and 7.07-7.52 (8H, m, Ar-H).

Thermolysis of 3-Methyl-2-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (228)

Experiment 1

The cyclopentadiene *exo*-adduct (228b) (0.17g, 0.75mmol) was heated under reflux in anhydrous toluene (11ml) under nitrogen. The reaction was followed by t.l.c. and was judged to be incomplete after 34.2h. Evaporation of solvent at this point gave a brown oil, which after chromatography on preparative SiO_2 plates gave the 'thial polymer' (230) (95mg) and the bicyclic lactone (232) (18mg).

Experiment 2

The cyclopentadiene *exo*-adduct (228b) (0.10g, 0.45mmol) was heated in anhydrous toluene (43ml) under reflux for 15h under nitrogen. The reaction mixture was evaporated to dryness and ^1H n.m.r. spectroscopy showed the starting adduct: ene product (231a) was *ca.* 2:1.

Experiment 3

The cyclopentadiene adducts (228) (0.047g, 0.21mmol) was heated in xylene (20ml) with 2,6-di-tert-butyl-*p*-cresol (264) (0.1mol. equiv.) at 110°C for 15h. Nitrogen, which had already passed through Fieser's solution[84], was bubbled through the reaction mixture during the reaction. Then the reaction mixture was evaporated to dryness and ^1H n.m.r. spectroscopy showed the ratio of starting adduct (228): ene product (231a) was *ca.* 1:2.

Preparation of Sodium S-(methoxycarbonylmethyl)Thiosulphate (83b) (Bunte salt)

Methyl bromoacetate (14.40g, 0.094mol) in acetone (4.7ml) and sodium thiosulphate pentahydrate (23.36g, 0.094mmol) in water (47ml) were shaken together for 3 min at room temperature. A homogenous solution resulted and completion of the reaction was confirmed by analytical t.l.c. The solvents were evaporated under reduced pressure with heating and the white solid residue was dried *in vacuo* over P_4O_{10} for 8h, then extracted with hot, ethanol (120ml). The hot extracts were filtered. When the filtrate was cooled to $0^{o}C$, the 'Bunte salt' (83b) separated as white crystals (10.23g, 0.049mol, 52%); ν_{max} (KBr) 1720, 1214, 1047 and 650cm^{-1}. The i.r. spectrum was essentially the same as that of a sample prepared by R.A. Lewis[76].

Preparation of Methyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (264).

Freshly distilled cyclopentadiene (0.95g, 0.014mol) was added to a suspension of the 'Bunte salt' (83b) (2.99g, 0.014mol) and calcium chloride dihydrate (2.10g, 0.014mol) in methanol (35ml). Triethylamine (1.44g, 0.014mol) was added dropwise to the stirred mixture and stirring was continued for 24h at room temperature. The reaction mixture was acidified with 5% hydrochloric acid (40ml) and extracted with dichloromethane (3 x 30ml). The combined extracts were washed successively with 5% hydrochloric acid (20ml) water (20ml), 0.5M aqueous sodium carbonate (20ml), and water (2 x 20ml), and were dried ($MgSO_4$) and evaporated to afford a yellow liquid. The crude product was distilled by the Kugelrohr method to afford methyl 2-thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (264) as a colourless liquid (1.70g, 10mmol, 72%), b.p. 90°C (0.04 mbar); ν_{max} (liquid film) 1737 cm^{-1}. The ^1H n.m.r. spectrum showed an unchanged *endo:exo* ratio (7:3); δ 1.51-1.91 (m, *exo*- and *endo*-7-H_2), 3.32 (s, *exo*-3-H), 3.52-3.84 (m, *exo*- and *endo*-4-H), 3.69 (s, *endo*-OCH_3), 3.77 (s, *exo*-OCH_3), 4.04-4.20 (m, *exo*- and *endo*-1-H), 4.43 (d, *J* 3.0 Hz, *endo*-3-H), 5.86-6.02 (m, *exo*- and *endo*-5-H), 6.41 (dd, *J* 3.0 and 6.0 Hz, *exo*-6-H), and 6.41 (dd, *J* 3.8 and 5.4 Hz, *endo*-6-H).

Preparation of Methyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (264)

The carboxylic acids (225) (0.61g, 3,9mmol) was added with stirring to a solution of methanolic hydrogen chloride prepared from acetyl chloride (0.1ml) and dried (Mg) methanol (12ml). The reaction mixture was kept at room temperature and

protected from moisture by a guard tube containing silica gel. The mixture was then diluted with dichloromethane (40ml), washed successively with 0.5M aqueous sodium carbonate (20ml) and water (2 x 20ml) and was dried ($MgSO_4$) and evaporated to afford a yellow oil (0.63g). The oil (0.19g) was chromatographed on preparative SiO_2 plates to afford an unidentified compound as the major product (0.12g); ν_{max} ($CHCl_3$) 1730 cm^{-1} (ester). The ^1H n.m.r. spectrum suggested that this product was a methyl ester, δ 3.72 (s), and methyl 2-thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (264) (0.03g, 16%); ν_{max} ($CHCl_3$) 1730 cm^{-1}; δ 1.68 and 1.93 (ABq, J 8.5 Hz, 7-H_2), 3.34 (br.s, 3-H), 3.57 (br.s, 4-H), 3.77 (s, OCH_3), 4.14 (br.s, 1-H), 5.96 (dd, J 3.5 and 5.5 Hz, 5-H), and 6.40 (dd, J 2.2 and 5.0 Hz, 6-H).

Preparation of 3-Methyl-2-butenyl bromoacetate (274a)

Following the literature procedure[46], 3-methyl-2-buten-1-ol (5.36g, 0.062mol) and pyridine (10ml) in dichloromethane (40ml) were stirred in an ice bath. The reaction mixture was kept dry by a guard tube containing silica gel. Bromoacetyl bromide (16.33g, 0.081mol) in dichloromethane (60ml) was added dropwise to the mixture up slowly to room temperature and stirring was continued for 0.5h. Then the mixture was poured into ice (100g) and extracted with dichloromethane (3 x 100ml). The combined dichloromethane layers were washed with 2.5M sulphuric acid (30ml) and water (2 x 50ml) and were dried (Na_2SO_4) to give a dark orange oil (7.66g, 0.037mol, 60%). The crude product (3.78g, 0.018mol) was distilled (Kugelrohr) to give the pure 3-methyl-2-butenyl bromoethanoate (274a)(3.13g, 0.012mol 63%, overall yield 38%), b.p. 60-65^oC (0.1 mbar) [lit.[46] b.p. 63-66^o (0.5 mmHg)] (Found: C, 40.46; H, 5.41; Br, 38.62. Calc.

for $C_7H_{11}BrO_2$, C, 40.60; H, 5.36; Br, 38.59%); ν_{max} (liquid film) 1740 cm^{-1}; δ 1.73 (br.s, CH_3), 1.77 (br.s, CH_3), 3.84 (s, CH_2Br), 4.65 (br.d, *J* 7.0 Hz, OCH_2), and 5.40 (br.t, *J* 7.0 Hz, C=CH).

Preparation of 2-Methyl-2-propenyl bromoethanoate

2-Methyl-2-propen-1-ol (2.71g, 0.038mol) in dichloromethane (25ml) was esterified with bromoacetyl bromide (9.85g, 0.049mol) in dichloromethane (40ml), as described in the foregoing experiment, to give the bromo ester (6.0g, 0.032mol, 83%). The crude product (4.02g, 0.021mol) was distilled (Kugelrohr) to give the pure 2-*methyl*-2-*propenyl bromoethanoate* (3.56g, 0.018mol, 88%, overall yield 73%), b.p. 120-130° (3mbar) (Found: C, 37.65; H, 4.75; Br, 41.74. $C_6H_9BrO_2$ requires C, 37.33; H, 4.70; Br, 41.39%); ν_{max} (CCl_4) 1744 cm^{-1}; δ 1.79 (br.s, CH_3) 3.88 (s, CH_2Br), 4.62 (br.s, OCH_2), 4.99 and 5.03 (2 x br.s, $C=CH_2$).

Preparation of Sodium S-(3-Methyl-2-butenyloxycarbonylmethyl) Thiosulphate (274b)

3-Methyl-2-butenyl bromoacetate (274a)(2.07g, 0.01mol) in acetone (5ml) and sodium thiosulphate pentahydrate (2.48g, 0.01mol) in water (5ml) were shaken together for 15min at room temperature and 2min at *ca.* 40°C. A homogenous layer then resulted and completion of reaction was confirmed by analytical t.l.c. Solvents were evaporated under reduced pressure with heating. The white solid residue was then dried *in vacuo* over P_4O_{10} for 8h and extracted with chloroform (2 x 30ml) and the extracts were filtered. The filtrate was evaporated to give essentially pure 'Bunte salt' (2.89g, 0.01mol,

100%). The 'Bunte salt' (274b)was crystallized from acetone and the white crystals (1.51g, 52%) were dried *in vacuo* at 40°C for 1h (Found: C, 31.95; H, 4.15; S, 24.59. $C_7H_{11}O_5NaS_2$ requires C, 32.10; H, 4.23; S, 24.45%); ν_{max} (KBr) 1740, 1210, 1055, and 670 cm^{-1}; δ 1.69 (br.s, CH_3), 1.78 (br.s, CH_3),3.95 (br.s, CH_2S), 4.69 (br.d, *J* 7.0 Hz, OCH_2), 5.36 (br.t, *J* 7.0 Hz, C=CH); δ (D_2O; standard: Bu^tOH, δ 1.28) 1.78 (br.s, CH_3), 1.81 (br.s, CH_3) 3.94 (s, CH_2S), 4.75 (br.d, *J* 7.0 Hz,)CH_2), and 5.48 (br.t, *J* 7.0 Hz, C=CH).

Preparation of Sodium S-(2-Methyl-2-propenyloxycarbonylmethyl) Thiosulphate

2-Methyl-2-propenyl bromoacetate (0.81g, 4.2mmol) in acetone (2ml) and sodium thiosulphate pentahydrate in water (2ml) were stirred for 1h at room temperature. Solvents were evaporated under reduced pressure with heating. The white solid residue was extracted with hot ethanol (6ml) and the extract was filtered. The filtrate was evaporated to give a white solid mass. The 'Bunte salt' was crystallized from acetone and the white crystals (0.27g, 26%) were dried *in vacuo* at 40°C for 1h (Found: C, 28.75; H, 3.23; S, 25.66. $C_6H_9O_5NaS_2$ requires C, 29.03; H, 3.23; S, 25.83%); ν_{max} (KBr) 1742, 1708, 1660, 1214, 1040, and 648 cm^{-1}; δ (D_2O; standard:Bu^tOH, δ 1.28) 1.82 (br.s, CH_3), 4.02 (s, SCH_2), 4.70 (br.s, OCH_2), 5.09 (br.s, $C=CH_2$).

Treatment of Sodium S-(Ethoxycarbonylmethyl) Thiosulphate with Triethylamine in the Presence of Cyclopentadiene in Different Solvent Systems

In order to find out the right solvent system for the preparation of various cyclopentadiene cycloadducts esters from the 'Bunte salt' several experiments using acetone and water in different ratios as solvents were carried out.

Generally, freshly distilled cyclopentadiene (1 mol. equiv.) was added to a suspension of the 'Bunte Salt' (χ mmol) and calcium chloride dihydrate (1 mol. equiv.) in an acetone:water mixture. Then triethylamine (1 mol. equiv.) was added dropwise to the stirred mixture. After 24 h stirring at room temperature the reaction mixture was acidified with 5% hydrochloric acid (10ml) and then extraced with chloroform (3 x 15ml). The combined chloroform extracts were washed with 5% hydrochloric acid (10ml), water (10ml), 0.6M aqueous sodium carbonate (10ml), and water (2 x 10ml) and were then dried ($MgSO_4$) and evaporated.

