The synthesis of sulphur-containing thromboxane analogues

Thesis

THE SYNTHESIS OF SULPHUR-CONTAINING THROMBOXANE ANALOGUES

A thesis submitted for the degree of

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by

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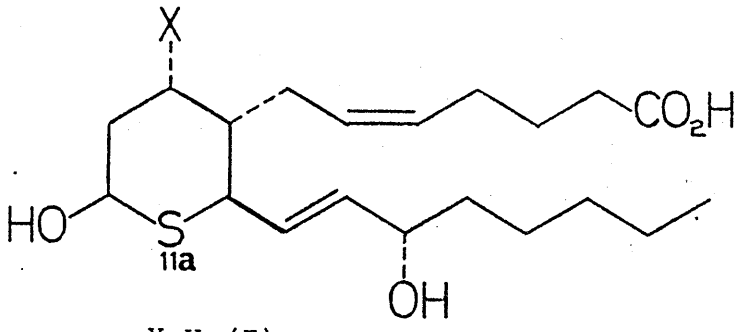
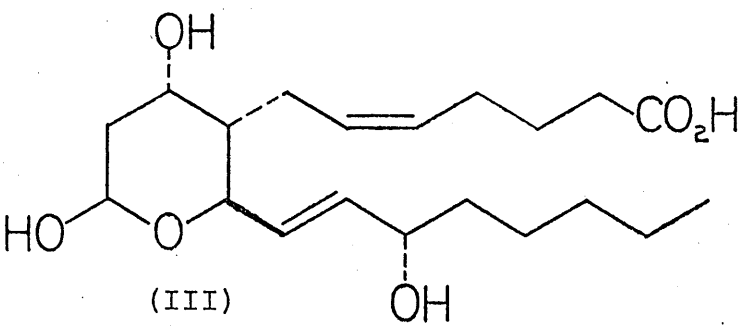
ABSTRACT

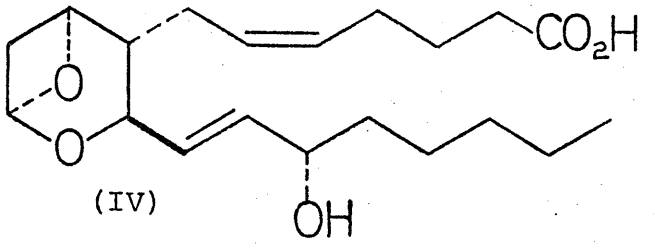
Synthetic routes were devised leading towards 9-deoxy-11a-thiathromboxane B_2 (I) and 11a-thiathromboxane B_2 (II); these are structural analogues of the natural substance thromboxane B_2 (TXB_2, III), which is the biologically stable product resulting from the rapid hydrolysis of active thromboxane A_2 (TXA_2, IV; half-life 30 seconds). It was hoped that the sulphur analogues, (I) and (II), of TXB_2 might exhibit biological activity of the same order as TXA_2 (IV) but in a more stable molecule. Since TXA_2 (IV) promotes blood platelet aggregation, it may well be that a more stable analogue would act as an antagonist and so inhibit platelet aggregation.



X=H (I)
X=OH (II)



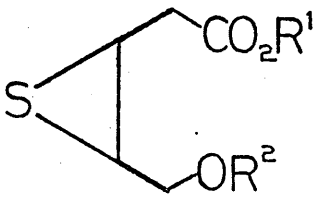
(III)



(IV)

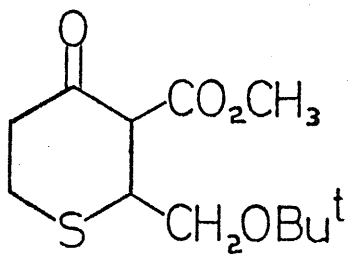
The synthetic targets (I) and (II) both contain a thiane ring, and of the three synthetic approaches attempted, two involved formation of the thiane ring towards the end of the route, whereas the other commenced with the formation of the thiane ring.

For the first synthetic route the key intermediates were disubstituted thiirans of type (V). A number of attempts to make these failed in the later stages of the reaction sequence.



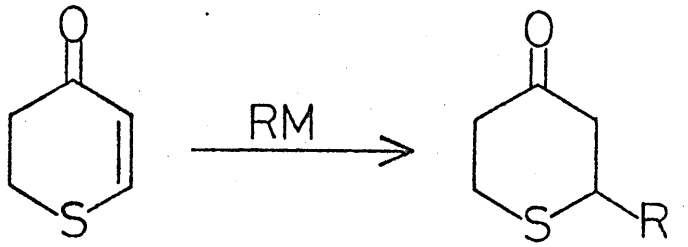
(V)

For the second synthetic route the key stage was a Michael reaction to give the 2,3-disubstituted thian-4-one (VI). However, the isolated product was the result instead of an ester/thiol-ester exchange process.



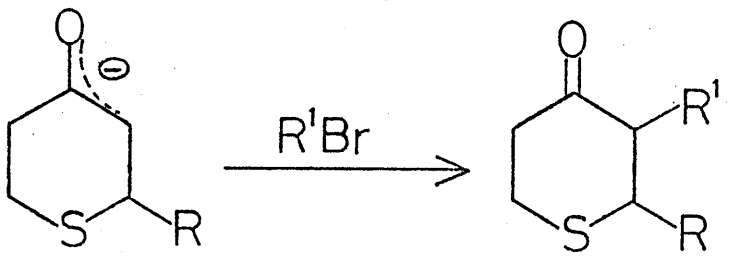
(VI)

The third route involved a detailed investigation of organocuprate conjugate addition reactions to dihydrothiinone (VII), leading to 2-substituted thian-4-ones.



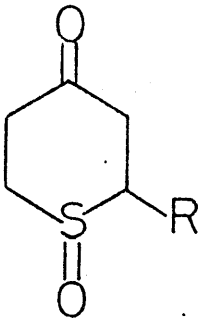
(VII)

Attempts to extend this procedure to the synthesis of 2,3-disubstituted thian-4-ones (VIII) by alkylation of the intermediate enolate were not successful; instead ring-opening occurred.

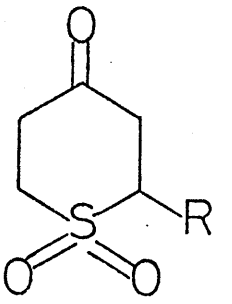


(VIII)

Further investigations of organocuprate conjugate addition reactions were made using the sulphoxide and sulphone corresponding to (VII). These led to the formation of 2-substituted derivatives (IX) and (X), without ring-opening at sulphur; however, extension of the sequence to yield 2,3-disubstituted compounds was not practicable.



(IX)



(X)

Acknowledgements

I would like to thank Dr. R. J. K. Taylor and Dr. J. D. Coyle for their advice and encouragement over the past three and a half years.

I am grateful to the Open University for financial support (Research Assistantship).

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EXPERIMENTAL

CHAPTER 1

Introduction

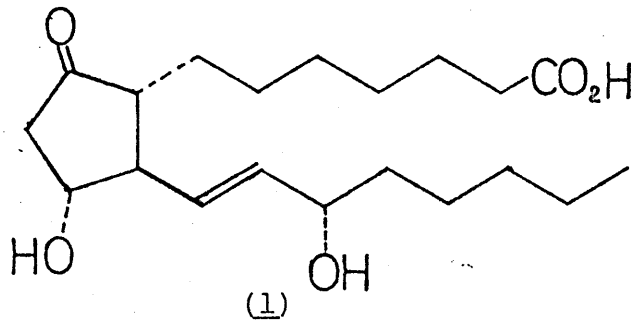
Prostaglandins and Thromboxanes

Chapter 1 Introduction

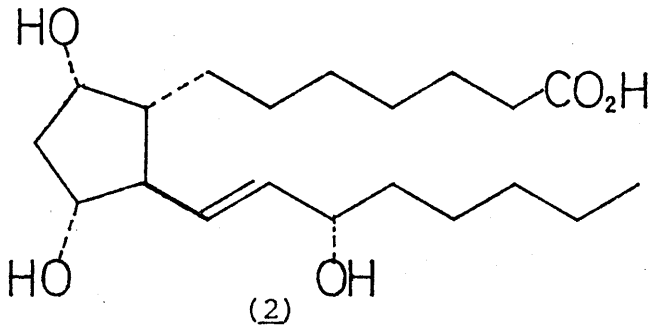
Prostaglandins and Thromboxanes

1.1 Prostaglandins and Prostaglandin Biosynthesis

The name prostaglandin was given originally to a lipid fraction of human seminal fluid which was found to stimulate isolated strips of uterine muscle.[1] Hampered by technical difficulties in the isolation of prostaglandins, and because of interest in other natural products, investigation remained dormant for a long time. Almost three decades elapsed between the discovery of the biological activity associated with prostaglandins and their structural elucidation. In 1960 Bergström and Sjövall isolated the crystalline prostaglandins (1) and (2) from sheep seminal vesicles. Within a few years, Bergström and his students isolated and elucidated the structure of thirteen different prostaglandins.[2] It was at this point, when the isolation and structural determination proved that prostaglandins were responsible for the observed biological activity, that research in the area expanded.

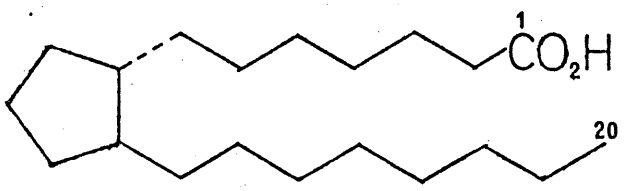


(1)



(2)

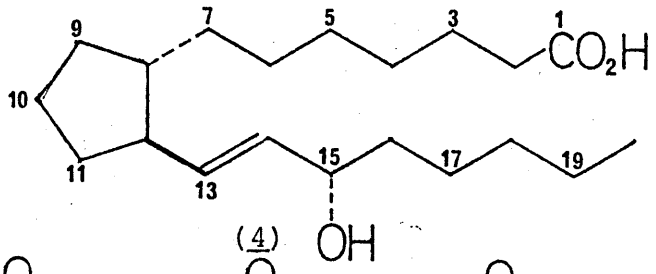
Prostaglandins (PG's) have generally been regarded as derivatives of prostanoic acid (3), a C-20 fully saturated carboxylic acid.



(3)

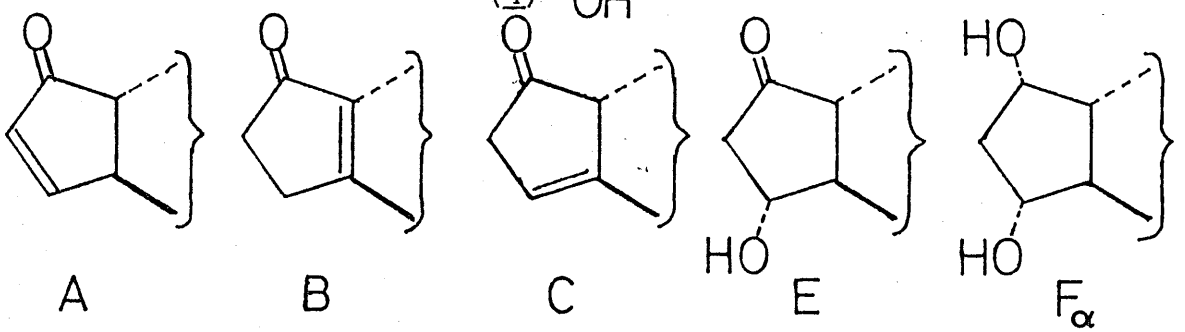
The full chemical names for prostaglandins and compounds with related structures are very long, but fortunately a useful trivial system has evolved[3] and this is shown in Figure 1. The numbering system and structural features which are common to all the natural substances are

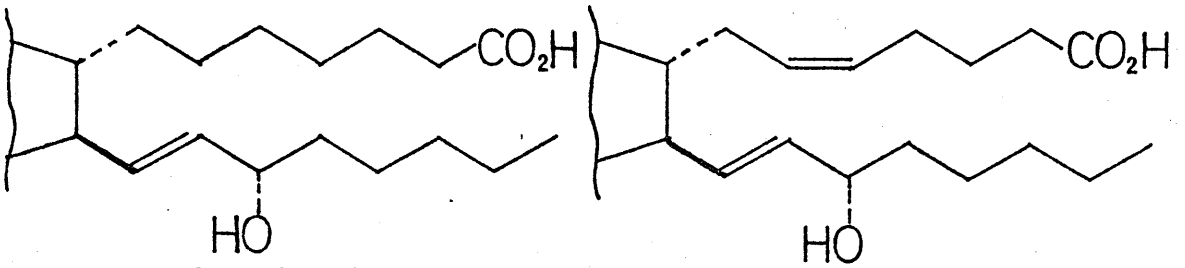
Figure 1



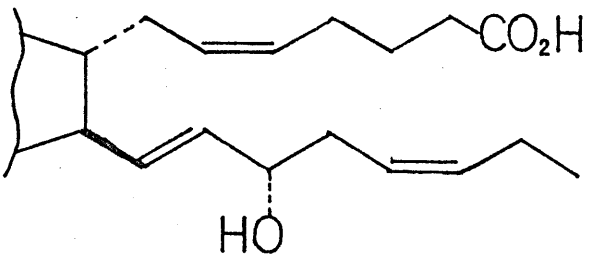
(4)

Numbering and common structural features of prostaglandins

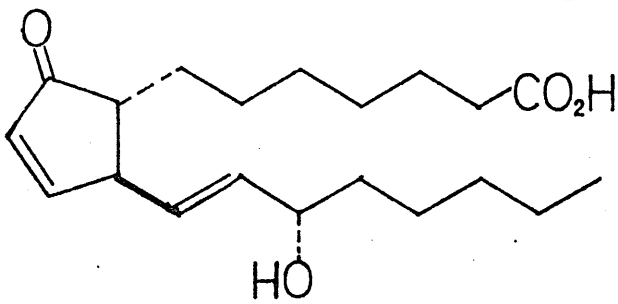




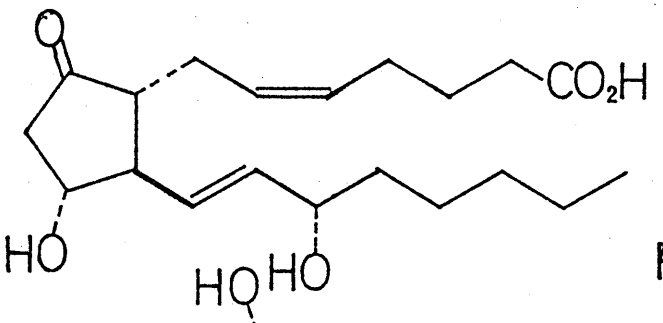
Subscript 1 Subscript 2



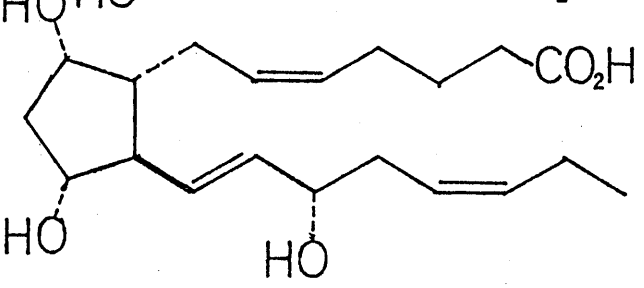
Subscript 3



PGA_1



PGE_2

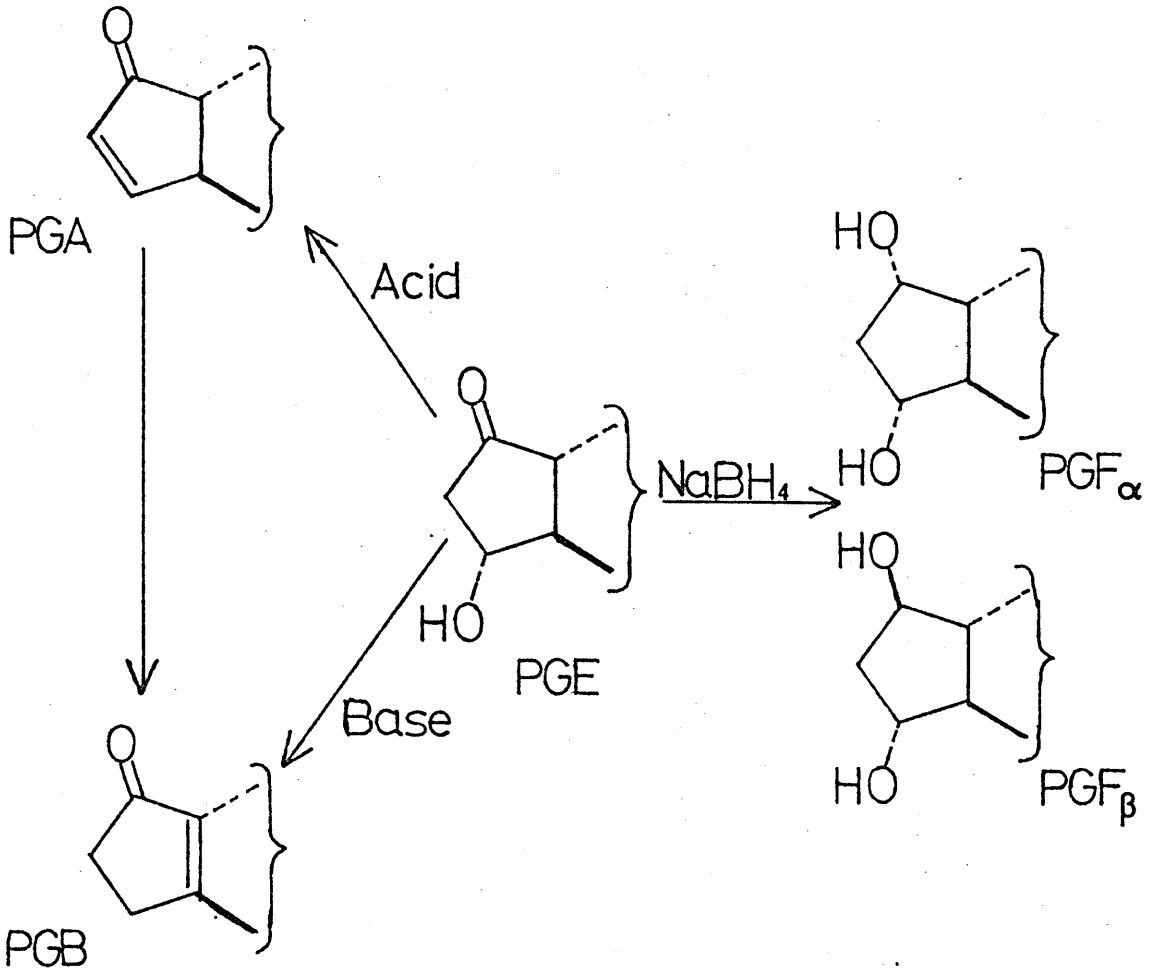


$PGF_{3\alpha}$

shown in formula (4). The compounds are named (PGA, PGB etc.) according to the substitution pattern in the five-membered ring and the number of double bonds in the side chains. All the primary prostaglandins are hydroxylated in the 15-position and contain a 13,14-trans-double bond. The degree of unsaturation of the side chains is indicated by the subscript numeral after the letter, thus prostaglandin PGA_1 has only the trans-double bond, while prostaglandin PGE_2 has in addition a cis-double bond in the 5,6-position.

Chemical reduction of a PGE yields two isomeric alcohols PGFα and PGFβ which is not found in nature. Stereochemistry is denoted in the conventional manner, that is the ring is assumed to be planar so that there are groups above the plane (β, thick line, the C-12 chain) and groups below (α, dotted line, the C-8 chain). The letters E and F in PGE and PGF refer to an early finding by Bergström and Sjövall that PGE and PGF compounds behave differently on partition between ether and phosphate buffer. The one more soluble in Ether was called PGE, whereas the other more soluble in phosphate buffer (Fosfate in Swedish) was called PGF. The letters A and B in PGA and PGB refer to the formation of these derivatives from PGE compounds by treatment with Acid and Base respectively.[4] The chemical relations between PGE, PGF, PGA and PGB compounds are depicted in Figure 2.

Figure 2



All other naturally occurring prostaglandins continue the alphabetical sequence, at the present time from PGA to PGI. The name prostaglandin, or sometimes prostanoid, is given to any compound which is structurally related to the natural substances.

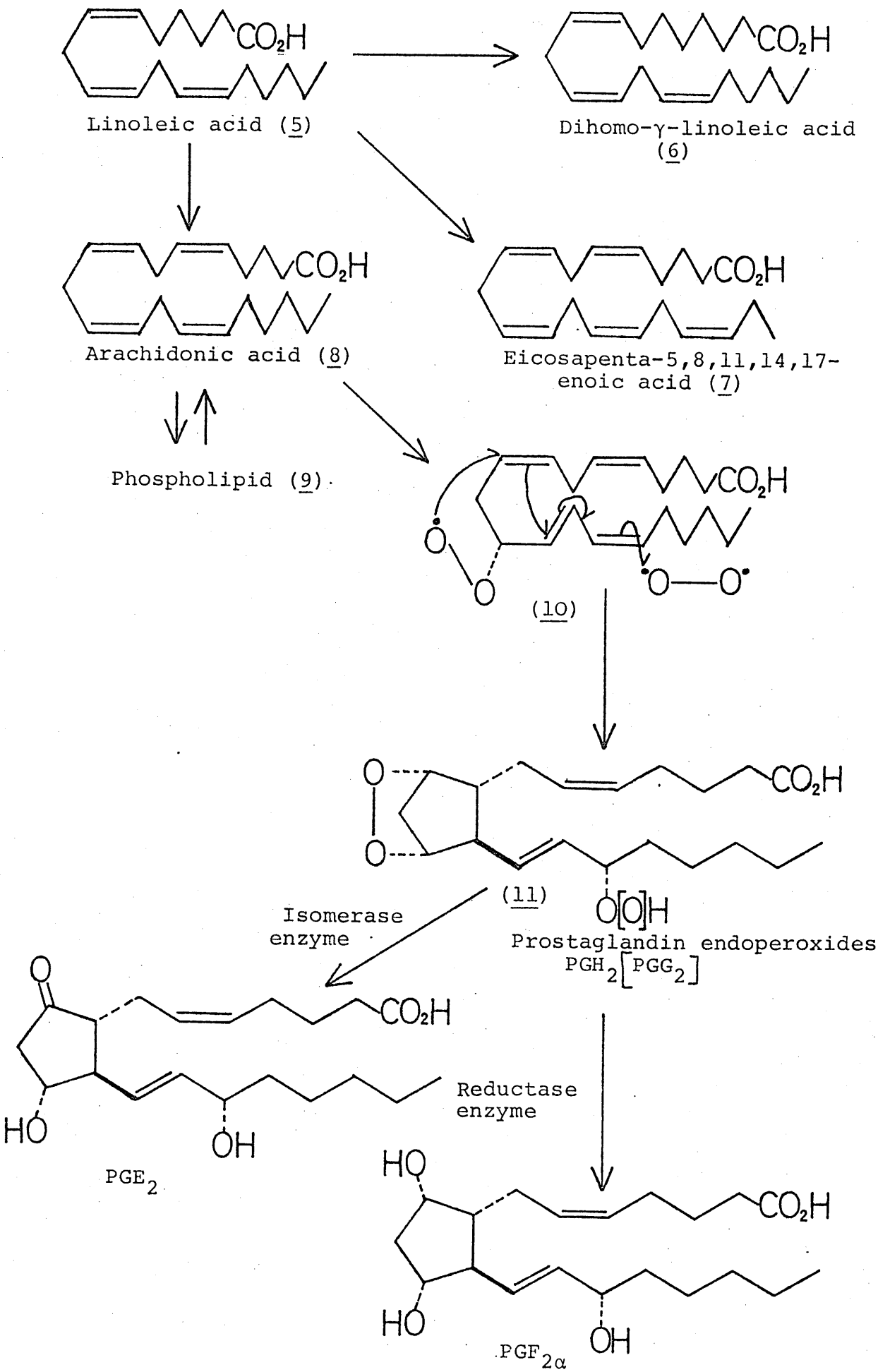
Prostaglandins have been implicated as local hormones in a multitude of important physiological processes.[5]

They affect the male and female reproductive systems, the gastrointestinal system, the cardiovascular and renal systems, and the nervous system. They are released when blood clots, and they are found when tissues become inflamed. However, the exact role of the prostaglandins in cellular regulation remains to some extent uncertain.

Since prostaglandins are not normally part of a mammalian diet they must be made in the body, and an important milestone in prostaglandin research was the elucidation of the main features of their biosynthesis. This is shown in a simplified form in Figure 3. The starting point is the essential dietary constituent linoleic acid (5) and this is readily converted into other fatty acids, for example arachidonic acid (8) which is stored in the body as a phospholipid (9). This therefore is a biosynthetic intermediate which is readily available in mammalian tissues and from which PG_2's are made by enzymatic processes via the peroxy intermediate (10) and the PG endoperoxides (11). The cyclooxygenase enzymes responsible are inhibited by aspirin and related compounds such as indomethacin, which thereby block the synthesis of all PG's from PGG_2 and PGH_2. Prostaglandins PG_1's and PG_3's are biosynthesised in a similar fashion via dihomo-γ-linoleic acid (6) and eicosapenta-5,8,11,14,17-enoic acid (7) respectively. This biology has been covered in several review articles.[6,7]

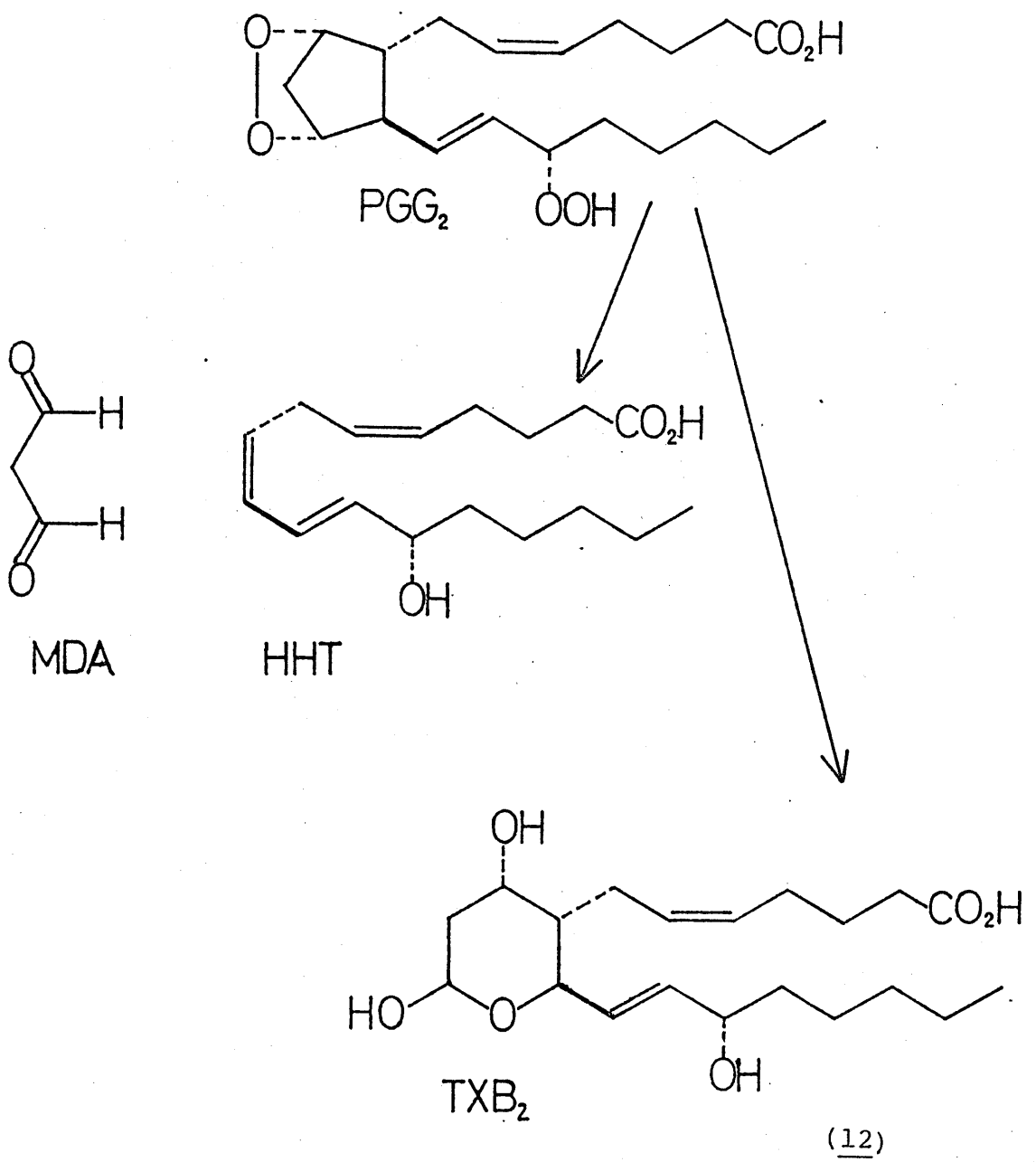
In 1973 Samuelsson isolated the endoperoxide intermediates PGG_2 and PGH_2.[8] In contrast to the previously discovered

Figure 3


Linoleic acid (5)
Dihomo-γ-linoleic acid (6)
Arachidonic acid (8)
Eicosapenta-5,8,11,14,17-enoic acid (7)
Phospholipid (9)
(10)
(11)
Prostaglandin endoperoxides
PGH2[PGG2]
Isomerase enzyme
Reductase enzyme
PGE2
PGF2α

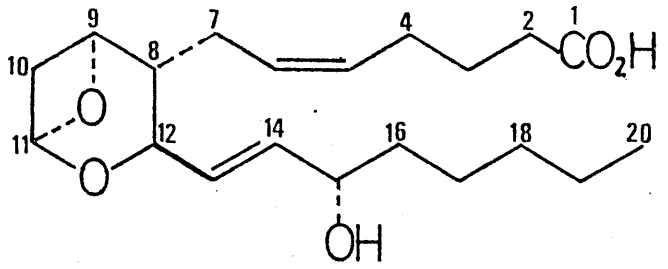
PG's, the endoperoxides have a short half-life of about 5 minutes in aqueous biological systems. The endoperoxides possess the ability to induce rapid irreversible aggregation of blood platelets. Two acids, thromboxane B_2 (TXB_2, 12) and 12-hydroxyheptadeca-5,8,10-trienoic acid (HHT), and malondialdehyde (MDA) were found to be the major metabolites of PGG_2 when incubated with human platelets (Figure 4).[8]

Figure 4



(12)

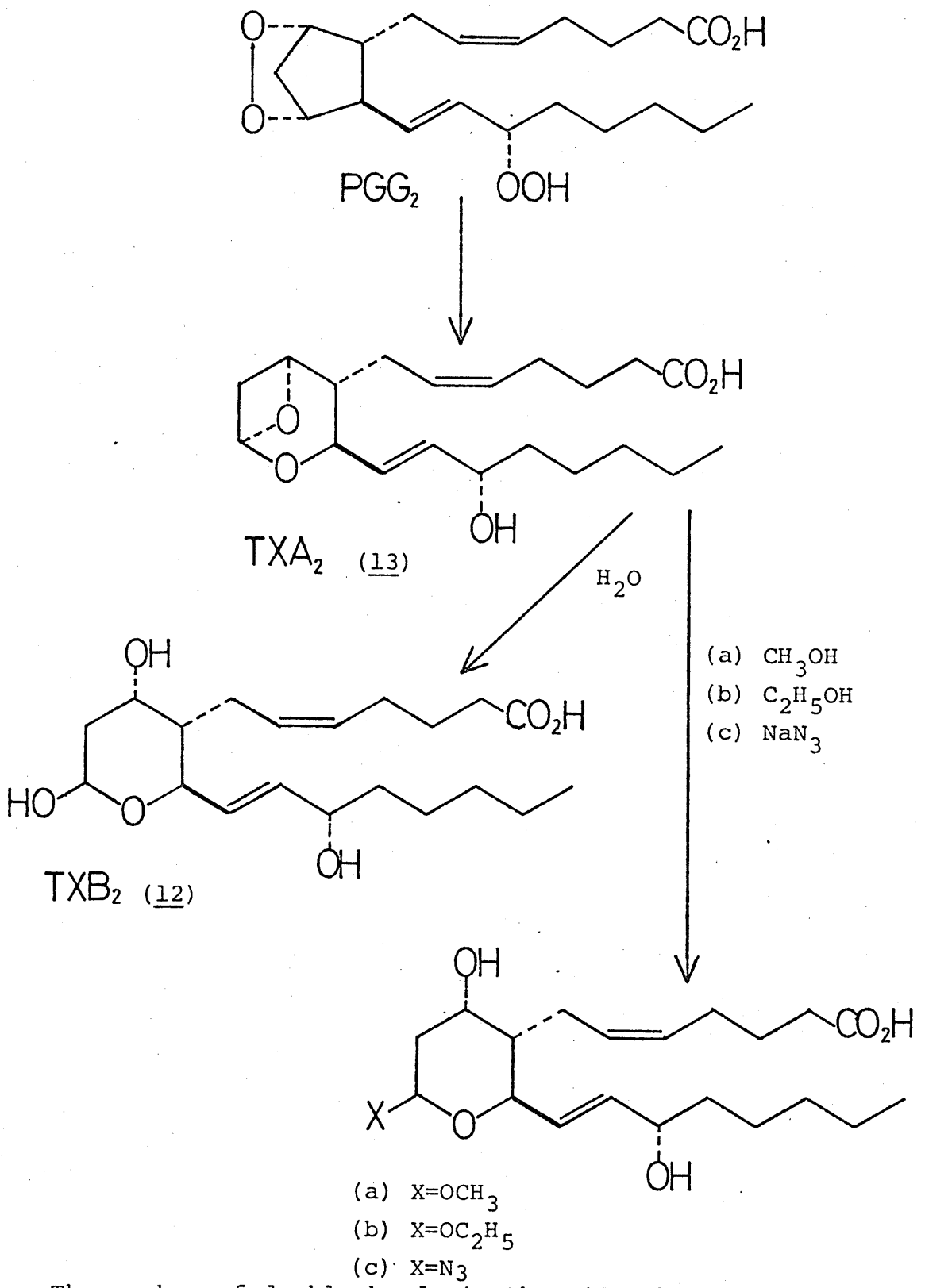
Thromboxanes (TX's) are distinguishable from prostaglandins by a 6-membered oxane ring in place of the cyclopentane ring. In the conversion of PGG_2 to TXB_2 in platelets, an extremely unstable intermediate (half-life 30 seconds) which rapidly hydrolyses to TXB_2 was identified. Trapping experiments (Figure 5) suggested the structure (13) and the compound was named thromboxane A_2 (TXA_2).



TXA_2 (13)

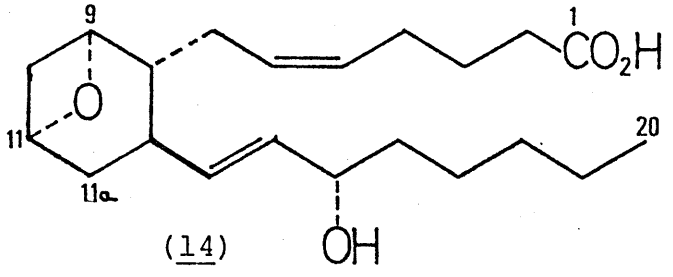
Thus, methanol, ethanol or sodium azide compete with water to afford the TXB_2 derivatives with the hemiacetal hydroxyl group substituted by methoxy, ethoxy and azido groups, respectively. These results are in agreement with the strained bicyclic structure assigned to TXA_2, which is expected to be very susceptible to nucleophilic attack at the acetal carbon to yield TXB_2 or its derivatives.

Figure 5



The number of double bonds in the side chains of thromboxanes is indicated in the same way as with the prostaglandins, butthe numbering of thromboxanes and

their analogues is such as to maintain a C-20 chain length with the oxygen (or other heteroatom) of the ring not being included in the numbering. An example of numbering is given by the thromboxane analogue (14).

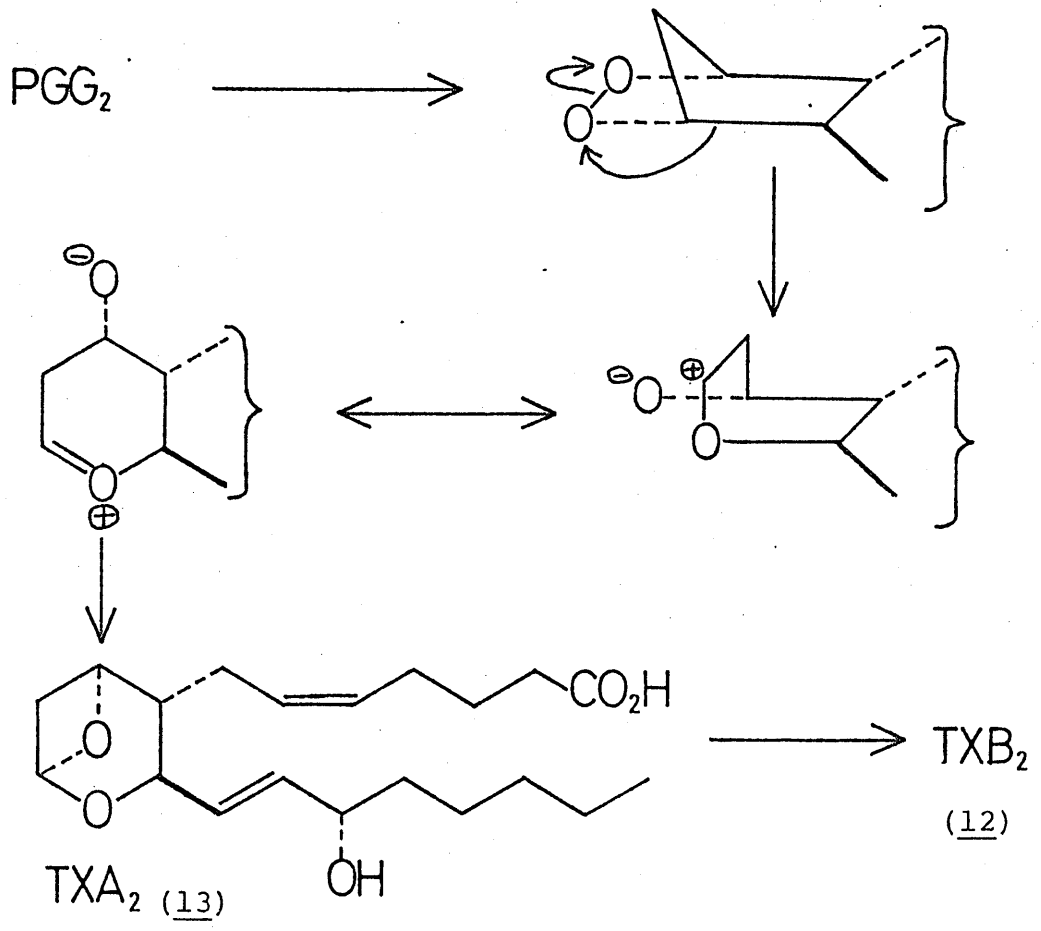


(14)

11a-methylene TXA_2

The rearrangement of PGG_2 to TXA_2 is thought to have the following mechanism (Figure 6).[6]

Figure 6

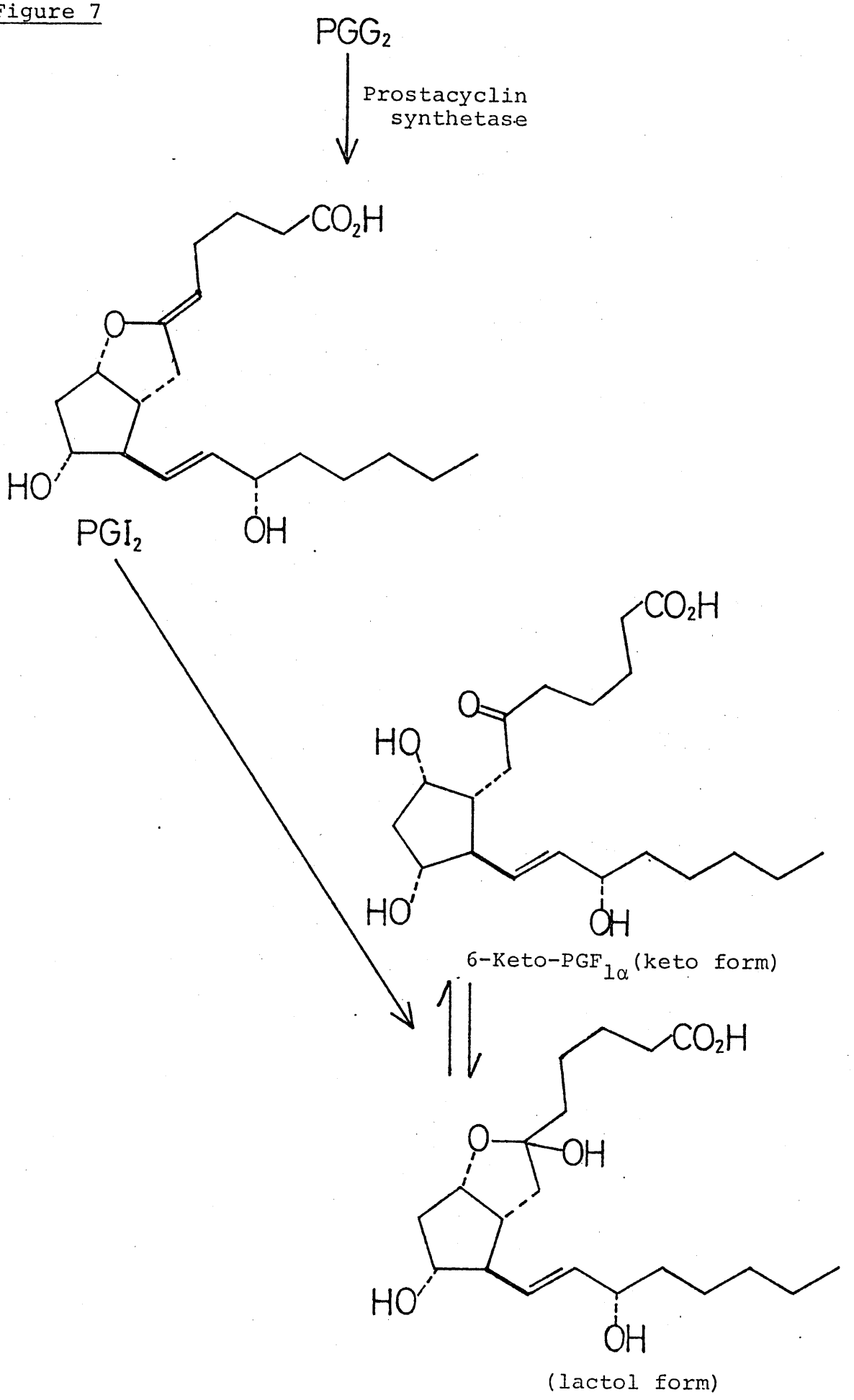


TXA_2 is a very potent aggregator of blood platelets, and the properties which were initially attributed to PGG_2 may well be caused by TXA_2. In addition, in 1969 Piper and Vane[9] described the release of a rabbit aorta contracting substance (RCS) from guinea pig lung, which had similar properties to TXA_2. Now this has been found to be a mixture of PGG_2 and TXA_2.

However, endoperoxides are not converted solely to thromboxanes, since Vane et al[5] recently discovered that endoperoxides are transformed by human arterial tissue into a new unstable substance. In most respects, the biological activity of this new substance is the opposite of TXA_2, including potent inhibition of platelet aggregation and smooth muscle relaxation. The chemical structure of this potent inhibitor of platelet aggregation was identified recently.[10] Since the structure contains a second ring system, the name prostacyclin (PGI_2) was adopted. Prostacyclin is rather unstable in aqueous acidic or neutral media, breaking down to 6-keto-$PGF_{1\alpha}$, in equilibrium with its lactol form (Figure 7).[7]

Thus PG endoperoxides serve as substrates for the generation of two labile substances with diametrically opposite biological effects. TXA_2 generated by platelets promotes aggregation, while PGI_2 produced by arterial tissue inhibits aggregation. In addition to its effects on platelets, prostacyclin may play a crucial role in preventing gastric

Figure 7


PGG2
Prostacyclin synthetase
CO2H
O
HO
PGI2
OH
CO2H
O
HO
HO
OH
6-Keto-PGF1α (keto form)
CO2H
O
OH
HO
OH
(lactol form)

ulceration, in preventing inflammation and in blood pressure regulation. These and other physiological processes may be regulated by the opponent actions of TXA_2 and PGI_2.

..2 Properties of Thromboxanes

Thromboxanes were so named because thromboxane A_2, identified as a metabolite of arachidonic acid in thrombocytes (platelets), contains an oxane ring and is a potent platelet aggregating agent. The number of double bonds in the side chains of prostaglandins usually does not fundamentally alter the biological properties, and prostaglandins E_1, E_2 and E_3 for example, have similar effects on vascular smooth muscle. However, a major exception to this general rule are the thromboxanes; thromboxane A_2 is potent aggregator of platelets, whereas thromboxanes A_1 and A_3 are not.[11] It now seems likely that, contrary to earlier reports, the endoperoxides do not themselves cause platelet aggregation but give rise to TXA_2 which does.[12] TXB_2, however, does not seem to be biologically active.

The generation of TXA_2 is essential to platelet aggregation, which leads to the formation of the hemostatic plug at the site of vascular injury, which is a very important function of platelets.[13] Recent evidence supporting the

essential role of TXA_2 in platelet aggregation has been provided by the development of selective inhibitors of thromboxane synthetase, such as hydroquinone or imidazole and its analogues,[14] which have little or no effect on prostaglandin endoperoxide formation. Interestingly, a deficiency of thromboxane synthesis has been described in a patient with habitual bleeding.[15] Aspirin can produce a bleeding disorder that is presumably also the result of an inhibition of TXA_2 formation. However, unlike imidazole, aspirin suppresses the synthesis of the prostglandin endoperoxides. As TXA_2 originates from the latter, its synthesis is also decreased. Therefore, in contrast to imidazole, aspirin is non-selective in its effects on prostaglandin, prostacyclin and thromboxane synthesis.

Since the discovery that anti-inflammatory agents (aspirin, indomethacin) are potent inhibitors of prostaglandin synthetase,[16] primary prostaglandins have been thought to mediate the inflammatory process. However, administration of these prostaglandins does not fully mimic inflammation.[17] It is now thought likely that TXA_2 may be the active triggering agent in promoting acute inflammation.[18]

In addition to promoting platelet aggregation, TXA_2 contracts blood vessels at the site of its release from the aggregating platelets. Together these effects promote blood clotting. The blood clotting mechanism is essential to survival, but when it gets out of hand it can lead to thrombosis, the disease responsible for the highest

fatality rate amongst young and middle-aged men in the Western World. Any effective method of curing or preventing this disease would be of immense medicinal value, but unfortunately prostacyclin (PGI_2) and thromboxane A_2 (TXA_2) have very short half-lives and consequently would appear to be of limited clinical utility. For medicinal purposes TXA_2 antagonists and PGI_2 mimics are required. This has led synthetic chemists to design and synthesise stable analogues of these molecules, and this is a major area of research in the chemical and biological sciences.

Developments in Thromboxane Synthesis

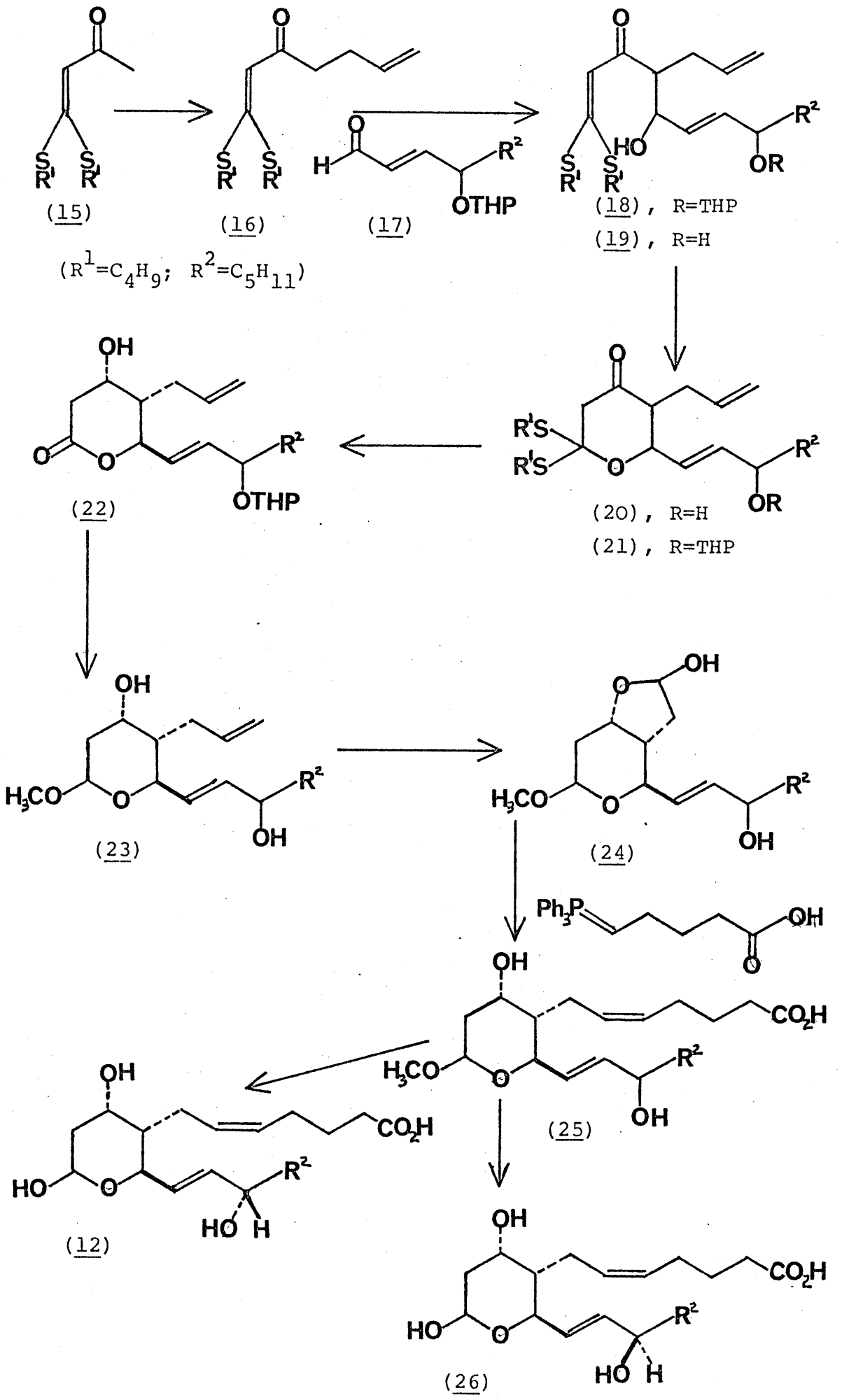
The recognition that TXB_2 is one of the major products of the biosynthetic system which converts arachidonic acid to prostaglandins has promoted efforts towards its synthesis. Developments have to date concentrated on preparing relatively large amounts of TXB_2, the hemiacetal derivative of TXA_2, in order to be able to study the compound's biological activity and role in the body.

Most of the routes to TXB_2 have involved the intermediacy of prostaglandins or prostaglandin precursors, a few have been total syntheses, and others have started with derivatives of D-glucose.

The total synthesis of TXB_2 has been described by Corey et al.[19] In this sequence, outlined in Figure 8, the enone (15) was alkylated with lithium di-isopropylamide (LDA)/allyl bromide to give (16), the lithium enolate of which was condensed with the aldehyde (17) furnishing (18) as a non-separable mixture of diastereoisomers which was used as such. Depyranylation of this intermediate led to (19) which, under acid conditions, cyclised to (20). The protected derivative (21), on reduction with $NaBH_4$, gave a diastereoisomeric mixture of alcohols from which the lactone (22) could be isolated after silver-induced removal of the thioketal function. Reduction, followed by subsequent methylation gave the cyclic acetal (23). Cleavage of the terminal methylene group by sequential exposure to osmium tetroxide/pyridine (to generate the diol) and sodium periodate led to the lactol (24). The final steps in the synthesis involved condensation of (24) with the ylide prepared from 4-carboxybutyltriphenylphosphonium bromide and sodium methylsulphinylmethylide in DMSO, followed by acidic hydrolysis and chromatographic separation of TXB_2 (12) from its C-15 epimer (26).

The first TXB_2 synthesis came from Schneider and Morge[20] in 1976, and it involved a four-stage synthesis from 9,15-diacetoxy-$PGF_2\alpha$ methyl ester (27) in an overall

Figure 8


(15)
(16)
(17)
(18), R=THP
(19), R=H
(R1=C4H9; R2=C5H11)
(20), R=H
(21), R=THP
(22)
(23)
(24)
(25)
(26)
(12)

yield of 25% (Figure 9). The crucial step in this synthesis is a ring-opening reaction initiated by the action of lead tetraacetate on the 11,12-bond, a reaction which has precedence in the steroid field and which occurs with particular ease in the case of homoallylic alcohols such as (27). The rather unstable acetoxyaldehyde (28) was directly converted to its dimethyl acetal (29) using trimethyl orthoformate and pyridinium chloride in methanol. Aqueous basic hydrolysis of (29) gave the trihydroxy acid (30). Acidic hydrolysis of (30) gave TXB_2 (12) as the major product along with its methyl acetal (31), from which it was separated chromatographically. TXB_2 was obtained as a crystalline solid, m.p. 92-94 ^{o}C.

Starting from the prostanoid precursor[21] (32) Nelson and Jackson[22] developed another route to TXB_2 (Figure 10). Treatment of (32) with florisil resulted in the formation of (33), which after reduction with $NaBH_4$ and protection as the 4-biphenylcarboxylate was hydroxylated with osmium tetroxide to afford (34). Cleavage of this diol with periodic acid led to the rather unstable aldehyde (35) which was reduced directly with $NaBH_4$ to afford (36). Differentiation of the two hydroxyl groups of (36) was achieved by Collins oxidation of its bis(trimethylsilyl ether) (37), leading to the aldehyde (38). Treatment of this intermediate with acid in methanol gave the acetal (39), which upon treatment with sodium methoxide in methanol yielded the alcohol (40). Oxidation of (40) with Collins reagent

Figure 9

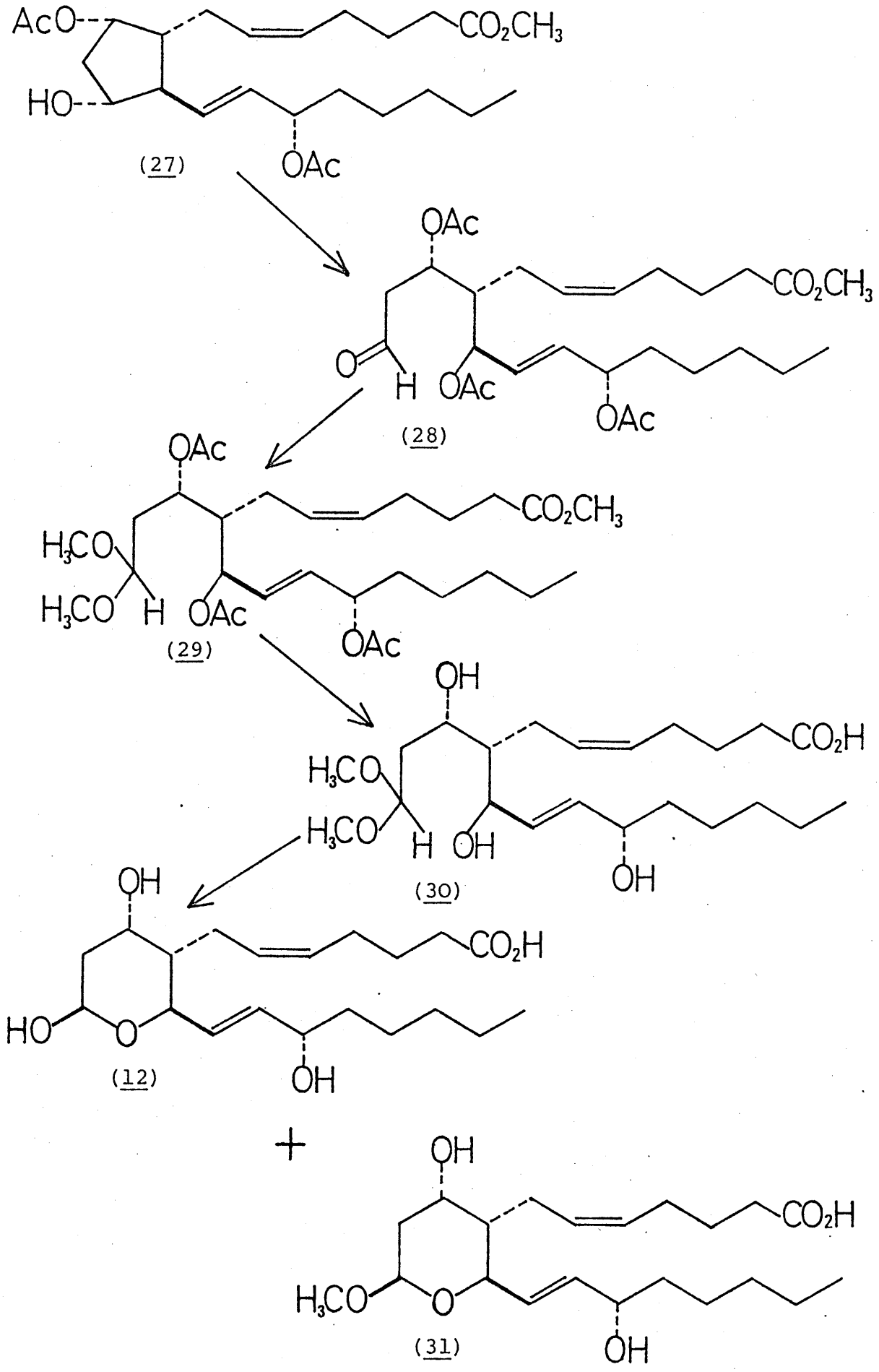
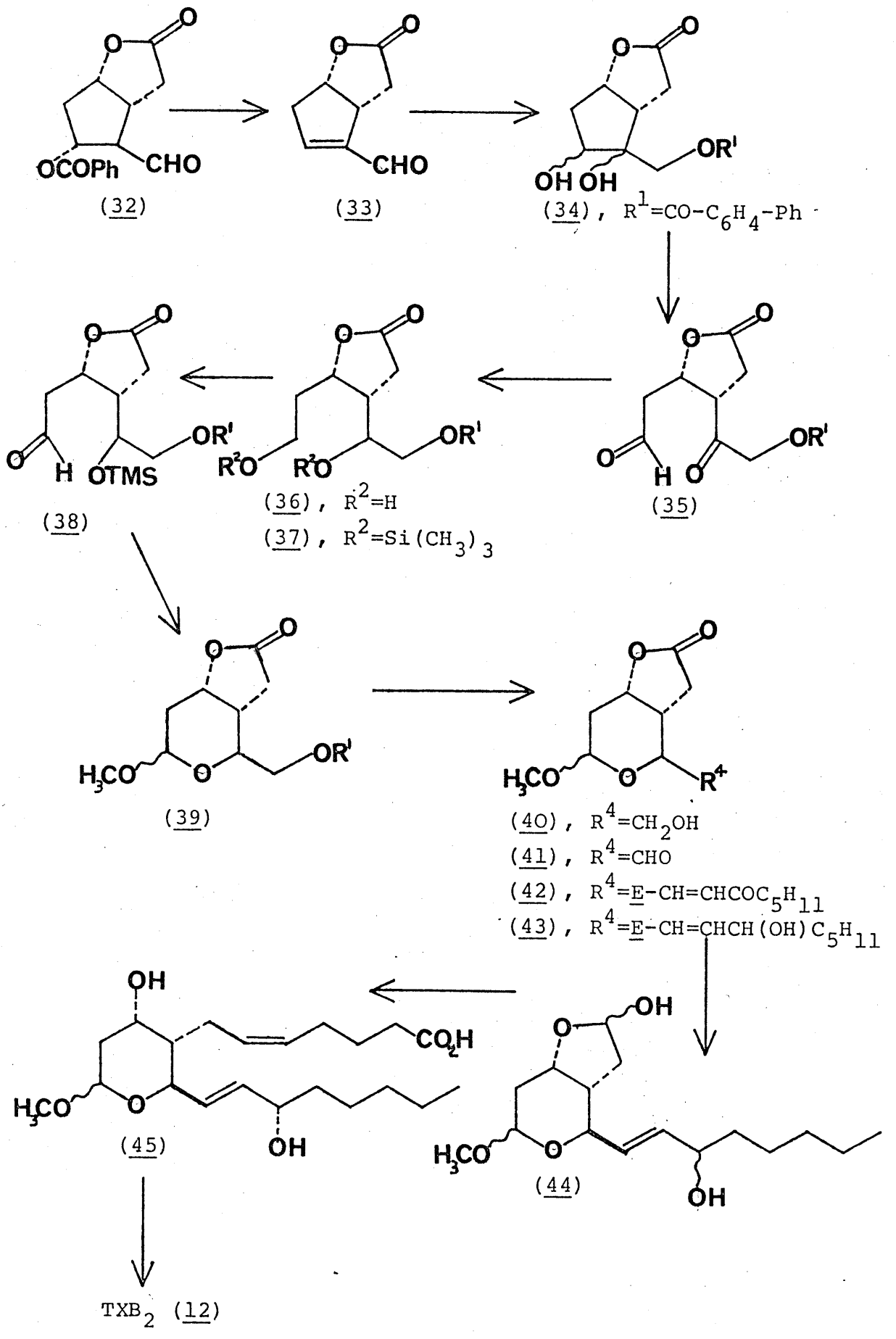

AcO
HO
CO_2CH_3
OAc
(27)
OAc
CO_2CH_3
O
H
OAc
OAc
(28)
OAc
CO_2CH_3
H_3CO
H_3CO
H
OAc
OAc
(29)
OH
CO_2H
H_3CO
H_3CO
H
OH
OH
(30)
OH
CO_2H
HO
O
OH
(12)
+
OH
CO_2H
H_3CO
O
OH
(31)

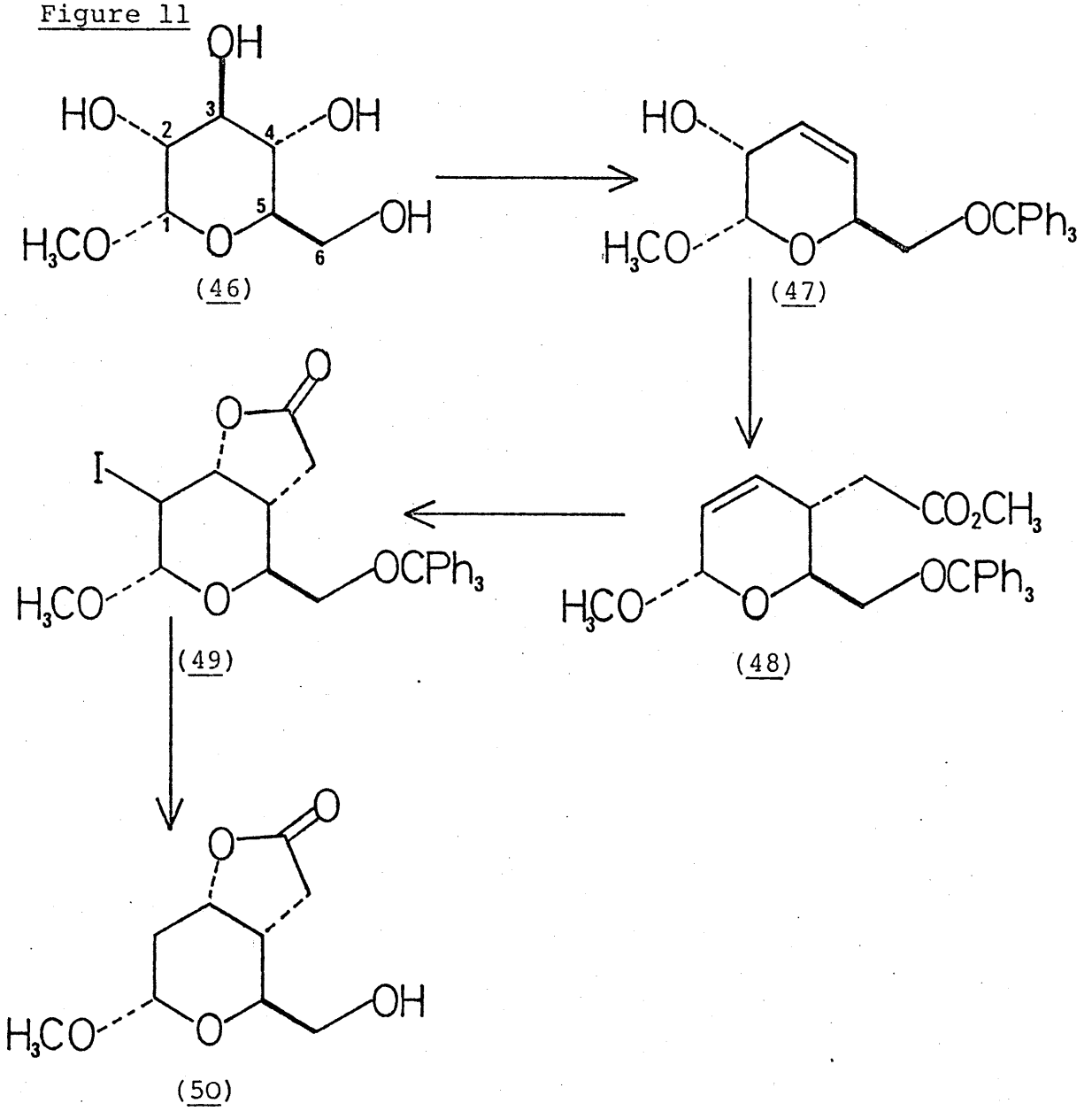
Figure 10


OCOPh
CHO
(32)
CHO
(33)
OH OH
OR'
(34), R1=CO-C6H4-Ph
OR'
H O
(35)
OR'
R2O
OR'
(36), R2=H
(37), R2=Si(CH3)3
H OTMS
OR'
(38)
H3CO
OR'
(39)
H3CO
R4
(40), R4=CH2OH
(41), R4=CHO
(42), R4=E-CH=CHCOC5H11
(43), R4=E-CH=CHCH(OH)C5H11
OH
OH
(44)
OH
CO2H
H3CO
OH
(45)
TXB2 (12)

gave (41), which when treated with the ylide prepared from dimethyl 2-oxoheptylphosphonate and potassium t-butoxide in THF gave (42). The remaining steps in the sequence followed standard prostaglandin methodology and involved (i) reduction of (42) with zinc borohydride to give (43), (ii) reduction of (43) with diisobutyl-aluminium hydride to give (44), (iii) treatement of (44) with the ylide prepared from 4-carboxybutyltriphenyl-phosphonium bromide and sodium methylsulphinylmethylide in DMSO to give (45) as two 15-hydroxyl epimers, (iv) hydrolysis of (45) to give TXB_2 (12).

A number of syntheses of TXB_2 take a carbohydrate approach.[23,24] TXB_2 can be considered as a D-glucoside in which positions 4 and 6 are the sites of C-branching and chain extension. Thus, the syntheses were based on the stereo-specific introduction of the acid side chain at C-4 and appropriate chain extension at C-6 in α-methyl-D-glucoside (46) (Figure 11).

Figure 11



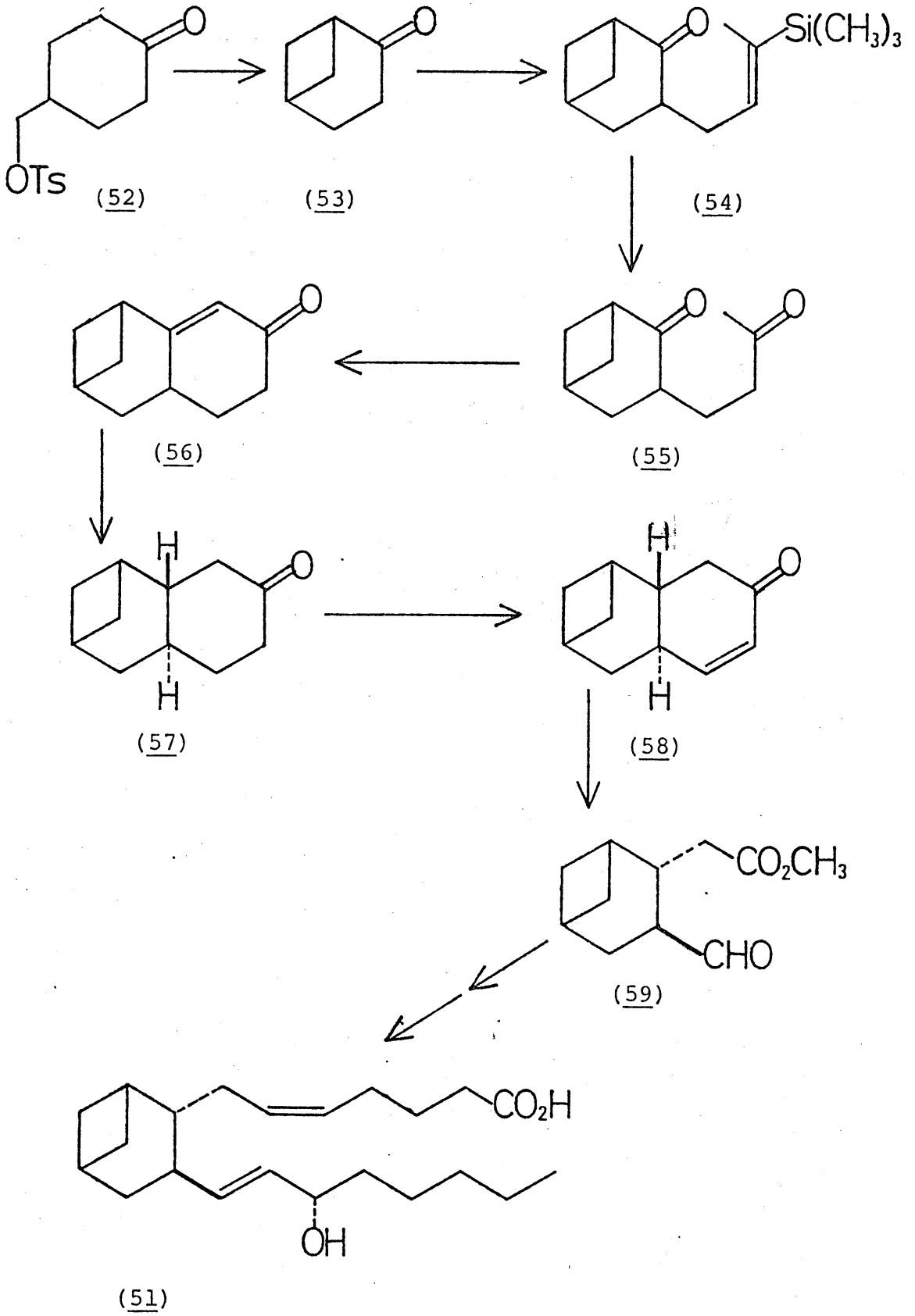
(46) was converted by a known and highly efficient series of sequential hydroxyl group activations to give (47). The allylic alcohol (47) when subjected to the conditions of the orthoester Claisen rearrangement[25] (trimethyl orthoacetate, propanoic acid, xylene) gave ester (48). Alkaline hydrolysis of (48) followed by reaction with potassium iodide-iodine gave the iodolactone (49), which was deiodinated with tributyltin hydride; after this the

trityl group was removed to give the hydroxylactone (50). This hydroxylactone was converted by standard methodology to TXB_2, as described above. This synthesis is an example of the use of carbohydrates as chiral intermediates in organic synthesis, an approach based on recognising hidden "sugar" components in the carbon skeletal framework of natural products.[26]

TXA_2 is found to be extremely labile and highly biologically active, so for these reasons stable structural analogues of TXA_2 have been synthesised in order that studies of their biological action may be made.

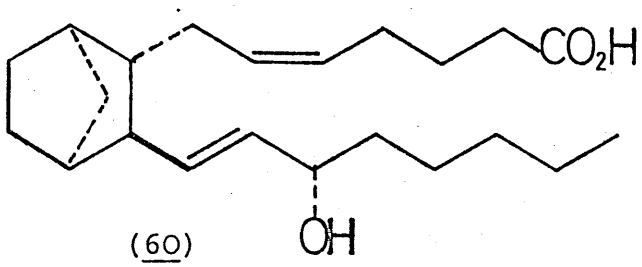
Japanese workers[27] have synthesised 9a,11a-dimethylene TXA_2 (51) in which oxygen atoms in the cyclic moiety of natural TXA_2 have been replaced by carbon atoms (Figure 12). The tosylate (52), prepared from ethyl 4-hydroxybenzoate in six steps, was treated with sodium bis(trimethylsilyl)amide in benzene to give the bicyclic ketone (53). Alkylation of (53) gave (54). Epoxidation of (54) with m-chloroperbenzoic acid and subsequent treatment with formic acid gave the diketone (55), which was transformed into the enone (56) with aqueous KOH in methanol. Reduction of (56) with lithium/liquid ammonia/t-butanol and then Jones oxidation yielded the tricyclic ketone (57). Conversion of (57) to the enone (58) was effected by bromination, then dehydrobromination of the resulting bromoketone. Oxidation of (58) with osmium

Figure 12



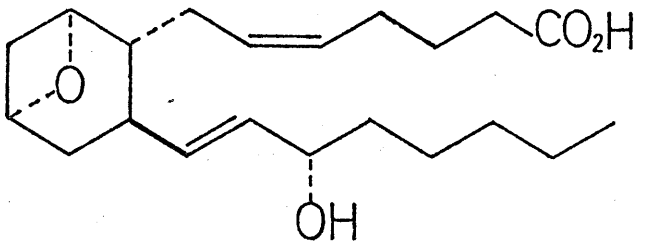
(52) (53) (54) (55) (56) (57) (58) (59) (51)

tetroxide followed by a reductive work-up gave the dihydroxyketone, which was cleaved oxidatively with lead tetraacetate to give the formylester (59).
The synthesis of (51) and its C-15 epimer was completed by chain extensions of (59) using the usual sequence already described. Nicolau et al[28] have also very recently described the synthesis of (51) by a similar method, while Barraclough[29] has described the synthesis of (60), a structurally related analogue.



(60)

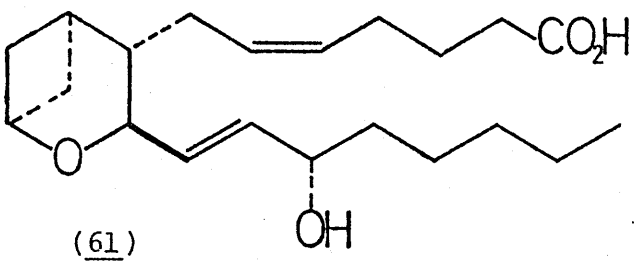
Maxey and Bundy[30] have synthesised 11a-methylene thromboxane A_2 (14) in which the 11a-oxygen atom of the bicyclic acetal has been replaced by a methylene group. This chemically stable molecule was prepared in the hope that it would mimic the activity of TXA_2 itself, thus greatly simplifying the pharmacological evaluation of the parent compound.



(14)

The strategy of replacing an oxygen atom with a methylene unit has provided chemically stable, biologically active mimics of several other unstable prostaglandins e.g. PGH_2.[31] Preliminary experiments indicate that 11a-methylene thromboxane A_2 (14) inhibits PGH_2-induced human platelet aggregation.

Corey et al[32] have synthesised 9a-methylene TXA_2 (61) in which the 9a-oxygen atom of the bicyclic acetal has been replaced by a methylene group.

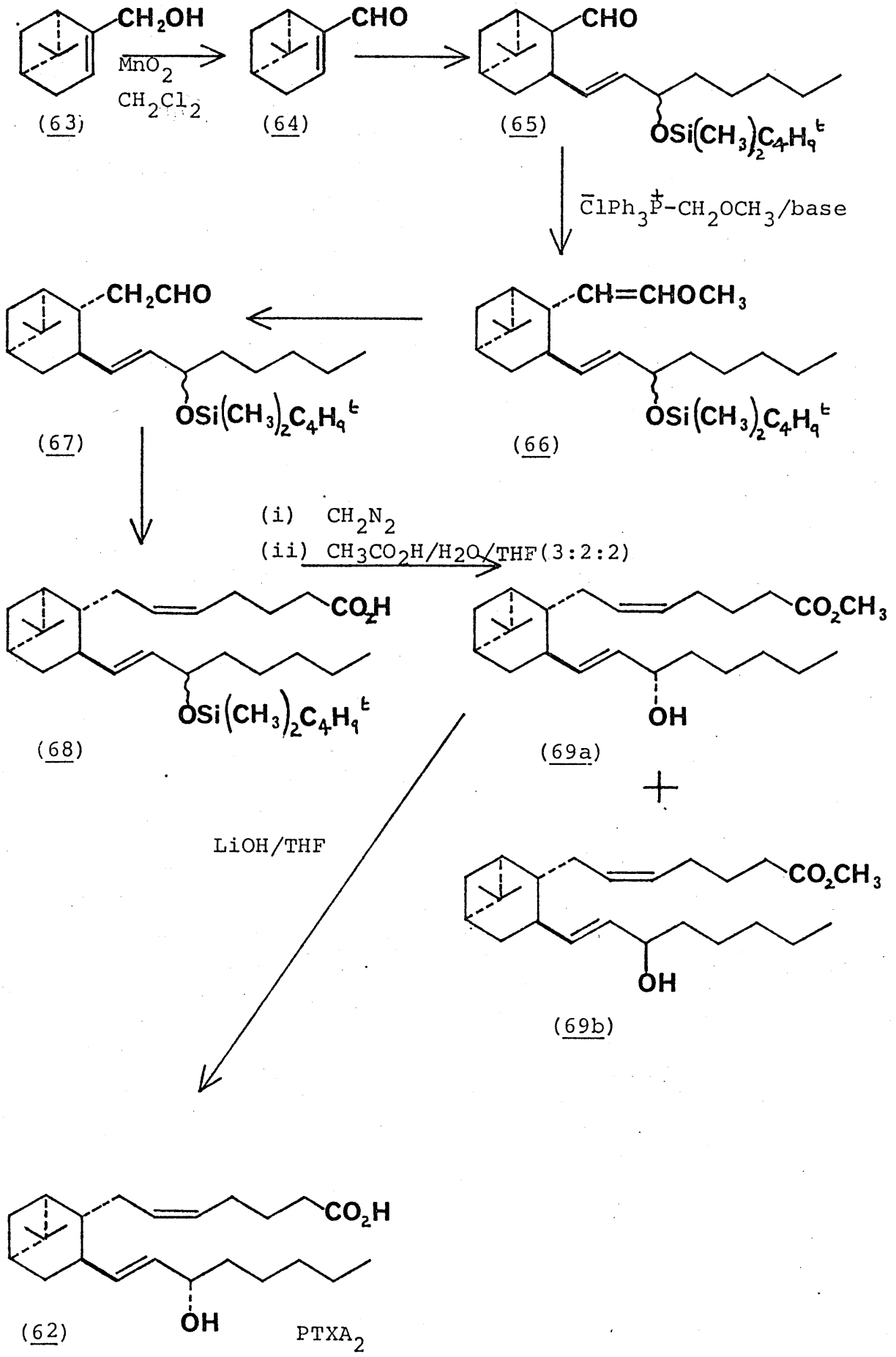


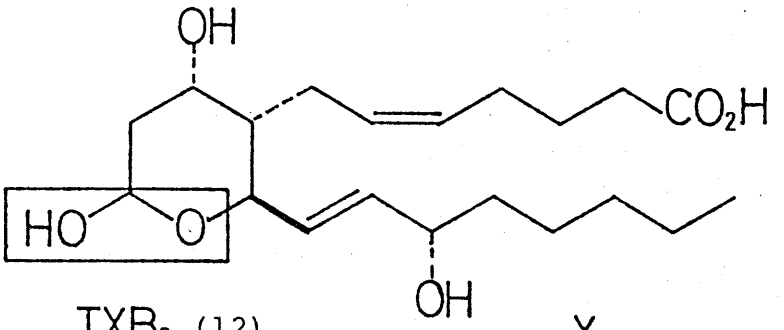
(61)

Nicolau et al[33] have recently synthesised pinane-thromboxane A_2 ($PTXA_2$, 62) in which the ether linkages of TXA_2 are replaced by carbon groupings. $PTXA_2$ was synthesised from (-)-myrtenol (63) as outlined in Figure 13.

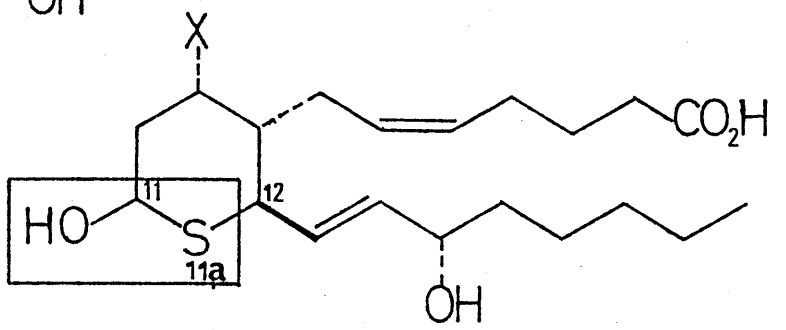
(-)-Myrtenol (63) was efficiently (95%) converted to the α,β-unsaturated aldehyde (64), which underwent smooth 1,4-addition with a mixed organocuprate to give the aldehyde (65). Condensation of (65) with methoxymethylene-triphenylphosphorane in toluene/THF gave the enol ether (66) from which the aldehyde (67) was liberated quantitatively. The upper side chain was completed by the standard prostaglandin Wittig reaction, leading, after diazomethane treatment, to the methyl ester of the protected TXA_2 analogue (68). Deprotection of the hydroxyl group led to the methyl esters (69a) and (69b), which were separated by chromatography. Hydrolysis of the more polar compound (69a) gave $PTXA_2$ (62) quantitatively. In preliminary tests both (62) and its C-15 epimer showed activity as TXA_2 antagonists. Caton el al[34] have also recently synthesised pinane-TXA_2 by a similar synthetic route.

Figure 13


CH2OH
MnO2
CH2Cl2
CHO
CHO
OSi(CH3)2C4H9t
(63)
(64)
(65)
ClPh3P-CH2OCH3/base
CH=CHOCH3
CH2CHO
OSi(CH3)2C4H9t
(66)
(67)
(i) CH2N2
(ii) CH3CO2H/H2O/THF(3:2:2)
CO2H
CO2CH3
OH
(68)
(69a)
LiOH/THF
CO2CH3
OH
(69b)
CO2H
OH
(62)
PTXA2



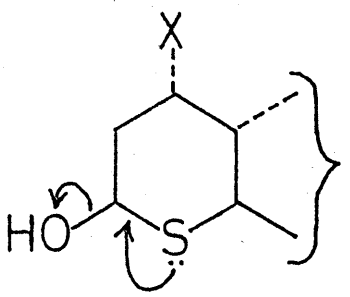
TXB_2 (12)

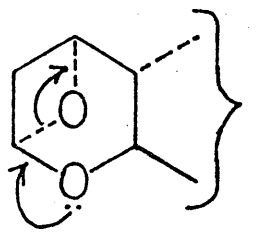


X=H (70) 9-deoxy-11a-thiathromboxane B_2

X=OH (71) 11a-thiathromboxane B_2

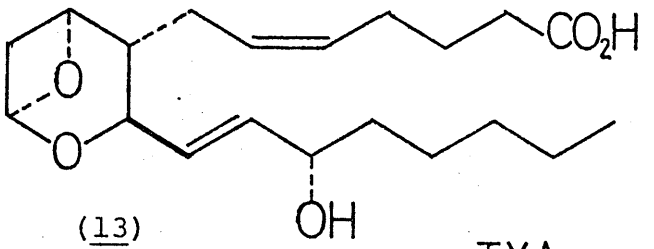
The synthetic targets of the work are the thiathromboxane analogues (70) and (71) in which the hemiacetal linkage of TXB_2 has been replaced by the more reactive α-hydroxy sulphide group. Analogues (70) and (71) contain a good leaving group at C-11 as does TXA_2:





Synthetic Objectives and Retrosynthetic analogues

Since TXA_2 promotes platelet aggregation it may well be the case that a more stable analogue, would act as an antagonist and so inhibit blood platelet aggregation. Analogues of TXA_2 that inhibit thromboxane synthetase or antagonise TXA_2 would be of great interest in the pharmaceutical field.

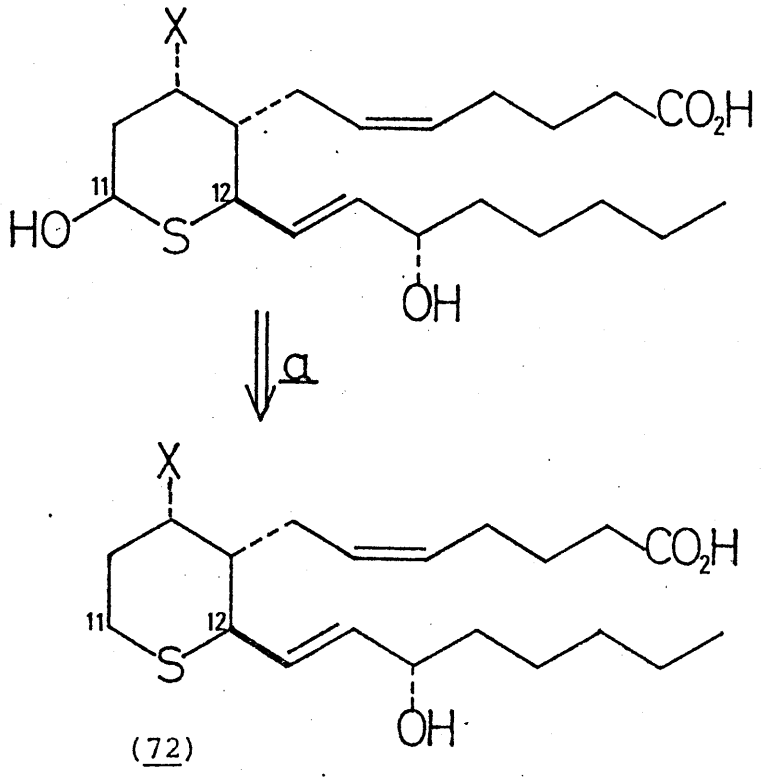


(13) TXA_2

The work described in this report is based on the observation that, in contrast to the potent TXA_2, TXB_2 is biologically stable. It is hoped to modify the structure of TXB_2 to obtain a biological activity of the same order as TXA_2 in a more stable molecule.

The synthetic targets all contain a thiane ring and three synthetic approaches to the target molecules are described (Chapters 2,3,4), two of which involve formation of the thiane ring towards the end of the synthetic route, the other commencing with the formation of the thiane ring.

In a retrosynthetic analysis the key precursor molecule is the disubstituted thiane derivative (72).

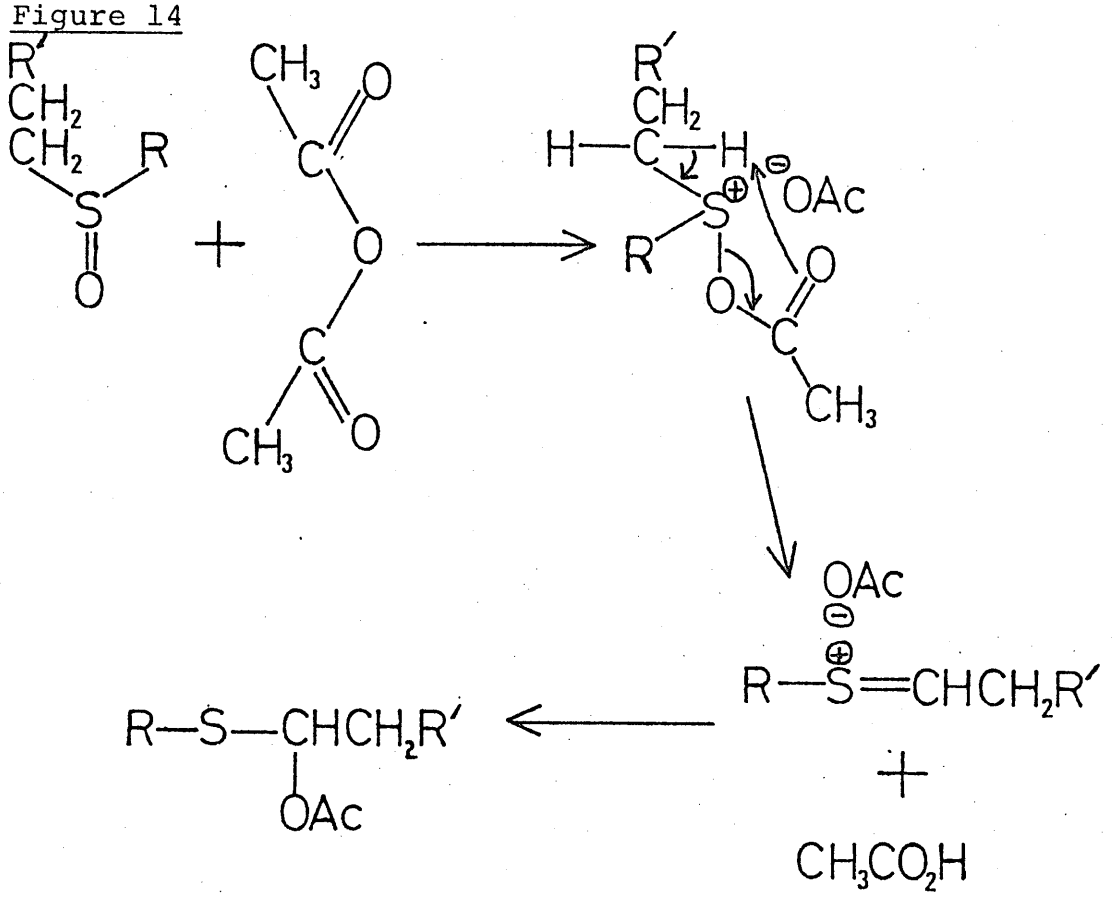


(72)

Step a in the forward process consists of oxidation followed by a Pummerer rearrangement, then hydrolysis. The oxidation of the sulphide to the sulphoxide can be carried out with one of several oxidants, for example, sodium metaperiodate or m-chloroperbenzoic acid, the temperature of reaction needing to be controlled to

prevent further oxidation to the sulphone.[35] This is followed by a Pummerer rearrangement which is the reaction of a sulphoxide bearing at least one α-hydrogen with hot acetic anhydride to give an α-acetoxy sulphide.[36] A possible mechanism for the rearrangement is shown in Figure 14.