Expt.	Bunte salt (mmol)	Solvent ratio[a]	Total vol. (ml)	Yields[b,c] (%)
1	2.8	2:1	10.8	54
2	2.9	2.5:1	12.6	48
3	2.4	2.8:1	9.5	51
4	1.2	3.4:1	13.2	59
5	2.6	5:1	9.0	72
6	3.6	7:1	10.5	76
7	3.6	ethanol	9.0	78

[a] Ratio of acetone:water, unless stated otherwise.

[b] Yields before any purification step.

[c] The ^1H n.m.r. spectra of the crude products showed the cycloadducts were accompanied by traces of disulphide.

Attempted Conversion of 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylic acid (225) to Its Acid Chloride (265)

Oxalyl chloride (0.55g, 4.3mmol) in dry benzene (0.54ml) was added slowly to the carboxylic acid (225) (0.27g, 1.7mmol) After 15min, the reaction mixture was heated under reflux for 3.5h and evaporated. The i.r. spectrum of the residue showed no carbonyl bands attributable to the carboxylic acid (225) or its acid chloride (265). The ^{1}H n.m.r. spectrum of the crude product was uninformative.

Preparation of 3-Methyl-2-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (228)

Method 1 Using *N,N'*-carbonyldiimidazole (226) as condensing agent with n-butyl-lithium as catalyst.

The carboxylic acids (225) (0.37g, 2.4mmol) (*endo*:*exo*, 7:3) in dichloromethene (5ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (0.47g, 73% purity, 1.05 mol. equiv.) at room temperature and the reacion mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-buten-1-ol (227) (0.20g, 2.2mmol) and n-butyl-lithium (1.58M, 0.2ml) in dichloromethane (2ml) were added. Stirring was continued for 8h. The reaction mixture was diluted with dichloromethane (40ml), washed with 0.5M aqueous sodium carbonate (20ml), and water (2 x 15ml) and dried (Na_2SO_4) and evaporated. The residue (0.46g) was chromatographed on a silica (HF_{254}) column, eluted with chloroform-light petroleum (1:4), then with chloroform-light petroleum (1:1) to afford the pure *endo*-ester (228a) (0.24g) and *exo*-ester (228b) (0.12g) and a mixture of both isomers (228) (0.08g) (total yield 0.44g, 2.0mmol, 91% from the alcohol). The separate isomers were distilled (Kugelrohr)

to afford 3-*methyl*-2-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*--3-endo-*carboxylate* (228a) as a colourless liquid, b.p. 110-120°C (0.2-0.25mbar) (Found: *m/z* 224.0850. $C_{12}H_{16}O_2S$ requires M^+, 224.0871); ν_{max} (liquid film) 1734 cm^{-1}; δ 1.62 (m, 7-H_2), 1.68 (br.s, CH_3), 1.72 (br.s, CH_3), 3.76 (br.s, 4-H), 4.08 (br.s, 1-H), 4.41 (d, *J* 4.0 Hz, 3-H), 4.56 (br.d, *J* 7.0 Hz, OCH_2), 5.3 (br.t, *J* 7.0 Hz, C=CH), 5.86 (dd, *J* 3.0 and 5.5 Hz , 5-H), and 6.47 (dd, *J* 3.0 and 6.0 Hz, 6-H), and 3-*methyl*-2-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (228b) as a colourless liquid, b.p. 105-110°C (0.1mbar) (Found: C, 64.22; H, 7.33. $C_{12}H_{16}O_2S$ requires C, 64.25; H, 7.19%) (Found: *m/z* 224.0863. $C_{12}H_{16}O_2S$ requires M^+, 224.0871); ν_{max} (liquid film) 1736 cm^{-1}; δ 1.63 and 1.93 (ABq, *J* 9.5 Hz, 7-H_2), 1.70 (br.s, CH_3),1.73 (br.s, CH_3), 3.29 (s, 3-H), 3.53 (br.s, 4-H), 4.10 (br.s, 1-H), 4.64 (br.d, *J* 7.0 Hz, OCH_2), 5.38 (br.t, *J* 7.0 Hz, C=CH), 5.87 (dd, *J* 2.5 and 5.0 Hz, 5-H), and 5.92 (dd, *J* 3.0 and 5.5 Hz, 6-H).

Method 2 Using *N,N'*-carbonyldiimidazole (226) as condensing agent at elevated temperature

The carboxylic acids (225) (*endo:exo*, 7:3), (0.58g, 3.7 mmol) in dry tetrahydrofuran (THF) (6ml) was stirred for 2h with *N,N'*-carbonyldiimidazole (0.63g, 3.9mmol, 1.05 mol.equiv) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-buten-1-ol (227) (0.32g, 3.7mmol) in dry THF (2ml) was added and the mixture was refluxed for 31h. Solvents were removed under reduced pressure with slight heating. The residue was diluted with water (10ml) and extracted with ether (4 x 15ml). The combined ethereal extracts were washed with 0.6M aqueous

sodium carbonate (15ml) and water (2 x 15ml) and were dried ($MgSO_4$) and evaporated. The ^1H n.m.r. spectrum of the residue (0.65g, 2.9mmol) revealed that the *endo:exo* ratio was unchanged. The crude product (55mg) was chromatographed on a preparative SiO_2 plate to afford pure 3-*methyl*-2-*butenyl* 2-*thiabicyclo*[2.2.1]-5-*ene*-3-*carboxylate* (228) (34mg, overall yield from alcohol, 62%). The ^1H n.m.r. spectrum agreed well with that of a sample of the ester prepared before.

Method 3 Using cyclohexylcarbodiimide as condensing agent.

The carboxylic acids (225) (*endo:exo* 7:3) (0.30g, 1.9mmol) 3-methyl-2-buten-1-ol (0.16g, 1.9mmol), and p-toluenesulphonic acid (17mg) were dissolved in pyridine (1.7ml). After the addition of cyclohexylcarbodiimide (0.47g, 2.3mmol, 1.2mol equiv.), the reaction mixture was stirred at room temperature for 25h. Then dichloromethane (50ml) was added and the mixture was washed with water (20ml), 1M hydrochloric acid (60ml), water (20ml), dilute aqueous sodium hydroxide (20ml), and water (3 x 20ml), and was dried ($MgSO_4$) and evaporated. The residue (0.25g) was chromatographed on preparative SiO_2 plates to afford 3-*methyl*-2-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*carboxylate* (228) (0.23g, 1.0mmol, 54%) with an unchanged *endo:exo* ratio. The ^1H n.m.r. spectrum agreed well with that of a sample of the ester prepared before.

Method 4 By treatment of sodium *S*-(3-methyl-2-butenyloxy-carbonylmethyl) thiosulphate (274b) with triethylamine in the presence of cyclopentadiene

Triethylamine (0.30g, 3.0mmol) was slowly added with stirring to a suspension of the 'Bunte salt' (0.53g, 2.0mmol),

calcium chloride dihydrate (0.47g, 3.2mmol), and freshly distilled cyclopentadiene (0.35g, 5.3mmol) in acetone-water (7:1) (8ml). Stirring was continued for 24h at room temperature and dichloromethane (50ml) was added. The mixture was washed with dilute hydrochloric acid (20ml) and water (2 x 15ml), dried ($MgSO_4$), and evaporated to afford 3-*methyl*-2-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*carboxylate* (228) (0.33g, 1.5mmol, 75%) as a light yellow mobile oil. The ^1H n.m.r. spectrum of the crude product showed that the *endo*- and *exo*-esters were the only products. The crude mixture was chromatographed using preparative SiO_2 plates to afford a mixture of the pure esters (228) (0.29g, 1.3mmol, 65%). as a colourless oil.

Attempted Preparation of 3-Methyl-2-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (228) Using Ethyl Chloroformate as Condensing Agent.

The carboxylic acids (225) (*endo:exo*, 7:3) (0.16g, 1.0mmol) and redistilled triethylamine (0.11g, 1.1mmol) in dichloromethane (3ml) were treated with ethyl chloroformate (0.11g, 1.0mmol) with stirring at 0°C, with a guard tube containing silica gel to exclude moisture. After 1h the reaction mixture was diluted with dichloromethane (20ml), washed with ice-water (10ml), dried (Na_2SO_4), and evaporated to afford the mixed anhydrides as a yellow oil (0.22g, 96%) with the *endo:exo* ratio unchanged; ν_{max} 1817 and 1733 cm^{-1}; δ 1.35 (t, *J* 7.0 Hz, *endo*-CH_3), 1.37 (t, *J* 7.0 Hz, *exo*-CH_3), 1.54-1.98 (m, *endo*- and *exo*-7-H_2), 3.38 (s, *exo*-3-H), 3.67 (br.s, *exo*-4-H), 3.84 (br.s, *endo*-4-H), 4.33 (q, *J* 7.0 Hz, *endo*-OCH_2), 4.36 (q, *J* 7.0 Hz, *exo*-OCH_2), 4.51 (d, *J* 4.0 Hz, *endo*-3-H), 5.97 (dd, *J* 3.0 an 5.5 Hz, *endo*- and *exo*-5-H), 6.45 (dd, *J* 3.0 and 5.5 Hz, *exo*-6-H),

nd 6.54 (dd, *J* 3.0 and 5.5 Hz, *endo*-6-H).

The crude mixed anhydrides (270) (*endo:exo*, 7:3) (0.22g, 0.96mmol) prepared in the foregoing experiment were stirred with triethylamine (0.40g, 4.0mmol) and 3-methyl-2-buten-1-ol (85mg, 0.99mmol) in dichloromethane (5ml) for 1.5h at room temperature. Dichloromethane (30ml) was added and the mixture was washed with dilute hydrochloric acid (10ml) and water (10ml), dried ($MgSO_4$), and evaporated. The residue (0.19g) was then chromatographed on preparative SiO_2 plates to afford an inseparable mixture (0.14g) of the 3-methyl-2-butenyl *endo*- and *exo*-ester (228) (74%) and the corresponding ethyl *endo*- and *exo*-esters (77) (26%). The ^1H n.m.r. spectrum showed that the *endo:exo* ratio had changed from 7:3 to 1:1.3.

Attempted Preparation of 3-Methyl-2-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (228) by Transesterification

The methyl ester cyclopentadiene cycloadducts (264) (*endo:exo*, 7:3) (0.56g, 3.3mmol), 3-methyl-2-buten-1-ol (0.31g, 3.6 mmol) and potassium t-butoxide (0.04g) were refluxed in dry benzene (6ml) in the presence of 5A molecular sieves (3.83g) for 3.5h. The reaction mixture was cooled, filtered, and diluted with ether (50ml). The mixture was washed with water (2 x 20ml), dried ($MgSO_4$), and evaporated *in vacuo* with heating to afford a yellow oil (0.48g); ν_{max} ($CHCl_3$) 1736 cm^{-1}. The ^1H n.m.r. spectrum suggested that the cycloadducts had decomposed but a signal for a methyl ester, δ 3.77 (s), was observed.

Preparation of 4-Methyl-3-pentenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (259)

The carboxylic acid (225) (0.30g, 1.9mmol) (*endo:exo*, 2:1) in dichloromethane (5ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (0.31g, 1.9mmol) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 4-methyl-3-penten-1-ol (0.17g, 1.7mmol) and n-butyllithium (0.2mmol) in dichloromethane (2ml) were added. Stirring was continued for 8h at room temperature. The reaction mixture wsa diluted with dichloromethane (40ml), washed with 0.5M aqueous sodium carbonate (20ml), and water (2 x 15ml) and dried (Na_2SO_4) and evaporated under reduced pressure with slight heating. The residue (0.40g) was chromatographed on a silica (HF_{254}) column, eluted with chloroform-light petroleum (1:4), then with chloroform-light petroleum (1:1) to afford 4-*methyl*-3-*pentenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (259a) (0.22g) (Found: *m/z* 238.1032. $C_{13}H_{18}O_2S$ requires M^+, 238.1027); ν_{max} (liquid film) 1730 cm^{-1}; δ 1.61 (br.s, CH_3), 1.68 (br.s, CH_3) 1.61-1.81 (m, 7-H_2), 2.28 (br.q, *J* 7.5 Hz, C=C-CH_2), 3.73 (br.s, 4-H), 4.02 (t, *J* 7.0 Hz, OCH_2), 4.07 (br.s, 1-H), 4.40 (d, *J* 4.5 Hz, 3-H), 5.08 (br.t, *J* 7.5 Hz, C=CH), 5.86 (dd, *J* 3.0 and 5.5 Hz, 5-H), and 6.45 (dd, *J* 3.0 and 5.5 Hz, 6-H), and 4-*methyl*-3-*pentenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (259b) (0.12g) (Found: *m/z* 238.1026. $C_{13}H_{18}O_2S$ requires M^+, 238.1027); ν_{max} (liquid film) 1732 cm^{-1}; δ 1.54-2.01 (m, 7-H_2), 1.61 (br.s, CH_3), 1.67 (br.s, CH_3), 2.31 (br.q, *J* 7.0 Hz, C=C-CH_2), 3.27 (s, 3-H), 3.50 (br.s, 4-H), 4.08 (br.s, 1-H), 4.10 (t, *J* 7,0 Hz, OCH_2), 5.10 (br.t, *J* 7.5 Hz, C=CH), 5.92 (dd, *J* 3.0 and 5.5 Hz, 5-H), and 6.36 (dd, *J* 3.0 and 5.8 Hz, 6-H). The pure esters (259), were obtained in a combined yield of 75% from the alcohol.

Preparation of Diphenylphosphinic Acid

A literature method was followed[78]. Chlorodiphenylphosphine (50g, 0.23 mol) was added dropwise with stirring to water (150ml). After the addition was completed, sodium hydroxide (19g, 0.475mol) was added in small portions with stirring so that the temperature did not exceed 50°C. Immediately after the addition of the base, hydrogen peroxide (30% solution, 20ml) was added in 2ml portions maintaining the temperature of the solution between 40 and 60°C. After the oxidation was complete , 6N hydrochloric acid was added dropwise till the pH of the solution was about 2. The mixture was cooled, filtered and the filter cake was washed with 0.06M hydrochloric acid (100ml), ice cold water (100ml) and benzene (10ml), Recrystallization afforded pure diphenylphosphinic acid (21.9g, 44%) as white needles, m.p. 192-196°C (from ethanol). (lit.[78] m.p. 193-195°C); ν_{max} (KBr) 1440, 1180, 1130 and 960 cm^{-1}.

Preparation of Diphenylphosphinoyl chloride (267)

To a stirred suspension of diphenylphosphinic acid (10.8g, 0.049mol) in dried (Na) benzene (50ml), thionyl chloride (20ml), 0.27mmol) was added in one portion. The mixture was heated with stirring under reflux for 2.5h, then was allowed to cool to room temperature. The volatile products were removed under reduced pressure (18mmHg) with slight heating and the remaining viscous yellow oil was distilled to afford pure diphenylphosphinoyl chloride (267) (9.81g, 42mmol, 85%), b.p. 141-143°C (0.2mmHg) [lit.[79] b.p. 139°C (0.15mmHg)]; ν_{max} (CCl_4) 1433, 1249, 1236, 1116, and 948 cm^{-1}.

Preparation of 2-Methyl-2-propenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (273)

Method 1 Using *N,N'*-carbonyldiimidazole as condensing agent with n-butyl - lithium as catalyst

The carboxylic acids (225) (0.78g, 5.0mmol) (*endo:exo*, 7:3) in dried (Na) tetrahydrofuran (THF) (5ml) was stirred for 2h with *N,N'*-carbonyldiimidazole (0.86g, 5.3mmol) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 2-methyl-2-propen-1-ol (0.36g, 5.0mmol) and n-butyl-lithium (15% w/w, 0.47g) in dried (Na) THF (4ml) were added. After stirring was continued for 4h, solvents were removed under reduced pressure with slight heating. The residue was diluted with water (10ml) and extracted with ether (4 x 20ml). The combined ethereal layers were washed successively with 0.6M aqueous sodium carbonate (15ml), and water (3 x 10ml), and were dried (Na_2SO_4) and evaporated to afford a brown oil (0.93g). The oil (0.10g) was chromatographed on preparative SiO_2 plates to afford the pure *endo*-ester (273a) (0.33g) and *exo*-ester (273b)(0.14g) (total yield 0.47g, 79%). The separate isomers were distilled to afford 2-*methyl*-2-*propenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (273a) as a colourless liquid, b.p. 90-95°C (0.1mbar) (Found C, 62.82; H, 6.90; S, 15.46. $C_{11}H_{14}O_2S$ requires C, 62.82; H, 6.71; S, 15.25) (Found *m/z* 210.0717. $C_{11}H_{14}O_2S$ requires M^+, 210.0714); ν_{max} (CCl_4) 1740 cm^{-1}; δ 1.66 (m, 7-H_2), 1.73 (br.s, CH_3), 3.79 (m, 4-H), 4.01 (m, 1-H), 4.48 (d, *J* 2.5 Hz, 3-H), 4.50 (s, OCH_2) 4.96 (br.d, *J* 4.0 Hz, C=CH_2), 5.92 (dd, *J* 2.8 and 5.3 Hz, 5-H), and 6.49 (dd, *J* 2.5 and 5.5 Hz, 6-H), and 2-*methyl*-2-*propenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (273b) as a colourless liquid, b.p. 90°C (0.13mbar) (Found: *m/z* 210.0720.

$C_{11}H_{14}O_2S$ requires M^+, 210.0714); ν_{max} (liquid film) 1738 cm^{-1}; δ 1.67 and 1.93 (ABq, J 8.5 Hz, 7-H_2), 1.77 (br.s, CH_3), 3.34 (s, 3-H), 3.57 (m, 4-H), 4.02 (m, 1-H), 4.58 (br.s, OCH_2), 4.98 (br.d, J 5.5 Hz, C=CH_2), 5.93 (dd, J 3.5 and 5.0 Hz, 5-H), and 6.39 (dd, J 2.5 and 5.5 Hz, 6-H).

Method 2 Using diphenylphosphinoyl chloride (267) as condensing agent

The carboxylic acids (225) (0.50g, 3.2mmol) (*endo:exo*, 7:3), diphenylphosphinoyl chloride (267) (0.76g, 3.2mmol), and *N*-methylmorpholine (0.65g, 6.4mmol) in dichloromethane (6ml) were stirred together at -20°C for 1h and the reaction mixture was kept dry by a guard tube containing silica gel. Then the reaction mixture was allowed to warm to room temperature for 0.5h and was refluxed for 1min. 2-Methyl-2-propen-1-ol (0.23g, 3.2mmol) and redistilled triethylamine 10.65g, 6.4mmol) were added to the mixture and reflux was continued for 14h. Then the reaction mixture was diluted with dichloromethane (40ml), washed successively with water (20ml), 5% hydrochloric acid (20ml) water (20ml), 0.5M aqueous sodium carbonate (20ml), water (3 x 20ml), and dried (Na_2SO_4) and evaporated to afford a brown liquid (0.54g). The ^1H n.m.r. spectrum showed that the crude product was composed of the cycloadducts (273) (*endo:exo*, 1:1) (94%) and the phosphinate ester (274) (6%). The liquid was chromatographed on a silica (HF_{254}) column, eluted with chloroform-light petroleum (1:4), then with chloroform-light petroleum (1:1) to afford the pure cycloadducts (273) (0.47g, 2.2mmol, 70%), whose ^1H n.m.r. spectrum agreed well with that of a sample prepared earlier, and 2-*methyl*-2-*propenyl diphenylphosphinate* (274) as a yellow solid (0.034g) (Found: *m/z* 272.0959.

$C_{16}H_{17}O_2P$ requires M^+, 272 0966); ν_{max} (KBr) 1440, 1220 and 1048 cm^{-1}; δ 1.75 (s, CH_3), 4.42 (d, J 7.5 Hz, OCH_2), 4.99 (br.d, J 11.0 Hz, $C=CH_2$), 7.36-7.60 (m, 2-aryl and 4-aryl-H), and 7.77-8.02 (m, 3-aryl-H).

Preparation of *trans*-2-Buten-1-ol.

trans-Crotonaladehyde (1.19g, 17mmol) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.19g, 5mmol) in dired (Na) ether (10ml) in an ice-bath under nitrogen. After the last addition of crotonaldehyde, the reaction mixture was allowed to warm up to room temperature and stirring was continued for 20min. Ice-water (20ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was poured into a mixture of ice (2g) and 10% sulphuric acid (10ml). The mixture was extracted with ether (2 x 20ml) and the combined ethereal layers were washed with water (10ml), and were dried ($MgSO_4$), and evaporated under reduced pressure with slight heating. The residual liquid (0.76g) was distilled to afford *trans*-2-buten-1-ol (0.54g, 7.5mmol, 44%), b.p. 120-122°C [lit.[64] 121.2°C (754mmHg)]; ν_{max} 1673 cm^{-1}; δ 1.58 (br.s, OH, exch. with D_2O), 1.71 (d, J 3.0 Hz, CH_3), 3.97-4.23 (m, OCH_2), and 5.59-5.82 (m, HC=CH).

Preparation of *trans*-2-Butenyl 2-Thiabicyclo[2.2.1]hept-5-ene 3-carboxylate (178).

Method 1 Using *N,N'*-carbonyldiimidazole as condensing agent with n-butyl-lithium as catalyst

The carboxylic acids (225) (0.95g, 6.1mmol) (*endo:exo*, 1:1) in dichloromethane (6ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (1.21g, 80% purity, 6.4mmol) at room temperature and

the reaction mixture was kept dry by a guard tube containing silica gel. Then *trans*-2-buten-1-ol (0.45g, 6.2mmol) and n-butyl-lithium (1.58M, 0.5ml) in dichloromethane (2ml) were added. Stirring was continued for 10h. The reaction mixture was diluted with dichloromethane (40ml), washed with 0.5M aqueous sodium carbonate (20ml) and water (2 x 20ml), and was dried (Na_2SO_4), and evaporated to afford a brown liquid (1.21g). The liquid was chromatographed on a silica (HF_{254}) column to afford trans-2-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (278a) as a colourless liquid (0.39g) (Found: *m/z* 210.0692. $C_{11}H_{14}O_2S$ requires M^+, 210.0715); ν_{max} (liquid film) 1732cm^{-1}; δ 1.64 (m, 7-H_2), 1.68 (d, *J* 6.0 Hz, CH_3), 3.74 (m, 4-H), 4.07 (m, 1-H), 4.42 (d, *J* 4.0 Hz, 3-H), 4.5 (d, *J* 6.0 Hz, OCH_2), 5.34-6.02 (m, HC=CH), 5.87 (dd, *J* 3.5 and 5.5 Hz, 5-H), and 6.47 (dd, *J* 2.8 and 5.8 Hz, 6-H), and trans-2-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (278b) as a colourless liquid (0.43g) (Found: *m/z* 210.0706. $C_{11}H_{14}O_2S$ requires M^+, 210.0714); ν_{max} (liquid film) 1730 cm^{-1}; δ 1.52-1.82 and 1.90 (ABq, *J* 10.0 Hz, 7-H_2), 1.70 (d, *J* 4.0 Hz, CH_3), 3.28 (s, 3-H), 3.54 (br.s, 4-H), 4.10 (br.s, 1-H), 4.57 (d, *J* 6.2 Hz, OCH_2), 5.37-6.07 (m, HC=CH), 5.92 (dd, *J* 2.5 and 5.5 Hz, 5-H), and 6.37 (dd, *J* 2.5 and 5.3 Hz, 6-H), and a mixture of both isomers (278) (0.19g). The pure esters (278) were obtained in a combined yield of 79% from the carboxylic acids.