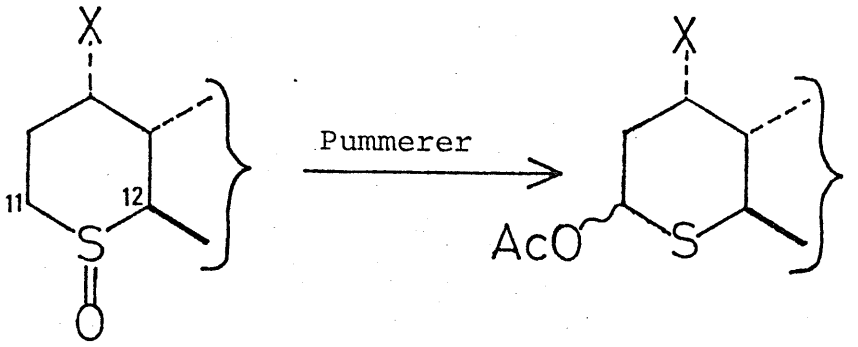
Figure 14



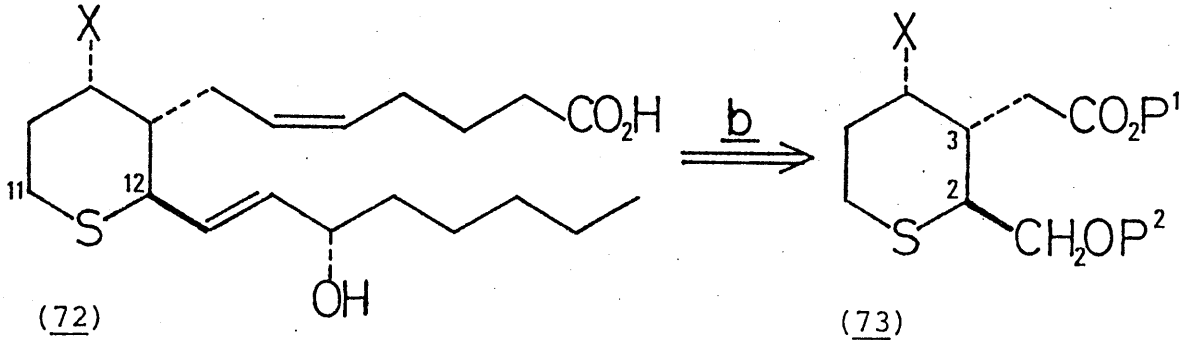
A common by-product in the Pummerer rearrangement is the corresponding α,β-unsaturated sulphide R-S-CH=CH-R'. However, it has recently been found that this conversion can be carried out in acetic anhydride containing trifluoroacetic anhydride at room temperature, thus minimising the possibility of the elimination of a hydrogen atom β-

to the sulphoxide group at high temperatures.[37] The conversion of the α-acetoxysulphide to the required α-hydroxysulphide group can be achieved by basic or acidic hydrolysis.

A variety of reaction conditions may have to be investigated in order to achieve the necessary regiospecificity in this reaction. Only the C-11 acetate (not the C-12 acetate) is required.



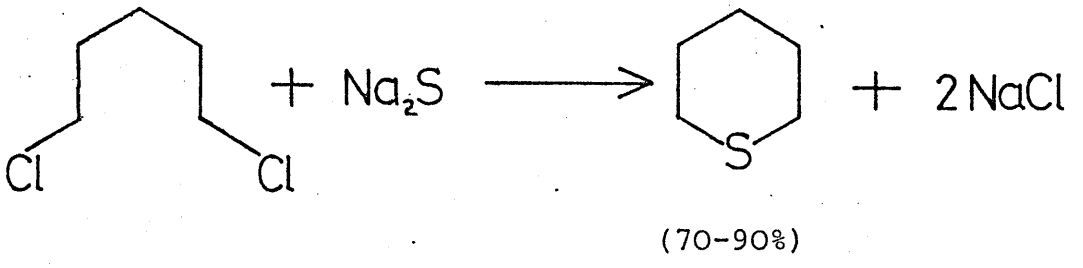
Continuing the retrosynthetic analysis, possible dislocations are shown below:



(72) (73)

In the forward process of step b, the Wittig reactions employed in many prostaglandin syntheses[38] could be used to form the required side chains at C-2 and C-3 of the thiane ring, using a CHO group at C-2 and a CH_2CHO group at C-3. These reactions would allow the introduction of the correct stereochemistry.
So the target molecule is now the relatively simple disubstituted thiane derivative (73) where P^1, P^2 are protecting groups that allow the side chains to be regiospecifically converted into aldehyde groups.

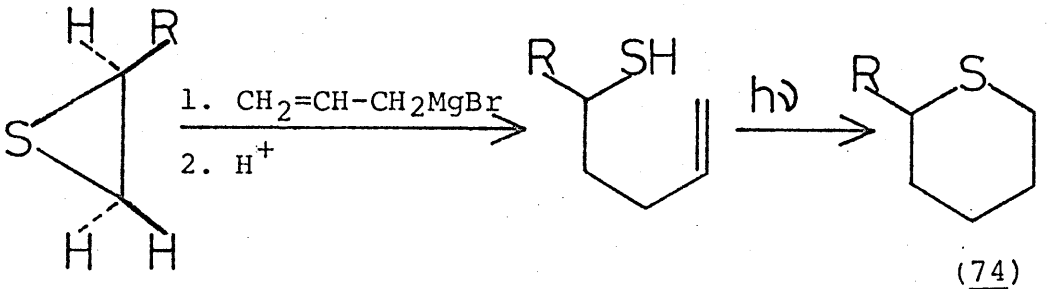
There are a number of methods available for constructing substituted thiane rings.[39,40,41,42,43] The most widely used method consists of refluxing an aqueous alcoholic solution of a dihalide with sodium sulphide:[40]



(70-90%)

However, this method can lead to substantial amounts of thiolane by-products, and also disubstituted substrates can prove difficult to prepare.

A photochemical method for thiane formation has been used extensively, involving the intramolecular cyclisation of compounds containing a thiol group and a carbon-carbon double bond. The reaction we decided to investigate first was discovered by Dronov:[44]

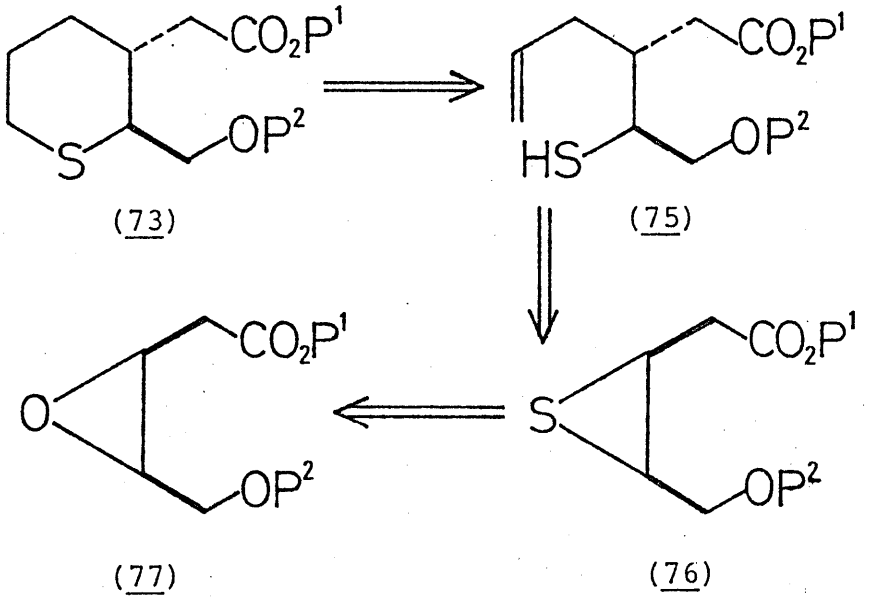


(74)

R=H, CH_3 or C_4H_9

Such reactions involving monosubstituted thiols derived from monofunctionalised thiirans to give monosubstituted thianes (74) have been well documented in the literature,[43,44] and there are examples of related radical induced cyclisations.[42] This latter example, when related to the need to obtain a differentially protected disubstituted thiane (73) leads to the retrosynthetic analysis depicted in Figure 15, and would lead to a synthesis of the 9-deoxy analogue (70, X=H).

Figure 15



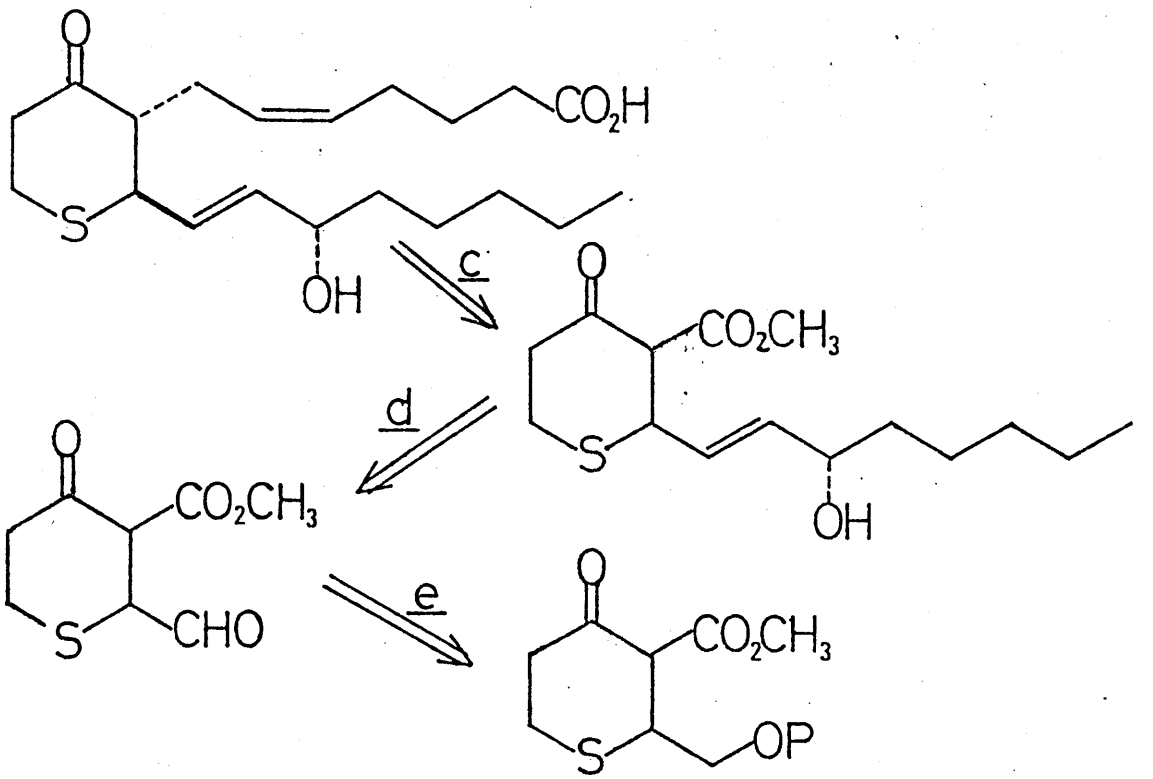
(73) (75)

(77) (76)

This approach, which appeared veryversatile is described in Chapter 2.

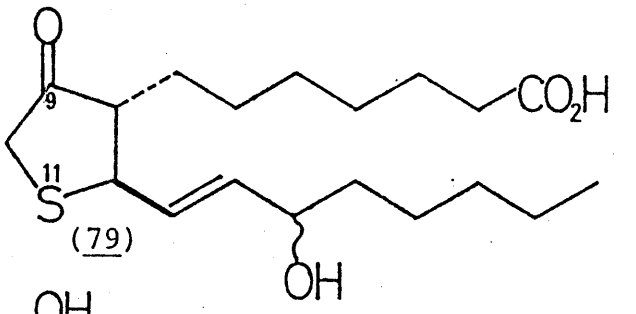
An alternative retrosynthetic analysis is shown in Figure 16.

Figure 16

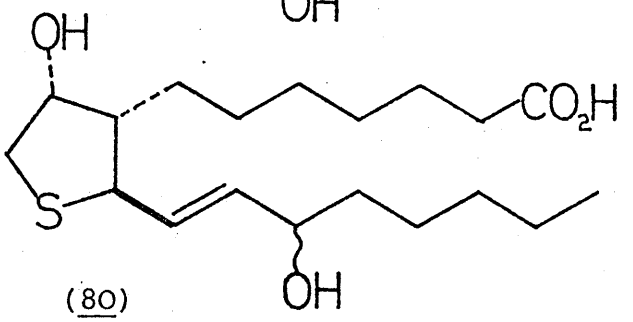


(78)

In the forward process, step c involves an alkylation reaction, whilst step d consists of a Wittig bond-forming reaction and oxidation and step e the hydrolysis of protecting group P to form an aldehyde functional group. This strategy has been used to make 11-thiaprostaglandins (79) and (80).[45]



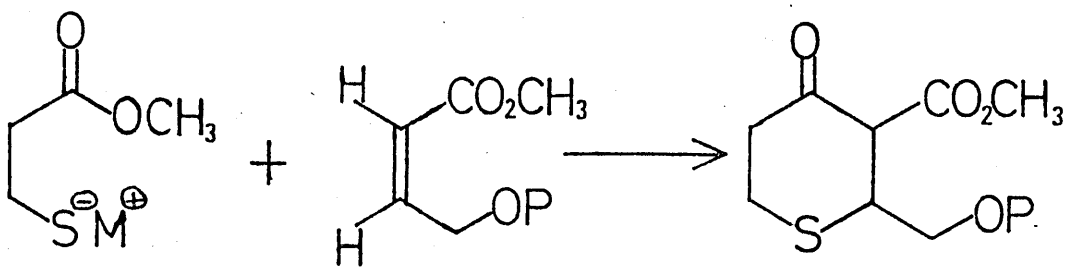
(79)



(80)

The key synthetic intermediate in this approach (Figure 16) is (78), a 2,3-disubstitutedthian-4-one. This compound (78) could possibly be constructed by the Michael addition of a thiolate anion (81) to a difunctionalised alkene (82), followed by an internal Claisen condensation, as shown in Figure 17.

Figure 17

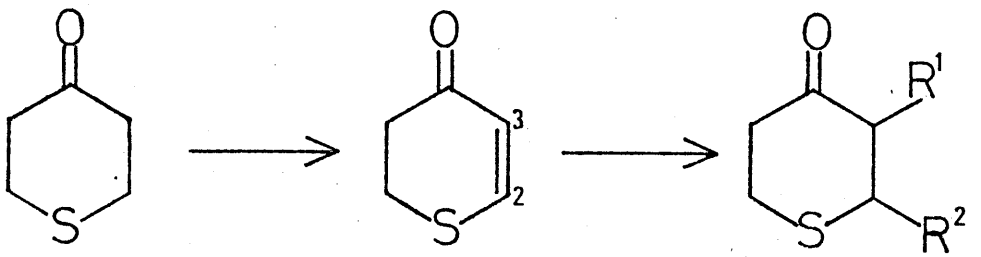


(81) (82) (78)

A similar reaction has been used previously to construct the thiolane ring[46], (as opposed to the thiane ring) in the synthesis of 11-thiaprostaglandins.[45] This approach is described in Chapter 3.

An alternative synthesis of a disubstituted thian-4-one would involve the introduction of the two side chains in sequence to a performed thiane ring. This is the basis of the final approach (Chapter 4) in which thian-4-one (83) is formed first, and the side chains are added by means of new synthetic techniques to form carbon-carbon bonds at both C-2 and C-3 of the unsaturated derivative (84). This is depicted in Figure 18.

Figure 18



(83) (84) (85)

Thian-4-one (83) required for this approach is readily available,[47,48,49] and the preparation of the required unsaturated thianone, 2,3-dihydrothi-in-4-one (84) from (83) has recently been reported,[50,51] although it has not been employed in carbon-carbon bond forming reactions.

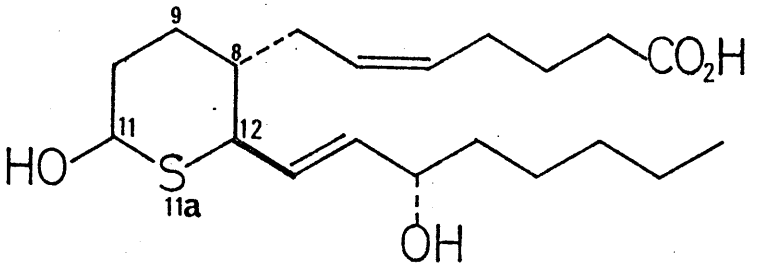
The approaches outlined for Chapters 2 and 3 involve formation of compounds with the thiane ring and parts of the required side chains (e.g. 73 and 78). However, the approach in Chapter 4 involves addition of the two side chains as complete preformed units to a pre-formed thianone ring.

CHAPTER 2

Routes to 9-Deoxy-11a-thiathromboxane B_2

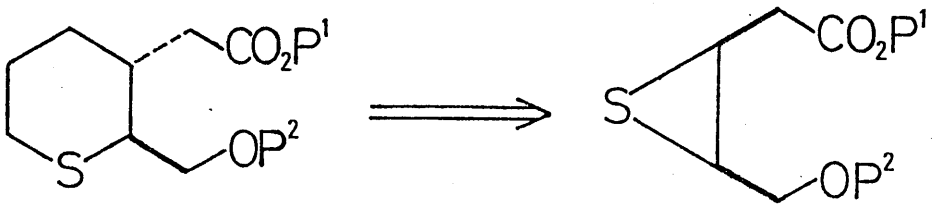
Chapter 2 Routes to 9-deoxy-11a-thiathromboxane B_2

The synthetic approach to 9-deoxy-11a-thiathromboxane B_2 (70) described in this chapter involves formation of the thiane ring at a stage where parts of both side-chains are present in the structure.



(70)

A precursor to (70) is a relatively simple disubstituted thiane derivative of type (73) where P^1, P^2 are protecting groups that allow the side-chains at C-8 and C-12 of (70) to be constructed. Working backwards from (73) leads to a key intermediate, a thiiran of type (76).

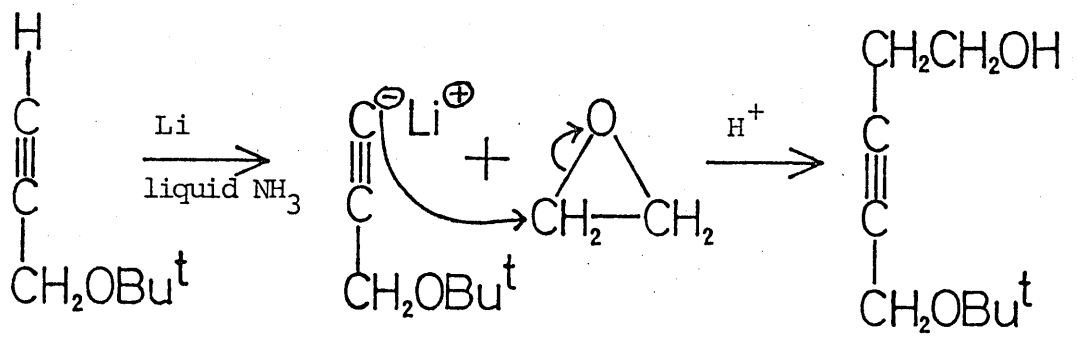


(73) (76)

This illustrates the need to obtain a differentially protected disubstituted thiiran (76) with groups which can be selectively removed, and which is a common intermediate to all the routes described.

The first attempted route towards a synthesis of 9-deoxy-11a-thiathromboxane B_2 (70) by this approach is shown in Figure 19. It was anticipated that the key thiiran ring-opening would be regioselective for steric reasons.

The first four steps in this route involve known manipulations of compounds containing an alkyne bond, and the actual syntheses have been adapted from analogous literature syntheses. 3-t-Butoxypropyne (87) was prepared from prop-2-yn-1-ol (86) by the acid-catalysed addition of the alcohol across the double bond of 2-methylpropene.[52] Abstraction of the terminal proton in (87) by lithium amide in liquid ammonia, and subsequent reaction of the lithio-acetylene with oxirane gave 5-t-butoxypent-3-yn-1-ol (88).[53,54]



(87) (88)

Figure 19

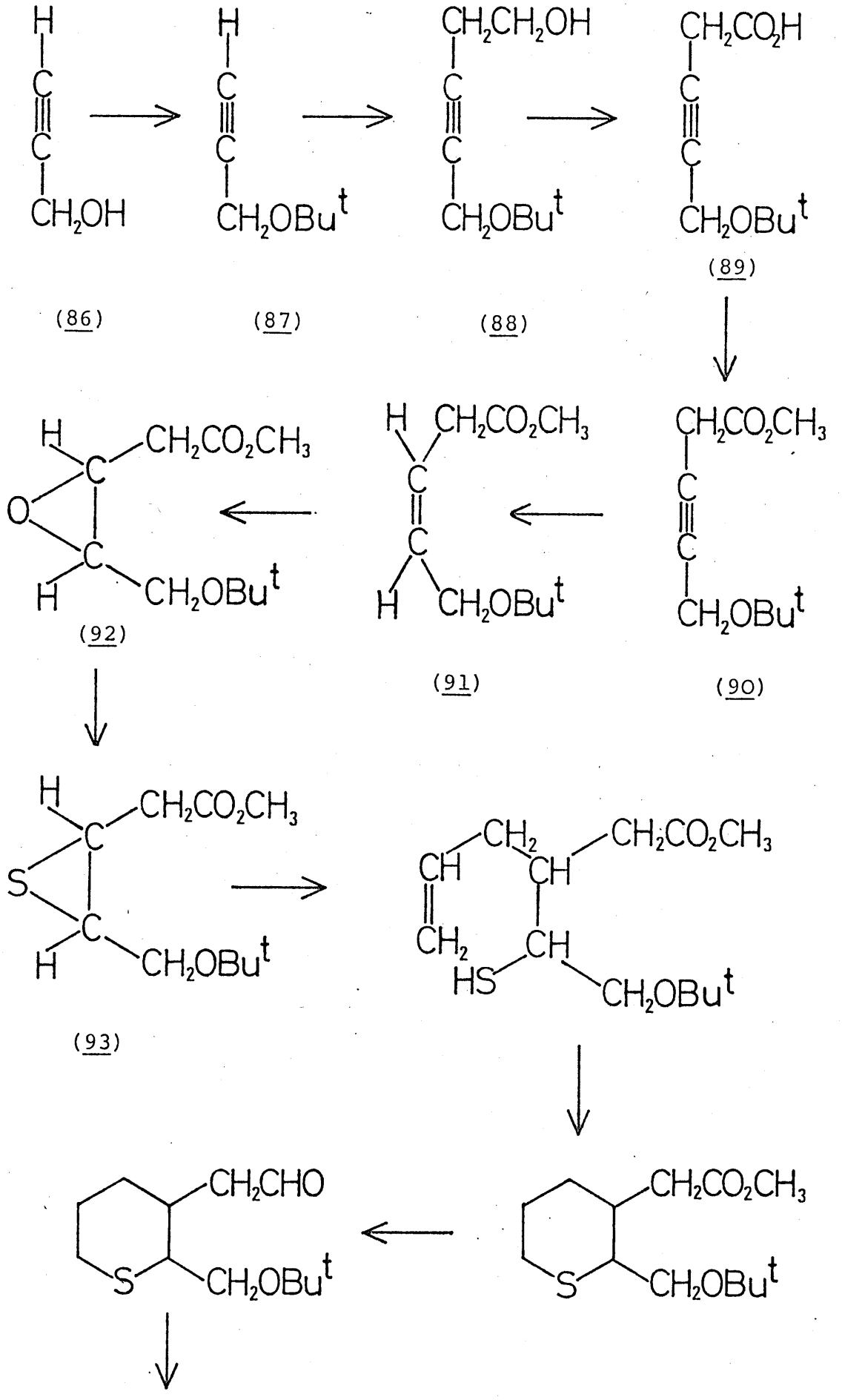
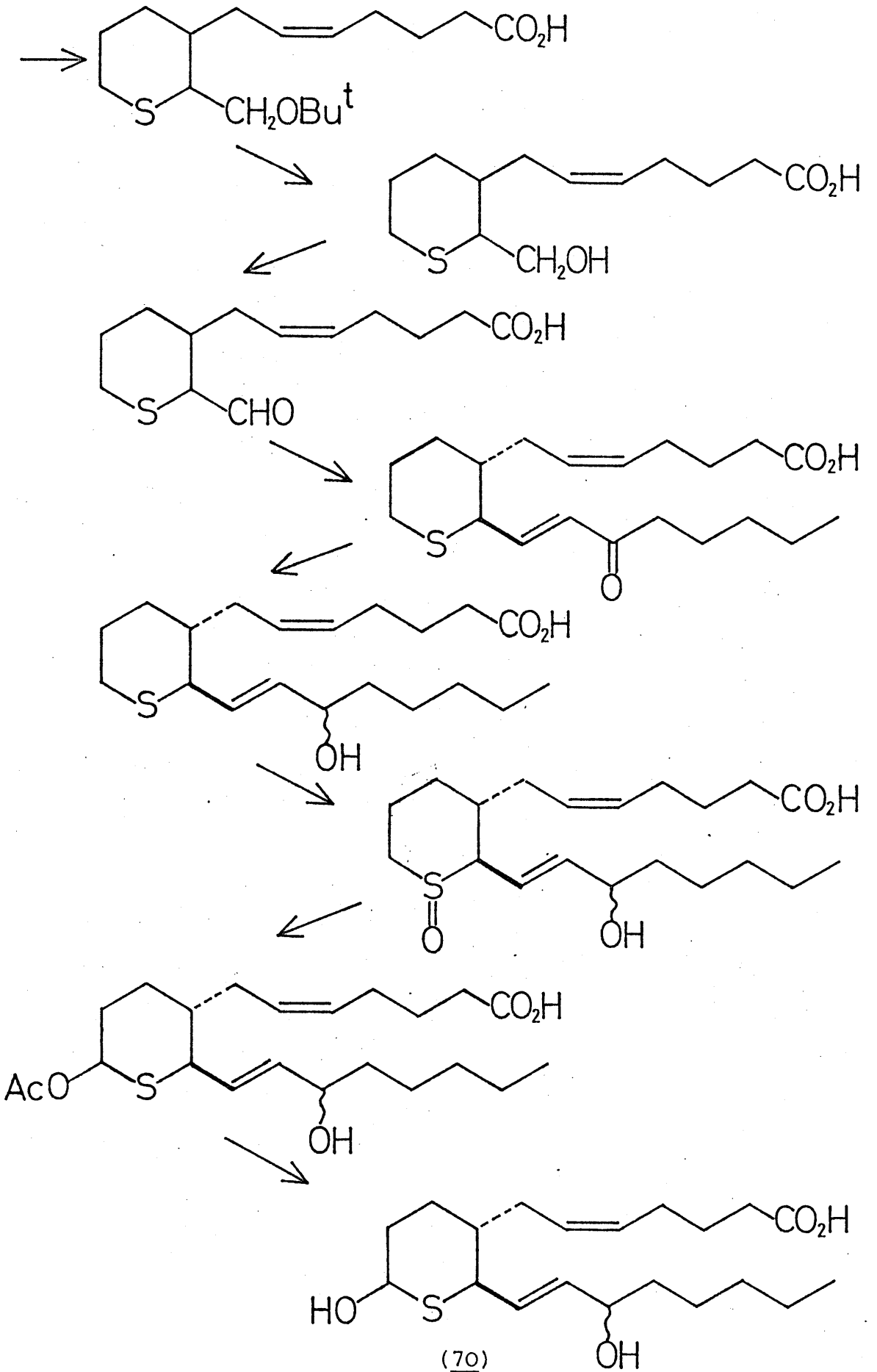
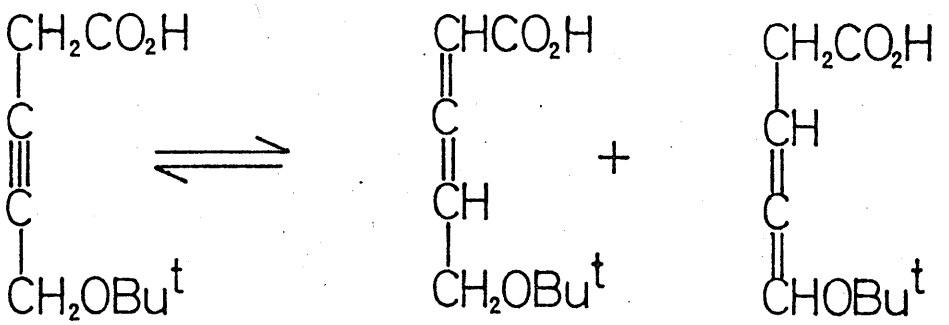


Figure 19 (cont'd)



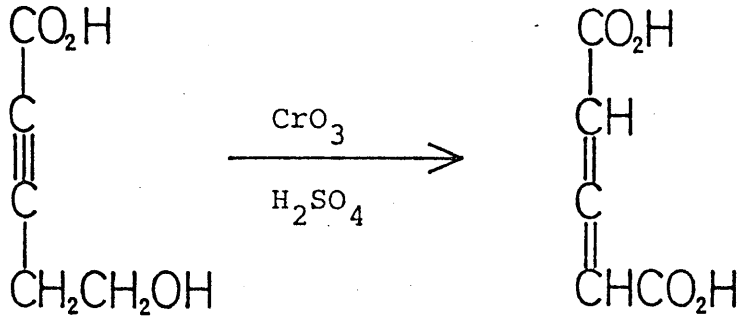
(70)

The hydroxy function in (88) was converted to an ester via the carboxylic acid. Oxidation of (88) to 5-t-butoxypent-3-ynoic acid (89) was achieved using chromic acid in acetone, a reagent frequently used in the alkyne field.[55] However, this reaction also gave a proportion (6%) of the allenic acids (94) and (95) produced by the propargylic rearrangement of (89).



(89) (94) (95)

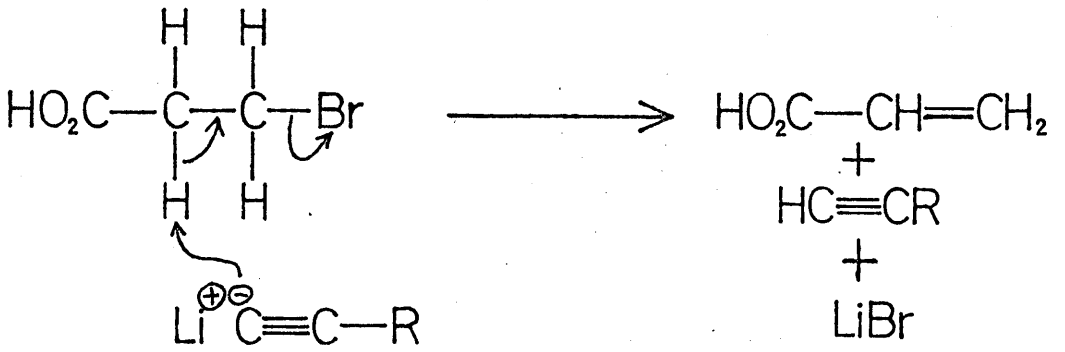
The possibility of such a rearrangement is always present as long as there is at least one hydrogen atom attached to a carbon atom next to a triple bond. A wide variety of bases of varying pK_b bring about such a rearrangement, e.g. sodium amide, alkali metal acetylides, potassium hydroxide and sodium carbonate. Acids will also give this conversion. The ease of rearrangement varies not only with the base strength, but also with the type of alkyne, the solvent and the temperature. The rearrangement has been observed in an acid medium when the chromic acid oxidation of the primary propargylic alcohol (96) yielded the rearranged allenic product (97), where no alkaline reagents were used even in the reaction work-up.[56]



(96) (97)

The conversion of (89) to its methyl ester, methyl 5-t-butoxypent-3-ynoate (90), was carried out in high yield by reaction with diazomethane.

Consideration had been given to the direct transformation of (87) to (90) by alkylation of the lithiated derivative of (87) with methyl 2-bromoacetate ($CH_3O_2C\text{-}CH_2Br$). However, for bromoacids ($HO_2C(CH_2)_nBr$; n=2,3) and their corresponding bromoesters, dehydrobromination becomes the predominant reaction owing to the electron withdrawing effect of the carboxylic acid or ester group.[57]

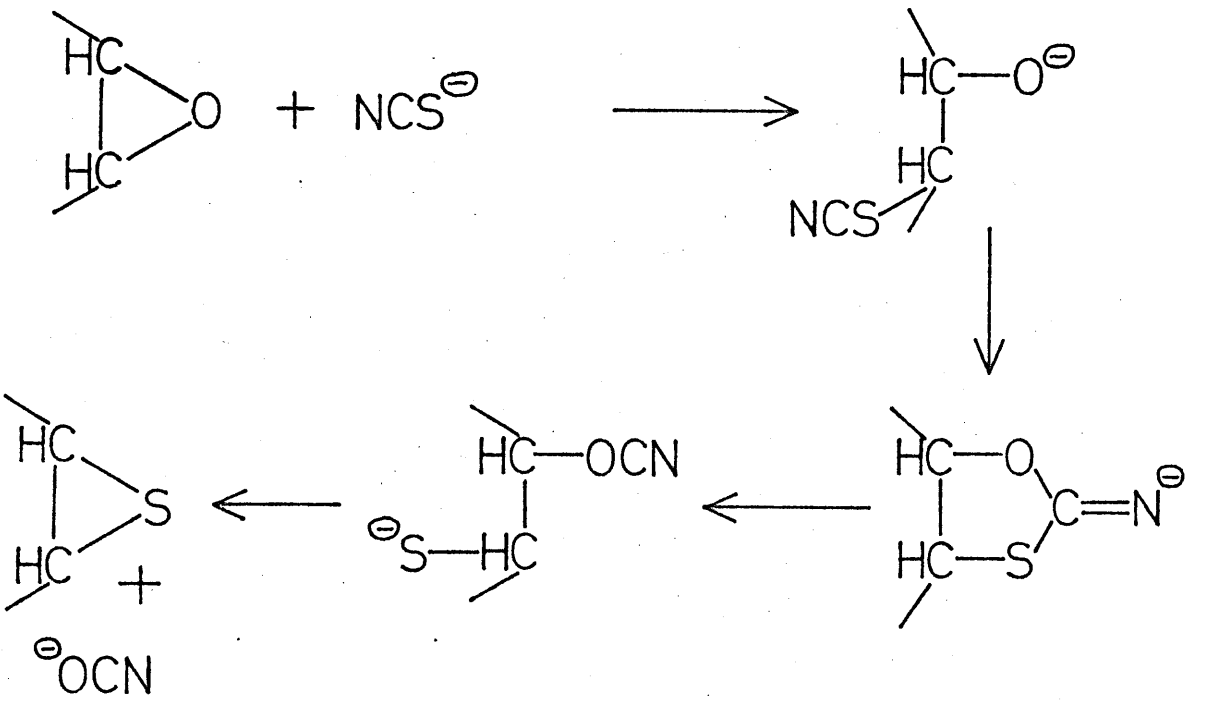


Brandsma[58] has also observed that ethyl 2-bromoacetate ($H_5C_2O_2C-CH_2Br$) yields polymeric products only in this reaction.

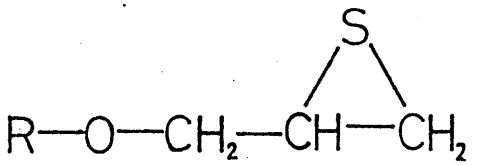
Atmospheric pressure hydrogenation of (90) with 5% palladium on charcoal gave methyl cis-5-t-butoxypent--3-enoate (91) in 84% yield. Epoxidation of (91) with m-chloroperbenzoic acid in dichloromethane gave methyl 5-t-butoxy-3,4-epoxypentanoate (92) in 60% yield.

Transformation of the oxiran (92) to the thiiran (93) proved to be unsuccessful after many attempts. The literature reports the reaction of oxirans with alkali metal thiocyanates or thiourea as being the most convenient procedure for the formation of thiirans on a preparative scale.[59,60] Ettlinger[61] has proposed that the formation of thiirans in these reactions involves the nucleophilic opening of the oxiran ring by the thiocyanate anion, the isomerisation of the resulting alkoxide anion[62] via a cyclic intermediate into a thiolate anion, and the conversion of the latter into the thiiran with elimination of the cyanate anion (Figure 20). According to this mechanism, the conversion of the oxiran ring into a thiiran ring should involve two Walden inversions in the trans-opening and trans-closure of the ring.

Figure 20



Most thiirans formed by this method have been monoalkylthiirans although some 2-alkoxymethylthiirans (96) have been synthesised,[62] and these are reported to be stable for long periods at room temperature.



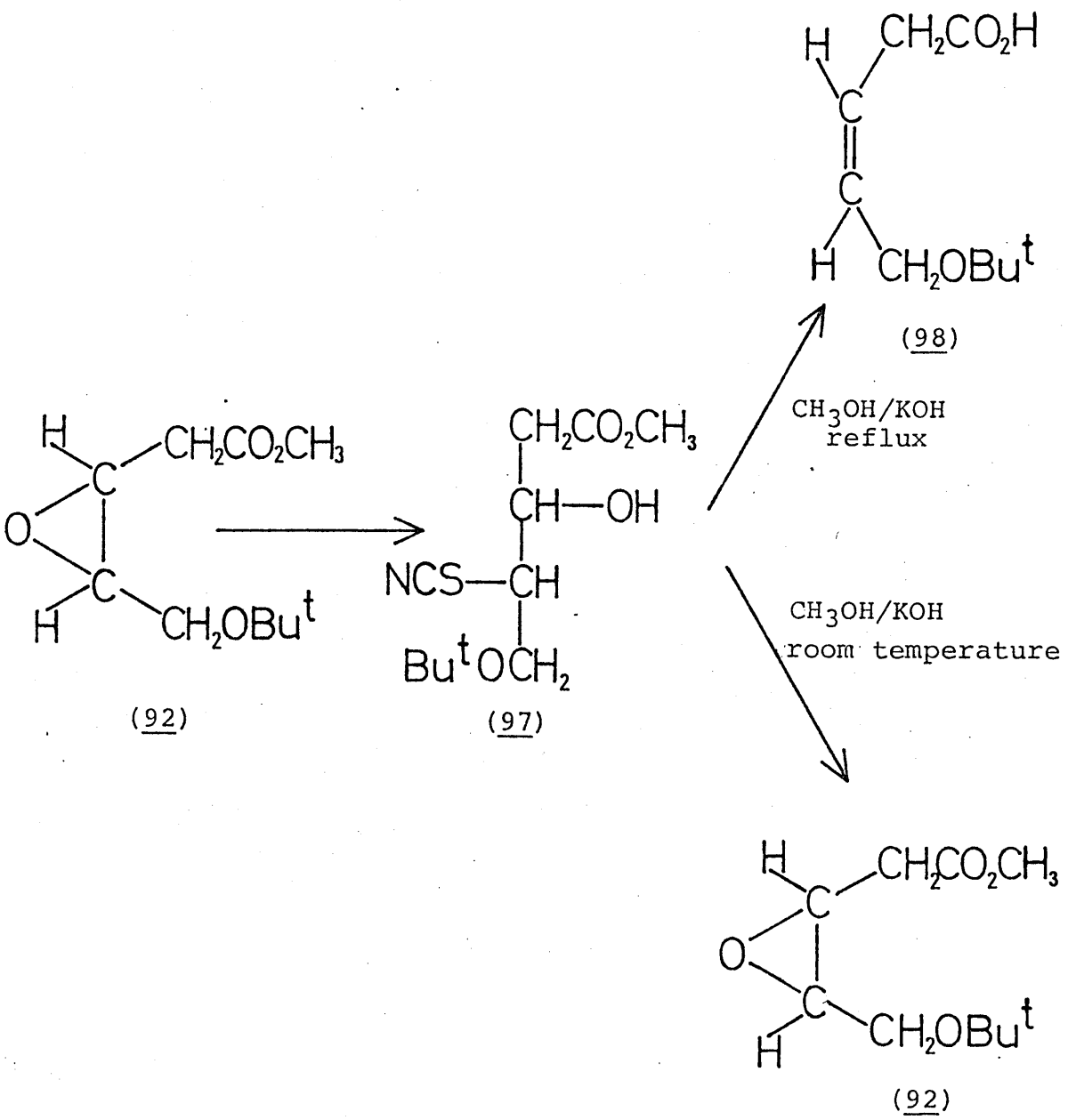
(96)

R = CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_5

The experimental procedure used for thiiran formation was that of Takeda,[63] which involved reaction of the oxiran (92) with a thiocyanic acid/ether complex, and

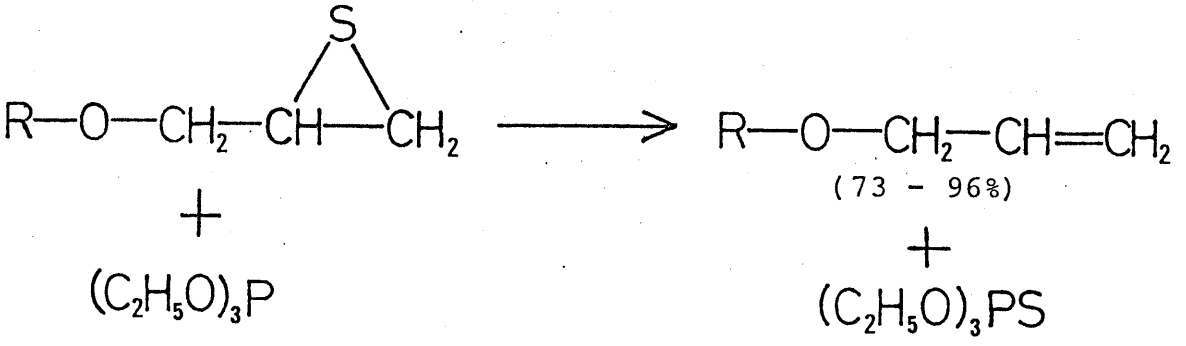
which allowed isolation of the intermediate thiocyanatoalcohol (97) derived from (92). However, attempts at subsequent ring-closure of this intermediate with the recommended methanolic potassium hydroxide reagent were not successful (Figure 21).

Figure 21



Various reaction temperatures were tried, from room temperature to reflux temperature. At reflux temperature the ester function was hydrolysed and further product decomposition occurred, the alkene (98) being formed, as shown by the tlc comparison with an authentic sample of (98); reaction at room temperature gave the oxiran starting material as shown by the tlc comparison with an authentic sample of (92).

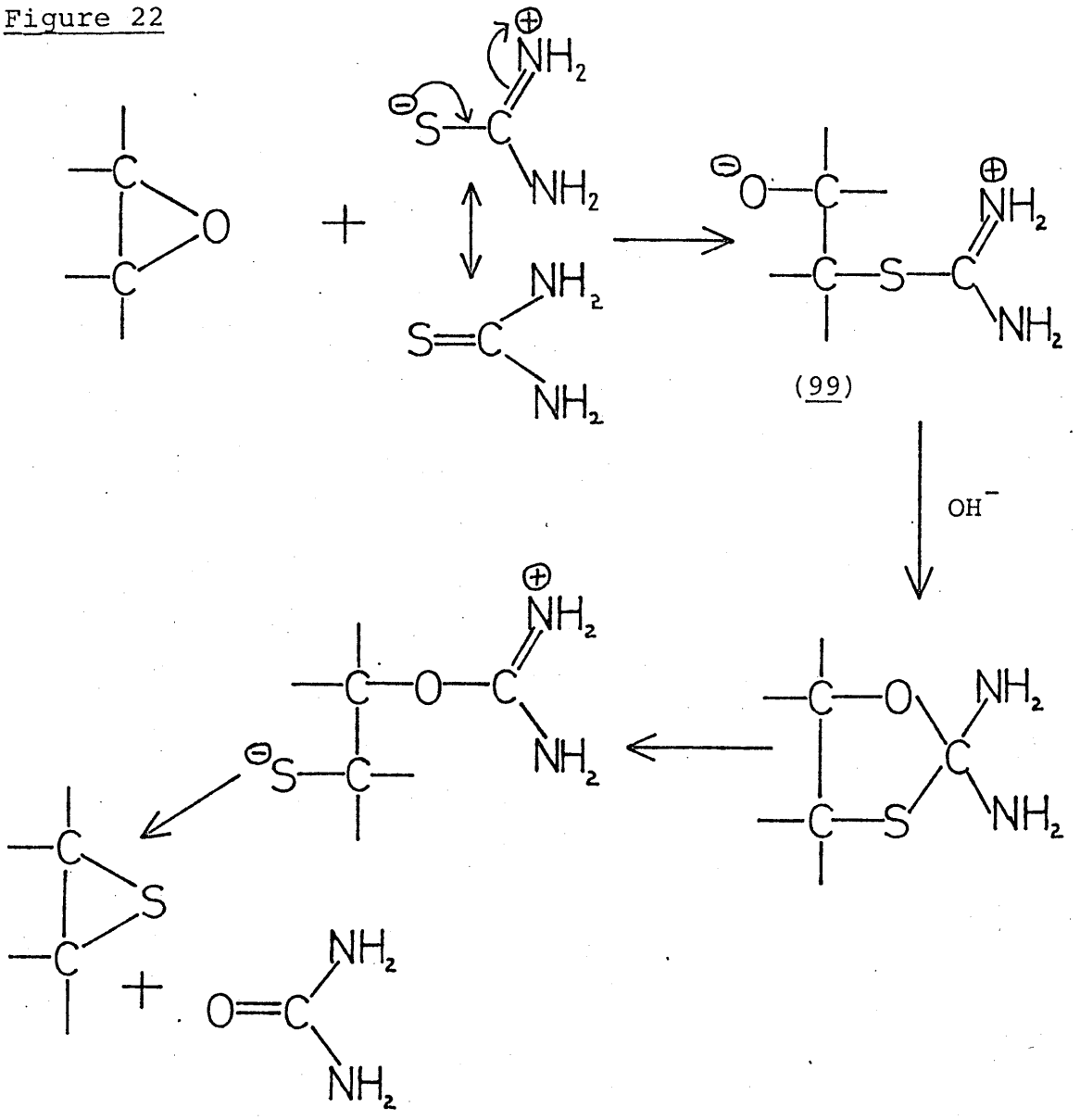
Alkene (98) was also detected when the oxiran (92) was treated with aqueous alcoholic potassium thiocyanate as described by Vierhapper.[42] This result was not surprising in the light of a report by Culvenor,[64] who showed that thiirans with electronegative groups attached to the thiiran ring cannot be obtained by this method because of the ease of elimination of sulphur in the course of their formation. The desulphurisation of 2-alkoxymethylthiirans by the nucleophilic reagent triethyl phosphite has been described by Schuetz[65]:



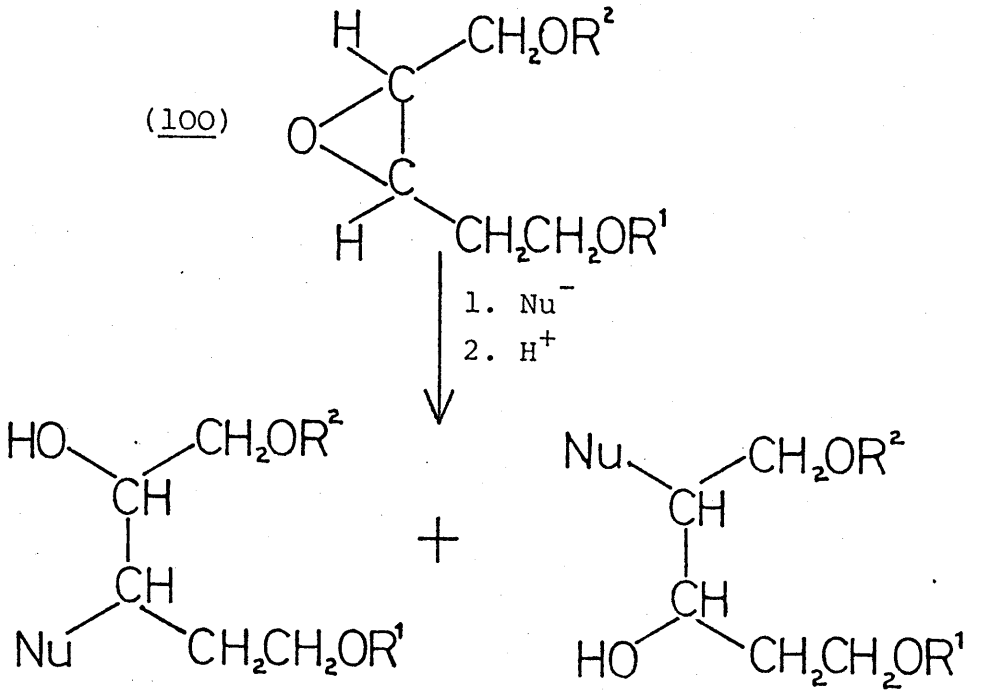
In conclusion it seems likely that the required thiiran(93) was formed but was further transformed to the corresponding alkene (98) by the action of methanolic alkali or other nucleophilic reagents present in the reaction mixture. However, investigations have established that under certain conditions of synthesis even thiirans which readily lose sulphur can be obtained from oxirans. For example, 2,3-diphenylthiirans were obtained in yields of 90% by the initial condensation of the corresponding oxirans with thiourea[66] and subsequent cautious alkaline treatment of the resulting isothiuronium salt (99), as shown in Figure 22.