Method 2 Using diphenylphosphinoyl chloride as condensing agent.

The carboxylic acids (225) (0.64g, 4.1mmol) (*endo:exo*, 7:3), diphenylphosphinoyl chloride (267) (0.89g, 3.7mmol), and *N*-methylmorpholine (0.83g, 8.2mmol) in dichloromethane (6ml) were stirred together at -15°C for 2h and the reaction mixture was kept dry by a guard tube containing silica gel. Then the reaction mixture was allowed to warm to room temperature for 0.5h and was refluxed for 10min. *trans*-2-Buten-1-ol (0.27g, 3.8mmol) and redistilled triethylamine (0.76g, 7.5mmol) were added to the mixture and reflux was continued for 14h. Then the reaction mixture was diluted with dichloromethane (40ml), washed successively with water (10ml), 5% hydrochloric acid (20ml), water (20ml), 0.5M aqueous sodium carbonate (20ml), and water (2 x 20ml), and dried (Na_2SO_4) and evaporated to afford a brown liquid (0.66g). ^1H n.m.r. spectrum showed that the crude product was composed of the carboxylic esters (278) (*endo:exo*, 1:1) (93%) and the phosphinate ester (*cf.* 274) (7%). The liquid was chromatographed on preparative SiO_2 plates to afford pure carvoxylic esters (278) (0.55g, 2.6mmol, 70%), whose ^1H n.m.r. spectrum agreed well with that of a sample prepared earlier, and trans-2-*butenyl diphenylphosphinate (cf.* 274) as a yellow oil (0.051g) (Found: *m/z* 272.0959. $C_{16}H_{17}O_2P$ requires M^+, 272.0966); ν_{max} ($CHCl_3$) 1440, 1215, and 1131 cm^{-1}; δ 1.66 (d, *J* 4.5 Hz, CH_3), 4.48 (br.t, *J* 6.0 Hz, OCH_2), 5.37-6.02 (m, HC=CH), 7.30-7.62 (m, 2-aryl and 4-aryl-H), and 7.62-8.00 (m, 3-aryl-H).

Preparation of 3-Methyl-2-cyclopenten-1-ol (257)

3-Methyl-2-cyclopenten-1-one (2.45g, 26mmol) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.45g) in dried (Na) ether (15ml) in an ice-bath under

nitrogen. After the last addition of the ketone, the reaction mixture was allowed to warm to room temperature and stirring was continued for 1h. Ice-water (20ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was extracted with ether (4 x 30ml). The combined ethereal layers were washed with water (20ml), and were dried (Na_2SO_4), and evaporated to afford a brown liquid (1.80g). The residual liquid (0.69g) was distilled (Kugelrohr) to afford 3-methyl-2-cyclpenten-1-ol (257) as a colourless liquid (0.64g, 66%), b.p. 50° (1.4mmHg); ν_{max} 1658 cm^{-1}; δ 1.54-2.62 (m, 4-H_2, 5-H_2 and CH_3), 1.88 (br.s, OH, exch. with D_2O), 4.83 (m, 1-H), and 5.47 (br.s, 2-H).

Preparation of 3-Methyl-2-cyclopentenyl 2-Thiabicyclo[2.2.1] hept-5-ene-3-carboxylate (279).

The carboxylic acids (225) (1.10g, 7.0mmol) (*endo:exo*, 5:6) in dichloromethane (5ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (1.40g, 80% purity, 7.4mmol) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-2-cyclopenten-1-ol (0.69g, 7.03mmol) and n-butyl-lithium (1.58M, 0.7ml) in dichloromethane (2ml) were added. Stirring was continued for 12h at room temperature and the mixture was refluxed for a further 3h. After cooling, the mixture was diluted with dichloromethane (40ml), washed with 0.5M aqueous sodium carbonate (30ml) and water (2 x 20ml) and was dried (Na_2SO_4) and evaporated to afford a brown oil (1.10g, 4.7mmol, 70%). ^1H n.m.r. spectrum showed the carboxylic esters (279) were the only product. The crude product was chromatographed on a Chromatotron (ethyl acetate:light petroleum, 15:85) to afford 3-*methyl*-2-*cyclo*-*pentenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*carboxylate* (279)

as a colourless oil (0.91g, 3.85mmol, 55%) (Found: *m/z* 236.0856. $C_{13}H_{16}O_2S$ requires M^+, 236.0871); ν_{max} (liquid film) 1726 cm^{-1}; δ 1.50-2.60 (m, 7-H_2 and CH_2CH_2), 1.82 (br.s, CH_3), 3.27 (s, *exo*-3-H), 3.53 (br.s, *exo*-4-H), 3.76 (br.s, *endo*-4-H), 4.11 (br.s, 1-H), 4.40 (d, *J* 4.5 Hz, *endo*-3-H), 5.49 (m, C=CH), 5.70 (m, OCH), 5.82-6.08 (m, 5-H), 6.38 (dd, *J* 2.5 and 5.0 Hz, *exo*-6-H), and 6.49 (dd, *J* 2.5 and 6.0 Hz, *endo*-6-H).

Preparation of 2-Propenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (281)

The carboxylic acids (225) (1.39g, 7.7mmol) (*endo:exo*, 7:3) in dichloromethane (8ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (1.42g, 90% purity, 1.05mol. equiv) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 2-propen-1-ol (0.45g, 7.7 mmol) and n-butyl-lithium (1.58M, 0.77ml) in dichloromethane (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (40ml), washed with aqueous sodium carbonate (0.5M, 20ml), water (2 x 15ml) and dried (Na_2SO_4) and evaporated to dryness. The residue was chromatographed on a silica (GF_{254}) column, eluted with chloroform-light petroleum (1:4), then with chloroform-light petroleum (1:1) to afford 2-*propenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (281a) (0.74g) ν_{max} (liquid film) 1735 cm^{-1}; δ 1.51-1.84 (m, 7-H_2), 3.81 (br.s, 4-H), 4.12 (br.s, 1-H), 4.47 (d, *J* 3.5 Hz, 3-H), 4.60 (d, *J* 5.8 Hz, OCH_2), 5.16-5.53 (m, $C=CH_2$), 5.70-6.17 (2H, m, 5-H and $CH=CH_2$) and 6.51 (dd, *J* 3.0 and 5.0 Hz, 6-H), and 2-*propenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (281b) (0.31g, (Found: *m/z* 196.0562. $C_{10}H_{12}O_2S$ requires M^+ 196.0558); ν_{max} 1735 cm^{-1}; δ 1.67 and 1.93 (ABq, *J* 9.0 Hz, 7-H_2), 3.34 (s, 3-H), 3.57 (br.s, 4-H),

4.14 (br.s, 1-H), 4.67 (d, *J* 5.0 Hz, OCH_2), 5.17-5.54 (2H, m, $C=CH_2$) 5.74-6.21 (2H, m, 5-H and $C\underline{H}=CH_2$) and 6.49 (dd, *J* 2.5 and 5.5 Hz, 6-H), and a mixture of both isomers (281) (0.32g). The pure esters (281) were obtained in a combined yield of 90%. The mixture of *endo*- and *exo*-esters were distilled (Kugelrohr) b p. 70-75°C (0 03mbar) (Found: C, 61.17; H 6.34; S, 16.29. $C_{10}H_{12}O_2S$ requires C, 61.19; H, 6.17; S, 16.34%).

Preparation of 3-Butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (287)

The carboxylic acids (225) (1.05g 6.7mmol) (*endo:exo*, 1:1.3) in dichloromethane (6ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (1.24g, 90% purity, 7.0mmol) at room temperature and the reaction was kept dry by a guard tube containing silica gel. Then 3-buten-1-ol (0.48g, 5.8mmol) and n-butyl-lithium (1.58M, 0.6ml) in dichloromethane (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (40ml), washed with aqueous sodium carbonate (0.5M, 20ml), water (2 x 20ml), dried (Na_2SO_4) and evaporated to dryness to afford a dark brown oil (1.23g). The crude product was chromatographed on a silica (HF_{254}) column, eluted with chloroform-light petroleum (1:4), followed by chloroform-light petroleum (1:1) to afford 3-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-5-endo-*carboxylate* (287a) as a colourless liquid (0.23g) (Found: *m/z* 210.0710. $C_{11}H_{14}O_2S$ requires M^+, 210.0714); ν_{max} (liquid film) 1735 cm^{-1}; δ 1.58-1.93 (m, 7-H_2), 2.38 (br.q, *J* 6.6 Hz, $C=CCH_2$), 3.28 (br.s, 4-H), 4.11 (br.s, 1-H), 4.14 (t, *J* 6.0 Hz, OCH_2), 4.44 (d, *J* 3.5 Hz, 3-H), 5.10 (br.d, *J* 11.0 Hz, $CH=C\underline{H}H$), 5.13 (br.d, *J* 17.0 Hz, $CH=CH\underline{H}$), 5.57-6.12 (m, $C\underline{H}=CH_2$), 5.89 (dd, *J* 2.5 and 5.0 Hz, 5-H), and 6.48 (dd, *J* 3.5 and 5.0 Hz, 6-H), and 3-*butenyl*

2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (287b) as a colourless liquid (0.30g) (Found: *m/z* 210.0707. $C_{11}H_{14}O_2S$ requires M^+ 210.0714); ν_{max} (liquid film) 1732 cm^{-1}; δ 1.67 and 1.93 (ABq, *J* 9.0 Hz, 7-H_2), 2.14 (br.q, *J* 7.0 Hz, C=CCH_2), 3.31 (s, 3-H), 3.56 (br.s, 4-H), 4.13 (br.s, 1-H), 4.23 (t, *J* 6.8 Hz, OCH_2), 5.11 (br.d, *J* 11.0 Hz, CH=C$\underline{H}$H), 5.14 (br.d, *J* 18.0 Hz, CH=CH$\underline{H}$), 5.60-6.10 (2H, m, 5-H and C$\underline{H}$=CH_2) and 6.40 (dd, *J* 2.5 and 5.5 Hz, 6-H), and a mixture of *endo*- and *exo*-isomers (0.60g). The pure esters (287) were obtained in a combined yield of 80%.