This procedure may have allowed the required difunctionalised thiiran to be obtained, although the acidic conditions employed for reaction would probably have led to removal of the ether and/or ester groups present. However, rather than try this a second route was investigated.

Figure 22

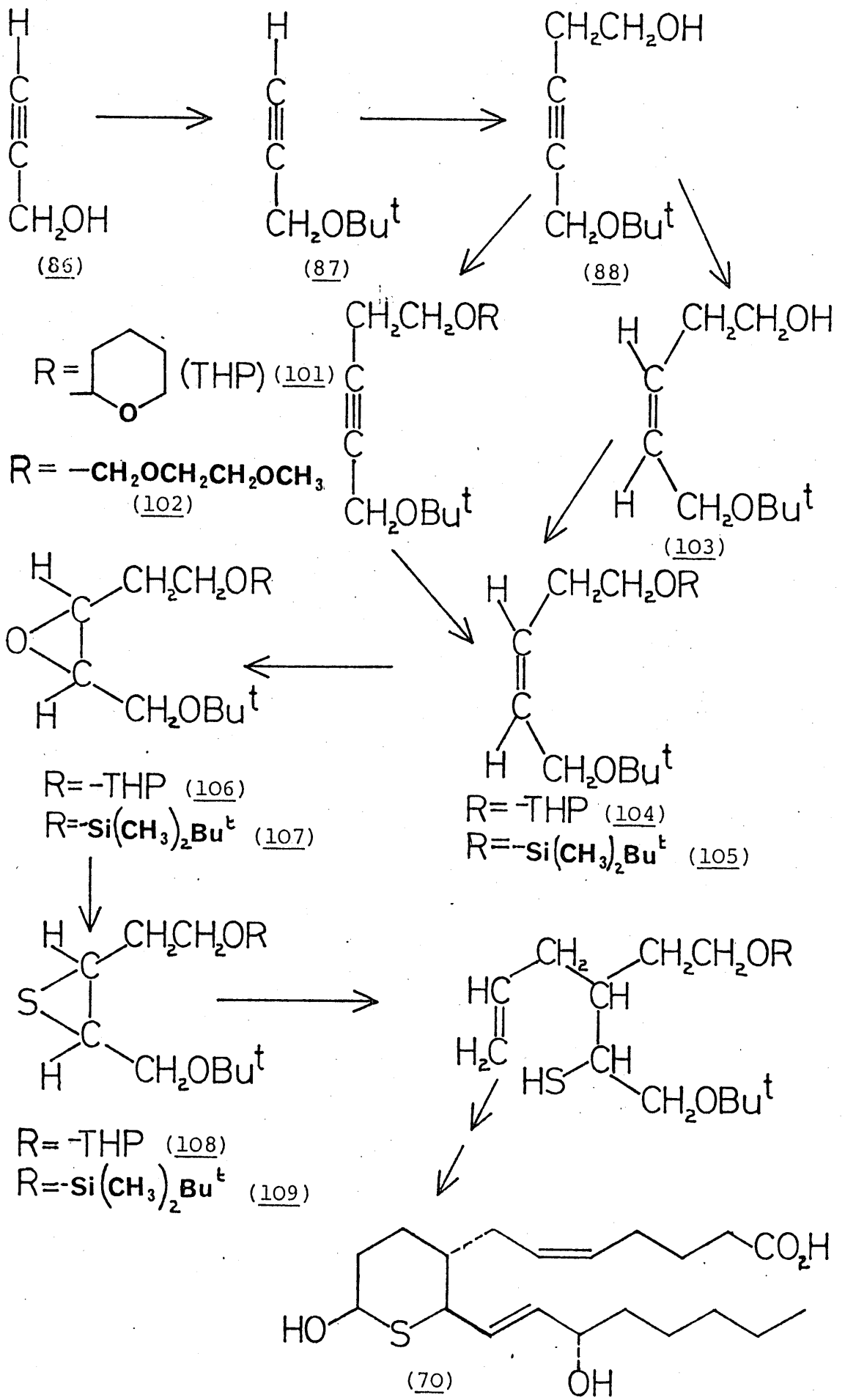


It was decided to have two ether groups in the molecule (e.g. 100), chosen so that each could be removed preferentially in the presence of the other. It was realised that subsequent nucleophilic ring-opening of the oxiran or thiiran was likely to be non-regioselective leading to a mixture of products e.g.



The preparation of compounds such as (100) is shown in Figure 23. Use was made of compound (88) which contains a tertiary-butoxy group, that requires fairly specific reaction conditions for its removal, either anhydrous trifluoroacetic acid or hydrogen bromide in acetic acid.[67] 1-t-Butoxy-5-tetrahydropyranyloxypent-2-yne (101) was prepared by the standard acid-catalysed addition of alcohol (88) to dihydropyran.[68] Another protecting group which has been described recently, the 2-methoxyethoxymethyl (MEM) group was also investigated, since it can be removed under essentially neutral aprotic conditions with anhydrous zinc bromide in dichloromethane.[69] MEM ethers are stable under a wide variety of conditions, including those attending the use of strong bases, reducing agents, organometallic reagents and mild acids. Selective cleavage of MEM

Figure 23

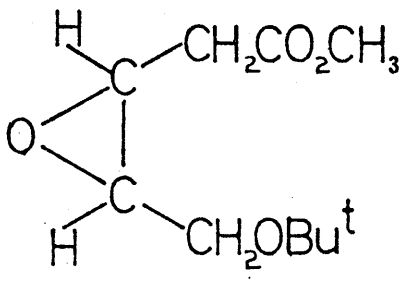

(86)
(87)
(88)
R = (THP) (101)
R = −CH2OCH2CH2OCH3
(102)
(103)
R= -THP (106)
R=-Si(CH3)2But (107)
R= -THP (104)
R=-Si(CH3)2But (105)
R= -THP (108)
R=-Si(CH3)2But (109)
(70)

ethers is possible in the presence of benzyl, tetrahydropyranyl, silyl and tertiary-butyl ethers. However, because of the difficulty experienced in preparing the MEM ether (102) and the relatively low yield obtained (40%) it proved to be of little synthetic value in this instance.

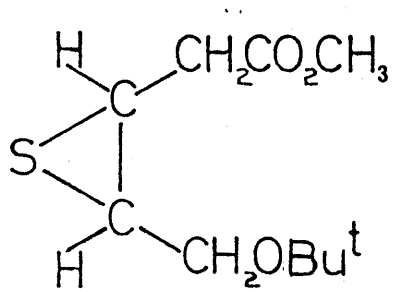
Hydrogenation of alkyne (101) at atmospheric pressure with 5% palladium on charcoal gave cis-1-t-butoxy-5-tetrahydropyranyloxypent-2-ene (104). This reduction was also accompanied by removal of the tetrahydropyranyl function giving the corresponding alcohol (103). This was probably due to the presence of a trace of mineral acid from the previous protection reaction. This problem was overcome by adding a small proportion of calcium carbonate to the reaction mixture prior to hydrogenation. To try to improve the yield of the protection and hydrogenation reactions (30%), the alternative sequence, hydrogenation then protection, was attempted, (88) to (103) to (104). The hydrogenation of (88) proceeded in high yield (87%) to give cis-5-t-butoxypent-3-en-1-ol (103), but the protection reaction (103) to (104) gave the required product in only 25% yield. As an alternative protecting group to the tetrahydropyranyl group, the tertiary-butyldimethylsilyl group was introduced into the synthesis by the transformation of (103) to cis-1-t-butoxy-5-t-butyldimethylsilyloxypent-2-ene (105) in 92% yield, using the procedure of Corey[70] with tertiary-

butyldimethylsilyl chloride and imidazole as catalyst in anhydrous dimethylformamide. This protecting group can be cleaved specifically by tetrabutylammonium fluoride in tetrahydrofuran at room temperature.

With alkenes (104) and (105) in hand their respective oxirans (106) and (107) were prepared by epoxidation with m-chloroperbenzoic acid in dichloromethane, with the addition of sodium hydrogen carbonate as a buffer to prevent any removal of the acid-sensitive protecting groups, as recommended by Anderson.[71] The conversion of the oxirans (106) and (107) into their respective thiirans (108) and (109) proved to be unsuccessful as in the analogous conversion of oxiran (92) to thiiran (93). The reasoning behind the failure to obtain thiiran (93) presumably also applies to the failure to obtain thiirans (108) and (109).



(92)

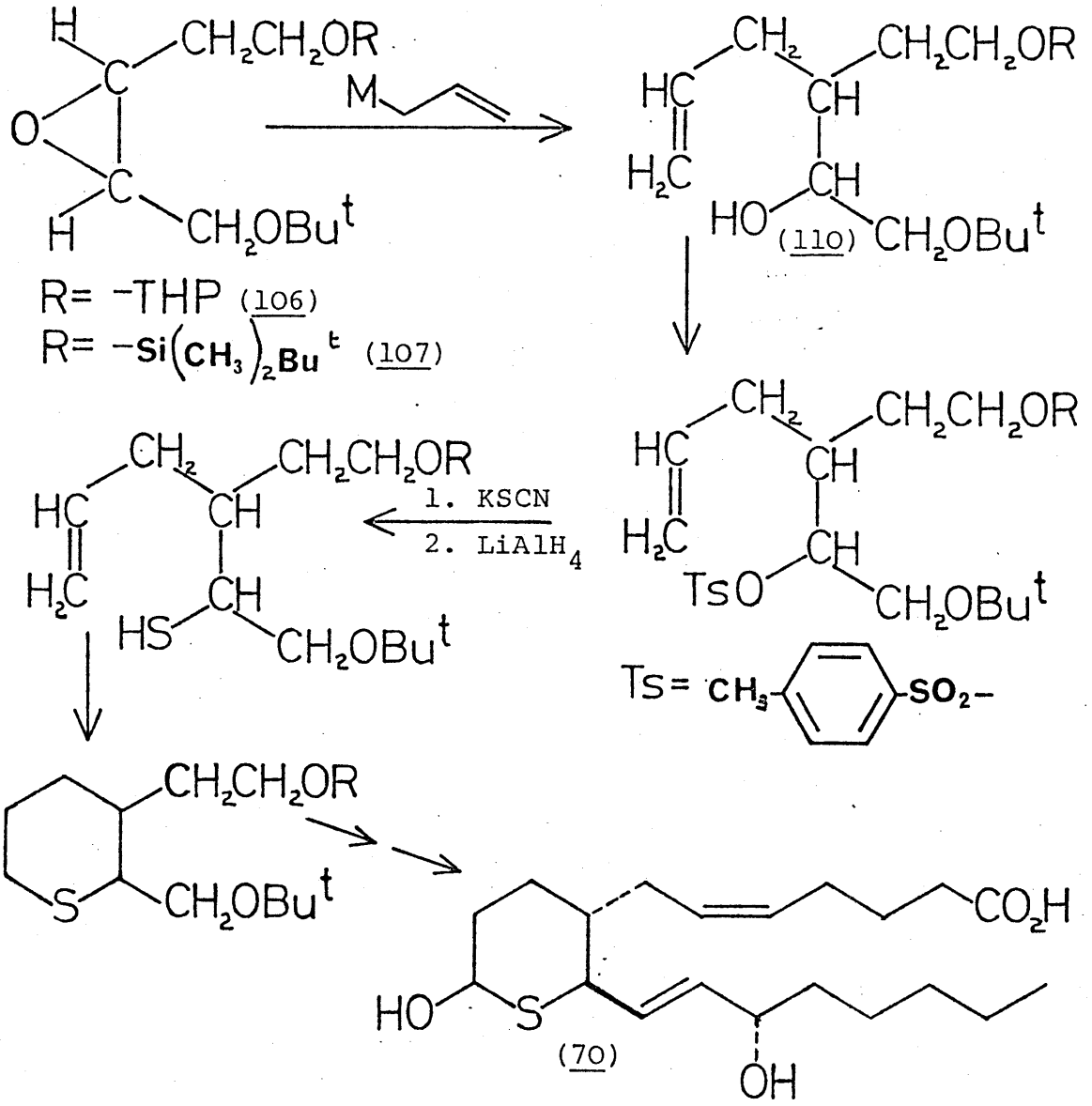


(93)

We therefore explored the alternative route shown in Figure 24. The nucleophilic ring-opening of oxirans (106) and (107) was investigated quite extensively, since the hydroxyl groups of the ring-opened products could easily be converted into a thiol group,[72] leading to the introduction of sulphur into the molecule as

required in the final 9-deoxy-11a-thiathromboxane B_2 (70).

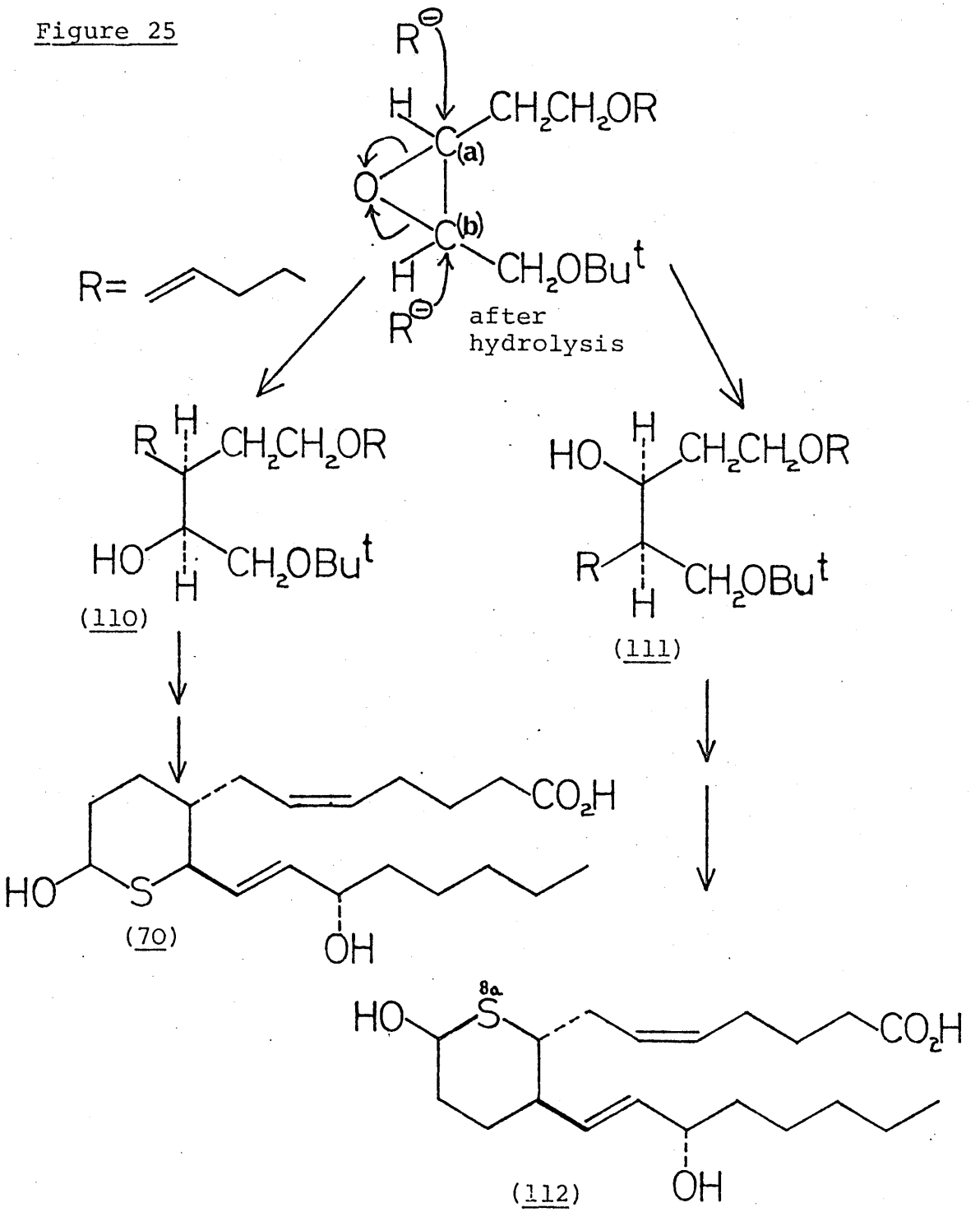
Figure 24



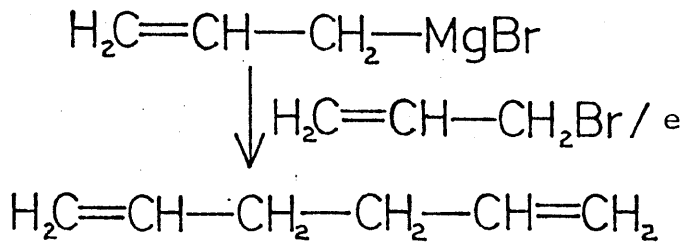
The influence exerted by substituents on the oxiran ring can be both steric and electronic in character,[73] and in the case of oxirans (106) and (107) there are electron-withdrawing substituents on each side of the oxiran group, so any prediction of the preferred site of attack by nucleophiles is difficult. As shown in

Figure 25, nucleophilic attack is possible at either carbon atom of the oxiran ring (a or b) giving the required product (110) or product (111). This route might therefore lead to both 9-deoxy-11a-thiathromboxane B_2 (70) and 11-deoxy-8a-thiathromboxane B_2 (112); both of the compounds would be of interest.

Figure 25

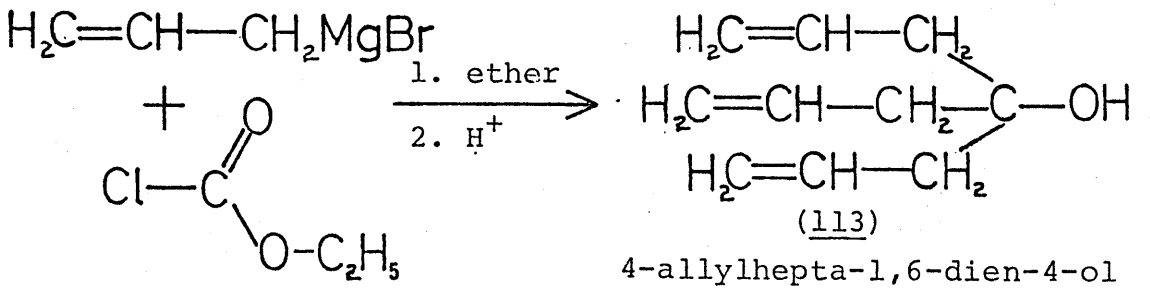


The reaction of oxirans (106) and (107) with allylmagnesium bromide was investigated first. Allylmagnesium bromide was prepared by the direct reaction of magnesium with allyl bromide in ether as solvent. An excess of magnesium (2.5 molar equivalents) was used in order to minimise the coupling of the Grignard reagent with unused allyl bromide to form hexa-1,5-diene:[74]



hexa-1,5-diene

Before use the Grignard solution was decanted from the excess of magnesium present. The formation of allylmagnesium bromide was checked by reacting it with ethyl chloroformate, following a literature procedure.[75] This gave the expected product (113) after work-up.



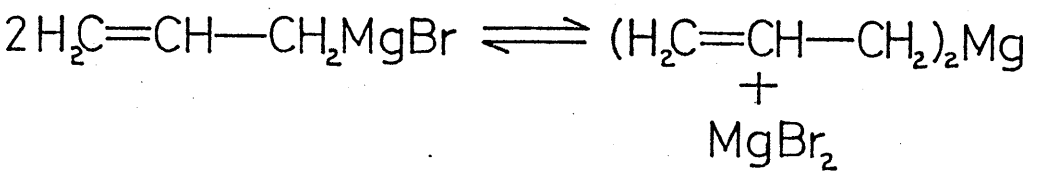
(113)

4-allylhepta-1,6-dien-4-ol

Incomplete reaction was observed when allylmagnesium bromide was reacted with (106) and (107), the reaction temperature and time making little difference to the product distribution. Nuclear magnetic resonance and infra-red evidence suggested that rearrangement

to a ketone had taken place, and at reflux temperature a non-polar product was formed, most probably a polymer of hexa-1,5-diene.

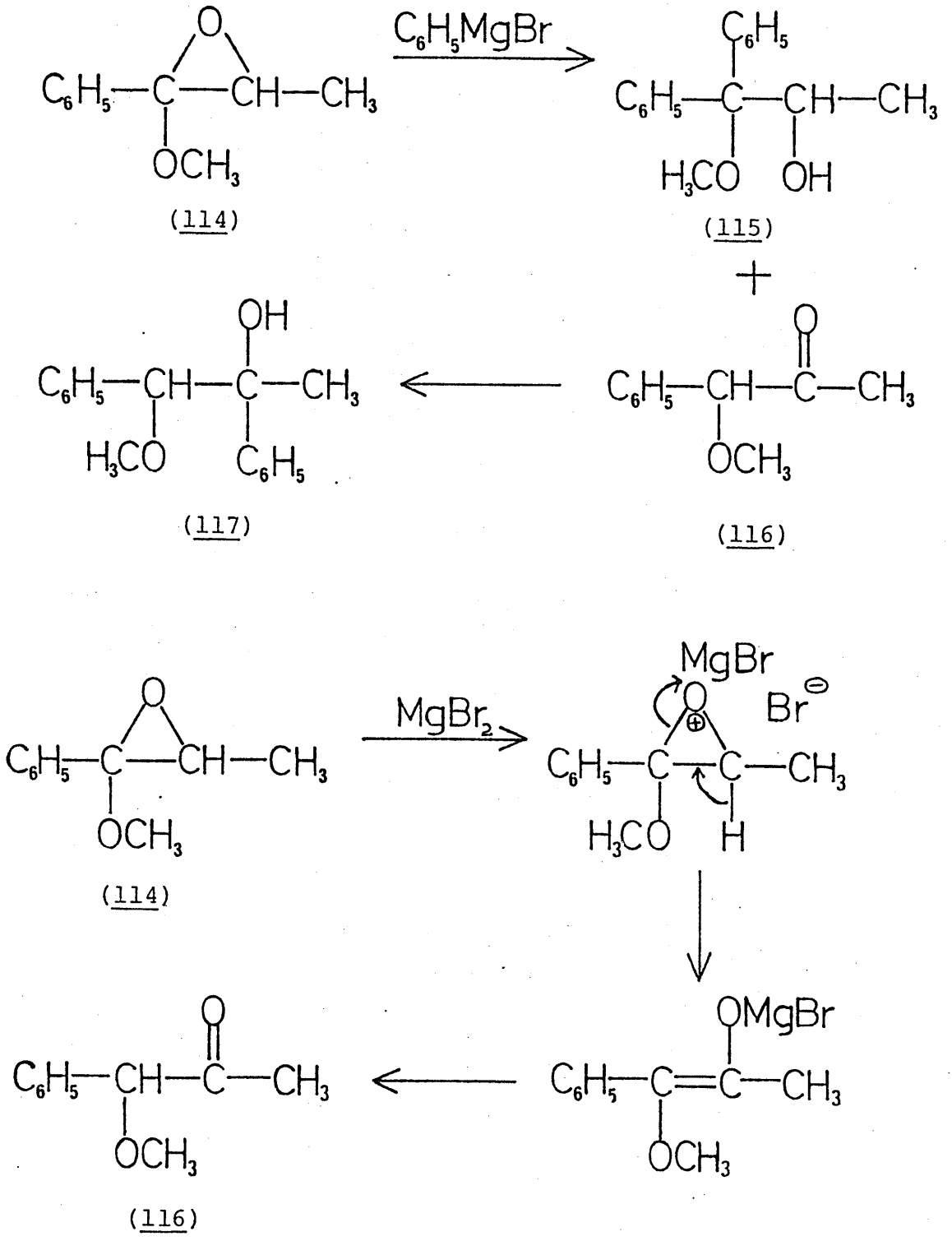
This result can be rationalised in view of the fact that an ethereal solution of allylmagnesium bromide always contains diallylmagnesium and magnesium bromide owing to the existence of the following equilibrium:



The presence of magnesium bromide in such solutions frequently leads to rearrangement of an oxiran to a carbonyl compound. So the products obtained from the reaction of an oxiran with a Grignard reagent often correspond to addition both to the oxiran itself and to its rearrangement product. Thus, two products were isolated from the action of phenylmagnesium bromide[76] on the oxiran (114), as shown in Figure 26.

Product (115) arises by direct attack of a phenyl anion on the carbon atom of the oxiran, while product (117) must arise by rearrangement of the oxiran to the ketone (116), followed by further reaction of this ketone with Grignard reagent. It was shown that the ketone (116) could be isolated in 80% yield by treatment of the oxiran with a solution of magnesium bromide in ether. Oxiran (114) is presumably rearranged

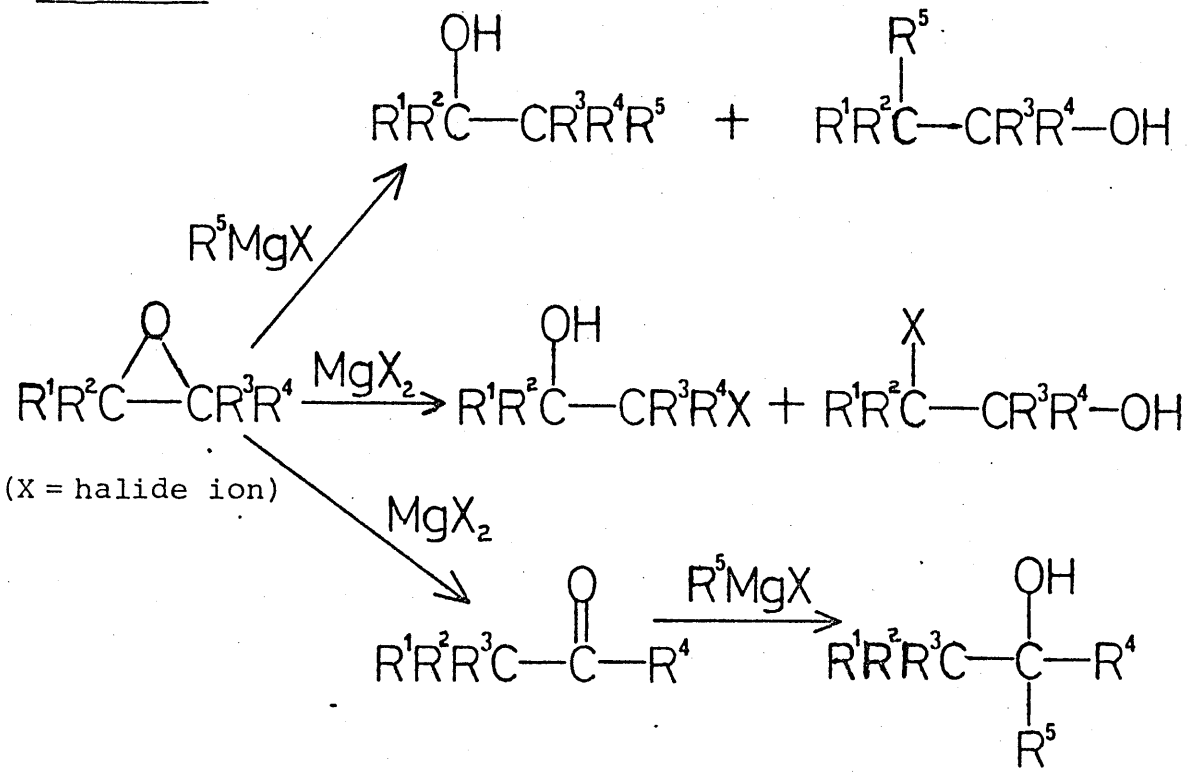
Figure 26



to (116) in the presence of magnesium bromide, by proton abstraction and accompanying oxiran ring-opening. A further complication sometimes arises from the attack of a halide ion on one of the oxiran carbon atoms, giving rise to a halohydrin.[76]

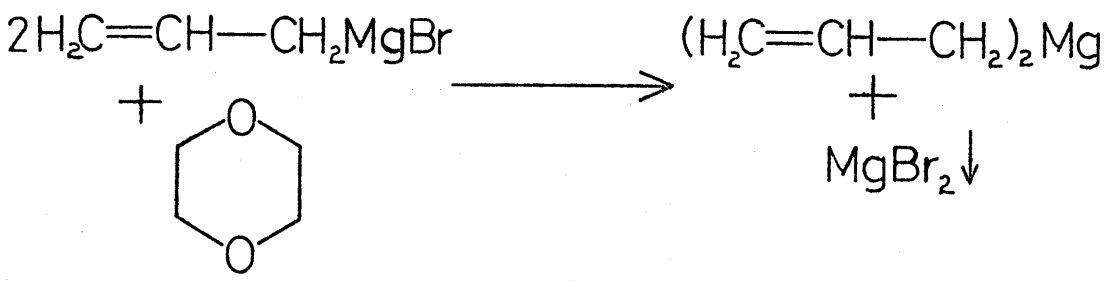
The five possible products in the reaction of a Grignard reagent with an oxiran are summarised below (Figure 27).

Figure 27



It has been demonstrated that dimethylmagnesium, methyllithium and lithium dimethylcuprate are far superior to the Grignard reagents with respect to the yield of nucleophilic ring-opened product.[77] Consequently, diallylmagnesium was prepared and reacted with oxirans (106) and (107). Diallylmagnesium was

prepared by adding 1,4-dioxan (4 molar equivalents) to allyl magnesium bromide whilst refluxing. This caused the magnesium bromide to precipitate out, which was filtered off under nitrogen to give a solution of diallylmagnesium:[78,79,80]

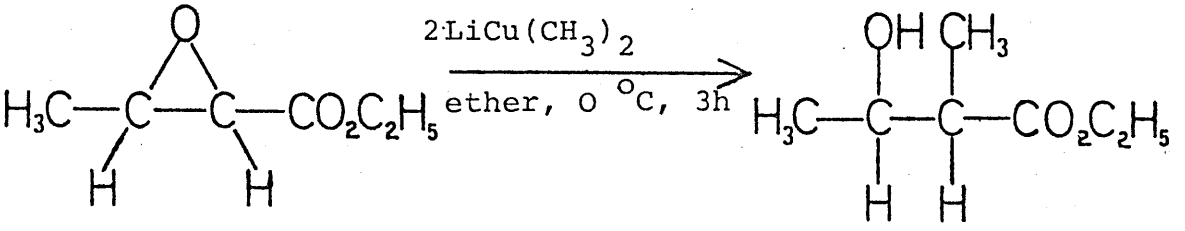


After several attempts, little reaction was detected between diallylmagnesium and oxirans (106) and (107), with a trace of a non-polar product being formed and starting material being recovered.

The next nucleophilic reagent investigated was allyllithium, which had to be synthesised by a transmetallation reaction between tetraallyltin and phenyllithium[81] (the reaction of allyl bromide in lithium results in extensive coupling between allyllithium and allyl bromide[82]). As with diallylmagnesium, no significant reaction between allyllithium and oxirans (106) or (107) was detected, only a trace of a non-polar product being formed.

In a final attempt to ring-open the oxirans (106) and (107), lithium diallylcuprate was prepared by the reaction of allyllithium with copper(I)iodide.[83] Little reaction was detected between this cuprate and

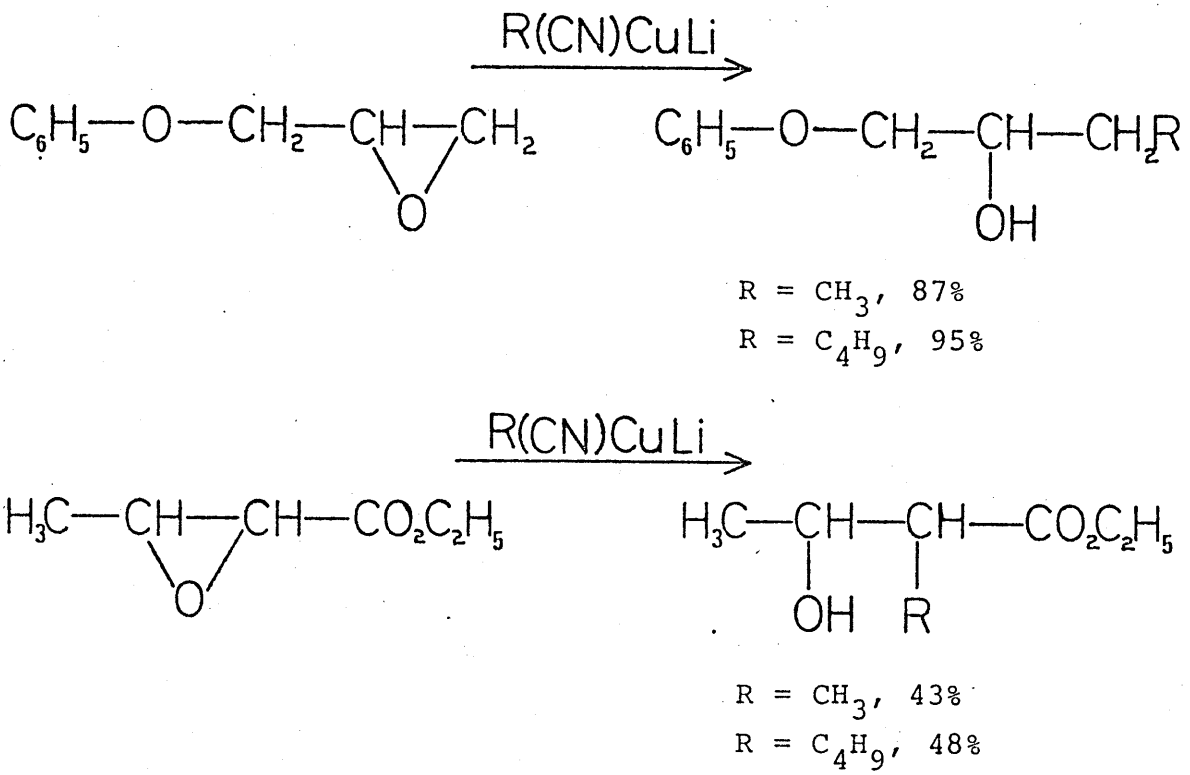
the oxirans. This is somewhat surprising, because it has been found that lithium dimethylcuprate and lithium diphenylcuprate are excellent reagents for the nucleophilic ring-opening of oxirans under mild conditions, being more reactive than the corresponding alkyllithiums.[84] Indeed it has been shown that lithium alkylcuprates are relatively inert toward saturated carbonyl moieties, and selective reaction at an oxiran ring in the presence of an unprotected carbonyl function is possible.



(67%)

It has been reported that lithium alkyl(cyano)copper(I) reagents such as $CH_3(CN)CuLi$, are effective in the ring-opening of oxirans using stoichiometric amounts of the cuprate reagents.[85] In these reactions the oxirans are attacked at the less hindered side of the oxiran group (Figure 28).

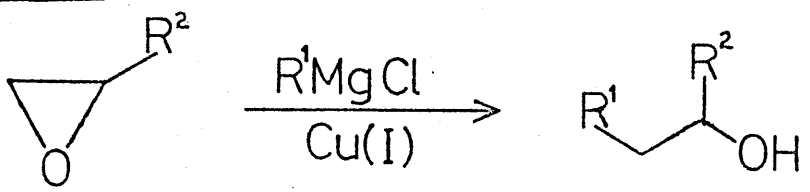
Figure 28



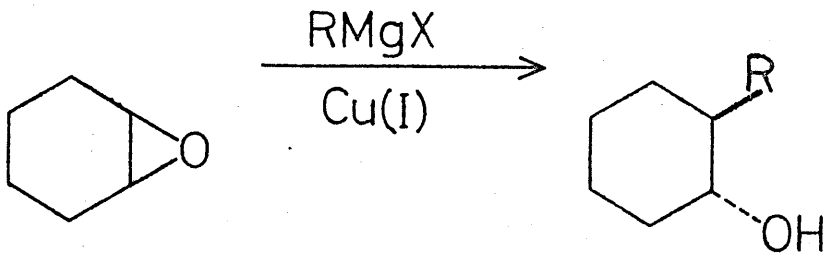
Possibly the allyl(cyano)copper(I) reagent would effectively ring-open oxirans (106) and (107) although this was not attempted.

Another possible method for ring-opening of oxirans (106) and (107) could be the copper-catalysed reaction with Grignard reagents. This has been reported to proceed in high yield under very mild conditions,[86] and allyl and vinyl Grignard reagents have been used (Figure 29).

Figure 29



R^1	R^2	Yield (%) with 10% CuBr	Yield (%) without catalyst
$CH_3-\overset{CH_3}{\overset{\vert}{C}}=CH_2$	CH_3	90	90
C_6H_5	CH_3	95	80
C_4H_9	CH_3	93	26



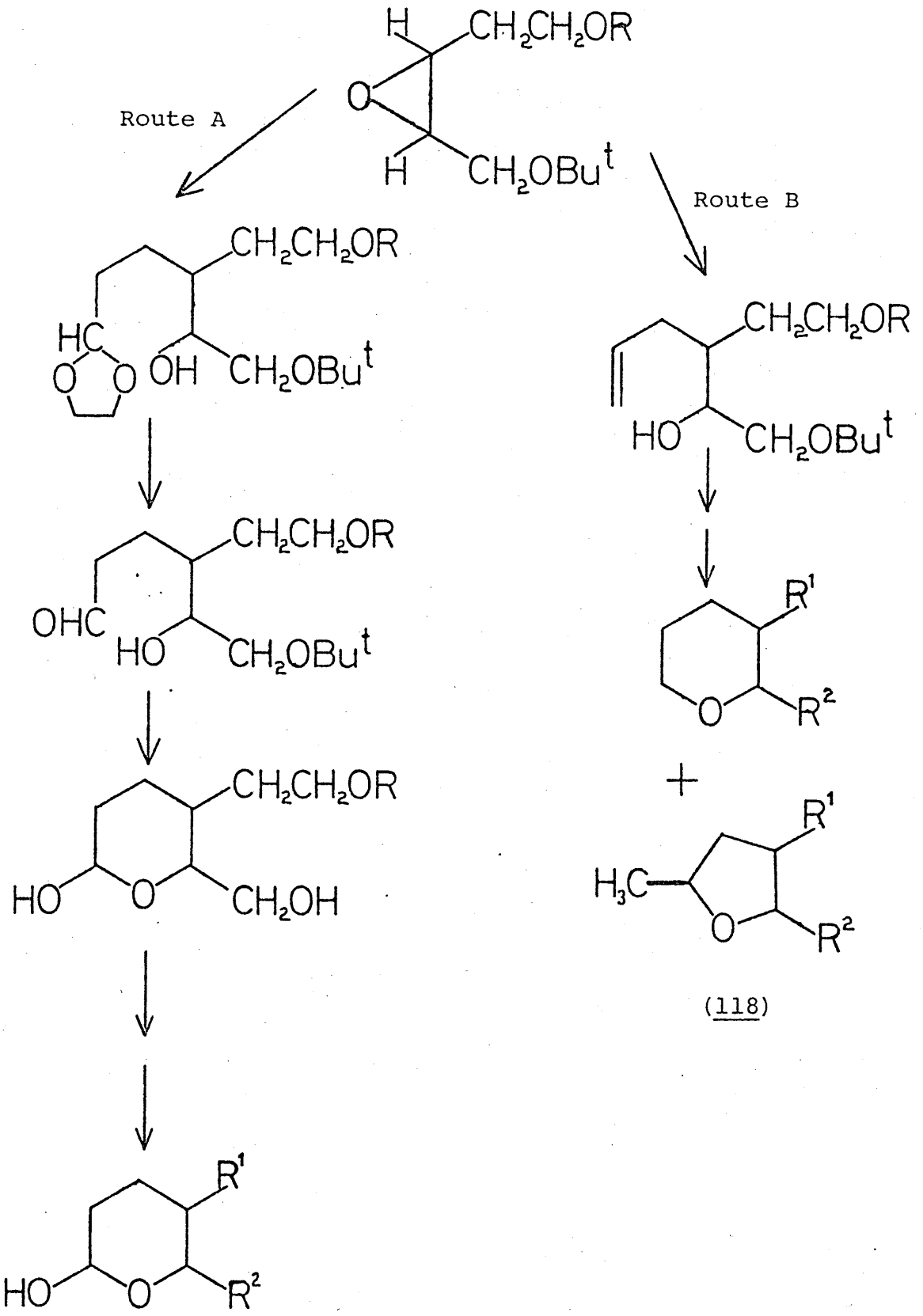
R	X	Yield (%) with 10% CuI	Yield (%) without catalyst
$CH_3-\overset{CH_3}{\overset{\vert}{C}}=CH_2$	Br	88	40
$(CH_3)_2C=CH-CH_2-$	Cl	86	86

Again, reaction is at the less hindered side of the oxiran group. The catalyst is a copper(I) salt, usually copper(I)bromide present in about 10% concentration with respect to the Grignard reagent. Monosubstituted oxirans are more reactive than disubstituted oxirans towards Grignards reagents and are less dependent upon copper catalysis.[86]

Oxirans such as (106) or (107) might themselves be useful intermediates, since in principle they can be

used to synthesise interesting oxa-thromboxane analogues as shown in Figure 30.

Figure 30



In this reaction scheme a likely by-product in the formation of the oxane ring system by Route B is the disubstituted methyloxolane (118) arising by attack at the more substituted alkene carbon atom. (118) would be the precursor to interesting oxaprostaglandin analogues.

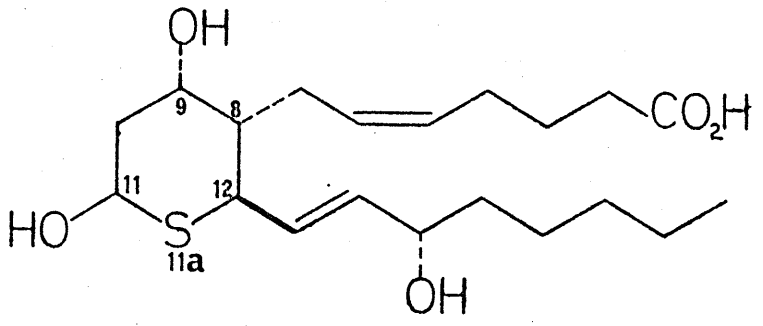
However, although this synthetic scheme has great potential, the lack of success in preparing disubstituted thiirans led us to try alternative synthetic procedures to prepare thiathromboxanes.

CHAPTER 3

Route to 11a-Thiathromboxane B_2

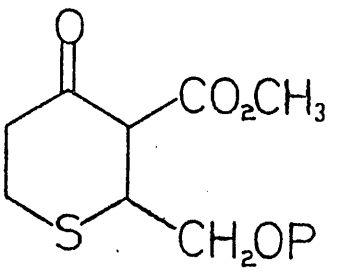
Chapter 3 Route to 11a-Thiathromboxane B_2

The synthetic approach to 11a-thiathromboxane B_2 (71) described in this chapter involves formation of the thiane ring at a stage where parts of both side-chains are present in the structure.



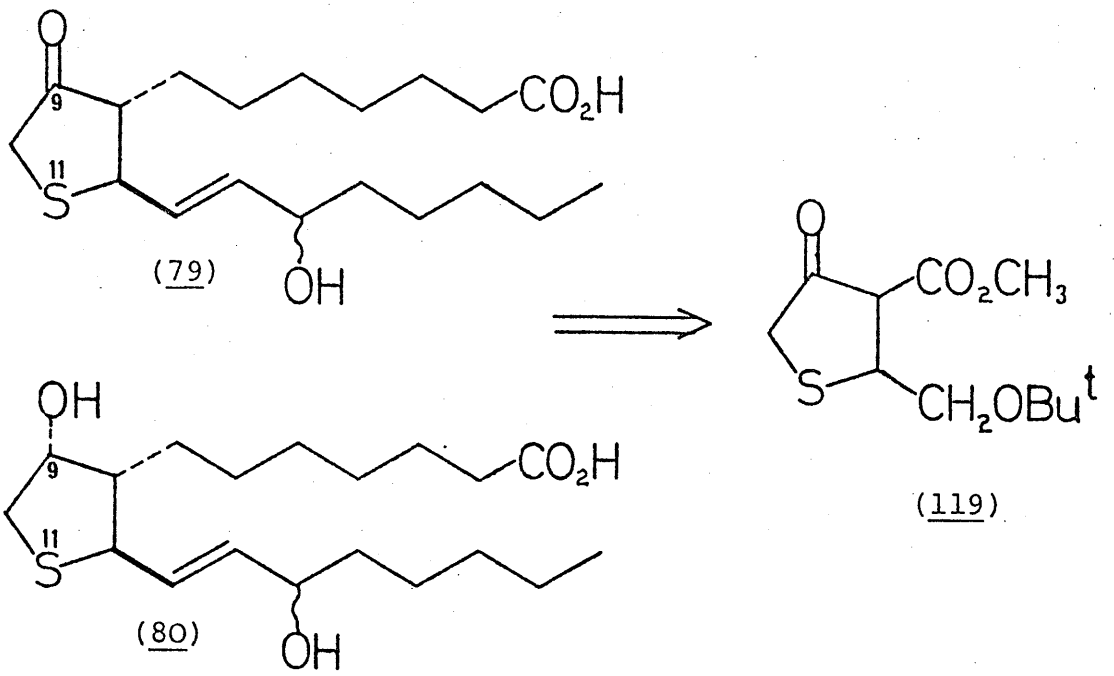
(71)

In this approach the thiane ring is formed at an earlier stage of the synthetic route than was the case in Chapter 2 (Figure 19), and as the key intermediate is a relatively simple disubstituted thianone of type (78), where P is a protecting group, which together with the methyl ester group, allows the side-chains at C-8 and C-12 of (71) to be constructed independently.



(78)

The synthetic route discussed has been used previously[45] to prepare 11a-thiaprostaglandins (79) and (80), where the key intermediate corresponding to (78) is (119).



(79) (80) (119)

Our attempted route towards 11a-thiathromboxane B_2 (71) is shown in Figure 31. The key step in this scheme is the cyclisation reaction (121) to (123).

3-t-Butoxypropyne (87) was prepared from prop-2-yn-1-ol (86) by acid-catalysed addition across the double bond of 2-methylpropene.[52] Abstraction of the terminal proton in (87) by ethylmagnesium bromide, and the subsequent reaction of the acetylenic Grignard reagent with dimethyl carbonate gave methyl 4-t-butoxy-2-ynoate (120) in 59% yield (Figure 32) after hydrolysis.[87]

Figure 31

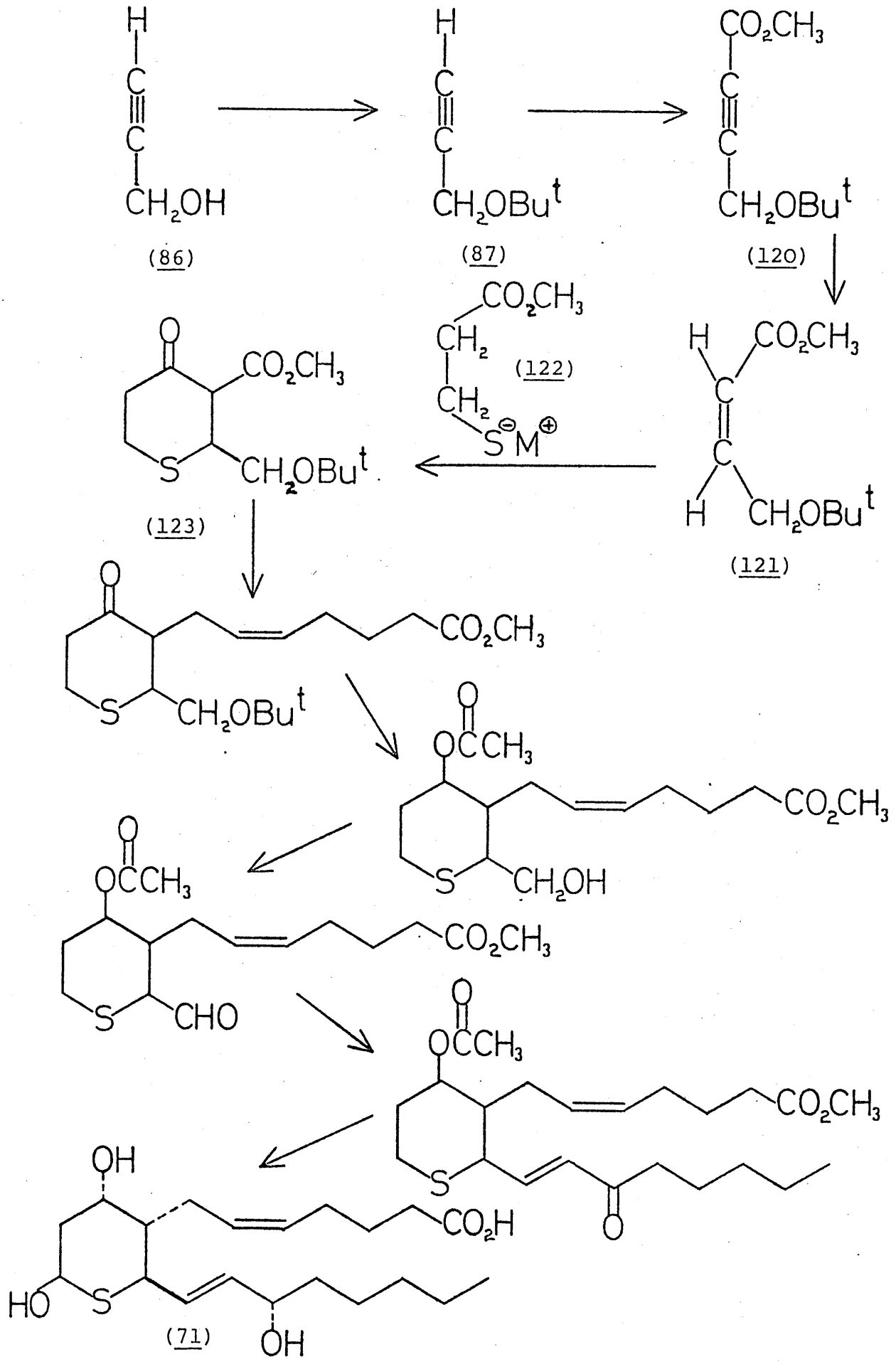
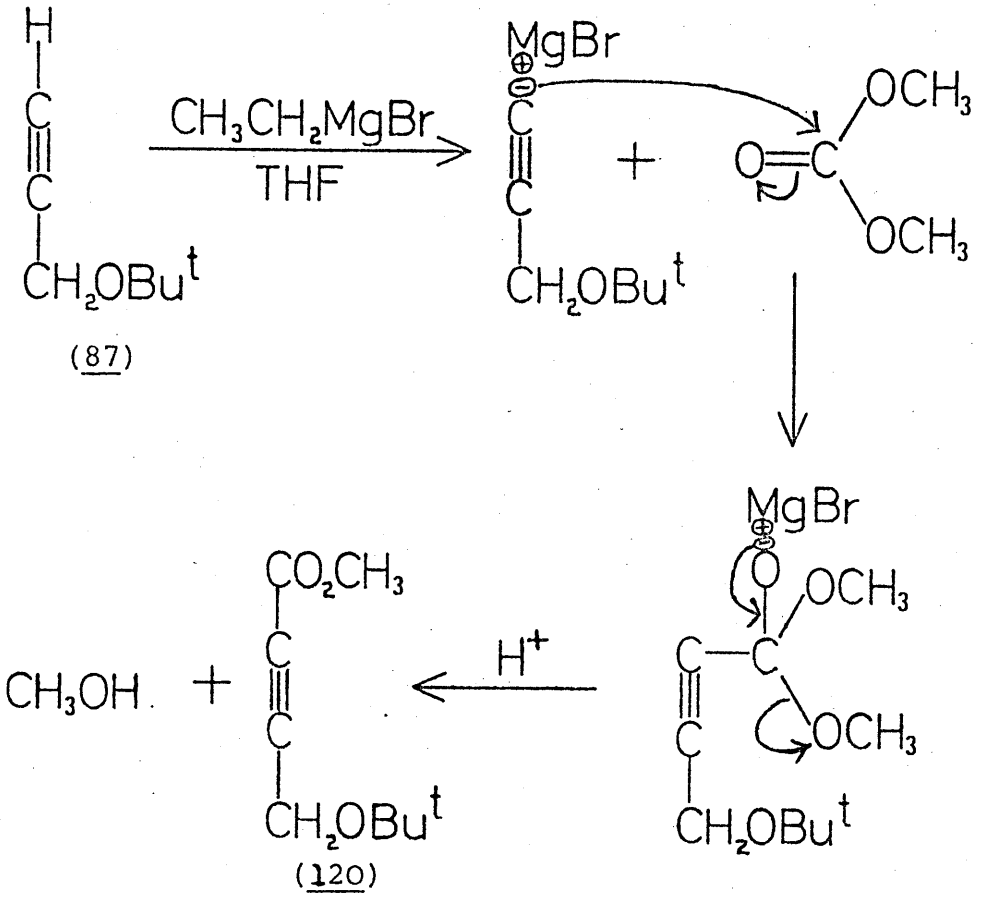


Figure 32

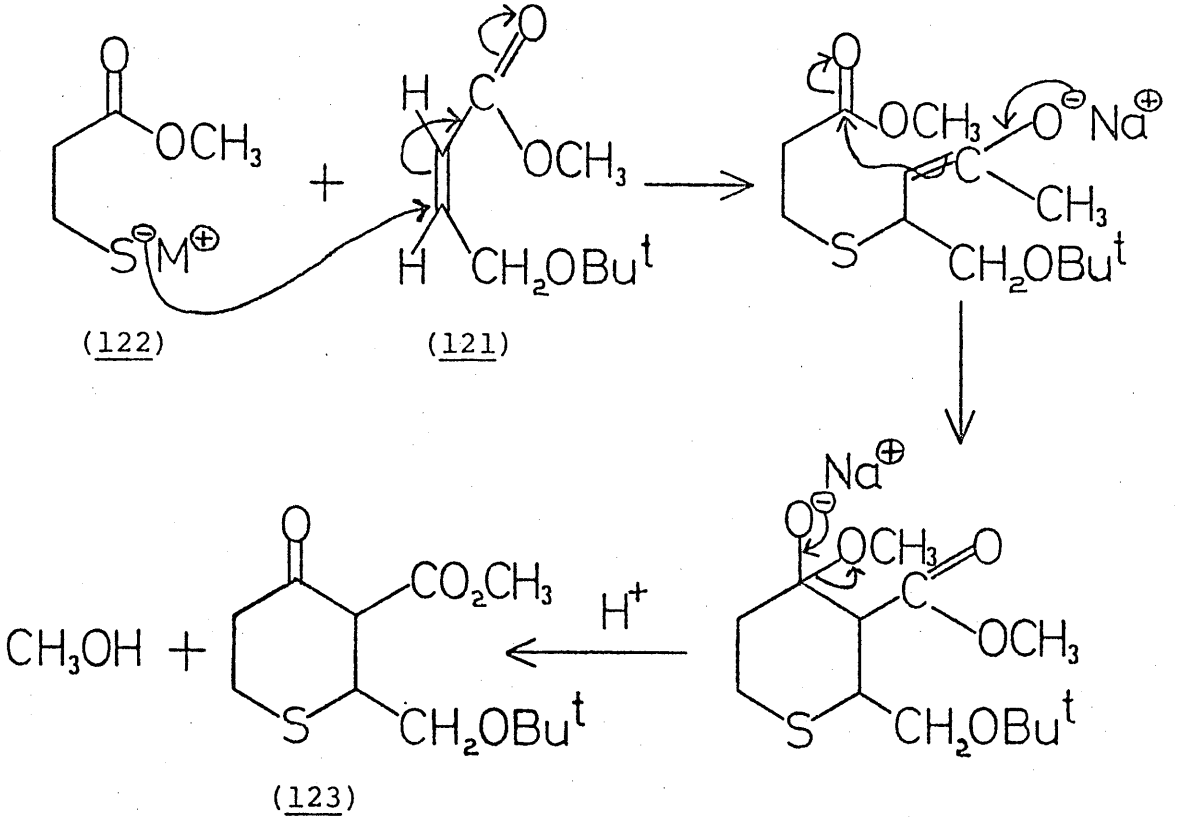


Atmospheric pressure hydrogenation of (120) with 5% palladium on charcoal gave methyl cis-4-t-butoxybut-2-enoate (121) in 45% yield.

The next step in this route (Figure 31) involves the formation of the disubstituted thianone ring by Michael addition of the sodium salt of methyl 3-mercaptopropanoate (122, M=Na) to methyl cis-4-t-butoxybut-2-enoate (121) followed by an internal Claisen condensation to give (123), a β-ketoester (Figure 33).

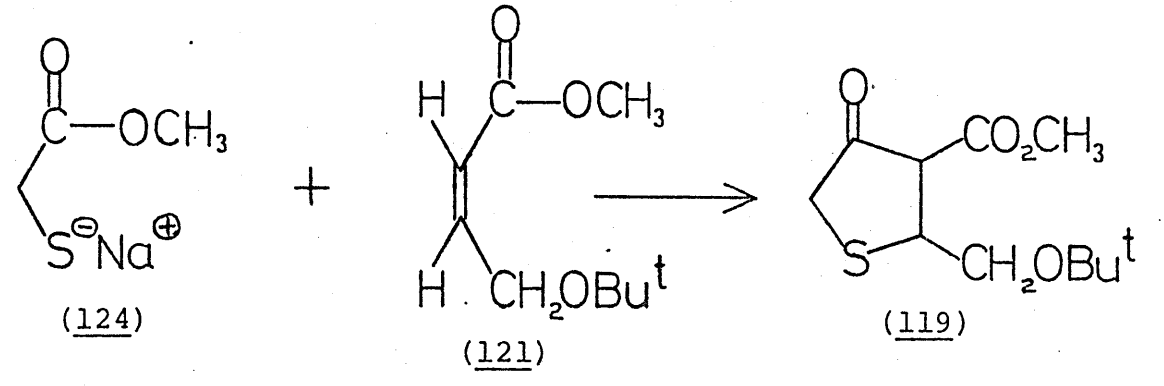
The attempted reaction is based on an analogous reaction reported in the literature,[45,46] and shown in Figure 34. However, in our reaction sodium methyl 3-mercaptopropanoate (122, M=Na) was used in place of sodium methyl mercapto-acetate (124).

Figure 33



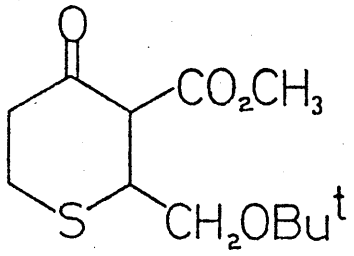
(122) (121) (123)

Figure 34

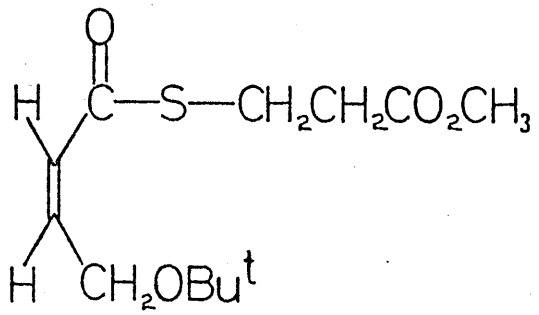


(124) (121) (119)

The product obtained from our reaction of compounds (121) and (122) was assigned the structure (125), rather than the required structure (123).



(123)

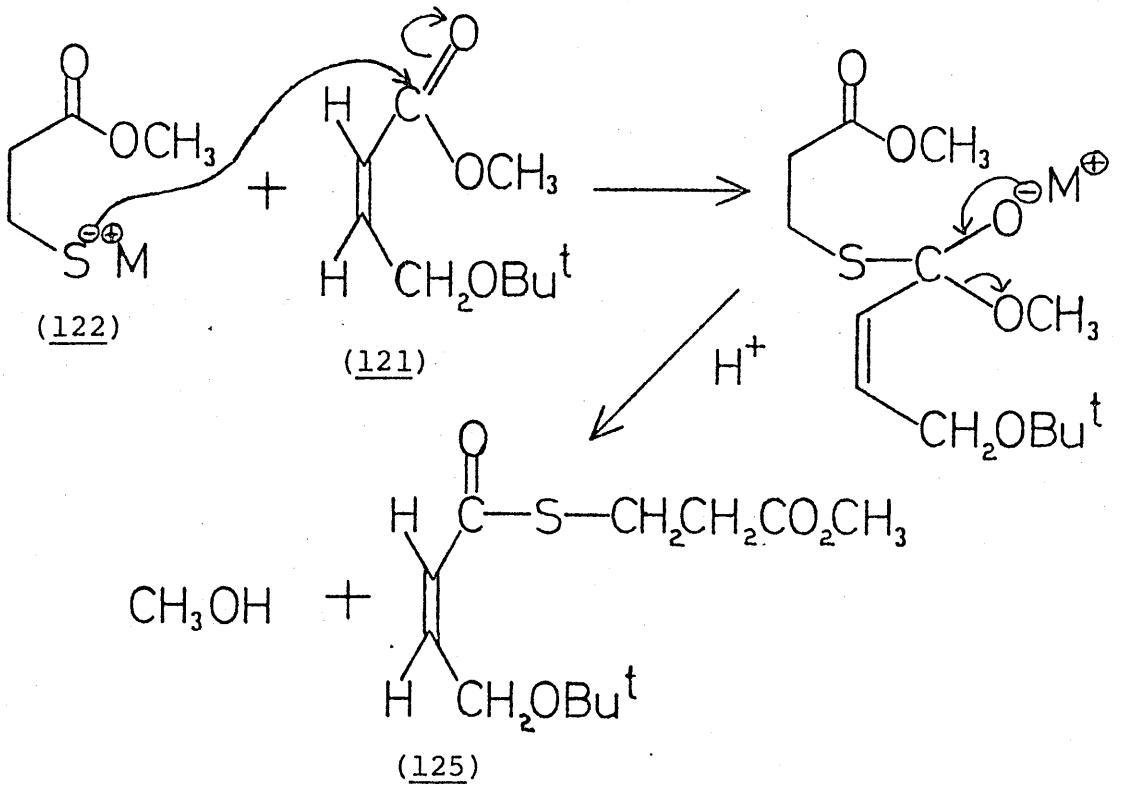


(125)

The ^{13}C-NMR spectrum showed two ester carbonyl carbons at 171.7 and 166.7 ppm, and two alkene carbons at 147.0 and 120.6 ppm. The ^{1}H-NMR spectrum showed two alkene protons at 6.06 and 7.00 ppm, the coupling constant (12 Hz) indicating a cis-configuration. Confirmation of structure (125) was obtained from infra-red evidence, which showed an ester carbonyl absorption at 1735 cm^{-1} together with an α,β-unsaturated thiolester at 1720 cm^{-1} and an alkene stretch at 1650 cm^{-1}. Product (125) presumably arose from an ester exchange reaction of the thiolate anion of (122) with the methyl ester group of (121) rather than the required Michael addition/Claisen condensation (Figure 35).

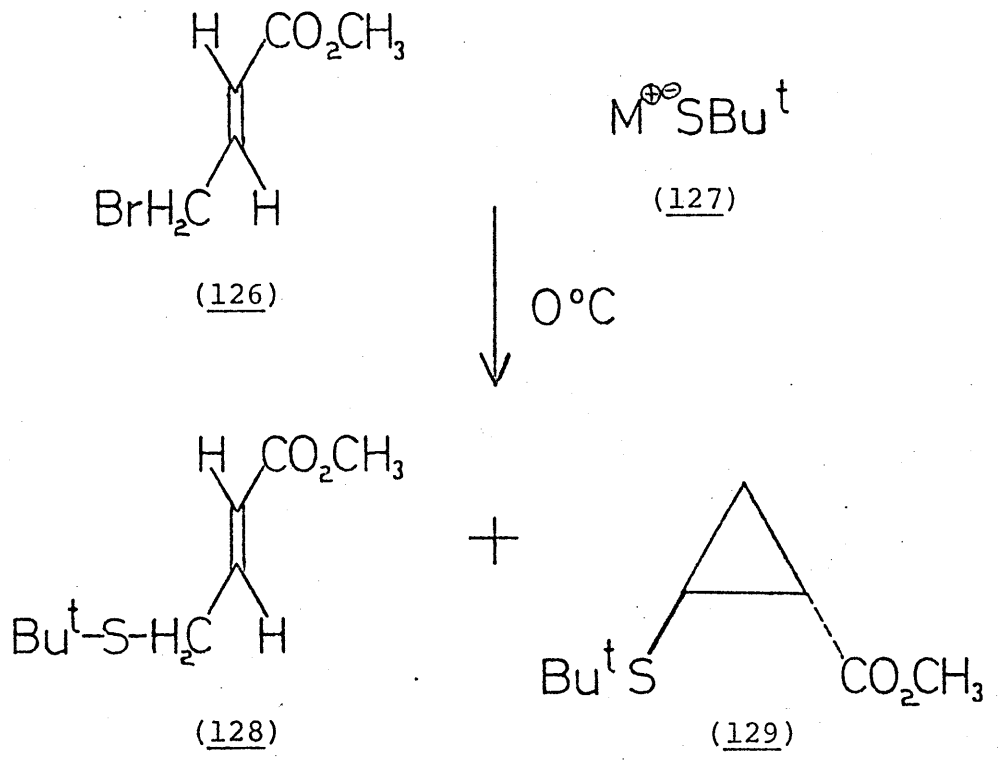
The yield of isolated product in the reaction between (122) and (121) was found to be dependent upon solvent and the thiolate gegenion. The reaction was carried out by forming either (i) the sodium salt of methyl 3-mercaptopropanoate (122, M=Na) with sodium hydride in dry diethyl ether or (ii) the lithium salt of methyl 3-mercaptopropanoate (122, M=Li) with butyllithium in dry diethyl ether, isolating these salts and then reacting them with methyl

Figure 35



cis-4-t-butoxybut-2-enoate (121) in either dry dimethyl-sulphoxide (DMSO) or dry diethyl ether. It was found that the highest yield of isolated product was obtained by using sodium hydride in diethyl ether, followed by reaction with (121) in dry diethyl ether. This dependency upon solvent and gegenion has been noted in other reactions involving thiolate anions. Little[88] investigated the reaction of methyl trans-4-bromobut-2-enoate (126) with alkali metal t-butylthiolates (127) in which two products (128) and (129) were formed, the ratio of these products depending on the solvent and thiolate gegenion (Figure 36).

Figure 36



In dichloromethane, THF, diethyl ether, benzene or pentane with lithium as the gegenion (127, M=Li), predominantly (129) was formed in yields of between 70-80%. This product results from a Michael addition, followed by a ring-closure reaction where lithium determines the site of predominant attack of thiolate ion (127). When the same reaction was conducted in dimethylformamide (DMF) or hexamethylphosphoramide (HMPA) only product (128) was formed, presumably because these solvents solvate the metal and effecively remove its influence upon the course of the reaction, allowing a different site of attack.

The reaction between the thiolate anion of (122) and difunctionalised alkene (121) did not lead to the required

disubstituted thianone (123) and despite extensive further investigations conditions could not be found which favoured the required Michael addition/Claisen condensation reactions. Alternative approaches were therefore explored.

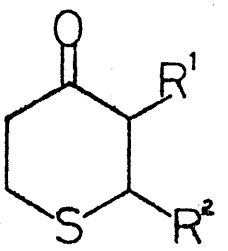
Chapter 4

A General Route To 2,3-Disubstituted Thian-4-ones

Chapter 4 A General Route To 2,3-Disubstituted Thian-4-ones

4.1 Introduction

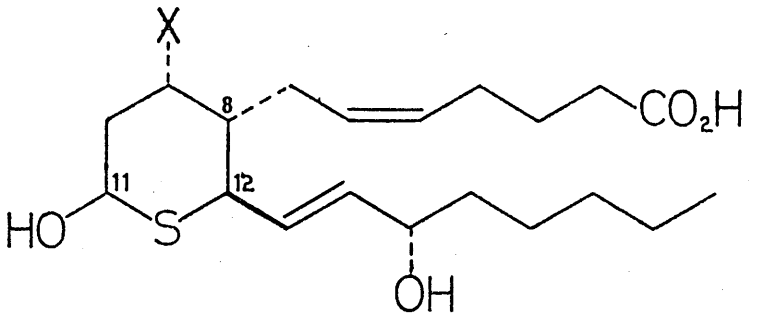
The approach described in this chapter was designed to synthesise 2,3-disubstituted thian-4-ones of general structure (85).



(85)

This approach was adopted with a view to the eventual synthesis of the target thiathromboxanes (70) and (71).

Thian-4-one and its substituted derivatives are useful synthetic intermediates. They have been used to prepare juvenile hormones[89] and have recently been employed as substrates for enzyme reductions.[90] Symmetrically substituted thian-4-ones can be prepared by a conventional

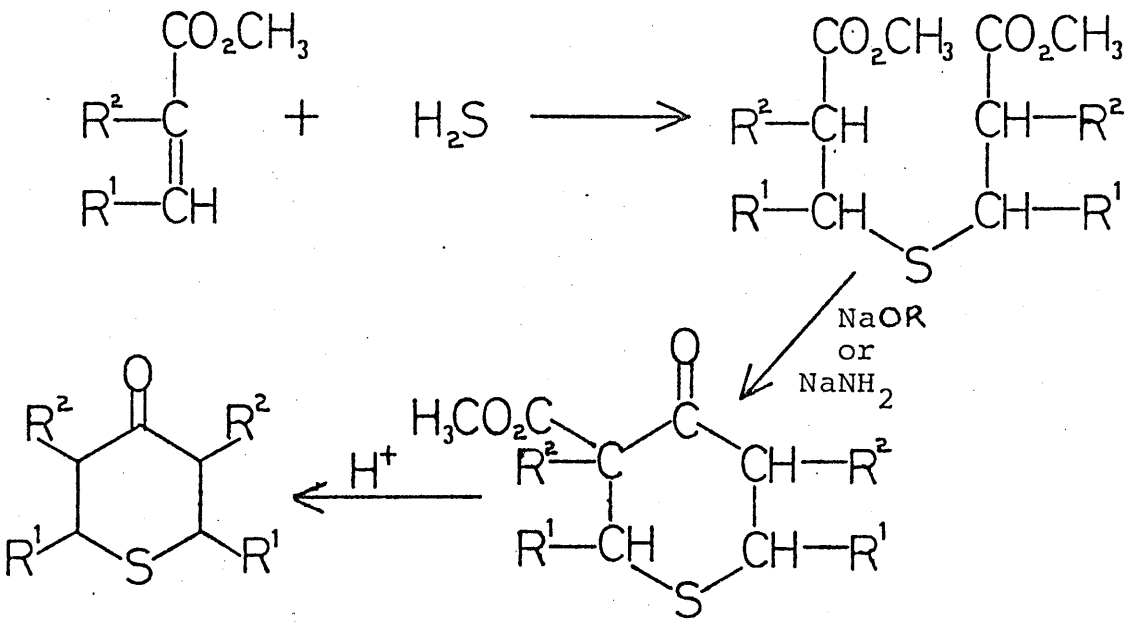


X = H(70) 9-deoxy-11a-thiathromboxane B_2

X = OH(71) 11a-thiathromboxane B_2

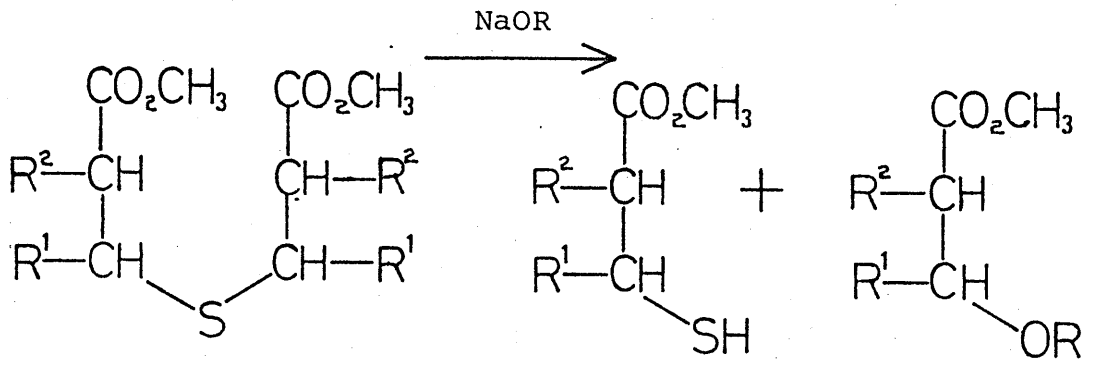
Dieckmann cyclisation approach[48] outlined in Figure 37.

Figure 37



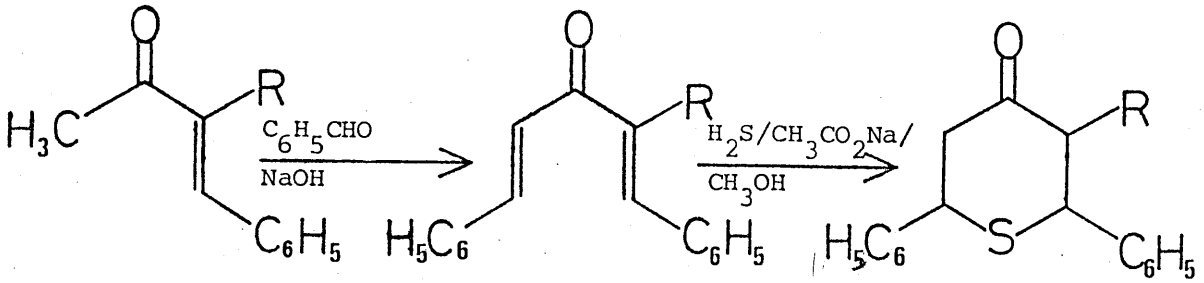
However this approach has proven to be both time-consuming and low-yielding, with yields of between 23 and 33%.[48] The reaction scheme has only been fully investigated when R^1 and R^2 are methyl or phenyl groups. A further limitation is that on reaction with sodium alkoxide, two major products are formed by cleavage of the sulphide linkage (Figure 38).[91] Hydrogen sulphide has also been detected by smell in these reactions.

Figure 38



Certain trisubstituted thian-4-ones have been prepared by the condensation of α,β-unsaturated ketones[92] with benzaldehyde in the presence of aqueous sodium hydroxide, to give the corresponding dienones, which when heated with sodium acetate and methanol in a stream of hydrogen sulphide gave the products in reasonable yields (Figure 39).[93]

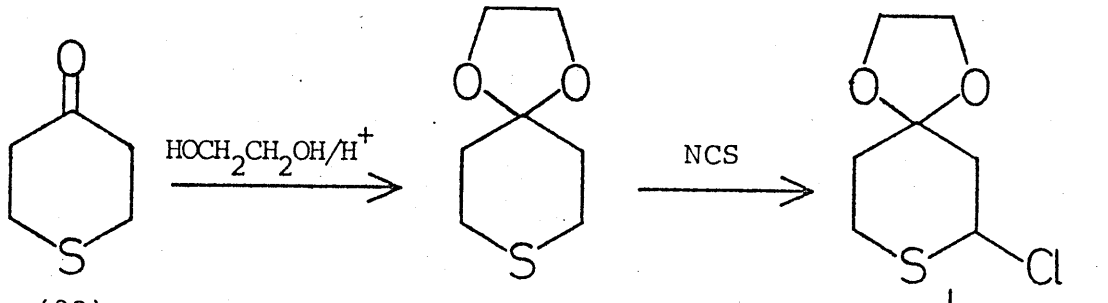
Figure 39



R = CH_3 (51%)
R = C_2H_5 (66%)

A three-stage route from thian-4-one (83) itself to 2-substituted derivatives (130) has recently been disclosed,[90] in which the ketone is protected as the dioxolane, N-chlorosuccinimide (NCS) is used to chlorinate position 2, and reaction with a Grignard reagent (RMgBr) followed by acid work-up gives thian-4-ones (130) in yields ranging from 30% to 37% as shown in Figure 40.

Figure 40



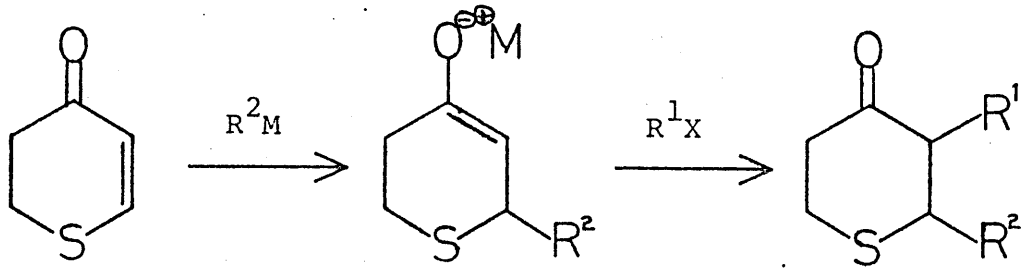
(83)

R	Yield (%)
$-CH_3$	30
$-CH_2CH_3$	33
$-CH(CH_3)_2$	36
$-C_6H_5$	37

(130)

However, these methods are not particularly versatile with respect to substitution. We required a general and efficient procedure for preparing 2,3-disubstituted thian-4-ones which was capable of being applied to thiathromboxane synthesis. We decided to investigate a new convergent synthesis of 2,3-disubstituted thian-4-ones based on organometallic conjugate addition (R^2M) - enolate alkylation (R^1X) reaction (Figure 41).

Figure 41

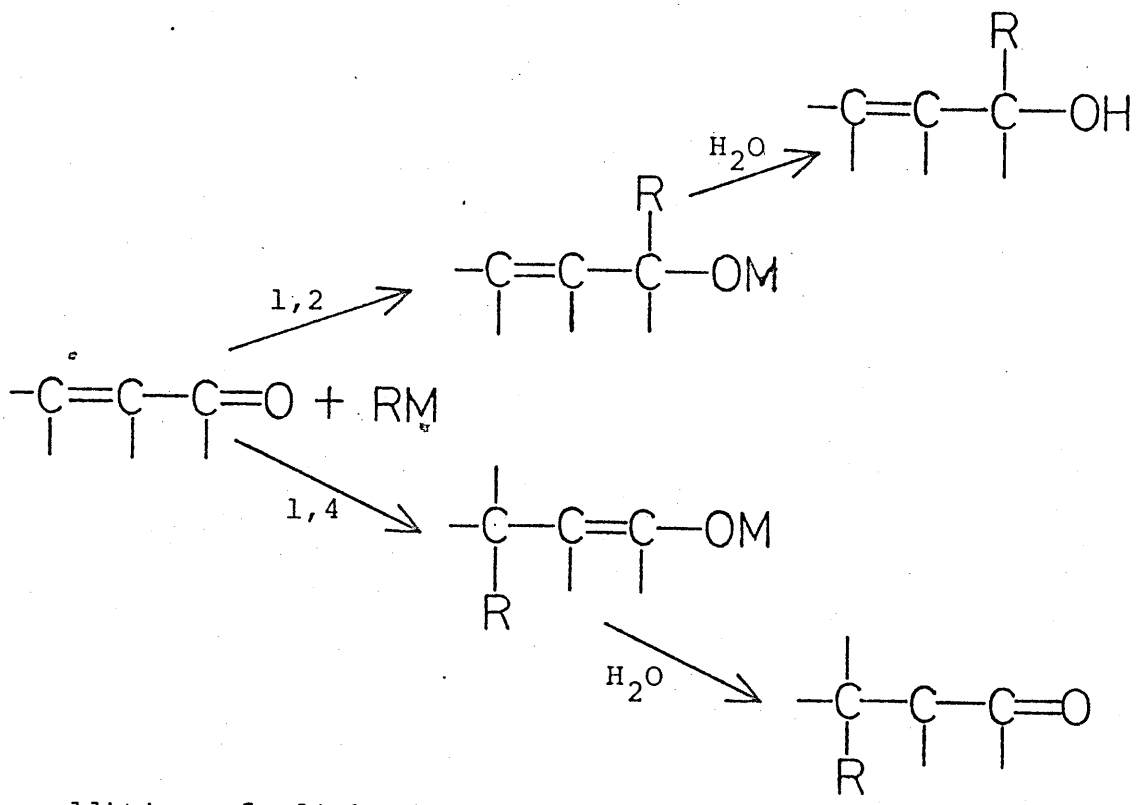


(84) (85)

The addition of an organometallic reagent to an α,β-unsaturated carbonyl compound occurs in one or both of two modes: attack at the carbonyl function produces a 1,2-adduct whereas reaction with the conjugated system gives a 1,4-adduct (Figure 42).

Organoalkali metal reagents derived from unstabilised carbanions (e.g. methyllithium, phenylsodium) generally add across the carbonyl group,[94] whereas enolates and other stabilised anions usually undergo Michael (1,4) addition.[95] Most unsaturated carbonyl functions react with organomagnesium reagents to give mixtures of 1,2- and 1,4- addition products.[96] Selective 1,4- or conjugate

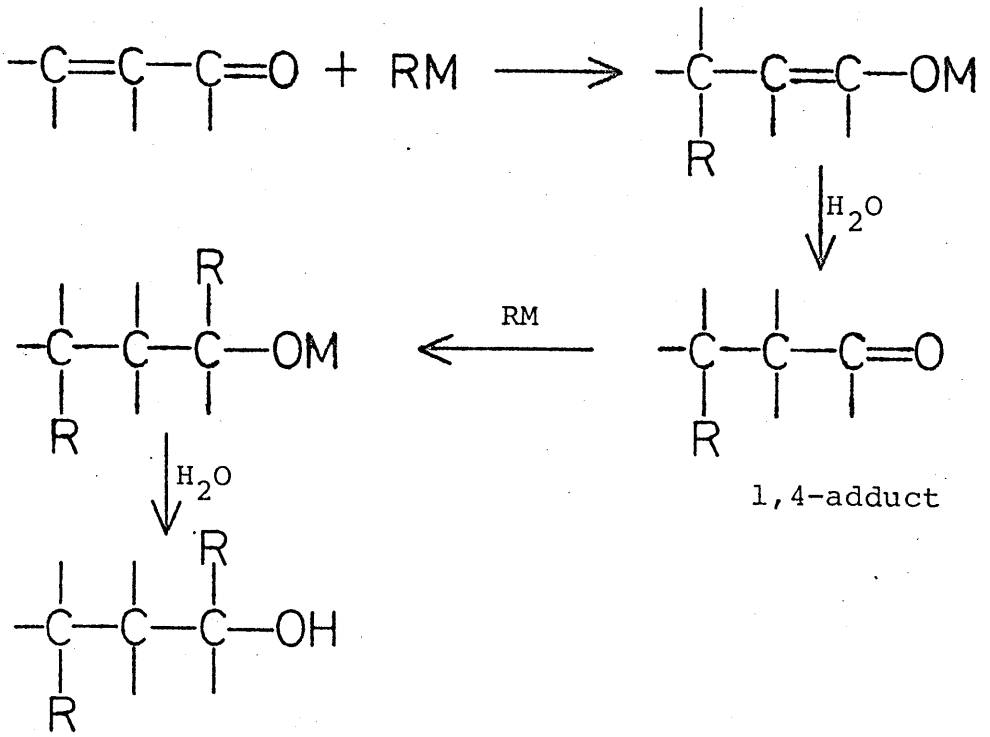
Figure 42



addition of aliphatic and aromatic groups to various unsaturated alkene and unsaturated alkyne carbonyl functions have been achieved successfully with organocopper reagents.[96] Grignard reagents in the presence of a catalytic amount of a copper salt also lead to 1,4-addition in the same way that stoichiometric organocopper reagents do, although the latter generally give conjugate adducts in higher yields and with greater stereoselectivity.[96] Based on observations accumulated during the past 15 years, some sound generalisations can be made on organocopper reactivity;[97] lithium dialkylcuprates (homocuprates, R_2CuLi) are more reactive than organocopper compounds (RCu), which in turn are more reactive than Grignard reagents in the presence of a catalytic amount of a copper salt (RMgBr/Cu(I)).

In organocopper reactions the work-up procedure can be critical in some cases. The major difficulty is the formation of a (1,4- plus 1,2-) di-adduct, arising presumably by hydrolysis of the intermediate enolate formed from conjugate addition followed by 1,2-addition of residual unhydrolysed organometallic species (Figure 43).

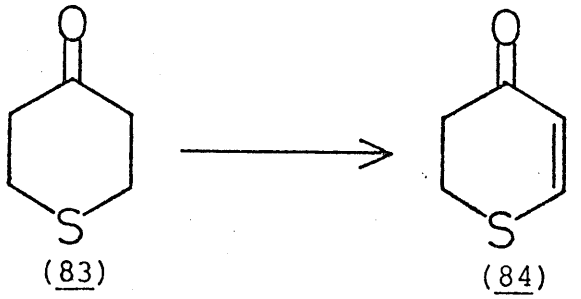
Figure 43



(1,4- + 1,2-) di-adduct

The quenching procedure devised to avoid this problem is to add 10% aqueous ammonium sulphate solution to the reaction mixture at -78 °C (or at the reaction temperature) and to stir vigorously whilst allowing the mixture to warm to room temperature. This seems to eliminate di-adduct (saturated alcohol) formation.[98]

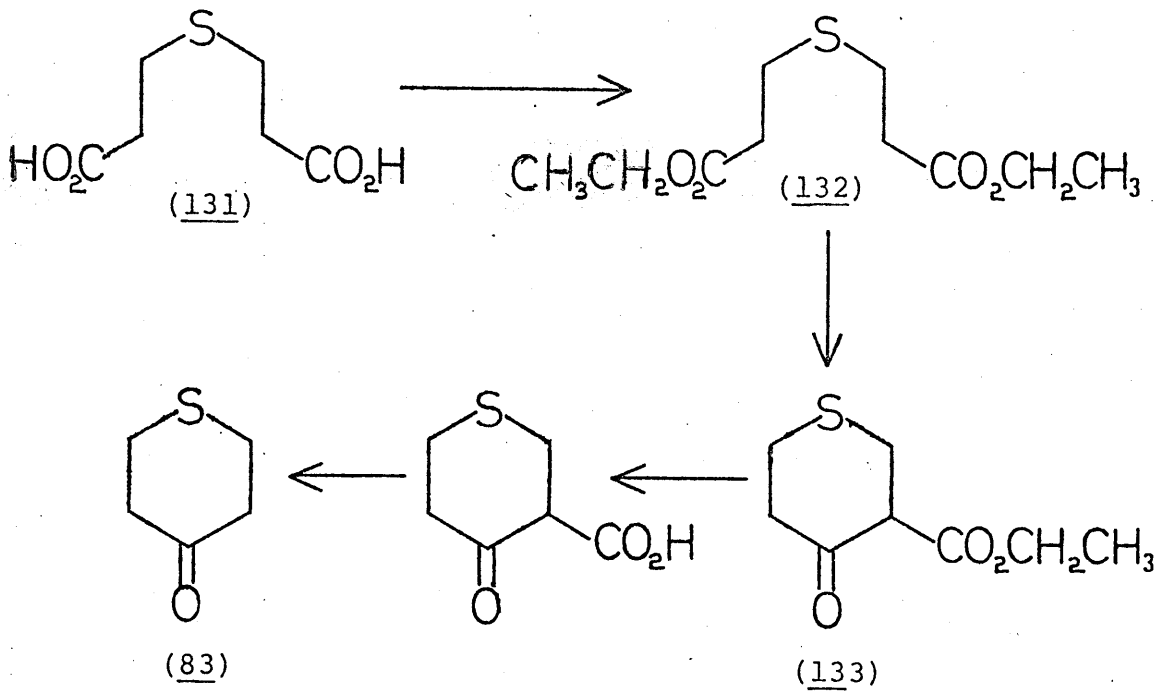
Having decided to use organocopper reagents initially we first had to prepare 2,3-dihydrothi-in-4-one (84), and a search of the literature showed that this was available from thian-4-one (83).