Preparation of 4-Pentenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (290)

The carboxylic acids (225) (0.93g, 6.0mmol) (*endo:exo*, 1:1) in dichloromethane (CH_2Cl_2) (10ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (1.24g, 75% purity, 6.3mmol) at room temperature and the reaction was kept dry by a guard tube containing silica gel. Then 4-penten-1-ol (0.52g, 6.0mmol) and n-butyl-lithium in CH_2Cl_2 (2ml) was added. Stirring was continued for 12h and the reaction mixture was diluted with CH_2Cl_2 (40ml), washed with aqueous sodium carbonate (0.5M, 20ml), water (2 x 20ml), dried (Na_2SO_4) and evaporated to give a dark brown oil (1.28g). The crude product was chromatographed on a silica (HF_{254}) column, eluted with chloroform-light petroleum (20-50%), to afford 4-*pentenyl* 2-*thiabicyclo*[2.2.1] *hept*-5-*ene*-3-endo-*carboxylate* (290a) (0.38g) as colourless liquid (Found: *m/z* 224.0868. $C_{12}H_{16}O_2S$ requires M^+, 224.0870); ν_{max} 1732 cm^{-1}; δ 1.61-1.98 (4H, m, 7-H_2 and $OCH_2C\underline{H}_2$), 2.16 (br.q, *J* 6.6 Hz, C=CCH_2), 3.79 (br.s, 4-H), 4.00-4.34 (m, 1-H), 4.12 (br.t, *J* 6.6 Hz, OCH_2), 4.46 (d, *J* 3.6 Hz, 3-H), 5.02

(br.d, *J* 10.4 Hz, CH=C<u>H</u>H), 5.07 (br.d, *J* 18.0 Hz, CH=CH<u>H</u>), 5.61-6.14 (m, C<u>H</u>=CH_2), 5.92 (dd, *J* 2.5 and 5.0 Hz, 5-H), and 6.51 (dd, *J* 3.0 and 5.0 Hz, 6-H), and 4-*pentenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (290b) as colourless liquid (0.39g) (Found: *m/z* 224.0887. $C_{14}H_{16}O_2S$ requires M^+, 224.0870); ν_{max} (liquid film) 1735 cm^{-1}; δ 1.57-2.02 (m, 7-H_2 and $OCH_2C\underline{H}_2$), 2.19 (br.q, *J* 6.6 Hz, C=CCH_2), 3.32 (s, 3-H), 3.56 (br.d, *J* 3.0 Hz, 4-H), 4.04-4.37 (m, 1-H), 4.20 (t, *J* 6.0 Hz, OCH_2), 5.02 (dd, *J* 2.0 and 9.0 Hz, CH=C<u>H</u>H), 5.07 (dd, *J* 2.0 and 18.0 Hz, CH=CH<u>H</u>), 5.62-6.10 (2H, m, 5-H and C<u>H</u>=CH_2) and 6.41 (dd, *J* 2.5 and 5.5 Hz, 6-H). The pure esters (290) were obtained in a combined yield of 57%.

<u>Preparation of 5-Hexenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (295)</u>

The carboxylic acids (225) (0.80g, 5.1mmol) (*endo:exo*, 7:3) in dichloromethane (8ml) was stirred for 2h with *N'N'*-carbonyldiimidazole (1.04g, 76% purity, 0.52mmol) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 5-hexen-1-ol (0.52g, 5.2mmol) and n-butnyl-lithium (1.58M, 0.4ml) in dichloromethane (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (40ml), washed with aqueous sodium carbonate (0.5M, 20ml), water (2 x 20ml), dried (Na_2SO_4) and evaporated to dryness. ^1H n.m.r. spectrum of the crude product showed it contained 5-hexenyl imidazole-*N*-carboxylate (294) (*ca.* 7%). The crude product was then chromatographed on a SiO_2 (HF_{254}) column, eluted with chloroform-light petroleum (10-50%), to give 5-*hexenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (295a) (0.46g) as colourless oil; ν_{max}

(liquid film) 1733 cm^{-1}; δ 1.26-1.88 (6H, m, 7-H_2 and $OCH_2(C\underline{H}_2)_2$), 2.10 (br.q, *J* 6.6 Hz, $C{=}CCH_2$), 3.79 (m, 4-H), 4.03-4.24 (m, 1-H), 4.11 (t, *J* 6.0 Hz, OCH_2), 4.46 (d, *J* 3.5 Hz, 3-H), 4.99 (br.d, *J* 11.0 Hz, CH=C<u>H</u>H), 5.03 (br.d, *J* 19.0 Hz, CH=CH<u>H</u>), 5.60-6.09 (2H, m, 5-H and C<u>H</u>=CH_2) and 6.51 (dd, *J* 3.0 and 5.5 Hz, 6-H), and 5-*hexenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-**exo**-*carboxylate* (295b) (0.50g) (Found: *m/z* 238.1034. $C_{13}H_{18}O_2S$ requires M^+, 238.1027); ν_{max} 1734 cm^{-1}; δ 1.20-2.32 (8H, m, 7-H_2 and $OCH_2(C\underline{H}_2)_3$), 3.32 (s, 3-H), 3.57 (br.d, *J* 2.0 Hz, 4-H), 4.06-4.30 (m, 1-H), 4.20 (t, *J* 6.0 Hz, OCH_2), 5.00 (br.d, *J* 10.0 Hz, CH=C<u>H</u>H), 5.04 (br.d, *J* 18.5 Hz, CH=CH<u>H</u>), 5.60-6.10 (2H, m, 5-H and C<u>H</u>=CH_2) and 6.42 (dd, *J* 2.5 and 5.5 Hz, 6-H), The pure esters (295) were obtained in a combined yield of 79%.

<u>Preparation of 3,4-Dimethylanisole</u>

3,4-Dimethylphenol (24.9g, 0.2mol), methyl iodide (31.86g, 0.26mol) and potassium carbonate (33.8g, 0.24mol) in acetone (150ml) were refluxed together with stirring for 7h. The reaction mixture was filtered and was evaporated under reduced pressure with slight heating. The residual liquid was diluted with ether (200ml), washed successively with ammonia (35%, 5ml), in water (50ml), and water (3 x 50ml), and dried (Na_2SO_4), and evaporated to afford a yellow liquid (25.6g). The liquid was distilled to afford pure 3,4-dimethylanisole (23.2g, 0.17mol, 85%), b.p. 200-201°C (lit.[80] b.p. 200-201°C) δ 2.16 (s, CH_3), 2.21 (s, CH_3), 3.74 (s, OCH_3), 6.52-6.74 (m, 6-aryl-H), 6.66 (br.s, 2-aryl-H), and 6.98 (br.d, 4-aryl-H). These values are in accord with measurement taken from the relevant spectrum (1.843A) in the 'Aldrich Library' of N.M.R. Spectra[81] .

Preparation of 1-Methoxy -4,5-dimethylcyclohexa-1,4-diene

Freshly distilled ammonia (*ca.* 150ml) was kept in liquid form in a three-necked round bottom flask, fitted with a condenser tube designed for acetone-carbon dioxide cooling and immersed in an acetone-carbon dioxide bath. The reaction mixture was kept dry by a guard tube containing potassium hydroxide pellets. After the addition of 3,4-dimethylanisole (6g, 44mmol) and methanol (8g), sodium (7g, 0.3mol) was added in small portions over 0.5h with stirring. A dark-blue sludge was formed. Stirring and cooling were continued for 2h. The apparatus was left open overnight in order to allow the ammonia to evaporate. Sodium residues were destroyed by ice-water mixture (10ml) and the mixture was extracted with ether (3 x 100ml). The combined ethereal layers were dried (K_2CO_3) and evaporated to afford a yellow liquid (4.92g). ^1H n.m.r. spectrum showed the liquid was composed of a mixture of the Birch reduction product (80%); δ 1.63 (br.s, 2 x CH_3), 2.66 and 2.68 (2 x br.s, $CH_2C{=}CCH_2$), 3.54 (s, OCH_3), and 4.60 (m, C=CH), and the starting anisole (20%).

Preparation of 3,4-Dimethylcyclohex-3-en-1-one

A crude product from the foregoing Birch reduction (3.5g), consisting mainly of 1-methoxy-4,5-dimethylcyclohexa-1,4-diene (*ca.* 80%) was shaken with a saturated solution of sodium hydrogen sulphite in water (10ml), prepared by dissolving sodium metabisulphite (15g) in water (15ml). After 11h, the reaction mixture was diluted with ether (20ml) and left standing at room temperature for 15min. The mixture was filtered and the filter cake was washed with ether (60ml). The bisulphite compound was stirred with sodium carbonate (3.20g) in ether-water

(3:1) (40ml). Stirring was continued for 0.5h and the mixture was filtered and the filtrate was extracted with ether (3 x 20ml). The combined ethereal layers were dried (Na_2SO_4), and evaporated to afford 3,4-dimethylcyclohex-3-en-1-one[82] (1.20g); ν_{max} ($CHCl_3$) 1710cm^{-1}; δ 1.69 and 1.73 (2 x br.s, 2 x CH_3), 2.44 (m, CH_2CH_2), and 2.81 (m, $COCH_2$).

Preparation of 3,4-Dimethylcyclohex-3-en-1-ol

3,4-Dimethylcyclohex-3-en-1-one (0.48g) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.44g) in dried (Na) ether (10ml) in an ice-bath under nitrogen. After the last addition of the ketone, the mixture was stirred for 1h at room temperature. Ice-water (10ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was extracted with ether (4 x 50ml). The combined ethereal layers were washed with brine (20ml), dried (Na_2SO_4) and evaporated under reduced pressure to afford a slightly yellow liquid (0.46g). The liquid was distilled to afford pure 3,4-dimethylcyclohex-3-en-1-ol (0.33g, 68%), b.p. 100-107^{o} (18mmHg); δ 1.63 (br.s, 2 x CH_3), 1.45-2.00 [m, 3 x CH_2 and OH (exch. with D_2O)], and 3.80-4.15 (m, 1-H).

Preparation of 3,4-Dimethyl-3-cyclohexenyl 2-Thiabicyclo[2.2.1] hept-5-ene-3-carboxylate (297)

The carboxylic acids (225) (0.16g, 1.0mmol) in dichloromethane (CH_2Cl_2) (4ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.19g, 81% purity, 1.05mol. equiv) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3,4-dimethyl-3-cyclohexen-1-ol. (0.13g, 0.97mmol) and n-butyl-lithium (1.58M, 0.1ml) in

CH_2Cl_2 (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with CH_2Cl_2 (30ml), washed with aqueous sodium carbonate (0.5M, 10ml), water (2 x 10ml) and evaporated to dryness. The crude product was chromatographed on preparative SiO_2 plates to give 3,4-*dimethyl*-3-*cyclohexenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (297a) as a colourless oil (0.08g) (Found: *m/z* 264.1157. $C_{15}H_{20}O_2S$ requires M^+ 204.1184); ν_{max} (liquid film) 1730 cm^{-1}; δ 1.52-2.64 (6H, m, $(C\underline{H}_2)_2C{=}CC\underline{H}_2$), 1.63 (br.s, 2 x CH_3), 3.79 (m, 4-H), 4.10 (br.s, 1-H), 4.44 (d, *J* 3.2 Hz, 3-H), 4.73-5.20 (br.s, OCH), 5.88 (dd, *J* 3.0 and 5.0 Hz, 5-H) and 6.48 (dd, 3.5 and 5.0 Hz, 6-H) and 3,4-*dimethyl*-3-*cyclohexenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (297b) as a colourless oil (0.12g); ν_{max} (liquid film) 1729 cm^{-1}; δ 1.50-2.60 (6H, m, $(C\underline{H}_2)_2C{=}CC\underline{H}_2$), 1.62 (br.s, 2 x CH_3), 3.30 (s, 3-H), 3.54 (m, 4-H), 4.12 (m, 1-H), 4.86-5.34 (br.s, OCH), 5.94 (dd, *J* 3.0 and 5.0 Hz, 5-H), and 6.39 (dd, *J* 3.0 and 5.0 Hz, 6-H). The pure esters (297) were obtained in a combined yields of 74%.

Preparation of 3-Methyl-3-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (298)

The carboxylic acids (225) (0.65g, 4.2mmol) in dichloromethane (5ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (0.84g, 80% purity, 1.05mol. equiv.) at room temperature and the reaction mixture was kept dry by a guard tube containing silica gel. Then 3-methyl-3-buten-1-ol (0.36g, 4.2mmol) and n-butyl-lithium (1.58M, 0.4ml) in dichloromethane (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (30ml), washed with aqueous sodium carbonate (0.5M, 10ml), water (2 x 20ml), dried (Na_2SO_4)

and evaporated. The crude product was chromatographed on a SiO_2 column, eluted with chloroform-light petroleum (10-50%), to give 3-*methyl*-3-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (298a) as a yellow oil (0.15g) (Found: *m/z* 224.0876. $C_{12}H_{16}O_2S$ requires M^+ 224.0871); ν_{max} (liquid film) 1734 cm^{-1}; δ 1.67 (m, 7-H_2), 1.79 (br.s, CH_3), 2.35 (br.t, *J* 7 Hz, C=CCH_2), 3.78 (m, 4-H), 4.11 (m, 1-H), 4.22 (br.t, *J* 7 Hz, OCH_2), 4.44 (d, *J* 3.5 Hz, 3-H), 4.78 and 4.85 (2 x br.s, C=CH_2), 5.91 (dd, *J* 3.5 and 5.5 Hz, 5-H), and 6.49 (dd *J* 3.5 and 5.5 Hz, 6-H), and 3-*methyl*-3-*butenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (298b) as a yellow oil (0.48g) (Found: *m/z* 224.0874. $C_{12}H_{16}O_2S$ requires M^+ 224.0871); ν_{max} (liquid film) 1732 cm^{-1}; δ 1.70 and 1.96 (ABq, *J* 9.0 Hz, 7-H_2), 1.77 (br.s, CH_3), 2.40 (br.t, *J* 7.5 Hz, C=CCH_2), 3.32 (s, 3-H), 3.58 (br.s, 4-H), 4.14 (br.s, 1-H), 4.30 (t, *J* 7.0 Hz, OCH_2), 4.74-4.94 (m, C=CH_2), 5.96 (dd, *J* 3.5 and 5.5 Hz, 5-H) and 6.41 (dd, *J* 2.5 and 5.5 Hz, 6-H), and a mixture of both isomers (298) (0.10g). The pure esters (298) were obtained in a combined yield of 77%.

Preparation of 3-Phenyl-2-propenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (299)

The carboxylic acids (225) (0.99g, 6.3mmol) (*endo:exo*, 1:3) in dichloromethane (CH_2Cl_2) (5ml) was stirred for 3h with *N,N'*-carbonyldiimidazole (226) (1.22g, 84%, 1.05mol.equiv.) at room temperature and the reaction mixture was kept dry by a guard tube contianing silica gel. Then 3-phenyl-2-propen-1-ol (0.85g, 6.6mmol) and n-butyl-lithium (1.58M, 0.6ml) in CH_2Cl_2 (2ml) were added. Stirring was continued for 12h. The reaction mixture was diluted with dichloromethane (30ml), washed with

aqueous sodium carbonate (0.5M, 20ml), water (2 x 20ml), dried (Na_2SO_4), and evaporated to dryness. The crude mixture was then chromatographed on a column (SiO_2), eluted with chloroform-light petroleum (2:8), then followed by chloroform-light petroleum (5:5) to give 3-*phenyl*-2-*propenyl* 2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-endo-*carboxylate* (299a) as a yellow oil (0.22g) (Found: *m/z* 272.0864. $C_{16}H_{16}O_2S$ requires M^+ 272.0871); ν_{max} (liquid film) 1738 cm^{-1}; δ 1.65 (m, 7-H_2), 3.80 (m, 4-H), 4.10 (br.s, 1-H), 4.49 (d, *J* 3.5 Hz, 3-H), 4.73 (d, *J* 6.0 Hz,)$CH_2)_3$ 5.92 (dd, *J* 2.5 and 5.5 Hz, 5-H). 6.24 (dt, *J* 6.0 and 16.0 Hz, C=C<u>H</u>CH_2O), 6.50 (dd, *J* 3.5 and 5.5 Hz, 6-H), 6.67 (d, *J* 16.5 Hz, C=C<u>H</u>Ph), and 7.20-7.52 (5H, m, Ar-H) and 3-*phenyl*-2-*propenyl* 2-*thia-bicyclo*[2.2.1]*hept*-5-*ene*-3-exo-*carboxylate* (299b) as a yellow oil (0.71g, (Found: *m/z* 272.0858. $C_{16}H_{16}O_2S$ requires M^+ 272.0871); ν_{max} (liquid film) 1733 cm^{-1}; δ 1.68 and 1.95 (ABq, *J* 10.0 Hz, 7-H_2), 3.35 (s, 3-H), 3.59 (m, 4-H), 4.13 (br.s, 1-H), 4.82 (d, *J* 6.0 Hz, OCH_2), 5.96 (dd, *J* 2.5 and 5.5 Hz, 5-H), 6.29 (dt, *J* 6.0 and 17.0 Hz, C=C<u>H</u>CH_2O), 6.39 (dd, *J* 3.5 and 5.5 Hz, 6-H), 6.70 (d, *J* 17.0 Hz, C=C<u>H</u>Ph), and 7.20-7.52 (5H, m, Ar-H), and a mixture of both isomers (0.16g). The pure esters (299) were obtained in a total yield of 60%.

Preparation of 9,10-Dihydro-12-hydroxymethyl-10,9-thiaethano-anthracene (304)

The carboxylic acid (234a) (0.64g, 2.4mmol) in dried (Na) tetrahydrofuran (THF) (5ml) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.16g) in dried (Na) THF (15ml) in an ice-bath under nitrogen. After the addition of the acid, the reaction mixture was allowed to warm up to room temperature and stirring was continued for 2h. Ice-water (20ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was poured into a mixture of ice (20g) and 10% sulphuric acid (30ml). The mixture was extracted with ether (4 x 50ml) and the combined ethereal layers were washed with brine (30ml), dried ($MgSO_4$) and evaporated under reduced pressure with heating. The residual solid (0.64g) was chromatographed on a column (SiO_2), eluted with chloroform-light petroleum (20-100%), to give 9,10-*dihydro*-12-*hydroxymethyl*-10,9-*thiaethano-anthracene* (304) (0.51g, 2.0mmol, 83%) m.p. 54-57°C (from dichloromethane) (Found: *m/z* 254.0769. $C_{16}H_{14}OS$ requires M^+ 254.0748); ν_{max} 3620-2500, 1470 and 1455 cm^{-1}; δ 1.66 (s, OH), 3.07-3.70 (3H, m, 11-H and CH_2), 4.81 (br.s, 9-H), 5.03 (s, 10-H), 7.00-7.52 (8H, m, Ar-H).

Preparation of 3,6-Dihydro-4,5-dimethyl-2-hydroxymethyl-2H-thiin (307)

The ethyl ester (314) (0.73g, 3.7mmol), prepared from a literature method[20], in dried (Na) ether (5ml) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.28g) in dried (Na) ether (10ml) in an ice-bath under nitrogen. After the addition of the ester, the reaction mixture was allowed to warm up to room temperature and stirring was continued

for 0.5h. Ice-water (20ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was extracted with ether (4 x 30ml). The combined ethereal layers were washed with brine (20ml), dried ($MgSO_4$) and evaporated to dryness to afford 3,6-*dihydro*-4,5-*dimethyl*-2-*hydroxymethyl*-2H-*thiin* (307) as a yellow oil; δ 1.67 (br.s, 2 x CH_3), 2.02-2.33 (m, 3-H_2), 2.82-3.22 (3H, m, 6-H_2 and 2-H) and 3.61 (d, *J* 7.0 Hz, OCH_2).

Thermal Conversion of the Anthracene Adduct (304) into the 3,3-Dimethyl-1,3-butadiene Adduct (307)

2,3-Dimethylbutadiene (0.36g, 10mol. equiv.) was added to the anthracene adduct (304) (0.11g, 0.43mmol) in anhydrous toluene (10ml) and the mixture was heated under reflux. After certain periods of time, solvents were removed under reduced pressure and the extent of transfer was determined by ^1H n.m.r. spectroscopy (Table 5).

Table 5

Time/h	extent of transfer /%
4	16
29.5	40
62.5	94
80	94

Preparation of 3-hydroxymethyl-2-thiabicyclo[2.2.1]hept-5-ene (301)

The ethyl ester (77) (0.75g, 3.4mmol) (*endo:exo*, 7:3) in dried (Na) ether (10ml) was added slowly to a stirring suspension of lithium aluminium hydride ($LiAlH_4$) (0.51g) in dired (Na) ether (10ml) in an ice-bath under nitrogen. After the last addition of the ester, the reaction mixture was allowed to warm

up to room temperature and stirring was continued for 1h. Ice-water (10ml) was added slowly to destroy the excess $LiAlH_4$ and the mixture was extracted with ether (4 x 30ml), washed with brine (20ml), dried ($MgSO_4$) and evaporated to dryness to afford 3-*hydroxymethyl*-2-*thiabicyclo*[2.2.1]*hept*-5-*ene* (301) as a colourless oil (0.52g, 3.3mmol, 97%), b.p. 80-90° (0.1-0.2mmHg, Kugelrohr) (Found: C, 59.13; H, 7.28; S, 22.45. $C_7H_{10}OS$ requires C, 59.12; H, 7.09; S, 22.55%) (Found: *m/z* 142.0450. $C_7H_{10}OS$ requires M^+ 142.0453); ν_{max} ($CHCl_3$) 3618 cm^{-1}. ^1H n.m.r. spectrum of the distillate showed unchanged *endo:exo* ratio (*ca.* 7:3). Separate *endo*-(77a) and *exo*-esters (77b) were reduced in the same way to form the *endo*-alcohol (301a) δ 1.48-1.80 (m, 7-H_2), 2.71 (s, OH, exch. with D_2O), 3.20-3.70 (3H, m, OCH_2 and 4-H), 3.80-4.10 (m, 3-H), 3.97 (br.s, 1-H), 5.77 (dd, *J* 3.5 and 5.5 Hz, 5-H), 6.36 (dd, *J* 3.3 and 5.8 Hz, 6-H), and the *exo*-alcohol (301b) δ 1.58 (br.s, 7-H_2), 2.30-3.24 (br.s, OH, exch. with D_2O), 2.94 (t, *J* 7.0 Hz, 3-H), 3.27 (br.s, 4-H), 4.65-4.10 (m, OCH_2), 4.02 (br.s, 1-H), 5.95 (dd, *J* 3.5 and 5.2 Hz, 5-H), and 6.30 (dd, *J* 2.8 and 6.0 Hz, 6-H) respectively.