(83) (84)

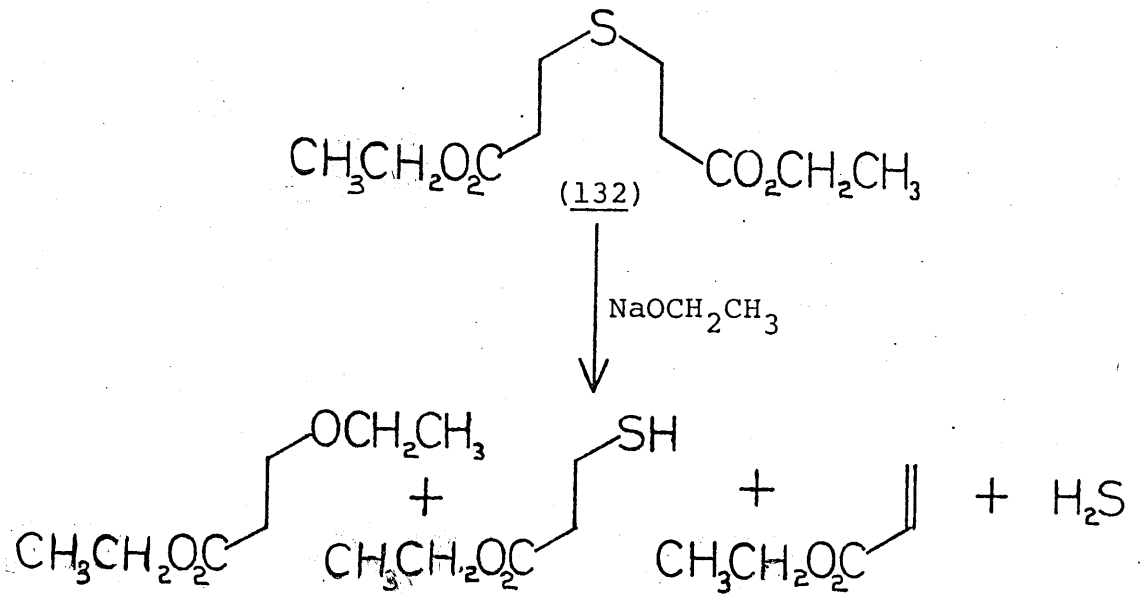
There are a variety of literature preparations of thian-4-one (83) but the yields quoted[47,48,49] could not be approached in our synthesis. The first approach we tried is shown in Figure 44.[47,48]

Figure 44



The first step involved the esterification of commercially available 3,3'-thiodipropanoic acid (131) with ethanol under acidic conditions, which gave diethyl 3,3'-thiodipropanoate (132) in 78% yield after distillation. The cyclisation step was the Dieckmann condensation reaction using sodium ethoxide in diethyl ether. This reaction gave varying yields of the required product, 3-ethoxycarbonylthian-4-one (133) according to the temperature of reaction and whether the sodium ethoxide used was prepared *in situ* or obtained commercially. The commercial product gave the highest yield of (133). Yields were improved by incorporating a small amount of ethanol in the reaction mixture. The condensation is reported to be accompanied by some cleavage of the sulphide linkage of the ester,[48] resulting in the formation of ethyl 3-ethoxypropanoate, ethyl 3-mercaptopropanoate, ethyl prop-2-enoate and hydrogen sulphide; the relative yields are not specified (Figure 45).

Figure 45

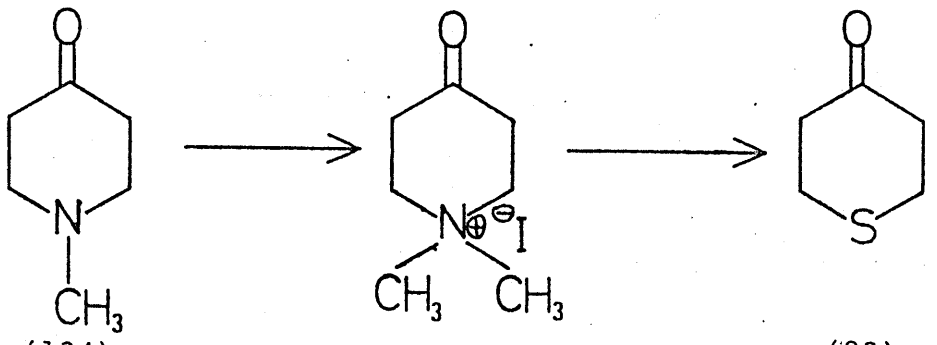


In our case the presence of hydrogen sulphide was detected by smell. Since this cleavage reaction was said to be more pronounced the higher the temperature, the reaction temperature was kept below 20 ^{o}C.

The final step involving hydrolysis and decarboxylation of (133) was accomplished by refluxing in 10% sulphuric acid, and this is where the yield was considerably reduced, from the literature yield[47] of 85% to 30%. Upon product isolation (including continuous ether extraction), a yellow insoluble oil was present together with the required thian-4-one (83). Repeated recrystallisation of the mixture from petroleum ether (40-60 ^{o}C) gave (83) as a colourless crystalline solid. The impurity could have been a product of the same sulphide cleavage as noted in the previous reaction.

The second approach we tried is shown in Figure 46.

Figure 46

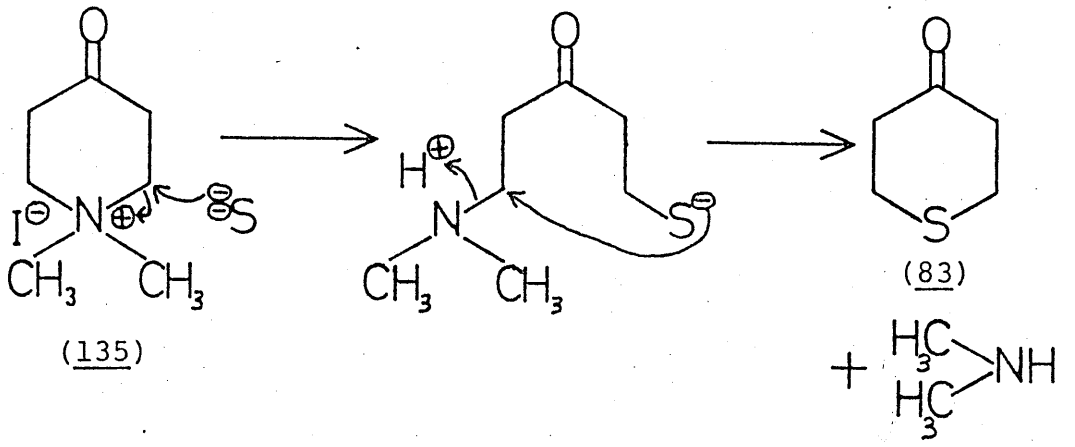


(134) (135) (83)

This procedure, devised by Johnson and Berchtold[49] involved the formation of 1,1-dimethyl-4-oxopiperidinium iodide (135) by reaction of the tertiary amine, 1-methyl-4-piperidone (134) with iodomethane. This

product proved to be hygroscopic and liable to decomposition to 1-methyl-4-piperidone (134) and so was used without further purification. The reaction of (135) with sodium sulphide under aqueous conditions, gave after acidification, thian-4-one (83) in 33% yield, compared to a literature yield[49] of 48%. This reaction involves the nucleophilic attack of the sulphide anion on the piperidone ring, which is repeated leading to the expulsion of dimethylamine (Figure 47).

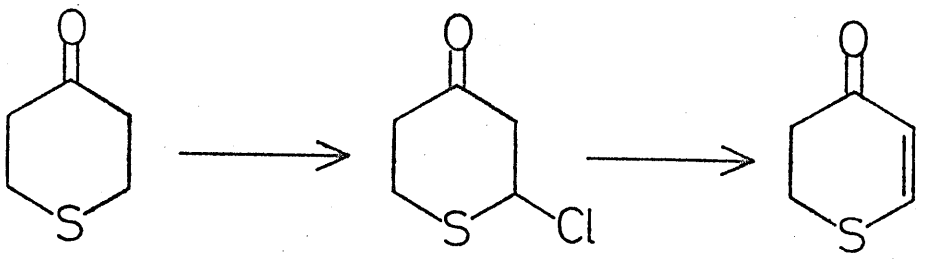
Figure 47



(135) (83)

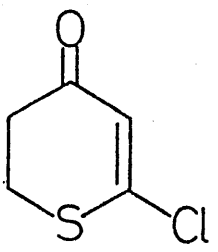
Thian-4-one (83) was then converted to its unsaturated derivative, 2,3-dihydrothi-in-4-one (84) which was required for the conjugate addition reactions. The first procedure followed, which was devised by de Waard et al (Figure 48)[51] involved chlorination of thian-4-one (83) with N-chlorosuccinimide (NCS) in benzene. This gave 2-chlorothian-4-one (136), which was then treated with 1,5-diazabicyclo[4,3,0]non-5-ene (DBN) to effect the required dehydrochlorination to give (84). The yield obtained by this method was 63% compared to the literature yield[51] of 70%.

Figure 48

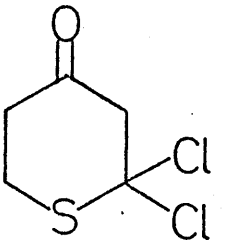


(83) (136) (84)

An impurity, which had a similar pmr (but with only one alkene proton) and a similar R_f value to the unsaturated thianone (84) was also isolated. This was most probably the chlorinated unsaturated thianone derivative (137) derived from 2,2-dichlorothian-4-one (138) by dehydrochlorination.



(137)



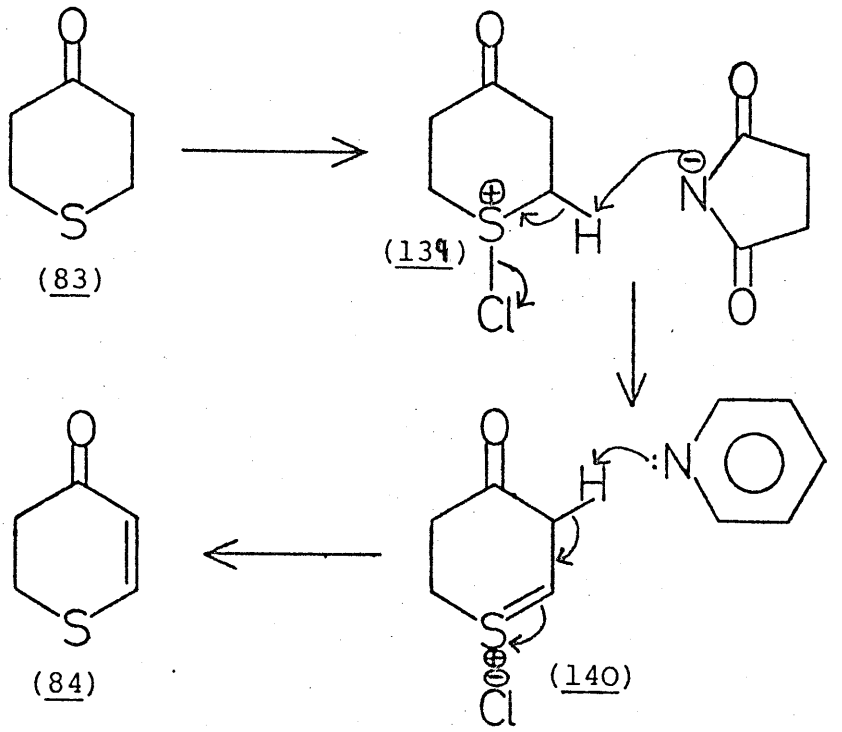
(138)

A suggested literature procedure[99] for giving selective 2-chlorination was attempted which involved a change of solvent from benzene to tetrachloromethane and a reaction temperature of $4 \pm 1\ ^{o}C$, but this gave no improvement. However, the required 2,3-dihydrothi-in-4-one (84) could be separated from the impurity by vacuum distillation.

An improved procedure for the formation of unsaturated thianone (84) involved a mild oxidative elimination

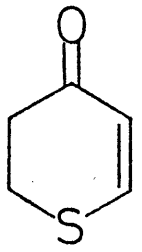
reaction employing NCS and pyridine as reagents (Figure 49).[50]

Figure 49

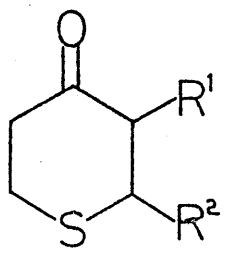


Thian-4-one (83) was initially converted by NCS to generate a chlorosulphonium salt (139), followed by formation of intermediate (140) with concurrent loss of succinimide. Under the basic conditions (pyridine) in which this reaction was conducted, the most acidic hydrogen was readily eliminated to give the required unsaturated thianone (84). This gave an isolated yield of 76%, compared to a literature yield[50] of 92%, with none of the previously formed impurity present.

Having optimised the yield of 2,3-dihydrothi-in-4-one (84) we proceeded to investigate the formation of 2,3-disubstituted thian-4-ones (85).



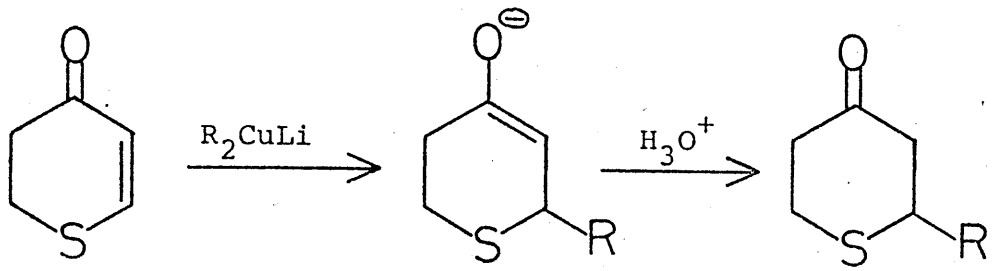
(84)



(85)

Initial investigations centred on the organocuprate conjugate addition reactions to (84) to form 2-substituted thian-4-ones (130) after quenching of the intermediate enolate (Figure 50). It was intended to optimise the yields of 2-substituted thian-4-ones (130) as a model study, before extending the procedure to the alkylation reactions leading to 2,3-disubstituted thian-4-ones (85).

Figure 50

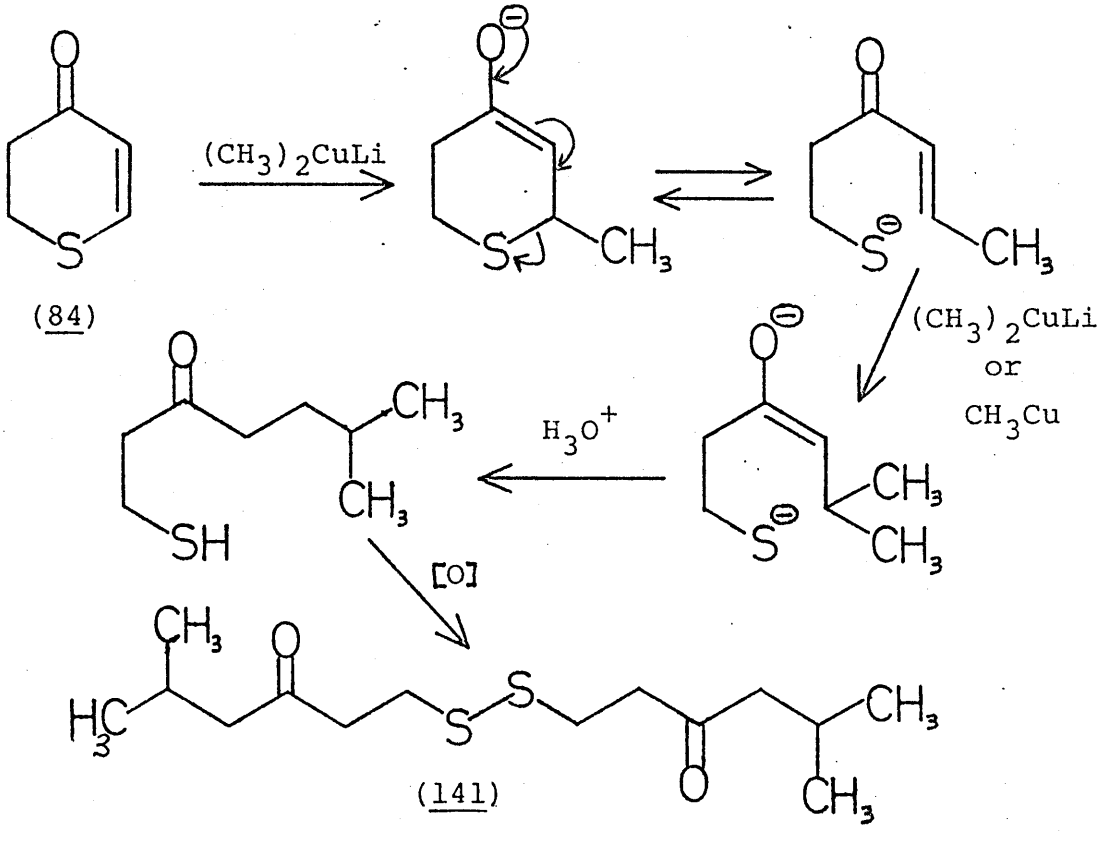


(84) (130)

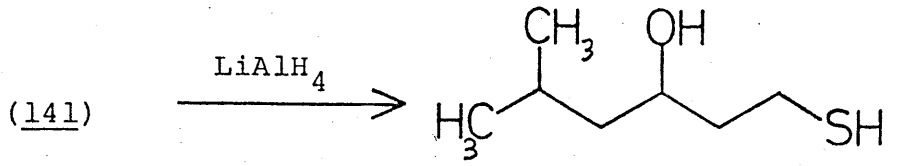
4.2 2-Substituted Thian-4-ones

Since organocopper reagents are the reagents of choice for conjugate addition reactions the preparation of 2-methylthian-4-one (130, R=CH_3) using lithium dimethylcuprate was investigated first. Lithium dimethylcuprate was prepared by the addition of methyllithium to purified copper (I) iodide in dry diethyl ether.[96] Treatment of 1.1 molar equivalents of this solution with 2,3-dihydrothi-in-4-one (84) in diethyl ether at 0 °C gave the disulphide (141) as the major product (38%), which presumably arose by ring-opening of the enolate followed by further reaction of organocuprate with the α,β-unsaturated carbonyl group and subsequent oxidation (Figure 51).

Figure 51



Proof of the disulphide structure was obtained from spectral data and by the reduction of (141) with lithium aluminium hydride[100] to give 1-mercapto-5-methylhexan-3-ol (142) in 78% yield.



(142)

Thiol (142) was relatively unstable to air oxidation, since a sample submitted for mass spectrometry had completely oxidised within a week so that a spectrum identical with that of the disulphide (141) was obtained.

This result (Figure 51) was not completely unexpected as thiolate anions have been previously shown to act as leaving groups in conjugate addition reactions of β-thioalkyl-α,β-unsaturated ketones, a second conjugate addition reaction then occurring (Figure 52).[101]

The introduction of both methyl groups during the conjugate addition reaction (Figure 51) could perhaps be explained by the scheme shown in Figure 53.

Figure 52

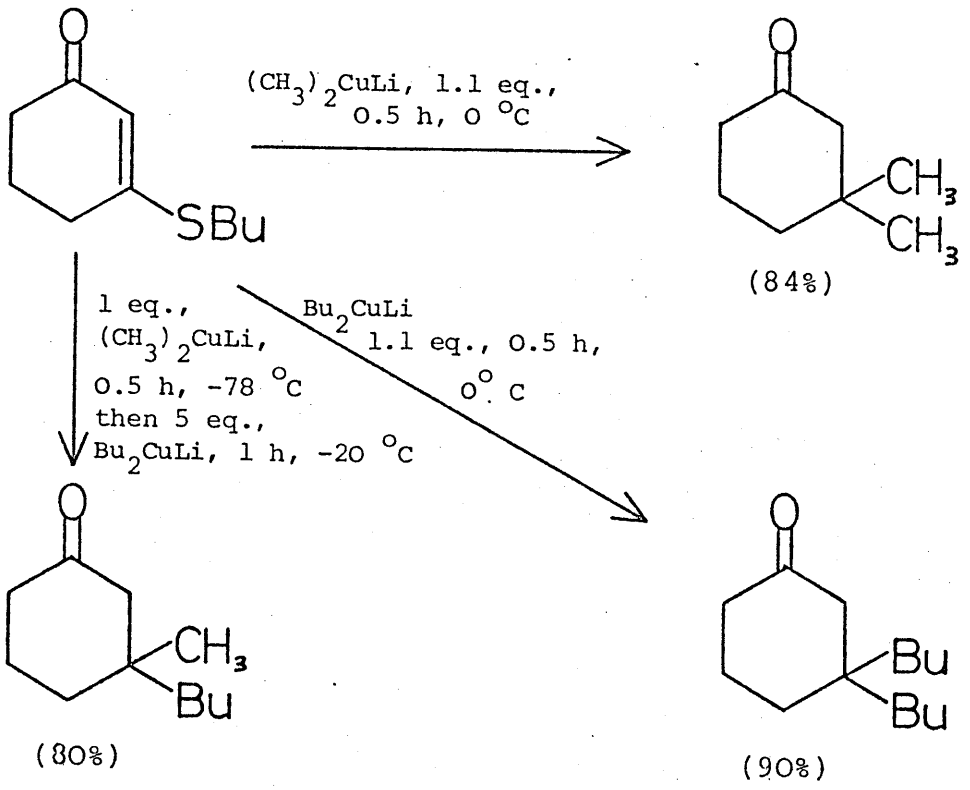
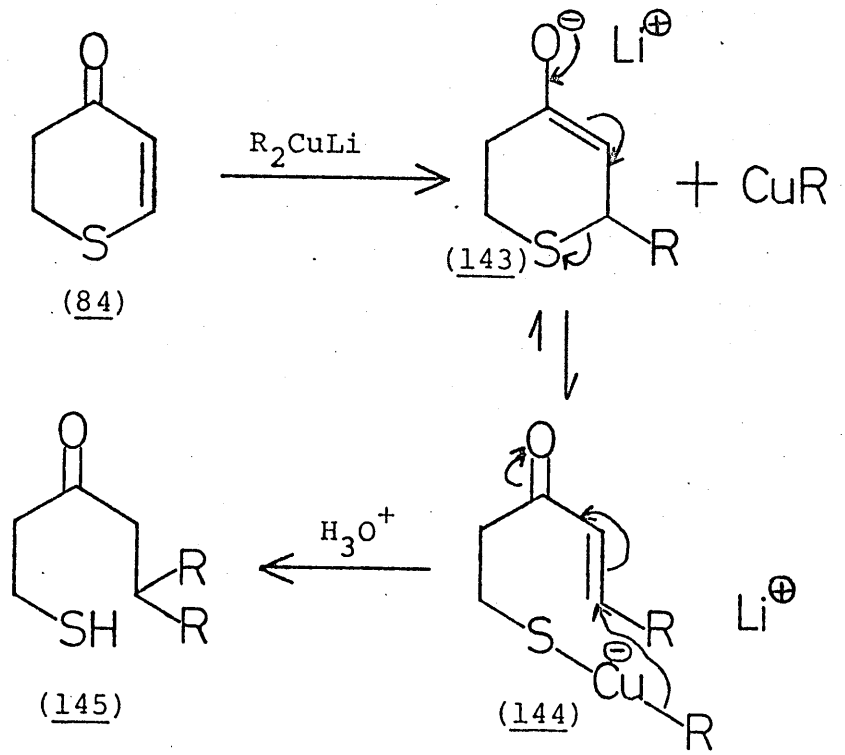
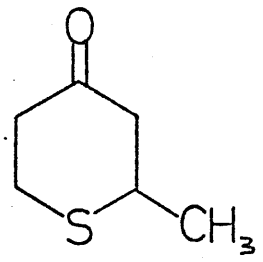


Figure 53



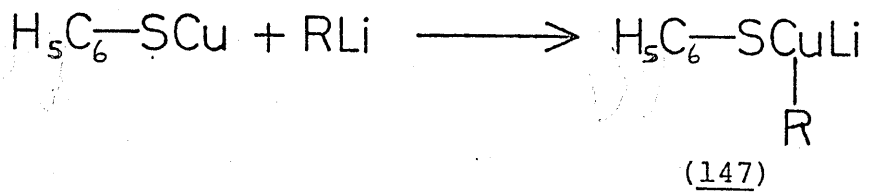
The initially formed enolate (143), upon ring-opening could form a cuprate (144), which by further conjugate addition and hydrolysis could give the 2-dialkylated product (145).

In the reaction under investigation (Figure 51), varying the ratio of the reactants had little effect, but lowering the temperature[102] to -78 °C did lead to the desired mono-conjugate addition product (146) but only in 23% yield.



(146)

With homocuprates (R_2CuLi) usually only one R group is transferred during the conjugate addition reaction, and as a result the other group is not utilised, creating a serious problem wherever the group is valuable or obtainable only by a multi-stage synthetic process. However, Posner[103] has reported that the organo(hetero)-cuprates, lithium alkyl(phenylthio)cuprates ($R(C_6H_5S)CuLi$) are easily prepared and are stable up to 0 °C. They allow easy work-up after reaction with the substrate, and they provide the highest efficiency in terms of the alkyl group which is transferred, whether this is a primary, secondary or tertiary alkyl group. Lithium alkyl-(phenylthio)cuprates (147) were prepared conveniently from phenylthiocopper(I) and alkyllithium reagents:[104]



(147)

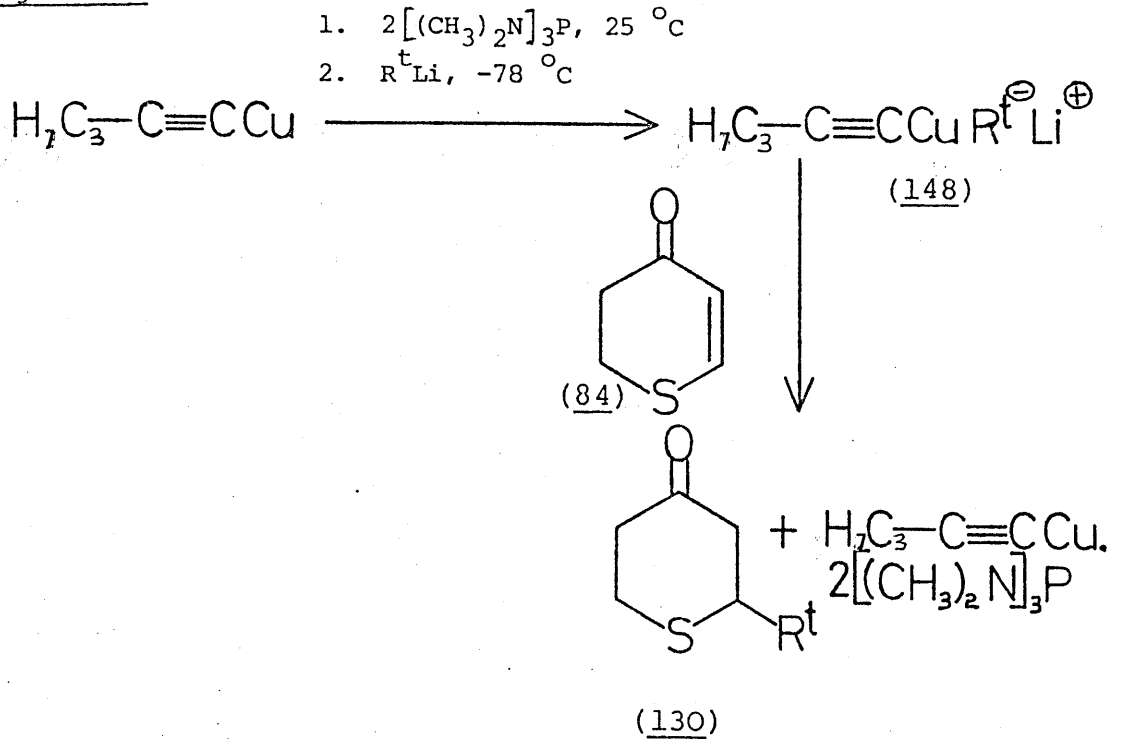
We thought that the use of these reagents might minimise further reaction as in Figure 53 and so raise the yield of 2-methylthian-4-one (146). However, treatment of 2,3-dihydrothi-in-4-one (84) with 2 molar equivalents of lithium methyl(phenylthio)cuprate (147, R = CH_3) at -78 °C, then warming to 0 °C, gave a product which was a mixture of components, almost all derived from thiophenol only. The same result was found when lithium butyl(phenylthio)cuprate (147, R = Bu) was used.

Heterocuprates (R^t R^r Cu Li) overcome the difficulties of only one group being transferred during conjugate addition reaction, since R^t represents the group to be transferred and R^r represents a residual group which is not transferred. The most common residual group is the pent-1-ynyl ($CH_3CH_2CH_2C{\equiv}C$) group first reported by Corey and Beames,[102] which remains tightly bound to copper during the reaction, and which upon isolation gives the volatile pent-1-yne easily separable from the reaction products.

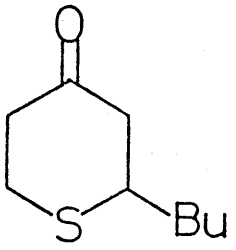
Therefore, the use of heterocuprates to effect conjugate addition to the unsaturated thianone (84) was investigated by using lithium alkylpent-1-ynylcuprates (148) prepared by the reaction between pent-1-ynylcopper[105]

and alkyllithiums in diethyl ether with added hexamethylphosphorus triamide (HMPT) to solubilise the pent-1-ynylcopper (Figure 54).

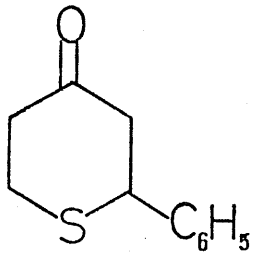
Figure 54



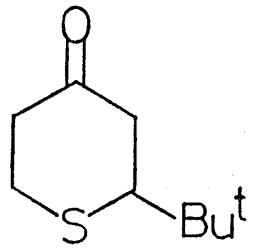
The reaction of methylpent-1-ynylcuprate (148, $R^t = CH_3$) with the unsaturated thianone (84) at -78 °C gave after an acid work-up[102] 2-methylthian-4-one (143) in 37% yield. This yield compares favourably with the yield of 30% obtained by Jones[90] using a three-stage route from thian-4-one (83), and with the yield of 25% obtained by Barkenbus[48] using the conventional Dieckmann cyclisation approach. The procedure for the preparation of 2-methylthian-4-one (143) was used to prepare 2-butylthian-4-one (149), 2-phenylthian-4-one (150) and 2-t-butylthian-4-one (151) with yields of 52%, 44% and 70% respectively.



(149)



(150)



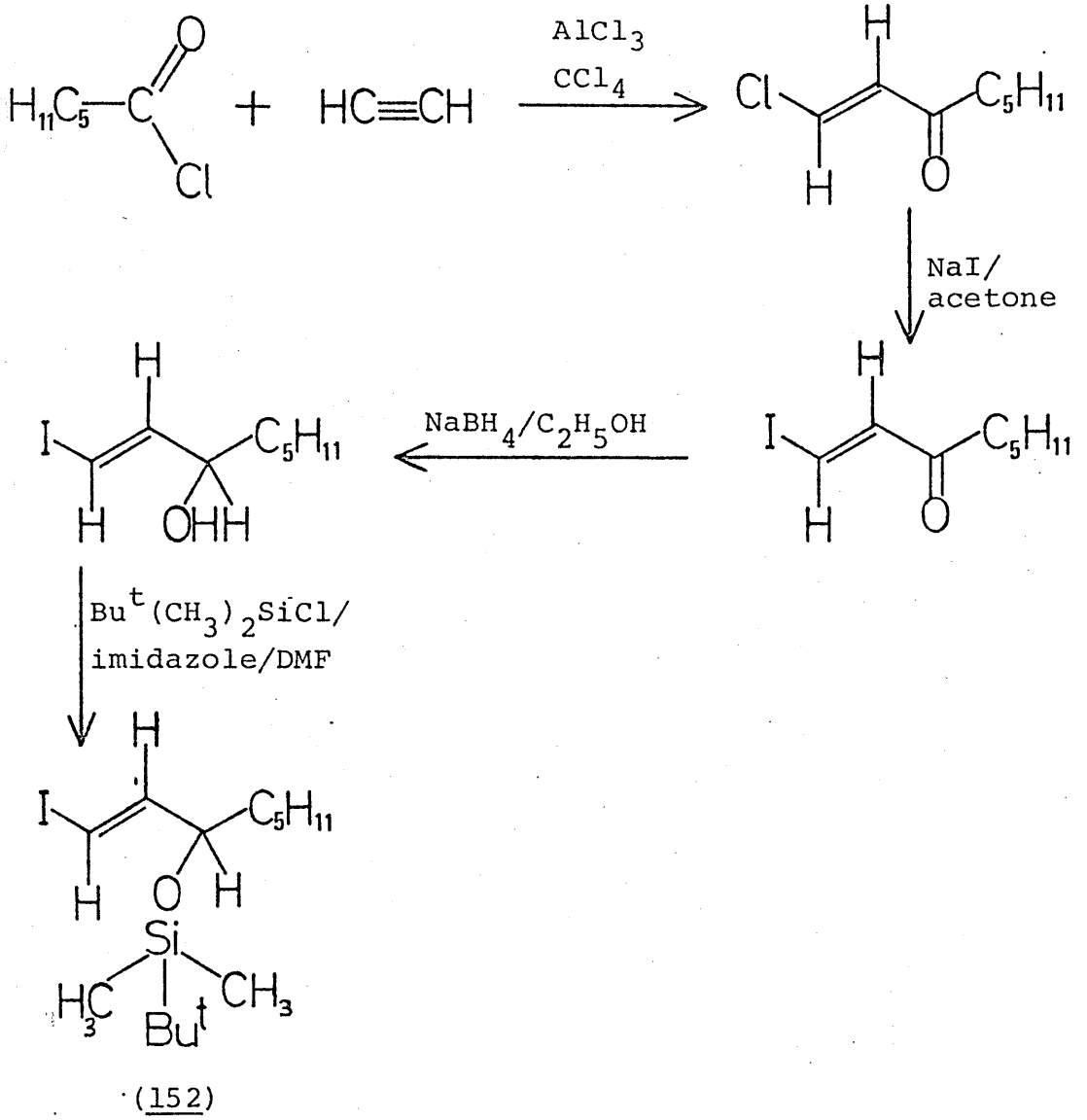
(151)

2-Phenylthian-4-one (150) is a known compound, the preparation of which is described by Jones[90] using a three-stage route from thian-4-one (83) in a yield of 37%.

For the C-2 side chain (R^2) of the target thia-thromboxane analogues, trans-3-(t-butyldimethylsilyloxy)-1-iodo-oct-1-ene (152) is required as starting material. This was prepared by the procedure of Corey and Beames[102] as shown in Figure 55.

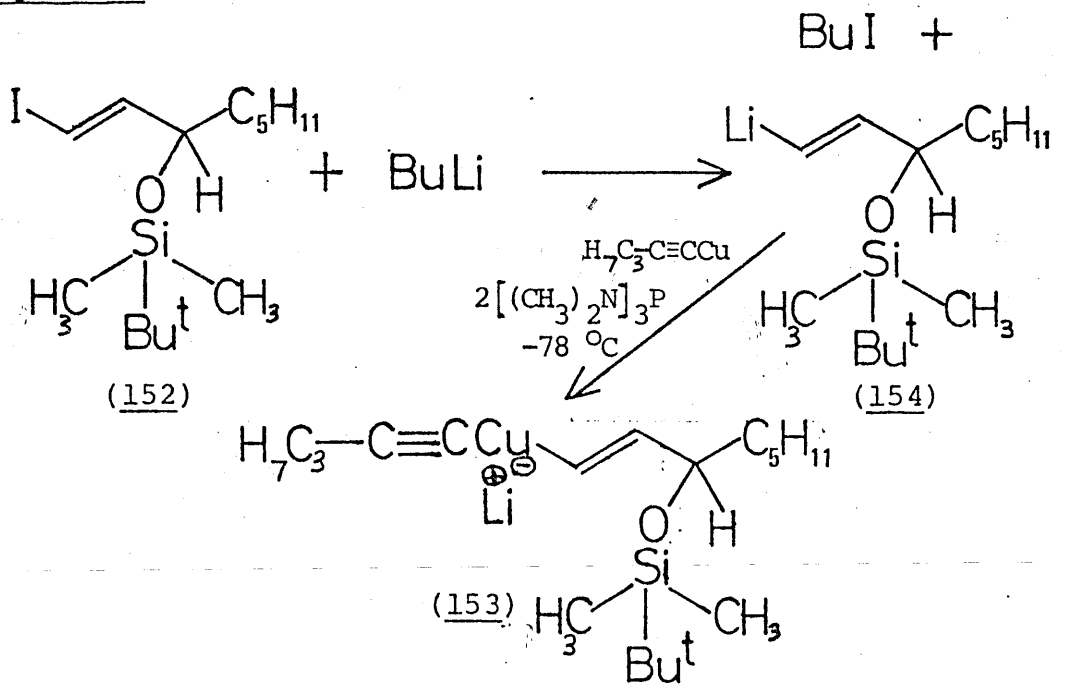
The mixed cuprate, lithium [trans-3-(t-butyldimethyl-silyloxy)oct-1-enyl] pent-1-ynylcuprate (153) was prepared by the reaction between one molar equivalent of butyllithium and trans-3-(t-butyldimethylsilyloxy)-1-iodo-oct-1-ene (152) to give the vinyl-lithium compound (154), which was treated with a solution of pent-1-ynylcopper and hexamethylphosphorus triamide in diethyl ether (Figure 56).

Figure 55



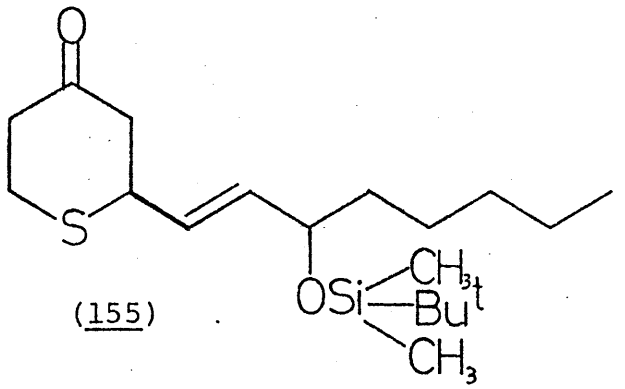
(152)

Figure 56



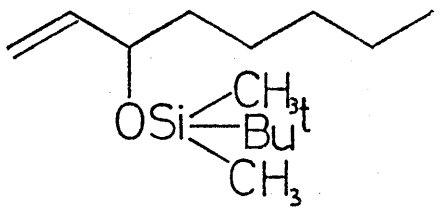
(152) (154) (153)

The addition of the unsaturated thianone (84) (precooled to -78 °C) to cuprate (153) gave 2-[trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] thian-4-one (155) in 28% yield after the usual acid work-up.



(155)

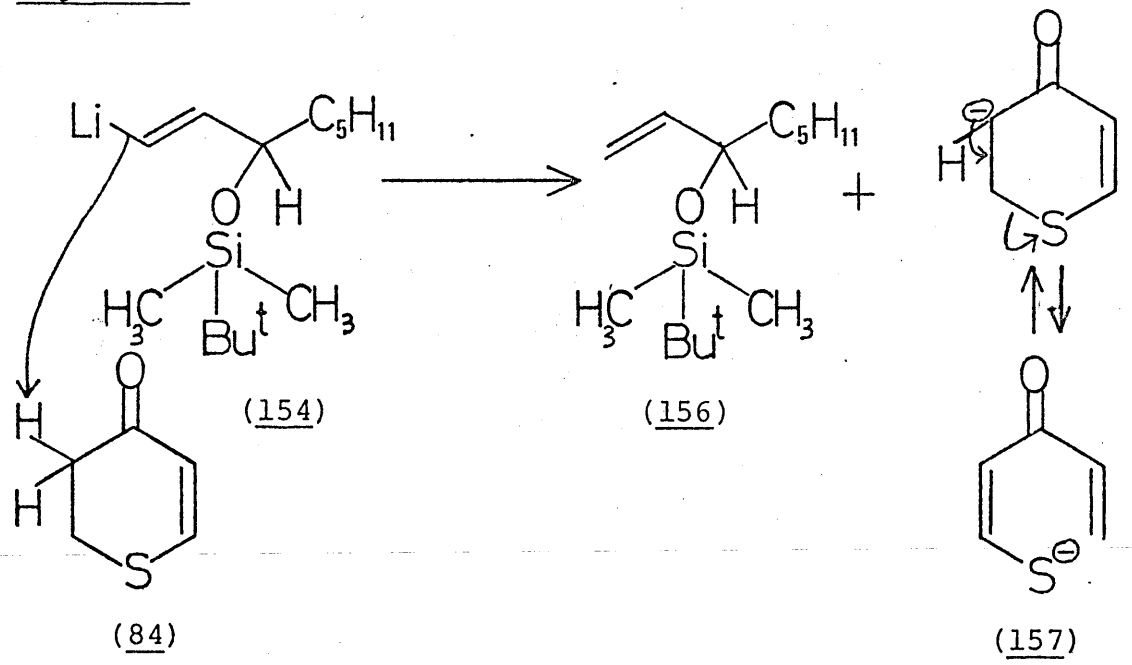
When 2 molar equivalents of tertiary-butyllithium were used to prepare the vinyl-lithium compound (154) as suggested by Corey[102] the yield of the required product (155) obtained was reduced to 16%. The use of tertiary-butyllithium was suggested since tertiary-butyl iodide, the initial product of lithium halogen exchange is converted to the innocuous products lithium iodide and 2-methylprop-1-ene, whereas butyl iodide could well interfere with the subsequent generation and use of the cuprate reagent.[102] The conjugate addition reaction leading to product (155) was accompanied by over 50% quenching of the vinyl-lithium compound (154) giving (156).



(156)

A possible explanation for this, and the low yield of the required product (155), could be that the methylene protons α to the carbonyl group in the unsaturated thianone (84) are acidic. The vinyl-lithium compound (154) or cuprate (153) might abstract a proton α to the carbonyl group (Figure 57) to give the ring-opened product (157), which would react further under the acid reaction conditions employed.

Figure 57



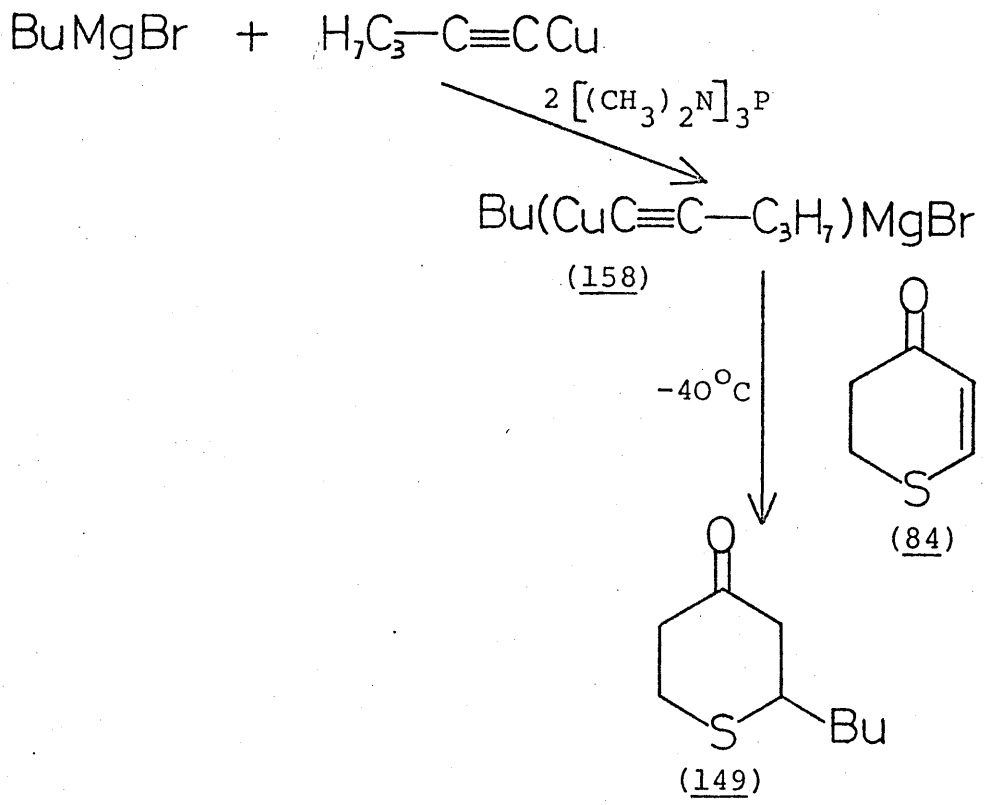
(84) (154) (156) (157)

When butyllithium was used to generate the vinyl-lithium compound (154) a small amount of 2-butylthian-4-one (149) was identified, and 2-t-butylthian-4-one (151) was formed in 2.5% yield when tertiary-butyllithium was used to generate (154). An attempt at increasing the yield of the required conjugate addition product (155) by quenching the reaction mixture with methanol at -78 °C,[106] led to the incorporation of methoxy groups into the product obtained, and so this procedure was not investigated further.

Preliminary studies carried out by S. Vassiliou at the University of East Anglia have shown that tributylphosphine-ligated organocopper reagents, i.e. RCu and 2-3 molar equivalents of tributylphosphine,[107] give increased yields of conjugate addition product when the unsaturated thianone (84) is the substrate.

Rivière[108] has developed magnesium organocopper reagents as efficient reagents for effecting conjugate addition to α,β-unsaturated ketones. Magnesium organocuprates have been found to have different stabilities and reactivities, and to be less basic than those of lithium organocuprates. They have been used in various syntheses of complex organic steroid molecules.[109] The mixed organocuprate reagent bromomagnesium butylpent-1-ynylcuprate (158) was prepared from the readily available butylmagnesium bromide and pent-1-ynylcopper. After the addition of hexamethylphosphorus triamide, the unsaturated thianone (84) was added in dry diethyl ether at -40 °C (Figure 58).

Figure 58



The usual acid work-up gave 2-butylthian-4-one (149) in 20% yield compared with 52% by the use of the corresponding lithium organocuprate (148, R^t=Bu).