Preparation of 9,10-Dihydro-12-(3-methyl-2-butenoyloxymethane)-10,9-thiaethanoenthrancene (310)

Dimethylacryloyl chloride (309) (0.70g, 6.0mmol) was added dropwise to a stirring solution of the alcohol (316) (0.30g, 1.2 mmol) and 2,4,6-trimethylpyridine (0.30g, 2.4mmol) in dried (Na) ether (8ml) in an ice-bath. Then the reaction mixture was allowed to warm up to room temperature and stirring was continued for 80h. The reaction mixture was diluted with dichloromethane (50ml), washed with water (20ml), dilute

hydrochloric acid (10ml), water (20ml), aqueous sodium carbonate (0.5M, 2 x 20ml), and water (2 x 20ml), and dried (Na_2SO_4) and evaporated to dryness. The crude product (0.31g) was chromatographed on preparative SiO_2 plates to afford 9,10-*hydro*-12-(3-*methyl*-2-*butenoyloxymethane*)-10,9-*thiaethano*-*anthracene* (310) (0.20g, 6.0mmol, 50%) as white solids, m.p. 107-108°C (from dichloromethane) (Found: *m/z* 336.1179. $C_{21}H_{20}O_2S$ requires M^+ 336.1184); ν_{max} 1711 and 1644 cm^{-1}; δ 1,90 and 2.16 (2 x br.s, 2 x CH_3), 3.47-4.12 (3H, m, CH_2 and 12-H), 4.73 (br.s, 9-H), 5.04 (br.s, 10-H), 5.77 (m, C=CH), and 7.06-7.48 (8H, m, Ar-H).

Thermolysis of 9,10-Dihydro-12-(3-methyl-2-butenoyloxymethane)-10,9-thiaethanoanthracene (310)

The anthracene cycloadduct (310) (0.057g, 0.17mmol) was heated under reflux in anhydrous toluene (5.3ml) under nitrogen for 4h. Evaporation of the solution to dryness and ^1H n.m.r. spectrum of the crude product showed the decomposition of the starting adduct (310) was *ca.* 14%.

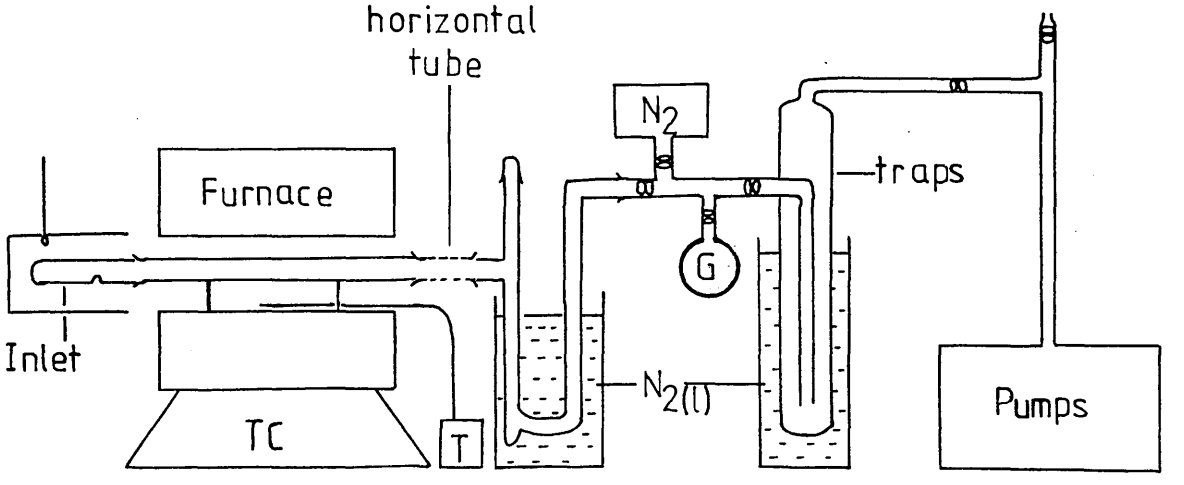
Preparation of 3-(3-Methyl-2-butenoyloxymethane)-2-thiabicyclo [2.2.1]hept-5-ene (314)

Dimethylacryloyl chloride (309) (0.29g, 2.4mmol) was added dropwise to a stirring solution of the alcohol (301) (0.17g, 1.2mmol) (*endo:exo*, 7:3) in pyridine (5ml) in an ice bath. Then the reaction was allowed to warm up to room temperature and stirring was continued for overnight. Water (20ml) was added to the reaction mixture and stirring was continued for 3h. The mixture was diluted with dichloromethane (150ml), washed with hydrochloric acid (2M, 40ml), water (30ml), aqueous sodium

hydroxide (1M, 30ml), water (2 x 20ml), and dried ($MgSO_4$) and evaporated to dryness to afford a dark brown oil. The crude product was chromatographed on preparative SiO_2 plates to afford 3-(3-*methyl*-2-*butenoyloxymethane*)-2-*thiabicyclo*[2.2.1] *hept*-5-*ene* (314) (*endo:exo*, 7:3) as a colourless oil (0.12g, 0.5mmol, 45%) (Found: *m/z* 224.8711. $C_{12}H_{16}O_2S$ requires M^+ 224.0865); ν_{max} ($CHCl_3$) 1711 and 1648 cm^{-1}; δ 1.47-1.78 (m, 7-H_2), 1.87 and 2.14 (2 x br.s, 2 x Me), 3.01 (dd, *J* 4.3 and 6.3 Hz, *exo*-3-H), 3.26 (br.s, *exo*-4-H), 3.47 (br.s, *endo*-4-H), 3.87 (dd, *J* 10.5 and 12.5 Hz, OCH_2), 3.93 (br.s, *endo*-1-H), 4.00 (br.s, *exo*-1-H), 4.34 (t, *J* 7.8 Hz, *endo*-3-H), 5.79 (dd, *J* 3.5 and 5.5 Hz, *endo*-5-H), 5.91 (dd, *J* 3.5 and 5.5 Hz, *exo*-5-H), 6.31 (dd, *J* 3.5 and 6.0 Hz, *exo*-6-H) and 6.38 (dd, *J* 3.0 and 5.5 Hz, *endo*-6-H).

Flash Vacuum Pyrolysis (FVP)

The apparatus used was based on the design of W.D. Crow, Australian National University. Similar apparatus is illustrated in the recent monograph by Brown[83]. The design was also adopted by Dr. Ian Gosney, Edinburgh University for his flash vacuum pyrolysis studies. Dr. Gosney kindly provided details for the construction of our apparatus.



G:Gauges T:Thermocouple

TC:Temperature control unit

Scheme 93

The essential features of the apparatus in our laboratory are shown in Scheme 93. The sample was volatilized from a horizontal inlet tube, heated in a Buchi Kugelrohr oven, through a 2.5 x 55cm silica tube, with the exception of the two experiments carried out in Dr. Gosney's laboratory using a 2.5 x 30cm silica tube. The silica tube was heated at temperatures in the range 430-600^{o}C by a laboratory tube furnace and the temperature was measured by a NiCr/NiAl (Type K) thermocouple situated at the centre of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. During

the thermolysis of anthracene cycloadducts, anthracene crystallized out in a short horizontal tube inserted between the furnace tube and the U-shaped trap as shown in Scheme 93, and volatile products were condensed in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure 10^{-2}-10^{-3} mmHg by an Edwards Model E2M8 rotary vacuum pump or at a pressure 10^{-4}-10^{-5} mmHg with the additional aid of a mercury diffusion pump. The pressure was measured by a Pirani gauge (1 atm-10^{-3} mmHg) or a Penning gauge (10^{-3}-10^{-7} mmHg), both situated between the U-shaped trap and the trap protecting the pump. The contact time in the hot zone was estimated to be in the range of 1-10 milliseconds at a pressure 10^{-2}-10^{-3} mmHg and in the range of 10-100 microseconds at a pressure of 10^{-4}-10^{-5} mmHg.

The pyrolysis conditions for each experiment are quoted as follows: Kugelrohr oven temperature, average pressure during pyrolysis, and furnace temperature.

Pyrolyses were generally carried out using 80-450mg of material. After the pyrolysis, the system was isolated from the pump and filled with nitrogen gas. The products were then dissolved out of the trap in dichloromethane and the solution was evaporated under reduced pressure with slight heating to afford the products.

FVP (in Edinburgh) of 3-Methyl-2-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (228b)

The cycloadduct (228b) (0.11g) was volatilized (80°C, 8 x 10^{-3} mmHg) through the FVP oven (silica tube, 2.5 x 30cm) maintained at 600°C. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (10ml). Evaporation of the solution to dryness afforded pure 3-*isopropenyl*-2-*mercaptobutan*-4-*olide*(231) (*cis:trans*, 1:3) as a colourless oil (73mg, 0.46mmol, 95%). The ^{1}H n.m.r. spectrum was the same as that of a sample prepared earlier.

FVP (in Edinburgh) of 4-Methyl-3-pentenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (259b)

The cycloadduct (259b) (84mg) was volatilized (100°C, 8 x 10^{-3} mmHg) through the FVP oven (silica tube, 2.5 x 30cm) at 600°C. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (10ml). Evaporation of the solution to dryness afforded 3-*isopropenyl*-2-*mercaptopentan*-5-*olide* (241) (*cis:trans*, 1;9) as a yellow oil (37mg, 0.22mmol, 62%) (Found: *m/z* 172.0559. $C_8H_{12}O_2S$ requires M^+, 172.0559. $C_8H_{12}O_2S$ requires 172.0558); ν_{max} ($CHCl_3$) 1730 cm^{-1}; δ 1.74 (br.s, *trans*-CH_3), 2.52 (d, *J* 3.5 Hz, *trans*-SH, exch. with D_2O), 3.82 (dd, *J* 3.5 and 9.5 Hz, *trans*-2-H), 4.38 (t, *J* 5.5 Hz, *trans*-5-CH_2) and 4.88 and 4.94 (2 x br.s, *trans*-C=CH_2).

FVP of 3-Methyl-2-butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (228)

The cycloadducts (228) (*endo:exo*, 7:3) (0.11g) were volatilized (80°C, 0.004 mmHg) through the FVP oven (see general methods) maintained at 600°C during a period of 12 min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). Evaporation to dryness afforded pure 3-*isopropenyl*-2-*mercapto*-*butan*-4-*olide* (231) (*cis:trans*, 1:2) as a colourless oil (75mg, 0.47mmol, 100%). The ^{1}H n.m.r. spectrum was the same as that of a sample prepared earlier.

FVP of 3-Methyl-2-butenyl 9,10-Dihydro-10,9-thiaethanoanthracene-12-carboxylate (233a)

The cycloadduct (233a) (0.40g), which was deposited on celite (0.1g) by evaporation of a dichloromethane (5ml) solution, was volatilized (180°C, 2 x 10^{-5} mmHg) through the FVP oven at 580°C during a period of 30min. Anthracene (0.23g) crystallized on the walls of the horizontal tube between the furnace and the trap. Volatile products were condensed in a trap cooled in liquid nitrogen and the products were dissolved out of the trap in dichloromethane (30ml). Evaporation of the solution to dryness afforded a yellow oil (0.15g, 0.95mmol, 80%). The ^{1}H n.m.r. spectrum showed that the crude product contained predominantly 3-*isopropenyl*-2-*mercaptobutan*-4-*olide* (231) (*cis:trans*, 2:3) with traces of impurities.

A similar FVP experiment was carried out. The cycloadduct (233a) (0.18g), which was deposited on celite (2.00g) by evaporation of a dichloromethane (5ml) solution, was volatilized (180°C, 3 x 10^{-5} mmHg) through the FVP oven at 600°C during a

period of 30min. The ^{1}H n.m.r. spectrum of the volatile products (0.083g) showed the presence predominantly of 3-*isopropenyl*-2-*mercaptobutan*-4-*olide* (231) (94%), anthracene (6%), and traces of impurities.