Grignard reagents with a catalytic amount of a copper salt, have been reported to give predominantly conjugate addition to α,β-unsaturated ketones.[96] The presence of even one mole per cent of a copper salt in the reaction medium also very markedly accelerates the overall rate of reaction.[98] The reaction between 2 molar equivalents of methylmagnesium iodide and the unsaturated thianone (84) with the presence of 0.25 molar equivalents of copper(II)-acetate gave the required product, 2-methylthian-4-one (143) in a 19% yield compared with 37% obtained by the use of lithium methylpent-1-ynylcuprate (148, R^t=CH_3). This

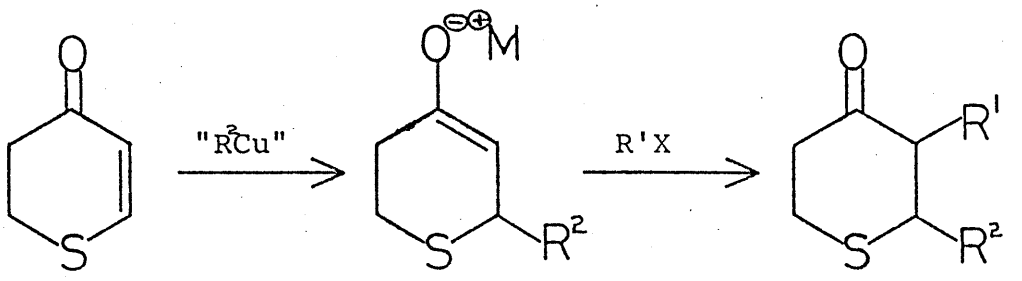
was accomplished by adding (84) and copper(II)acetate as a solution in dry THF to the Grignard reagent at -10 ^{o}C.[110] This stepwise addition of copper salt has been reported to cause a 10-30% increase in the yield of conjugate addition products.[111] Inverse addition, involving adding the Grignard reagent to a mixture of unsaturated substrate and copper catalyst has also led to a dramatic increase in the yields of conjugate addition products.[112] However, in our case a lower yield of conjugate addition product was obtained, with a greater proportion of other more polar products as indicated by tlc.

From these investigations of the conjugate addition reactions to 2,3-dihydrothi-in-4-one (84), the reagents of choice are the lithium alkylpent-1-ynylcuprates ($LiR^{t}CuC{\equiv}CC_3H_7$).

4.3 Attempted Alkylations and Silylations

An attempt was made to extend the conjugate addition procedure to the synthesis of 2,3-disubstituted thian-4-ones (85) by the *in situ* alkylation of the intermediate enolates (Figure 59).

Figure 59

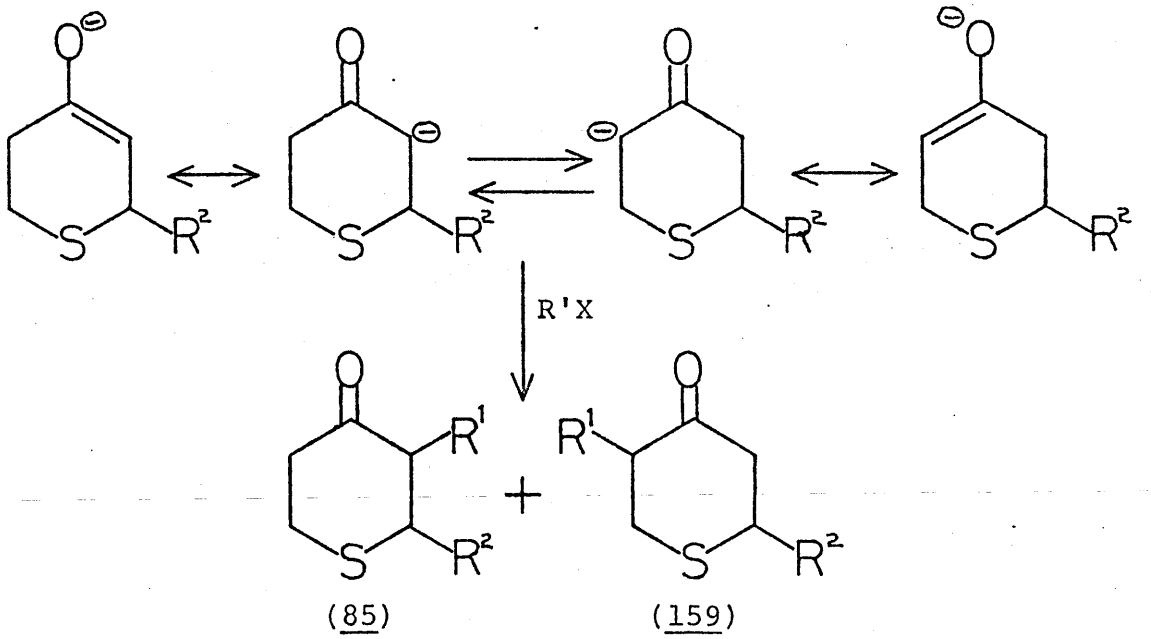


(84) (85)

This procedure is potentially an efficient method for introducing two different hydrocarbon groups, R^2 as a nucleophile and R^1 as an electrophile. Usually this would lead to a trans-stereochemical relationship.[113]

However, enolates once formed have been known to undergo proton transfer[113] and this could lead to the formation of structurally isomeric alkylated products in our system (Figure 60).

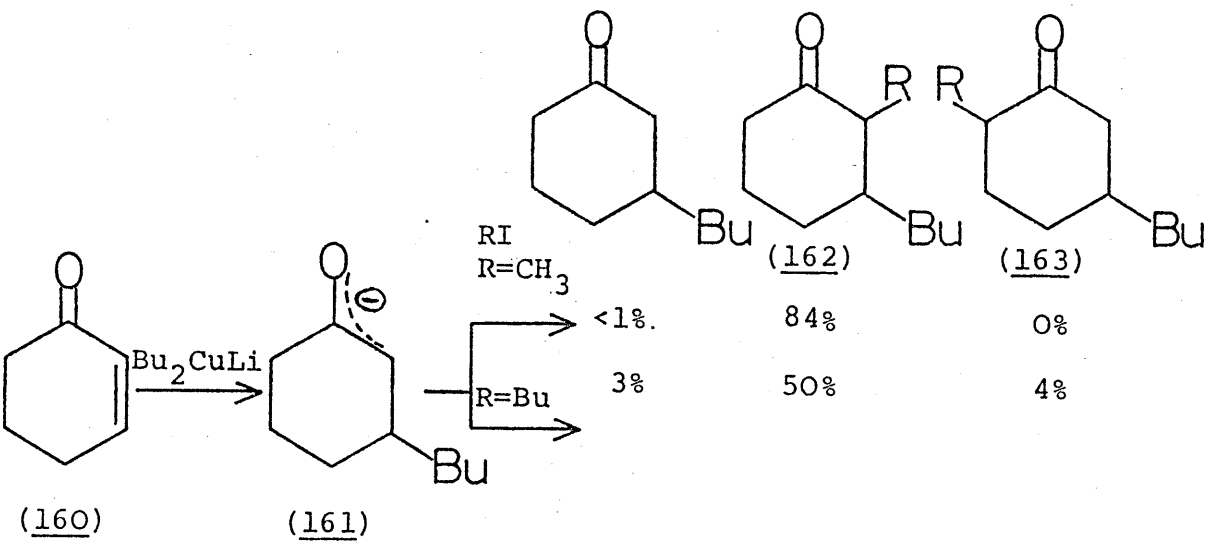
Figure 60



(85) (159)

For example, cyclohex-2-enone (160) reacts with excess lithium dibutylcuprate in THF at -78 °C to produce enolate (161); addition of excess iodomethane in HMPA at -78 °C, warming to between -40 and -30 °C and reaction at that temperature for 2 hours gave trans- and cis-3-butyl-2-methylcyclohexanones (162, R=CH_3) in a 7:1 ratio in 84% yield (Figure 61).[113]

Figure 61



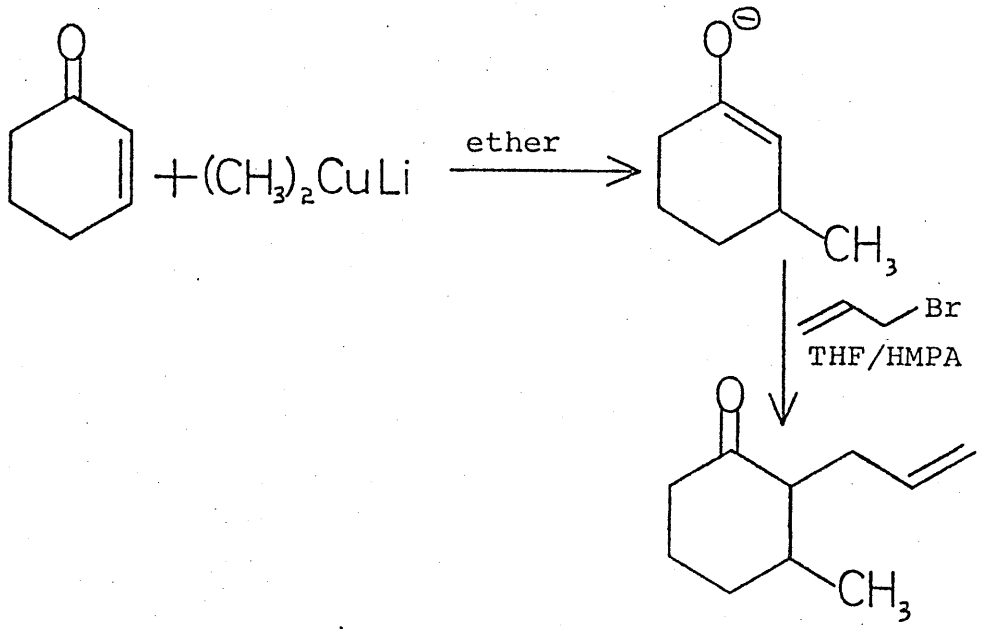
No 5-butyl-2-methylcyclohexanone (163, R=CH_3) was formed, which indicated that methylation is much faster than proton transfer of enolate (161) under the reaction conditions. Reaction of enolate (161) with iodobutane gave trans- and cis-2,3-dibutylcyclohexanones (162, R=Bu) in a 4.5:1 ratio in 50% yield, along with a small amount of 2,5-dibutylcyclohexanone (163, R=Bu) Therefore, it has been found that intermediate enolates may be alkylated regiospecifically in unhindered cases, without significant amounts of isomeric products arising from proton transfer being formed. A possible explanation for this is that organocuprate enolates are highly covalent and so less likely to undergo proton transfer.[114]

The solvent of choice for the maximum yield of conjugate addition product is usually diethyl ether,[96] whereas the intermediate enolates are not very reactive in diethyl ether. The solvent of choice for alkylation reactions is 1,2-dimethoxyethane (DME), alkylation being 10^5 times more effective than in diethyl ether. Since a DME-diethyl ether mixture is much less effective than DME on its own for alkylation, then nearly all the diethyl ether remaining from the conjugate addition reaction has to be removed prior to the addition of DME.[115] Both THF and HMPA have a rate-accelerating effect comparable to, but slightly less than that of DME.

Taking these findings into account the conjugate addition - enolate alkylation reaction was investigated. The butyl group was chosen for conjugate addition since this had given the highest yield of conjugate addition product to the unsaturated thianone (84), 2-butylthian-4-one (149), and the group is a linear chain, with no steric complications involved. THF was used as a solvent for conjugate addition and a mixture of THF and HMPA for the alkylation step. The alkylating reagent chosen was allyl bromide since this has given good yields of 2,3-disubstituted cyclohexanones (Figure 62).[115]

Allyl bromide is also significant because it has a similar haloalkane group to that in the reagent,[116] methyl cis-7-iodohep-5-enoate (164), required to construct the side chain in the target thiathromboxane molecules.

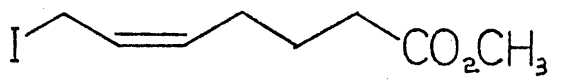
Figure 62



trans : cis

8 : 1

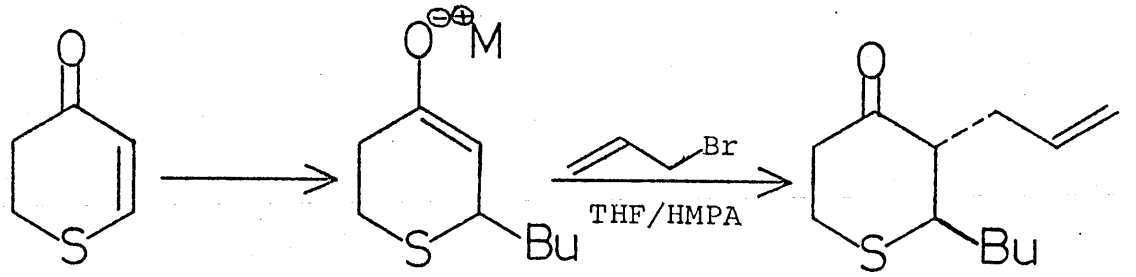
74%



(164)

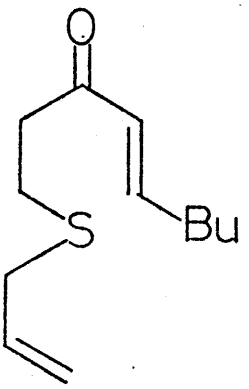
The attempted alkylation was effected by adding a mixture of allyl bromide (5 molar equivalents) and HMPA to the enolate (165) at -20 °C (Figure 63).

Figure 63



(84) (165) (166)

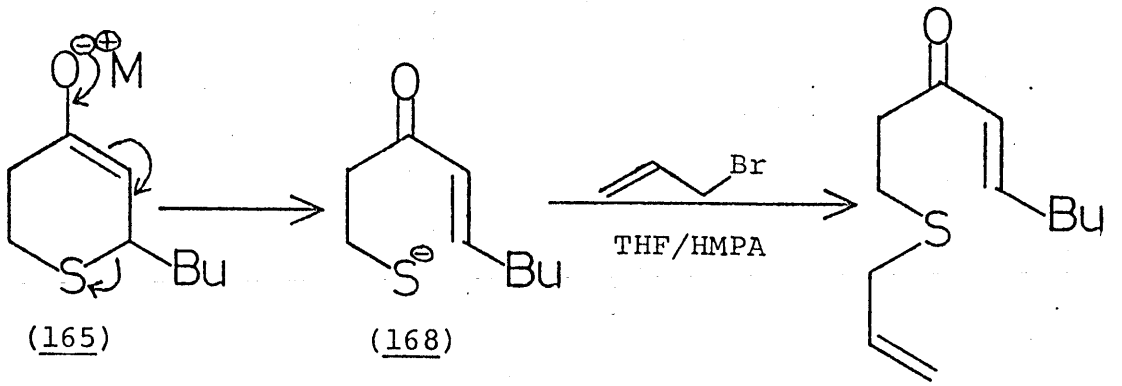
After the usual acid work-up and column chromatography of the crude product spectroscopic measurements indicated that the required product (166) had not been formed. ^{1}H-NMR indicated the presence of five alkene protons; the infra-red spectrum gave a C=C stretch at 1630 cm^{-1}, together with a C=O stretch at 1670 cm^{-1} implying conjugation with a C=C bond. The presence of a trans-alkene bond was indicated by a C-H bend at 950 cm^{-1}. The ^{13}C-NMR showed one carbonyl carbon atom present, together with four alkene carbon atoms. The mass spectrum confirmed the structure of the product as being trans-1-allylthionon-4-en-3-one (167).



(167)

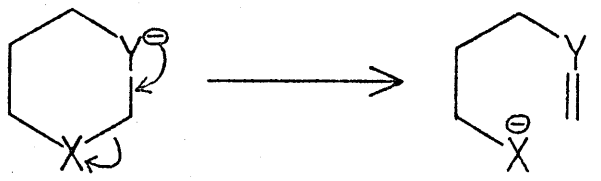
Presumably this compound was formed by ring-opening of the intermediate enolate (165) to give (168) which was then alkylated by allyl bromide at the sulphur atom (Figure 64).

Figure 64



(165) (168) (167)

The transformation of (165) to (168) can be represented by the general reaction (169) to (170):

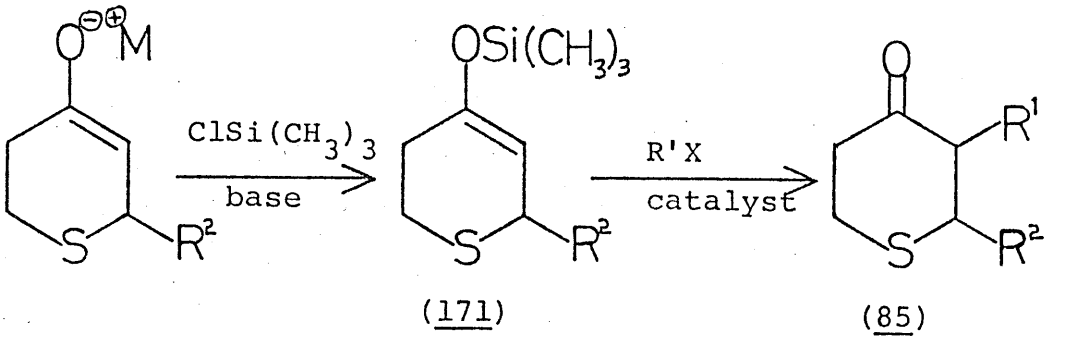


(169) (170)

Baldwin[117] has investigated the ring-closure of acyclic precursors by the nucleophilic attack of oxygen on conjugated double and triple bonds. By a consideration of bond lengths and the ring size it is possible to determine whether X and Y can attain the required transition state geometry, and so give an indication of whether ring-closure is favoured or disfavoured. The transformation (169) to (170) is classified as a retro-6-endo-trigonal process since in the (170) to (169) transformation, (i) the breaking bond (=Y) is endocyclic to the ring, (ii) the ring is 6-membered, and (iii) the geometry of the carbon atom undergoing the ring-closure reaction is trigonal. According to Baldwin the reverse process (170 to 169) would be favoured (if X was a first row element in the Periodic table). By analogy, in our reaction (165 to 168) Baldwin's rules would predict that the ring-opening reaction is favourable.

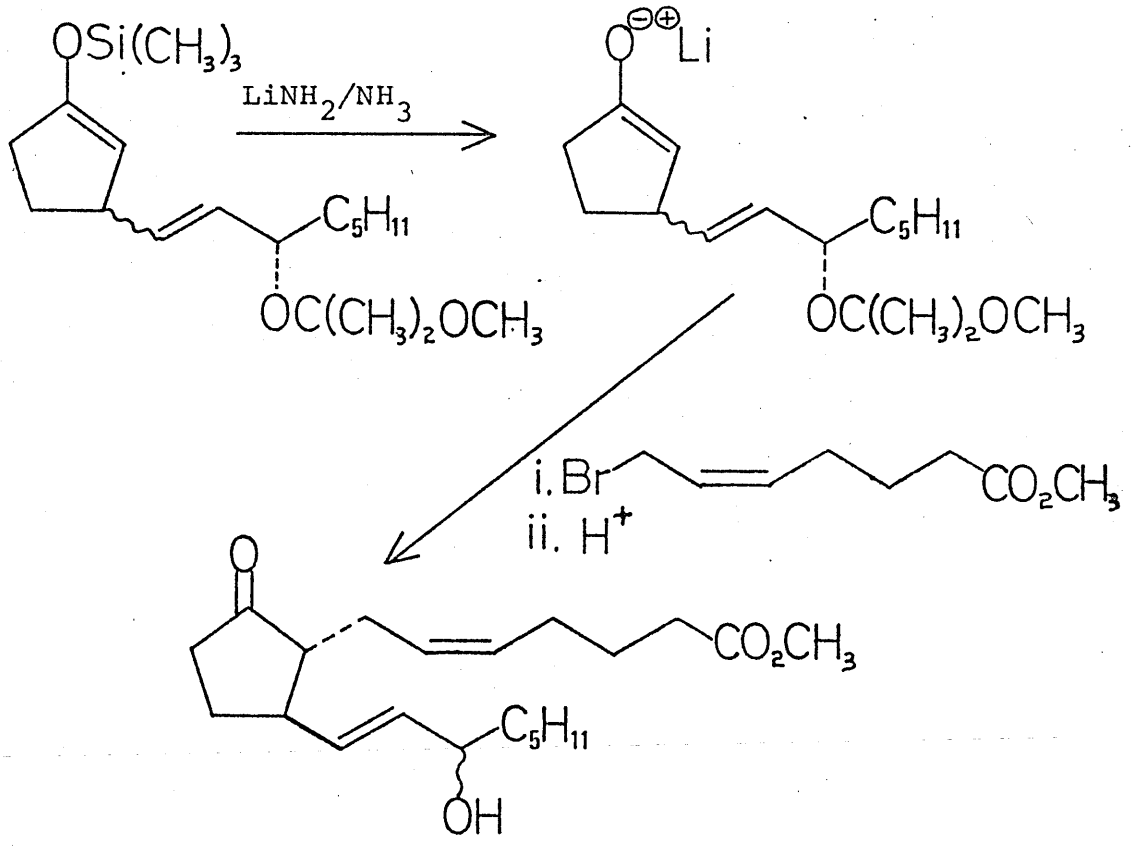
An alternative approach to prepare 2,3-disubstituted thian-4-ones was then attempted. This involved trapping the intermediate enolate as its trimethylsilyl ether (171) which might allow alkylation by Lewis acid catalysis (Figure 65).[118,119]

Figure 65



There are no published results to date in the prostaglandin field for alkylating silyl enol ethers directly. However, Patterson[120] has used silyl enol ethers in alkylation by regeneration of the enolates using lithium amide in liquid ammonia (Figure 66).

Figure 66

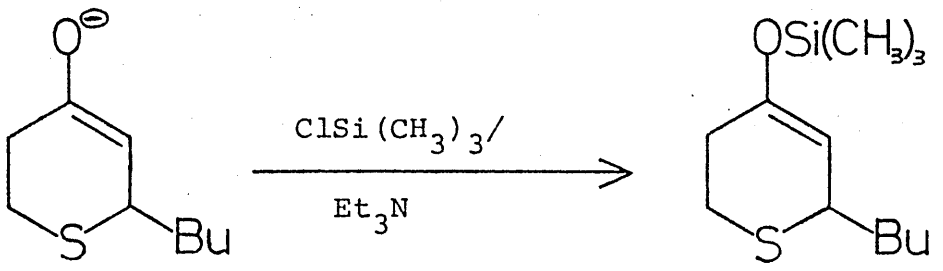


The direct alkylation of silyl enol ethers has also been carried out by Paterson using alkylating agents which give stable carbonium ions, e.g. methoxymethyl chloride, prenyl bromide.[118]

When lithium butylpent-1-ynylcuprate (148, R^t = Bu) was used for the conjugate addition reaction of the unsaturated thianone (84) to form enolate (165) the isolated product consisted of mostly HMPA, formed by the oxygenation of HMPT during work-up. An acid work-up would have removed the HMPA, but this treatment also removed the trimethylsilyl group. Attempts at removing the HMPA by distillation or column chromatography were unsuccessful.

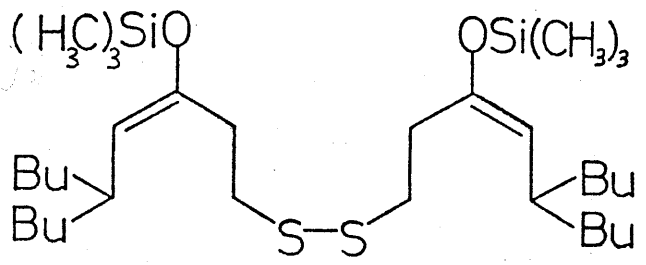
In order to avoid the use of HMPT, the homocuprate lithium dibutylcuprate (Bu_2CuLi) was used for the conjugate addition reaction to the unsaturated thianone (84), then the enolate (165) was trapped by adding a mixture of trimethylchlorosilane (7 molar equivalents) and triethylamine at -78 °C (Figure 67).

Figure 67



(165)

A basic aqueous work-up then allowed the crude product to be isolated.[121] However, the product decomposed when purification was attempted using silica, alumina or cellulose chromatography and when distillation was attempted. Column chromatography using Florisil was found to be the only satisfactory purification method.[122] Two compounds were obtained in 40% yield which had the same ^{1}H-NMR and infra-red characteristics, most probably isomers. The ^{1}H-NMR spectrum indicated that two butyl groups had been inserted into the molecule during the reaction. Together with mass spectral evidence this suggested that the product had the structure (172), bis(5-butyl-3-trimethylsilyloxynon-3-enyl)disulphide.

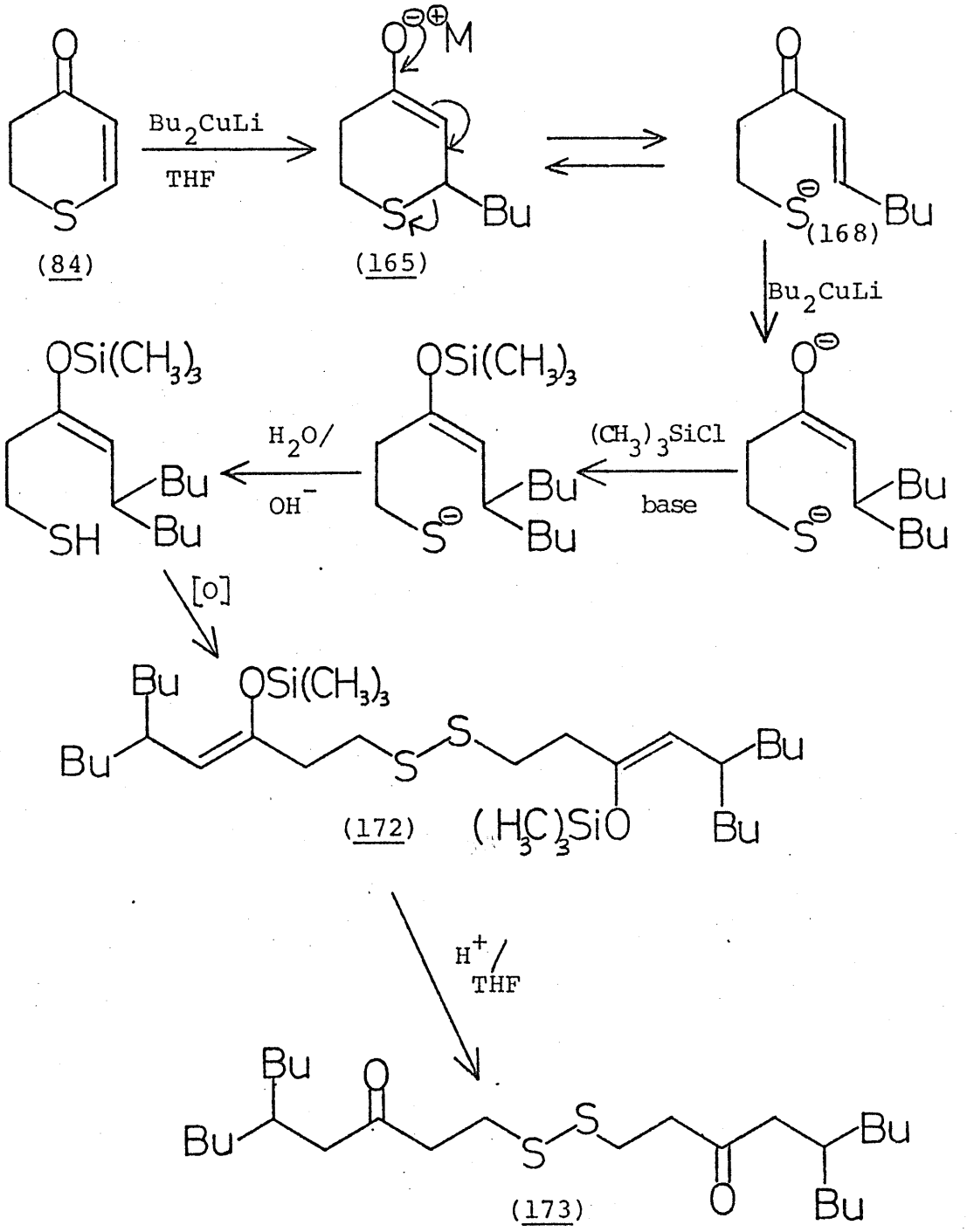


(172)

These compounds presumably arose by ring-opening of the enolate (165), followed by further reaction of organocuprate, then trimethylsilylation (Figure 68).

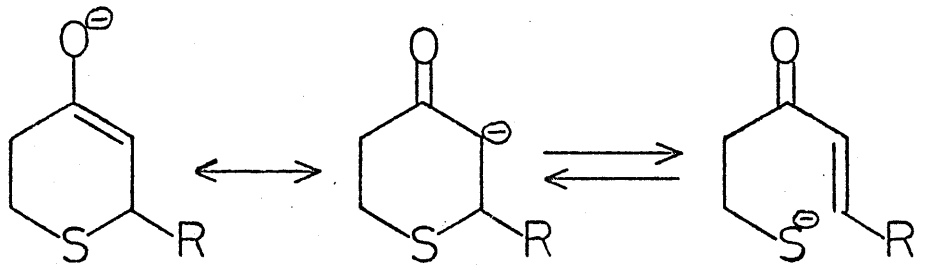
Further proof of the disulphide structure was obtained by hydrolysis of disulphide (172) with 10% HCl in THF to give bis(5-butyl-3-oxononyl)disulphide (173) in 67% yield.

Figure 68

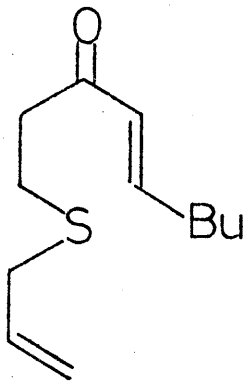


Attempted hydrolysis of disulphide (172) by passing down a silica gel column gave incomplete hydrolysis to (173).

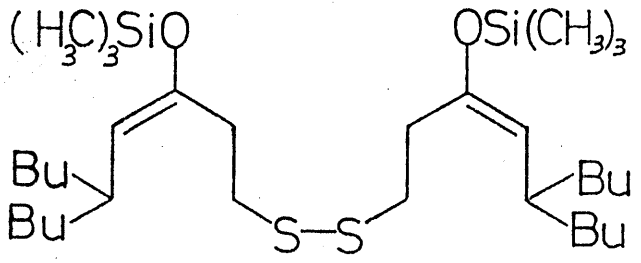
The observation that allylation of enolate (165) with allyl bromide gives S-allylation and silylation with trimethylchlorosilane gives O-silylation can be explained by a consideration of the Hard and Soft Acids and Bases Principle (HSAB) of Pearson.[123] This states that 'hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases'. A 'hard' acid (electron acceptor) or base (electron donor) is generally characterised by a small atomic radius, a high effective nuclear charge and a low polarisability, whereas a 'soft' acid or base implies all the opposite properties. The two anions (I and II) involved in this case can be considered as:



According to the HSAB, anion Ia($RO^{\ominus}$) is a hard base, whereas anions Ib($R_3C^{\ominus}$) and II($RS^{\ominus}$) are soft bases. Allyl bromide is classified as a soft acid and trimethylchlorosilane as a hard acid. Therefore by this principle allyl bromide should give the C-allylated or the S-allylated product, and in practice the S-allylated product (167) was formed. Trimethylchlorosilane, by the same principle, should give only the O-silylated product. This is found to be the case in practice, with disulphide (172) formed.



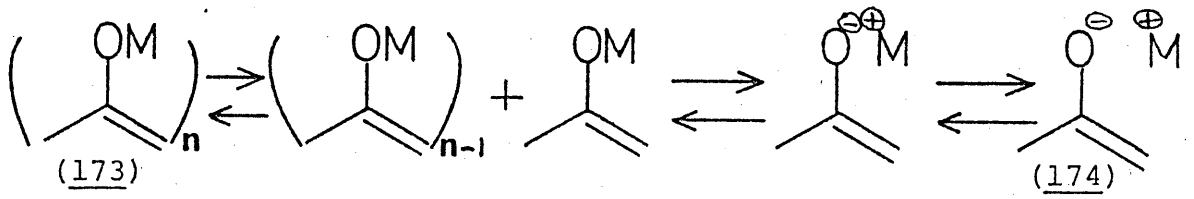
(167)



(172)

The reactivity of anions such as I and II with various electrophilic reagents also depends on the nature of the solvent present. Metal enolate solutions may consist of aggregates (dimers or trimers) in equilibrium with monomeric covalently bonded species, contact ion pairs and solvent-separated ion pairs (Figure 69).[124]

Figure 69



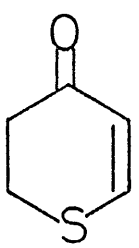
(173) (174)

The nature of the solvent has a profound influence on the degree of aggregation and the nature of the association between the enolate anion and the metal. This influences the reactivity of the enolate towards electrophilic reagents (allyl and alkyl halides). In non-polar solvents such as benzene or diethyl ether, the solubility of metal enolates is low, and in solution the metal enolate exists primarily in the aggregated form (173).

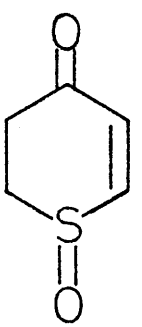
Dipolar aprotic solvents, such as THF or DME, solvate the metal cation and force the equilibrium towards monomeric species, and greatly enhance the enolate reactivity towards electrophilic reagents. Highly ionizing solvents, such as DMF, DMSO and HMPA solvate the metal cation and shift the equilibrium to solvent-separated ion pairs. Such species, (174), are highly nucleophilic so they will undergo reactions with alkylating reagents at very rapid rates, although the extent of O-alkylation is substantially increased.[124]

However, in the case of the formation of the S-allylated product (167), no allylation occurred unless HMPA was added to the reaction mixture. Perhaps a way of inducing C-allylation would be to vary the quantity of HMPA added, reducing the figure of 6 molar equivalents, so as to vary the nucleophilic character of the enolate.

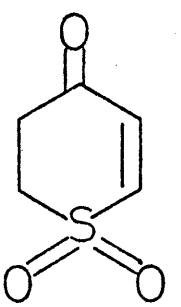
Since ring-opening and S-allylation occurred when conjugate addition-allyl trapping was attempted on 2,3-dihydro-thi-in-4-one (84), the same reactions were investigated with the corresponding sulphoxide (175) and sulphone (176).



(84)



(175)

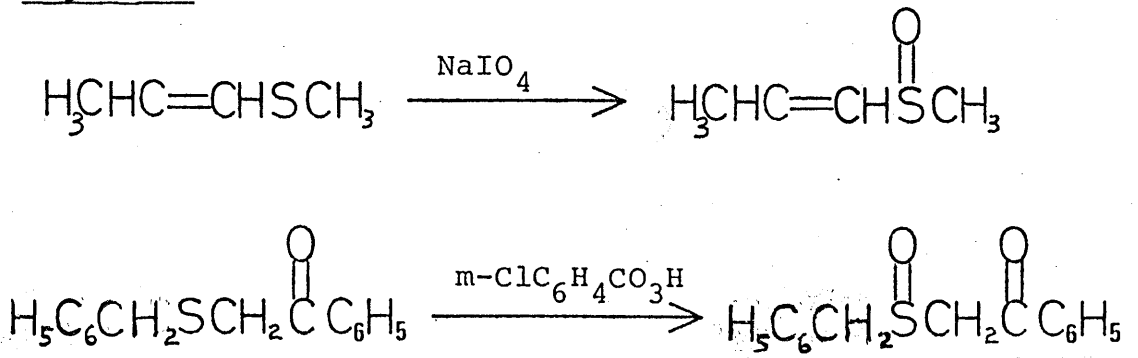


(176)

4.4 Reactions with 2,3-dihydrothi-in-4-one 1-oxide and 2,3-dihydrothi-in-4-one 1,1-dioxide

The literature procedure for the synthesis of 2,3-dihydrothi-in-4-one 1-oxide (175) involved oxidation of (84) with sodium metaperiodate in aqueous acetonitrile solution.[125] However, the reaction was not complete after several days using a large excess of reagent. An alternative procedure was developed which involved oxidation with one molar equivalent of m-chloroperbenzoic acid with chloroform as solvent. This gave the required sulphoxide (175) in 91% yield, but it was susceptible to decomposition on column chromatography. These oxidation procedures were employed because they have been reported to be selective reagents for oxidation of the sulphide function to the sulphoxide only, with no epoxidation of the double bond present, no further oxidation to the sulphone, and no oxidation of carbonyl functional groups (Figure 70).[126]

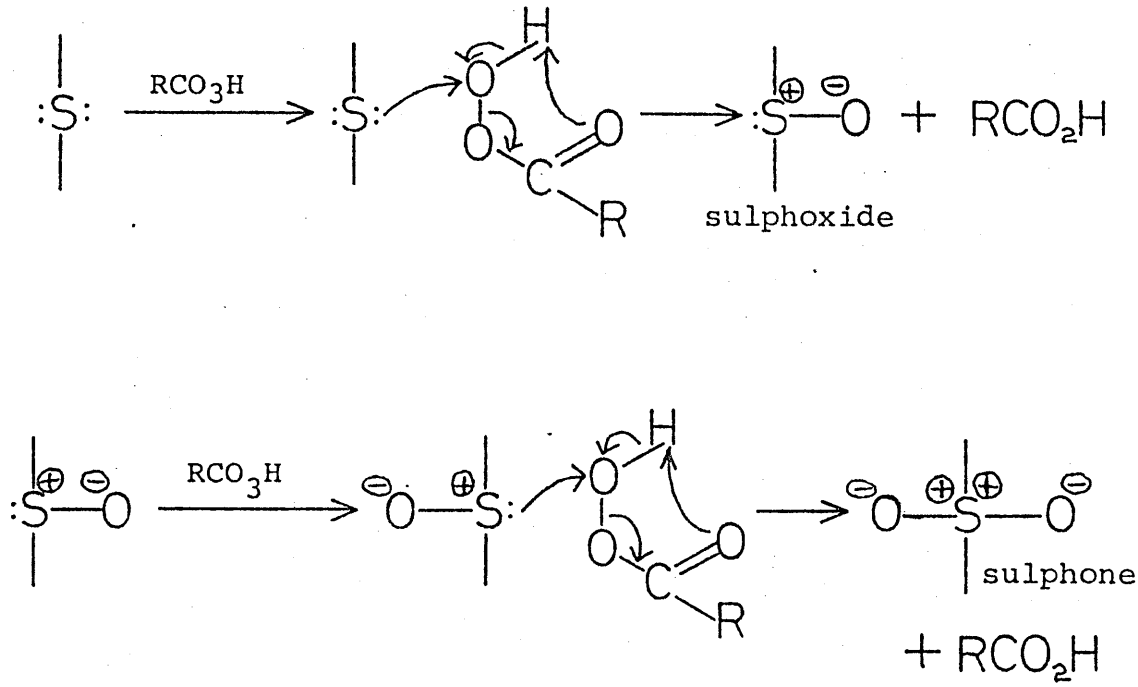
Figure 70



The oxidation of the unsaturated thianone (84) to sulphone (176) was accomplished by reaction with 2 molar equivalents of m-chloroperbenzoic acid in chloroform at -20 °C.[51] This gave 2,3-dihydrothi-in-4-one 1,1-dioxide (176) in 68% yield, and this did not decompose during column chromatography.

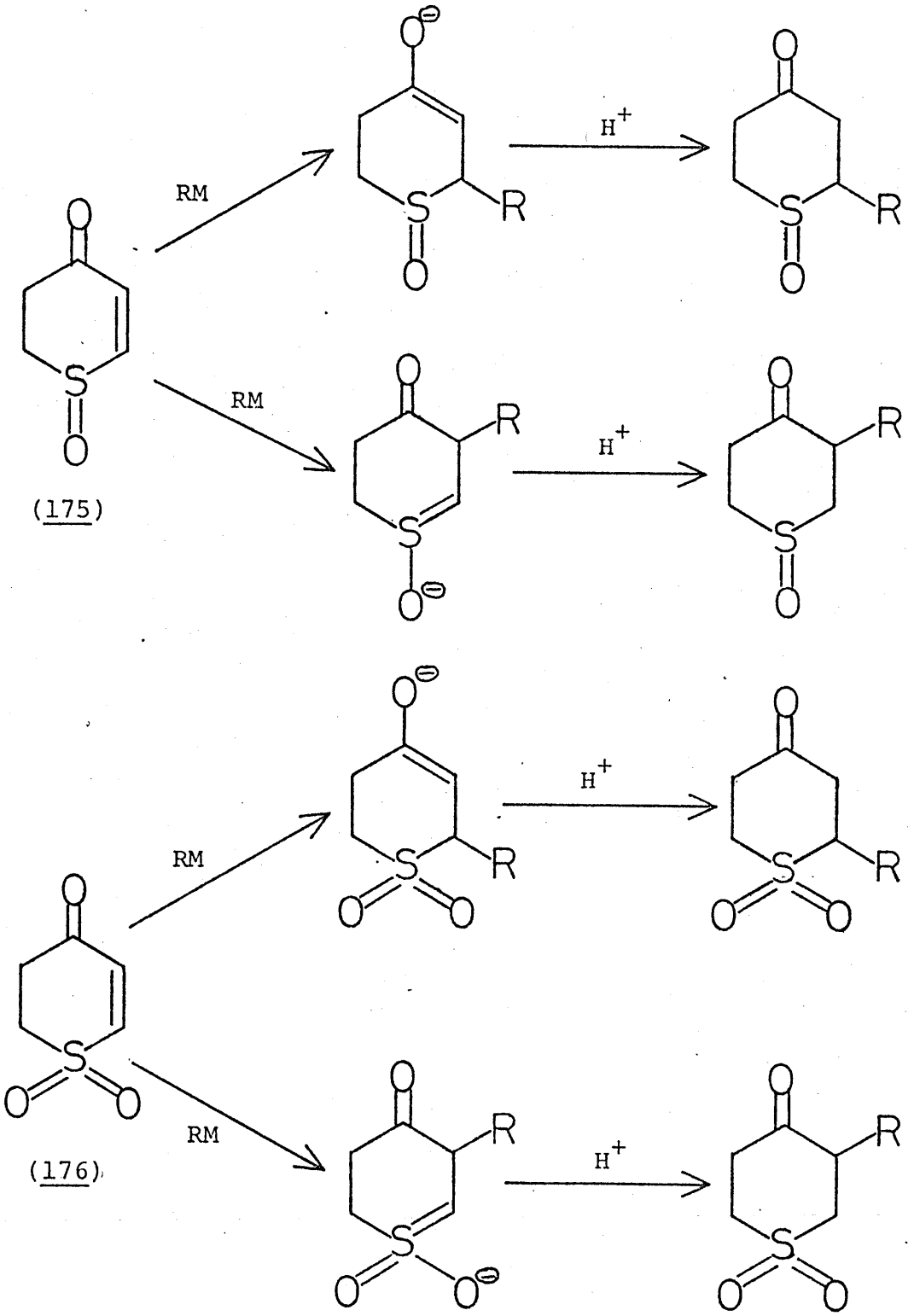
The mechanism of the sulphide and sulphoxide oxidations with peracids probably involves a nucleophilic oxygenation, with the nucleophilic attack by sulphur on an electronegative oxygen atom of the peracid, in a concerted process (Figure 71).[126]

Figure 71



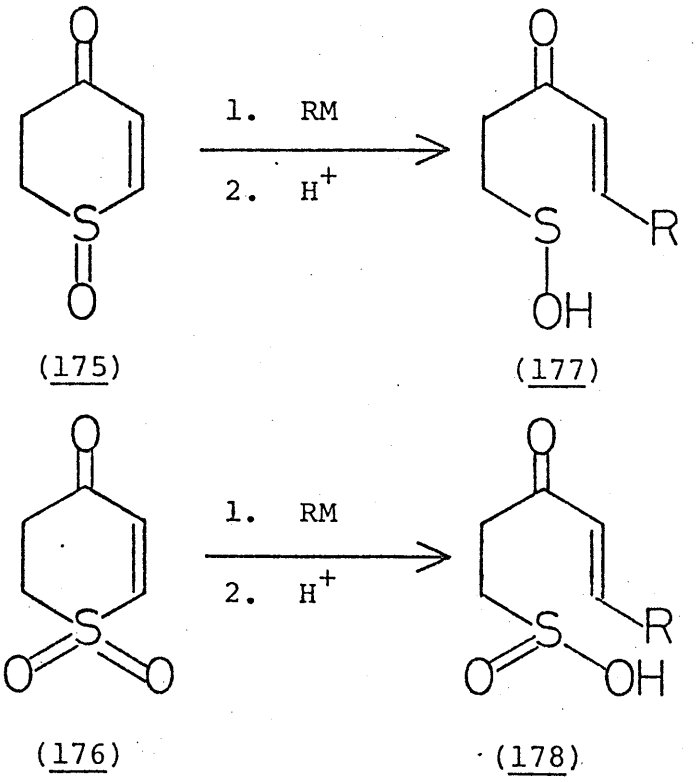
With sulphoxide (175) and sulphone (176) conjugate addition could occur at either end of the double bond, leading to either 2-substituted or 3-substituted derivatives (Figure 72).

Figure 72



Stirling[127] has investigated the leaving group ability of a series of groups in 1,2-elimination reactions and found the order $-SO_2 > -SO > -S$, so sulphones and sulphoxides would be expected to ring-open more easily than sulphides. If ring-opening did occur in these cases, then the sulphoxide (175) would give a sulphenic acid (177) and the sulphone (176) would give a sulphinic acid (178), as shown in Figure 73.