FVP of 4-Methyl-3-pentenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (259b)

The cycloadduct (259b) (0.16g) was volatilized (110°C, 3 x 10^{-3} mmHg) through the FVP oven at 500°C during a period of 10min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of a trap in dichloromethane (30ml). The solution was evaporated to afford 3-*isopropenyl*-2-*mercaptopentan*-5-*olide* (241) (*cis:trans*, 2:3) and traces of impurities as a colourless oil (0.11g, 0.64mmol, 99%); δ (200MHz) 1.68 (br.s, *cis*- and *trans*-CH_3), 1.73-2.25 (m, *cis*- and *trans*-4-CH_2), 1.99 (d, *J* 4.5 Hz, *cis*-SH), 2.42 (d, *J* 3.5 Hz, *trans*-SH), 2.55 (dt, *J* 9.9 and 5.8 Hz, *trans*-3-H), 2.82 (dt, *J* 5.0 and 10.5 Hz, *cis*-3-H), 3.75 (dd, *J* 3.5 and 9.9 Hz, *trans*-2-H), 3.98 (ddd, *J* 1.2, 4.8 and 5.0 Hz, *cis*-2-H), 4.23 (dt, *J* 11.5 and 4.1 Hz, *cis*-5-H), 4.32 (m, *trans*-5-CH_2), 4.46 (ddd, *J* 2.5, 5.8 and 11.4 Hz, *cis*-5-H), 4.74 and 4.93 (2 x br.s, *cis*-C=CH_2), and 4.81 and 4.88 (2 x br.s, *trans*-C=CH_2).

FVP of 2-Methyl-2-propenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (273b)

The cycloadduct (273b) (0.41g) was volatilized (80°C, 3 x 10^{-3} mmHg) through the FVP oven at 600°C during a period of 18 min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloro-

methane (30ml). The solution was evaporated to afford a yellow oil (0.15g 52%). The i.r. and ^{1}H n.m.r. spectra suggested that the crude product contained predominantly 2-*mercapto*-4-*methylene*-*pentan*-5-*olide* (276) and some impurities (Found: *m/z* 144; $C_6H_8O_2S$ requires M^+, 144.0245); ν_{max} ($CHCl_3$) 1726cm^{-1}; δ 2.42 (d, *J* 6.0 Hz, SH, exch. with D_2O), 3.92 (dt, *J* 5.5 and 7.5 Hz, 2-H), 4.88 (br.s, 5-H_2), and 5.04-5.27 (m, C=CH_2). The crude product was then chromatographed on a Chromatotron (ethyl acetate-light petroleum, 2:3). Four different fractions were collected but their ^{1}H n.m.r. spectra showed no signals for the lactone (276).

The foregoing experiment was repeated with the *exo*-cyclo-adduct (273b) (0.34g)(Kugelrohr oven temperature 80°C, pressure 3 x 10^{-3} mmHg, and furnace temperature 430°C). The ^{1}H n.m.r. spectrum of the crude product (0.17g, 73%) showed that a comparatively cleaner reaction had occurred, i.e. less impurities were formed. To facilitate purification, the crude product (0.17g) was treated with methyl iodide (1.7g, 0.012mol) under N_2 in anhydrous acetone saturated with potassium carbonate (4ml) for 4h at room temperature. The reaction mixture was then diluted with water (10ml), and extracted with dichloro-methane (3 x 20ml). The combined extracts were washed with water (10ml), dried (Na_2SO_4), and evaporated to afford a yellow oil (0.11g). The oil was chromatographed on preparative SiO_2 plates to afford 2-*methylthio*-4-*methylenepentan*-5-*olide* (277) (77mg, 0.49mmol, 30% from the cycloadduct) (Found: *m/z* 158.0397. $C_7H_{10}O_2S$ requires M^+, 158.0402); ν_{max} ($CHCl_3$) 1718 cm^{-1}; δ 2.24 (s, SCH_3), 2.70 (dd with fine splitting, *J* 4.5 and 17.0 Hz, 3-H), 3.07 (dd with fine splitting, *J* 6.0 and 17.0 Hz, 3-H'), 3.57 (dd, *J* 4.0 and 5.8 Hz, 2-H), 4.78 and 5.14 (ABq, *J* 15.0 Hz, 5-H_2), and 5.10 (m, C=CH_2).

FVP of *trans*-2-Butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (278)

The cycloadducts (278) (*endo:exo*, 13:16) (0.17g) was volatilized ($80^{o}C$, 4 x 10^{-3} mmHg) through the FVP oven at $600^{o}C$ during a period of 12min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The solution was evaporated to afford pure 3-*ethenyl*-2-*mercaptobutan*-4-*olide* (251) (*cis:trans*, *ca.* 1:1) as a colourless liquid (0.12g, 0.8mmol, 100%). The ^{1}H n.m.r. spectrum was the same as that of a sample prepared earlier.

FVP of 3 Methyl-2-cyclopentenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (279)

The cycloadducts(279) (0.18g) was volatilized ($80^{o}C$, 4 x 10^{-4} mmHg) through the FVP oven at $620^{o}C$ during a period of 15min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The solution was evaporated to give a yellow oil (0.07g, 54%). Both i.r. and ^{1}H n.m.r. spectra suggested either 4-*mercapto*-6-*methyl*-2-*oxa*-3-*oxobicyclo*[2.2.1]*oct*-6-*ene* (255) or 4-*mercapto*-6-*methylene*-2-*oxa*-3-*oxobicyclo*[2.2.1]*octane* (256) had been formed; ν_{max} ($CHCl_3$) 1760 and 1704 cm^{-1}; δ 2.19 (d, J 6.0 Hz, SH, exch. with D_2O), 3.96 (dd, J 6.0 and 9.0 Hz, 4-H), and 5.19 (dt, J 4.0 and 7.0 Hz, 1-H).

FVP of 2-Propenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-carboxylate (281)

The cycloadducts (281) (0.34g) (*endo:exo*, 3:2) was volatilized (100°C, 3 x 10^{-3} mmHg) through the FVP oven at 600°C during a period of 9 min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of a trap in dichloromethane (30ml). The solution was evaporated to afford a yellow oil with white solids (0.19g). The crude product was chromatographed on preparative SiO_2 plates to afford Δ^6-1,4-*oxathiepin*-2-*one* (282) as a yellow oil (0.08g, 0.61mmol, 36%) (Found: *m/z* 130.0091. $C_5H_6O_2S$ requires M^+, 130.0089); ν_{max} (liquid film) 1760 cm^{-1}; δ 3.39 (d, *J* 8.0 Hz, 5-H_2), 3.42 (s, 3-H_2), 5.65 (dt, *J* 6.0 and 8.0 Hz, 6-H), and 6.58 (d, *J* 6.0 Hz, 7-H).

Preparation of Methyl 6-oxo-3-thiahexanoate (284)

The *endo*-adduct of cyclopentadiene and 2-propenyl thioxo-acetate (281a) (0.14g, 0.71mmol) was volatilized (100°C, 5 x 10^{-3} mmHg), through the FVP oven at 450°C. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The solution was evaporated to afford a yellow oil with white solids (0.09g). The crude product was chromatographed on preparative SiO_2 plates to afford Δ^6-1,4-*oxathiepin*-2-*one* (282). The vinyl ester (282) in methanol (6ml) was treated with SiO_2 (1.3g) for 2h at room temperature. The reaction mixture was filtered and evaporated to dryness to afford *methyl 6-oxo-3-thiahexanoate* (284) (27mg, 0.17mmol, 23%) as a yellow oil (Found: m/z 162.0346. $C_6H_{10}O_3S$ requires M^+ 162.0316); ν_{max} (liquid film) 1732 cm^{-1}; δ 2.62-3.09 (4H, m, $S(CH_2)_2$), 3.27 (s, $COCH_2$), 3.77 (s, OCH_3),

and 9.76 (t, *J* 1.5 Hz, CHO).

FVP of 3-Butenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (287b)

The cycloadduct (287b) (0.18g) was volatilized (80°C, 6×10^{-4} mmHg) through the FVP oven at 600°C during a period of 8 min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The solution was evaporated to afford a yellow oil with white solids (0.10g). The solution was evaporated to afford a yellow oil with white solids (0.10g). The crude product was chromatographed using preparative SiO_2 plates to afford 6-*ethenyl* 1,4-*oxathiepan*-2-*one* (288) as a yellow oil (0.04g, 0.29mmol, 34%) (Found: *m/z* 144.0249. $C_6H_8O_2S$ requires M^+, 144.0245); ν_{max} ($CHCl_3$) 1738 cm^{-1}; δ 2.71-3.51 (m, 5-H_2), 3.25 and 3.60 (ABq, *J* 14.4 Hz, 3-H_2) 5.03 (dt, *J* 5.0 and 10.0 Hz, 6-H), 5.38 (br.d, *J* 10.0 Hz, *cis*-CH=C<u>H</u>), 5.48 (br.d, *J* 17.0 Hz, *trans*-CH=C<u>H</u>), and 5.97 (ddd, *J* 5.5, 10.0 and 17.0 Hz, C<u>H</u>=CH_2).

FVP of 4-Pentenyl 2-Thiabicyclo[2.2.1]hept-5-ene-3-*exo*-carboxylate (290b)

The cycloadduct (290b) (0.17g) was volatilized (100°C, 4×10^{-3} mmHg) through the FVP oven at 600°C during a period of 14 min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The solution was evaporated to afford a yellow oil with white solids (0.08g). The crude product was chromatographed on preparative SiO_2 plates to afford Δ^6-1,4-*oxathionin*-2-*one* (291) as a yellow oil (0.04g, 0.25mmol,

33%) (Found: *m/z* 158.0404. $C_7H_{10}O_2S$ requires M^+ 158.0402); ν_{max} (liquid film) 1745 cm^{-1}; δ 2.38 (dt, *J* 3.8 and 6.0 Hz, 8-H_2), 3.23 (s, 3-H_2), 3.36 (d, *J* 7.4 Hz, 5-H_2), 4.22 (t, *J* 5.0 Hz, 9-H_2), and 5.36-5.86 (m, 6-H and 7-H).

FVP of 5-Hexenyl 2-Thiabicyclo[2.2.1]bicyclohept-5-ene-3-*exo*-carboxylate (295b).

The cycloadduct (295b) (0.20g) was volatilized (100°C, 1 x 10^{-3} mmHg) through the FVP oven at 600°C during a period of 8 min. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The solution was evaporated to afford a yellow oil (0.12g). The crude product was chromatographed on preparative SiO_2 plates to afford a yellow oil (0.03g, 0.17mmol, 21%), which appeared as one spot on t.l.c. (R_f. = 0.31; chloroform-light petroleum, 6:4). The ^1H n.m.r. spectrum of the yellow oil suggested there was more than one compound present. The yellow oil was then chromatographed on preparative SiO_2 plates impregnated with $AgNO_3$[71] to give two compounds. Both the more polar compound (Found: *m/z* 172.0560. $C_8H_{12}O_2S$ requires M^+ 172.055%); ν_{max} (liquid film) 1739 cm^{-1}; and the less polar compound (Found: *m/z* 172.0557. $C_8H_{12}O_2S$ requires M^+ 172.0558); ν_{max} (liquid film) 1733 cm^{-1}; were obtained as yellow oils.

FVP of 3-(3-Methyl-2-butenoyloxymethane) 2-Thiabicyclo[2.2.1] hept-5-ene (214)

The cycloadducts (314) (0.25g) was volatilized (100°C, 3 x 10^{-3} mmHg) through the FVP oven at 600°C. The products were condensed in a trap cooled in liquid nitrogen and were dissolved out of the trap in dichloromethane (30ml). The

solution was evaporated to afford a yellow oil (0.08g, 45%); ν_{max} ($CHCl_3$) 1772 cm^{-1}. Attempted to purify the crude product on a Chromatotron (SiO_2; ethyl acetate-light petroleum, 3:7) resulted in intractable products.

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