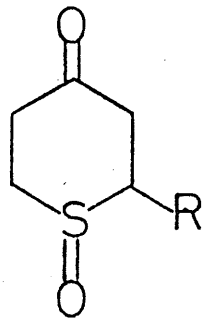
Figure 73



(175) (177)

(176) (178)

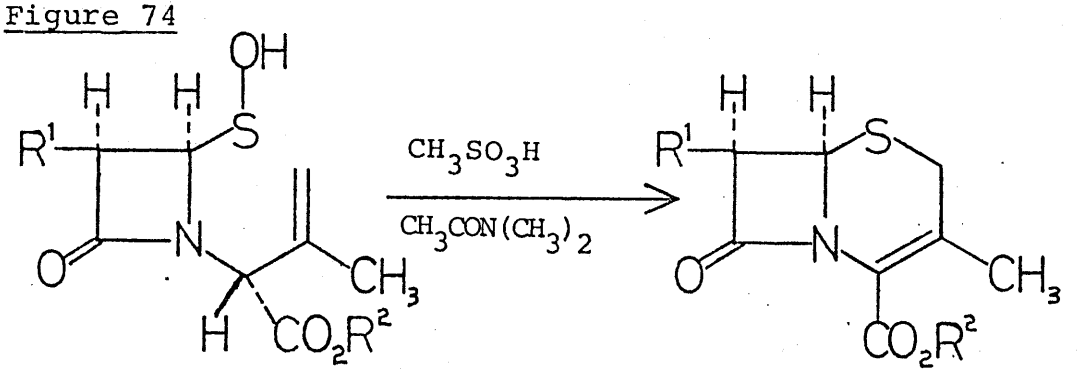
Sulphenic acid (177) if formed, would be likely to cyclise to give the required conjugate addition product (179).



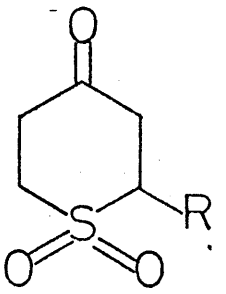
(179)

This cyclisation has precedence in the penicillin field (Figure 74).[128]

Figure 74



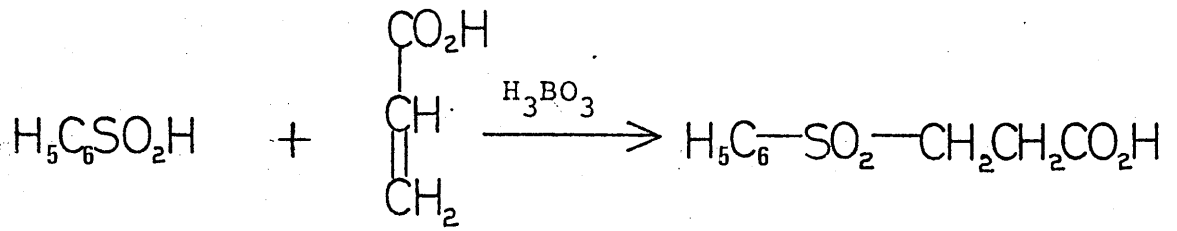
Sulphinic acid (178) if formed, would be likely to cyclise to give the required conjugate addition product (180).



(180)

The literature shows that sulphinic acids add to α,β-unsaturated carbonyl compounds to yield the corresponding sulphones, the reaction being catalysed by weak acids (Figure 75).[129] The nucleophilic centre of sulphenic and sulphinic acids is the sulphur atom.

Figure 75



In order to determine whether ring-opening takes place and at which end of the double bond conjugate addition occurs, then the reaction of butylpent-1-ynylcuprate ($C_3H_7C{\equiv}CCuBuLi$) with sulphoxide (175) was investigated.

However, the conjugate addition products could not be isolated, but only HMPA derived from the oxygenation of HMPT. To avoid the use of HMPT, the homocuprate, lithium dibutylcuprate (Bu_2CuLi) at -78 °C was used for this conjugate addition reaction with THF as solvent, since sulphoxide (175) was not soluble in diethyl ether. After the usual aqueous work-up a product (181) consisting of two components was obtained in 51% yield. The two components were separated by column chromatography and were found to give the same mass spectra with identical molecular masses. These are likely to be isomers with different configurations of the sulphoxide group, cis and trans with respect to the butyl group. In order to determine at which end of the double bond conjugate addition had occurred, a sample of 2-butylthian-4-one (149) prepared by the conjugate addition to the unsaturated thianone (84), was oxidised with one molar equivalent of m-chloroperbenzoic acid.[126] This oxidation gave a product in 85% yield with two components which had identical spectral characteristics to the product (181). This implied that conjugate addition to the sulphoxide (175) occurred at C-2 to give 2-butylthian-4-one-1-oxide (181) (Figure 76).

The reaction of lithium dimethylcuprate ($(CH_3)_2CuLi$) at -78 °C with the sulphoxide (175) gave under the same conditions 2-methylthian-4-one 1-oxide (182) in 12.5% yield, again consisting of two components (Figure 77). The low yield can probably be accounted for by the increased

water solubility of (182), containing a methyl group, over (181), containing a butyl group.

Figure 76

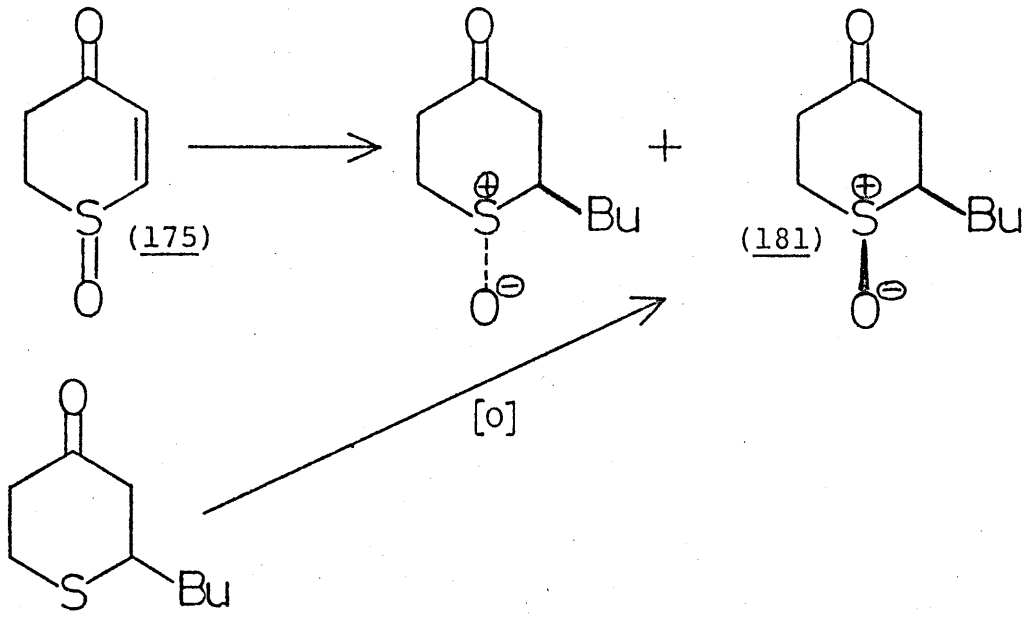
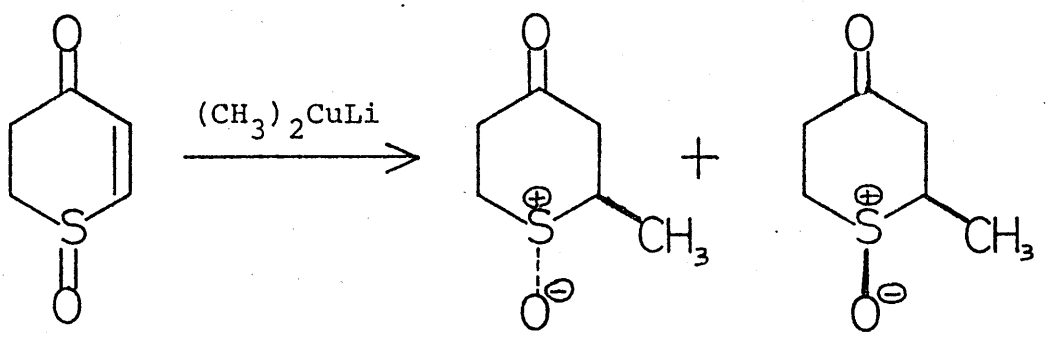


Figure 77



(175) (182)

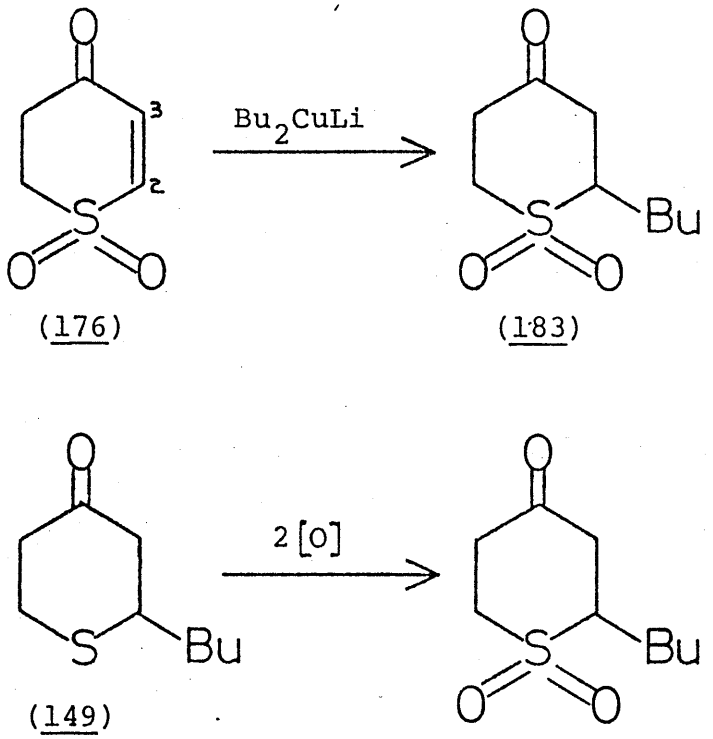
An attempt to bring about the conjugate addition of lithium diphenylcuprate to sulphoxide (175) under the same reaction conditions gave only biphenyl (C_6H_5-C_6H_5), with no sign of any 2-phenylthian-4-one 1-oxide. However, it has been reported that a major side product in some conjugate additions with R_2CuLi is the dimer RR.[130]

It was significant that the conjugate addition of homocuprates to the sulphoxide (175) did not lead to any products derived from ring-opening at sulphur, whereas the corresponding homocuprate conjugate additions to the unsaturated thianone (84) led to ring-opening at sulphur and to reaction with more homocuprate.

Reactions with the sulphone (176) were next investigated. The homocuprate lithium dibutylcuprate (Bu_2CuLi) at -78 ^{o}C in THF as solvent was used for the conjugate addition reaction with sulphone (176). After the usual aqueous work-up the major product was (183) isolated in 13% yield together with a minor product in 1.5% yield (Figure 78). The low yields are probably due to increased water solubility, although continuous extraction of the aqueous extracts with chloroform gave little further products.

In order to determine the regioselectivity of this conjugate addition reaction a sample of 2-butylthian-4-one (149) was oxidised with 2 molar equivalents of m-chloroperbenzoic acid.[131] This gave a single component product in 69% yield which had identical physical and spectral characteristics to the product (183), so conjugate

Figure 78

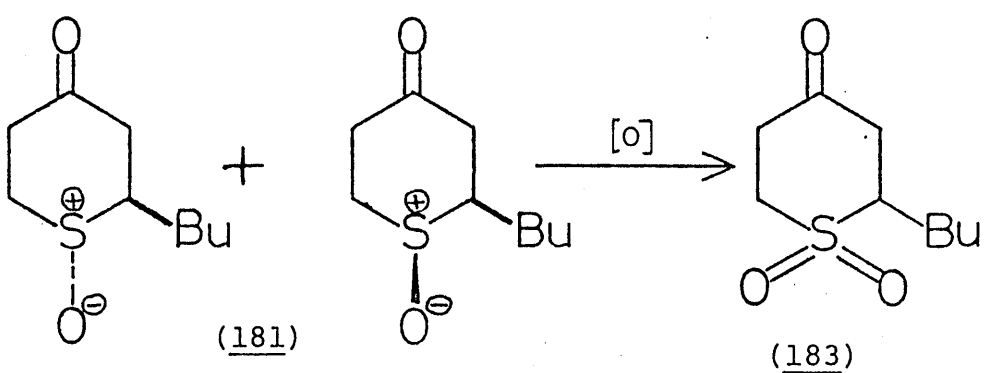


(176) (183)

(149)

addition had occurred at C-2 to give 2-butylthian-4-one 1,1-dioxide (183). Further proof of conjugate addition at the C-2 position was obtained by the oxidation of 2-butylthian-4-one 1-oxide (181), formed by the conjugate addition reaction with sulphoxide (175), with one equivalent of m-chloroperbenzoic acid.[126] This gave a product in 71% yield with identical physical and spectral properties as sulphone (183) (Figure 79).

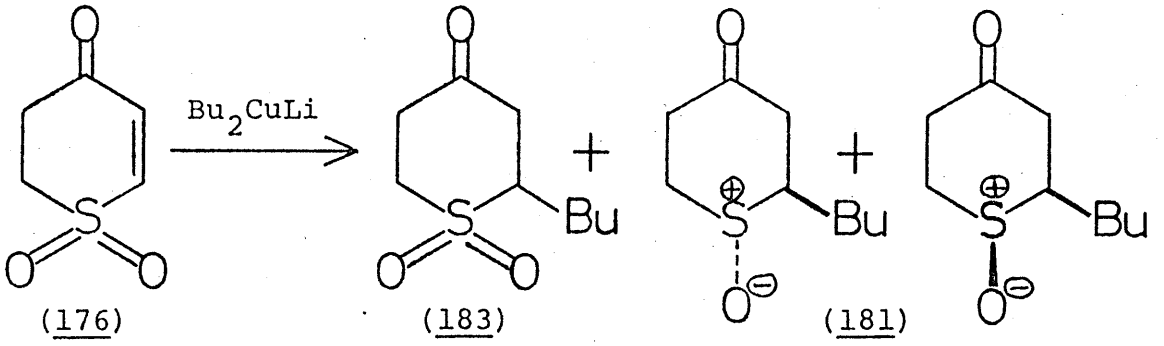
Figure 79



(181) (183)

The minor product from the sulphone conjugate addition reaction (Figure 78) consisted of two components which corresponded by tlc and by mass spectrum to 2-butylthian-4-one 1-oxide (181) (Figure 80).

Figure 80

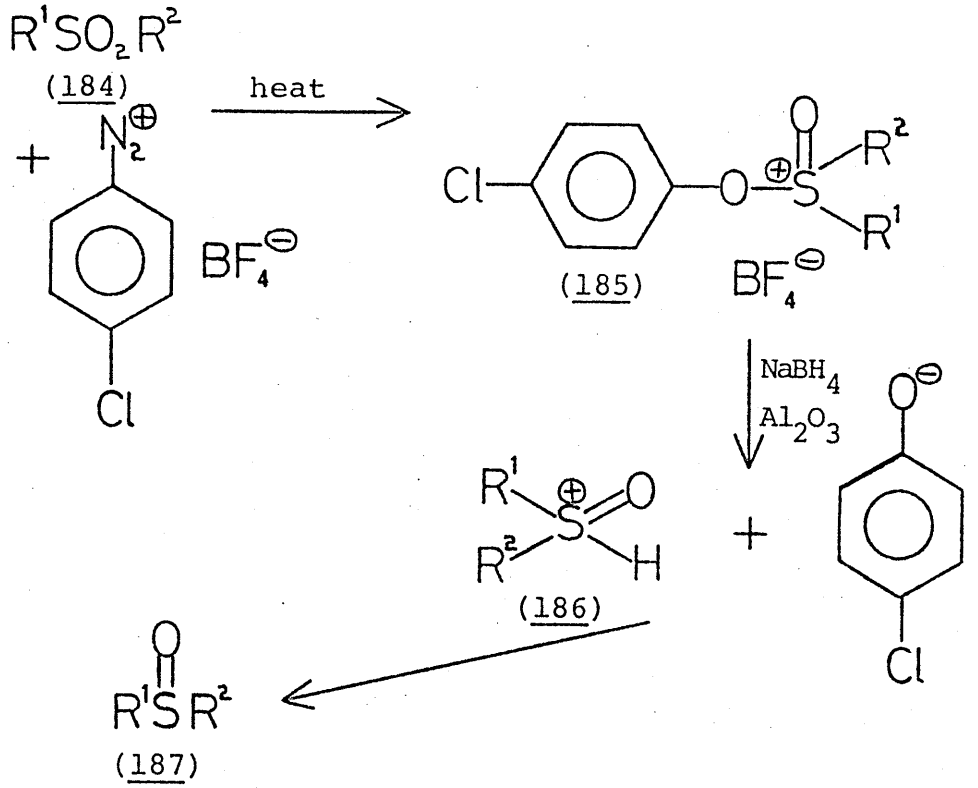


(176) (183) (181)

The reaction conditions required for the conjugate addition to an α,β-unsaturated ketone were thus accompanied by some reduction of a sulphone to a sulphoxide. Until very recently there was no reported procedure for reducing a sulphone to a sulphoxide. The only procedure[132] involves the reaction of a sulphone with a suitable electrophile, followed by nucleophilic reduction to give a sulphoxide. For example, reaction of a sulphone (184) with an arenediazonium salt at 70-80 °C forms an aryloxysulphoxonium salt (185) (Figure 81).

Reduction of this salt with sodium borohydride-alumina leads to the nucleophilic hydride displacement of the 4-chlorophenoxide anion and the formation of a species (186) which, by loss of a proton, is readily converted to

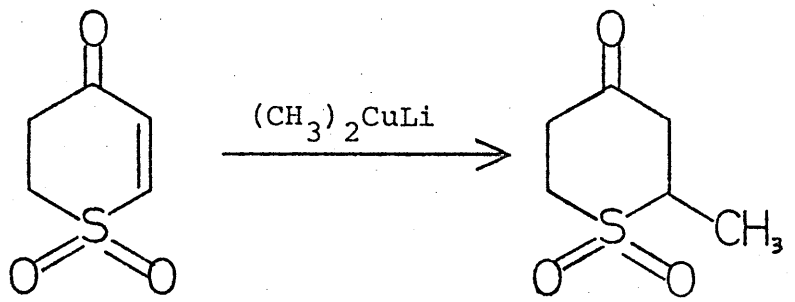
Figure 81



the sulphoxide (187). The finding that organocuprates can apparently convert a sulphone to a sulphoxide warrants further investigation, since it could represent a simple procedure for this conversion, filling an important gap in the functional group interconversion of organosulphur compounds.

The reaction of lithium dimethylcuprate ($(CH_3)_2CuLi$) at -78 °C with sulphone (176) gave 2-methylthian-4-one 1,1-dioxide (188) in a 22% yield (Figure 82). Owing to high water solubility of this sulphone, it had to be isolated by a continuous extraction process using chloroform.

Figure 82



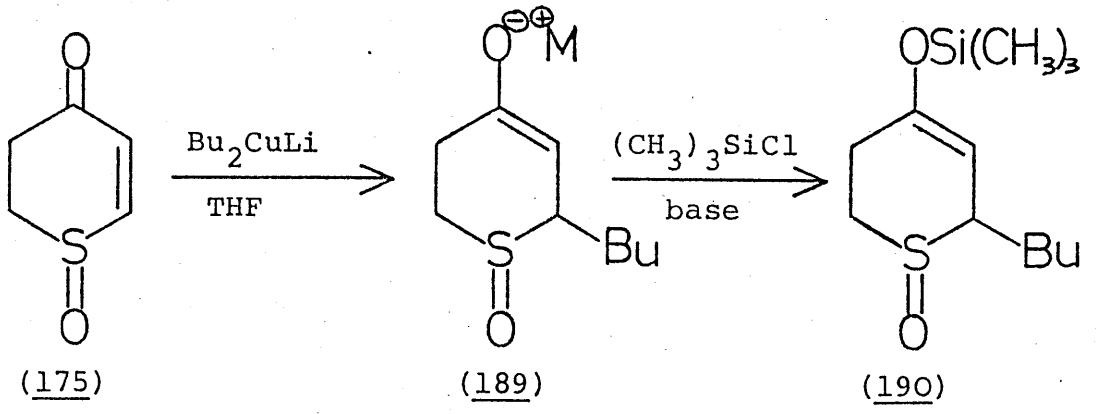
(176) (188)

Since the conjugate addition reactions to the sulphoxide (175) and the sulphone (176) did not lead to ring-opening at sulphur and addition occurred at C-2, then this procedure was extended with the intention of synthesising 2,3-disubstituted thian-4-one 1-oxides by alkylation of the intermediate enolates. An identical procedure was followed as that carried out for the conjugate addition and enolate allylation of 2,3-dihydrothi-in-4-one (84), that is, lithium dibutylcuprate in THF was used for the conjugate addition to sulphoxide (175), and a mixture of THF and HMPA together with allyl bromide was used for the allylation step. It was found that the presence or absence of HMPA made little, if any difference to the product obtained after the usual acid work-up. The crude product could not be visualised by any of the normal tlc spray reagents, whereas the crude product obtained after column chromatography and preparative plate chromatography could be weakly distinguished. The ^{1}H-NMR showed that in this product the thian-4-one ring and the butyl group were present, but there was little sign of any significant allylation. The mass spectrum and ^{13}C-NMR were also unsatisfactory, but the infra-red spectrum did show a C=O

stretch at 1710 cm^{-1}. An attempt was made to use iodomethane as the alkylating agent in the expectation that this would be a better electrophilic reagent with a better leaving group, than allyl bromide. However, this produced little, if any alkylation.

The alternative approach of trapping the intermediate enolate (189) and isolation as its trimethylsilyl ether (190) was then attempted (Figure 83).[40]

Figure 83

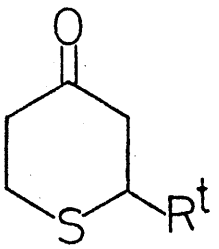


(175) (189) (190)

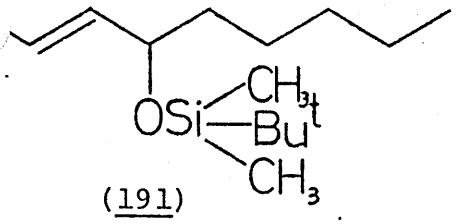
Lithium dibutylcuprate (Bu_2CuLi) was used for the conjugate addition reaction to form enolate (189), which was trapped by adding a mixture of trimethylchlorosilane (7 molar equivalents) and triethylamine at -78 °C. A basic aqueous work-up gave a very complex mixture of products, as evidenced by the tlc and the ^{1}H-NMR. Further attempts at trimethylsilylation were not investigated.

4.5 Conclusions

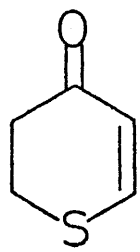
In summary, the work described in this chapter gives a good method for the preparation of 2-substituted thian-4-ones (130) with R^t=CH_3, Bu, Bu^t, C_6H_5 and the octenyl side chain (191).



(130)



(191)

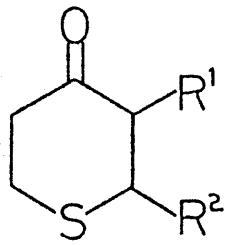


(84)

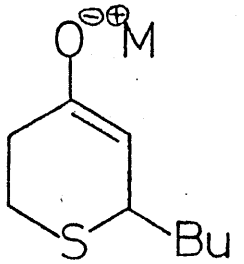
From investigations of various types of organocopper reagents, and change of reaction conditions the reagents of choice for conjugate addition to 2,3-dihydrothi-in-4-one (84) are the lithium alkylpent-1-ynylcuprates ($LiR^tCuC{\equiv}CC_3H_7$). However, an attempt to extend this procedure to the synthesis of 2,3-disubstituted thian-4-ones (85) by trimethylchlorosilane and allyl bromide trapping of the intermediate enolate (165) was not successful.

Conjugate addition reactions to sulphoxide (175) and sulphone (176) led to the formation of the corresponding 2-substituted derivatives without ring-opening at sulphur (Figure 84).

However trapping of the intermediate enolate was again unsuccessful.

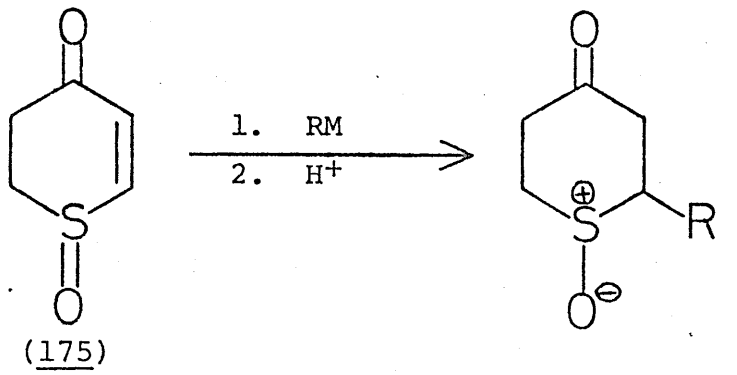


(85)

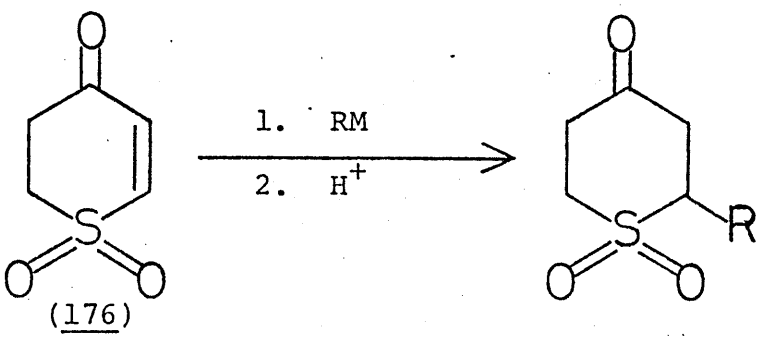


(165)

Figure 84



(175)



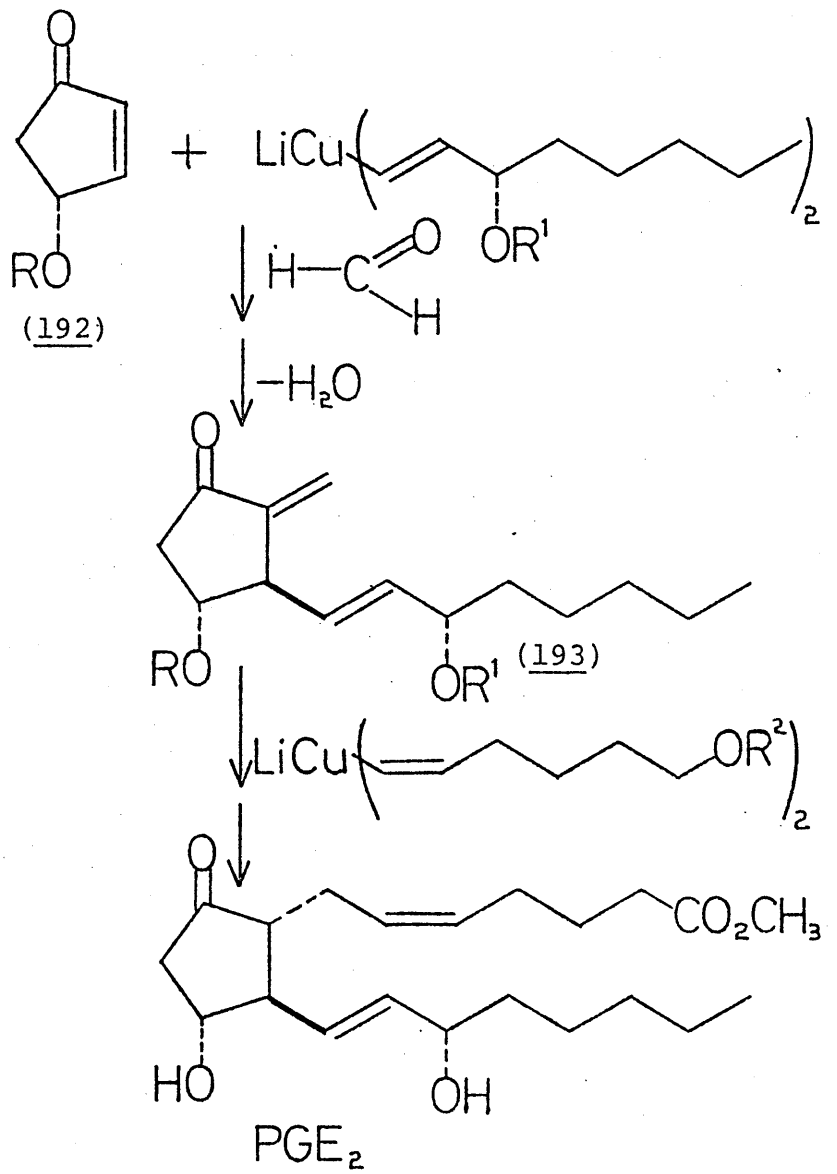
(176)

Further attempts to form 2,3-disubstituted thian-4-ones could include solvent variations[124] to vary the nucleophilicity of the enolate anion of (165), together with the use of more reactive C-alkylating species such as

carbonyl compounds.[97]

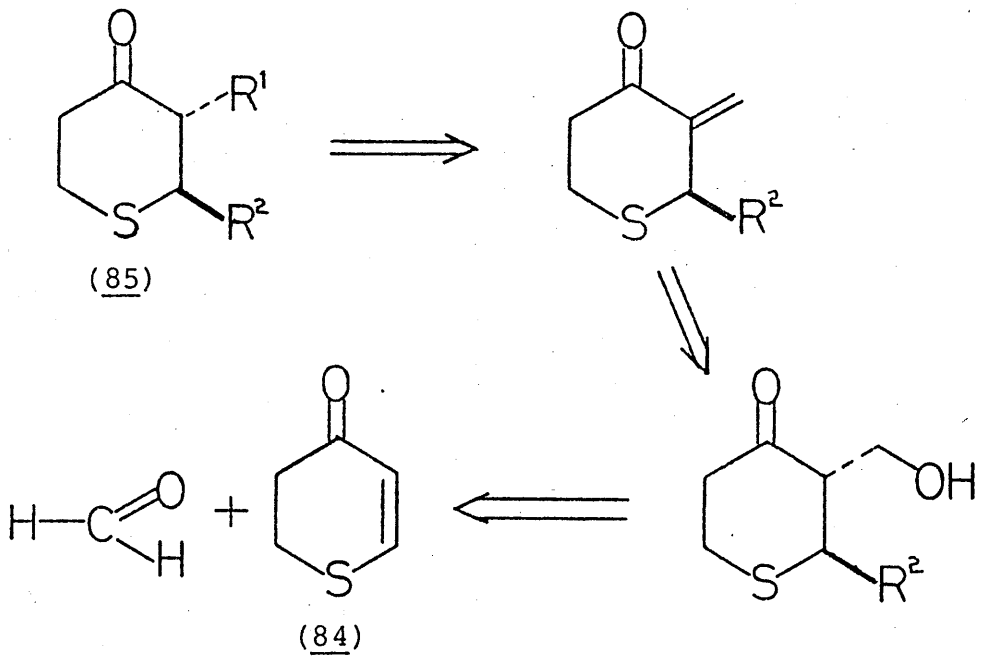
Stork[133] has developed a most effective method of cyclopentenone α,β-dialkylation for prostaglandin synthesis. 4-Alkoxycyclopenten-2-one (192) reacts with an eight-carbon vinylic cuprate and then with formaldehyde (i.e. an aldol condensation) to produce, after dehydration, a new α,β-unsaturated ketone (193) which then reacts with a different functionalised vinylic cuprate to form PGE_2 directly (Figure 85).

Figure 85



When applied to the synthesis of 2,3-substituted thian-4-ones the retrosynthetic analysis in Figure 86 is arrived at.

Figure 86



Trapping of the intermediate enolate, derived from conjugate addition to the unsaturated thianone (84) with formaldehyde may well provide a route to the required 2,3-disubstituted thian-4-ones (85).

CHAPTER 5

Experimental - General

EXPERIMENTAL - GENERAL

Infrared (IR) spectra were recorded using Pye-Unicam SP1000 or SP1050 infrared spectrophotometers, as liquid films or nujol mulls. Infrared absorption bands are expressed in reciprocal centimetres (cm^{-1}) measured against polystyrene calibration; only peaks yielding structural information are reported. Proton nuclear magnetic resonance (^{1}H - NMR) spectra were recorded using a Perkin-Elmer R12B instrument, and carbon-13 nuclear magnetic resonance (^{13}C - NMR) spectra were obtained on a Bruker WP60 instrument. Nuclear magnetic resonance peak positions are expressed as downfield shifts (δ) in parts per million from tetramethylsilane internal standard. Resonances are characterised as multiplet (m), quartet (q), triplet (t), doublet (d), singlet (s) or broad (br). Mass spectra (ms) were measured on an AEI MS50 instrument at 70 eV beam intensity. Analytical glc was performed on a Pye-Unicam Series 204 gas chromatograph with an SE52 column. Elemental microanalyses were performed at University College, London, University of Kent or University of East Anglia.

All reactions involving organometallic reagents were carried out in an inert atmosphere of prepurified nitrogen (passed through concentrated sulphuric acid, sodium hydroxide and

silica gel) with careful exclusion of oxygen and water. Prior to the introduction of reactants, the apparatus was dried at 120 °C in an oven and cooled in a stream of nitrogen.

Reagents and Solvents

The following reagents were obtained from commercial sources and were purified by distillation from calcium hydride: allyl bromide, hexamethylphosphoramide, triethylamine, trimethylchlorosilane, diethyl ether and tetrahydrofuran. Iodomethane was purified by percolation through a column of activated (Grade I) alumina followed by distillation. Copper(I)iodide was continuously extracted with tetrahydrofuran in a Soxhlet extractor for 12 h and dried at 25 °C under vacuum; the copper(I) iodide thus purified remained pure on standing for several months, and aliquots were used for reaction with organolithium reagents to generate organocuprates (R_2CuLi).

Benzene was dried by distilling from sodium wire and then standing over 5 A molecular sieves. Chloroform was purified by passing through a column of basic alumina (Grade I; 10 g per 14 ml of solvent), a procedure which also removes traces of water and acid. The chloroform was used directly. 1,4-Dioxan was purified by distillation from lithium aluminium hydride under nitrogen.

Alkyl and aryllithium reagents were obtained from Aldrich Chemical Co. or Ventron (Alfa Inorganics) as 1.0-2.0 M solutions in the solvents indicated : methyllithium (ether), butyllithium (hexane), t-butyllithium (pentane) and phenyllithium (benzene : ether, 7:3). The concentration of organolithium reagents was determined by a double titration procedure,[134] involving standard acid-base titrations. They were stored at 4 ^{o}C under nitrogen. The alternative method,[135] involving titration using diphenylacetic acid proved to be unsatisfactory owing to uncertainty in the location of the end point.

Most reactions were monitored by thin-layer chromatography (tlc), using mixtures of petroleum ether 60-80 ^{o}C (redistilled), diethyl ether (sodium dried), hexane (distilled) and acetone (AR) as eluants. Camlab 20 x 5 cm tlc plates (silica gel 60) were used and were developed by spraying with ammonium molybdate solution followed by heating. Ultraviolet visualisation was also used when possible. Column chromatography was carried out by using either Hopkin and Williams Silica gel 60 or florisil for the gradient elution technique, and Merck Silica gel 60, 400-230 mesh for the flash chromatography technique.[136]

CHAPTER 6

Routes to 9-Deoxy-11a-thiathromboxane B_2 (70)

Routes to 9-Deoxy-11a-thiathromboxane B_2 (70)

3-t-Butoxypropyne (87)

To prop-2-yn-1-ol (168 g, 3 mol) was added concentrated sulphuric acid (3 ml) dropwise with stirring. The flask was warmed to 35 °C and 2-methylpropene introduced from a cylinder. The flow was adjusted to give a slow stream (50 ml min^{-1}) emitted from the flask. The rate of absorption of gas increased with increasing temperature, so the flow was increased during the course of the reaction. The external temperature was then kept between 40 and 45 °C by water-bath cooling. After 2.75 h the evolution of heat subsided and the temperature gradually dropped. The flask was then warmed on a water-bath for 45 min at 40 °C and the gas flow was continued at about 300 ml min^{-1}. After this period the solution was poured into a saturated solution of NH_4Cl (100 ml) to which KOH (10 g) had been added. The product was dried with K_2CO_3, then distilled at reduced pressure. The product (87) was obtained as a colourless liquid, yield 272.9 g (81%) (lit.,[52] 75%). b.p. 38-46 °C/ 41 mm Hg (lit.,[52] b.p. 70 °C/90 mm Hg). $\delta(CDCl_3)$: 1.24 (s, 9H); 2.36 (m, 1H); 4.08 (m, 2H). $\nu_{max.}$ (liquid film): 3 270 (H-C≡ stretch) and 2 110 (C≡C stretch) cm^{-1}.

5-t-Butoxypent-3-yn-1-ol (88)

Liquid ammonia (500 ml) was cooled in a flask with a dry ice-acetone bath. Small pieces of lithium were added, and stirred until the blue colour persisted. Subsequently powdered iron(III) nitrate (0.06g) was dissolved in the ammonia. Immediately upon obtaining a uniform brown solution, lithium metal (3.0 g, 0.42 mol) was added in small pieces. The metal was completely converted in 1.25 h giving a grey-white suspension of lithium amide.

To this suspension (0.42 mol) was added 3-t-butoxypropyne (87, 45.0 g, 0.40 mol) over a period of 20 min. Foaming was prevented by adding a small volume of diethyl ether (5 ml).

The solution was transferred to a silvered Dewar flask (1.5 l capacity), and oxirane (19.5 g, 0.44 mol, pre-cooled in a dry ice-acetone mixture) was added in five equal portions at intervals of 1 h. After the addition of each portion the flask was swirled gently for 20 s, then closed by a stopper perforated by a curved tube filled with KOH pellets. After 42 h NH_4Cl solution (60 g in 300 ml of water) was added to the residue in the Dewar flask, together with diethyl ether (200 ml). The mixture was transferred to a separating funnel, and the lower aqueous layer subjected to continuous diethyl ether extraction for 24 h. The organic extract was dried over $MgSO_4$,

then rotary-evaporated. The resulting liquid was distilled at reduced pressure. The product (88) was obtained as a colourless liquid, yield 31.6 g (50.5%). b.p. 98-101 °C/ 3.3 mm Hg. $\delta(CDCl_3)$: 1.27 (s, 9H); 2.45(tt, J 2 and 7 Hz, 2 H); 3.5 (br, IH, disappears after addition of D_2O); 3.7 (t, J 7 Hz, 2 H); 4.05(t, J 2 Hz, 2 H). $\nu_{max.}$ (liquid film): 3 440 (O-H stretch) cm^{-1}. m/e: 156 (M^+); 141(M^+-CH_3); 111($M^+-CH_2CH_2OH$); 99($M^+-C_4H_9$).

5-t-Butoxypent-3-ynoic acid (89)

Chromic acid solution was prepared by diluting a mixture of chromium trioxide (10 g) and concentrated sulphuric acid (16 g) to 50 ml with water. The chromic acid solution (4.13 ml) was added by syringe to a stirred and cooled (ice-bath) solution of 5-t-butoxypent-3-yn-1-ol (88, 1.0 g, 0.0064 mol) in acetone (10 ml) over a period of 30 min. The resulting mixture was then stirred at room temperature for 2 h, poured into water (200 ml) and stirred well. The solution was ether extracted (3 x 75 ml), and the extracts dried with $MgSO_4$ then rotary-evaporated. The product (89) was obtained as an oil, yield 1.03 g (94%). $\delta(CDCl_3)$: 1.2(s, 9H); 3.3(t, J 2 Hz, 2 H); 4.05(t, J 2 Hz, 2 H); 5.9 (br s, IH, disappears after addition of D_2O). $\nu_{max.}$: 3 470 (O-H stretch); 2 240(C≡C stretch) and 1 740(C=O stretch) cm^{-1}.

Methyl 5-t-butoxypent-3-ynoate (90)

Diazald (N-methyl-N-nitroso-p-toluenesulphonamide) Kit was used for the generation of diazomethane.[137]

2-(2-Ethoxyethoxy)ethanol (35 ml) and diethyl ether (20 ml) were added to a solution of potassium hydroxide (6 g) in water (10 ml). This solution was placed in a flask (100 ml) fitted with a condenser, and placed in a water-bath maintained at 70 °C. As the distillation of the ether started a solution of Diazald (21.5 g) in ether (200 ml) was added through a dropping funnel over 40 min, the mixture being magnetically stirred. The rate of addition was adjusted until it equalled the rate of distillation. When the addition was complete, ether (40 ml) was added slowly and the distillation continued until the distillate was colourless. The combined ethereal distillate contained about 3 g of diazomethane, and was stored in a fridge. Diazomethane solution (250 ml) was added dropwise to 5-t-butoxypent-3-ynoic acid (89, 11.33 g, 0.067 mol) in dry diethyl ether (150 ml), whilst cooling in ice, until nitrogen evolution ceased. The solution was kept in ice for 30 min, then at room temperature for 3 h, and finally a warm water-bath (40 °C) for 2 h. The solution was dried with $MgSO_4$ and rotary-evaporated. The product (90) was obtained as a liquid, yield 11.81 g (95%). $\delta(CDCl_3)$: 1.2(s,9 H); 3.25(t, J 2 Hz, 2 H); 3.7(s, 3H); 4.05(t, J 2 Hz, 2 H). $\nu_{max.}$ (liquid film): 2 230(C≡C stretch) and 1 750(C=O stretch) cm^{-1}.

Methyl cis-5-t-butoxypent-3-enoate (91)

Methyl 5-t-butoxypent-3-ynoate (90, 3.0 g, 0.016 mol) in methanol (45 ml) containing 5% palladium on charcoal (0.11 g) was hydrogenated at atmospheric pressure until 361 ml of hydrogen were taken up. The catalyst was removed by filtration through celite, and the product was isolated by rotary-evaporation followed by distillation. The product (91) was obtained as an oil, yield 2.54 g (84%). b.p. 74-78 °C. $\delta(CDCl_3)$: 1.2(s, 9 H); 3.15(d, J 5 Hz, 2 H); 3.65(s, 3 H); 3.9(d, J 4 Hz, 2H); 5.65(m, 2 H). $\nu_{max.}$ (liquid film): 1 753 (C=O stretch) and 1 665 (C=C stretch) cm^{-1}.

Methyl 5-t-butoxy-3,4-epoxypentanoate (92)

Methyl cis-5-t-butoxypent-3-enoate (91, 4.39 g, 0.024 mol) was dissolved in dichloromethane (120 ml) at room temperature and magnetically stirred with m-chloroperbenzoic acid (85%, 5.74 g, 0.033 mol) at room temperature under nitrogen. After overnight stirring the m-chlorobenzoic acid was filtered off, dichloromethane (50 ml) was added, and the solution washed with 10% sodium hydrogen carbonate solution (3 x 25 ml), 10% potassium metabisulphite solution (3 x 25 ml), and finally water (100 ml). The organic extracts were dried with $MgSO_4$ then rotary-evaporated. The product (92) was obtained as an oil, yield 2.84 g (60%). $\delta(CDCl_3)$:

1.1(s, 9 H); 2.5(d, J 6 Hz, 2 H); 3.1(m, 2 H); 3.3(d, J 5 Hz, 2 H); 3.6(s, 3 H). $\nu_{max.}$ (liquid film): 1 750 (C=O stretch) cm^{-1}.

Attempted synthesis of Methyl 5-t-butoxy-3,4-epithiopentanoate (93)

Potassium thiocyanate (2.64 g, 0.0272 mol) in ice-water (5 ml) and diethyl ether (10 ml) was shaken with ortho-phosphoric acid (3.97 g), and the resulting pink thiocyanic acid solution separated and dried with $MgSO_4$. This solution was added to methyl 5-t-butoxy-3,4-epoxypentanoate (92, 0.24 g, 0.0012 mol) in diethyl ether (10 ml), and stirred for 3 h at room temperature. The solution was ether extracted (3 x 50 ml), the extracts being washed well with water (100 ml). The combined ether extracts were dried with $MgSO_4$ and rotary-evaporated to give methyl 5-t-butoxy-3-hydroxy-4-thiocyanatopentanoate (97, 0.29 g, 90%). $\nu_{max.}$ 3 430 (O-H stretch) and 2 140 (S-C≡N stretch) cm^{-1}.

Attempts were then made to form (93):

(i) The ester (97, 0.29 g, 0.0012 mol) was refluxed in 5% potassium hydroxide: methanol (21 ml) for 30 min, then allowed to stand overnight at room temperature. The solution was extracted with ether (3 x 50 ml), dried with

$MgSO_4$ and rotary-evaporated. The product obtained was an oil (0.20g) which gave decomposition on a tlc plate (ether: hexane, 1:1) and gave no C=O stretch in the infra-red spectrum.

(ii) The ester (97, 0.26 g, 0.0011 mol) was stirred overnight at room temperature with sodium methoxide (0.065 g, 0.0012 mol) in methanol (5 ml). Upon isolation the product obtained compared well with the product obtained in (i) above.

1-t-Butoxy-5-tetrahydropyranyloxypent-2-yne (101)

5-t-Butoxypent-3-yn-1-ol (88, 20.0 g, 0.128 mol) was stirred in benzene (400 ml) containing phosphorus oxychloride (48 drops) and dihydropyran (12.9 g, 0.14 mol) under nitrogen, whilst cooling in an ice-bath. The reaction was stood overnight at room temperature. The mixture was extracted with ether (3 x 150 ml), the extracts being washed well with water (300 ml). The combined extracts were dried with $MgSO_4$ and rotary-evaporated. The crude mixture was separated by column chromatography (silica gel 60-120 mesh) using gradient elution from petroleum ether 60-80 ^{o}C: ether (9:1) to petroleum ether 60-80 ^{o}C: ether (3:1). The product (101) was obtained as a colourless liquid, yield 19.1 g (62%). $\delta(CDCl_3)$: 1.2(s, 9 H); 1.6 (m, 6 H); 2.5(tt, J 2 and 8 Hz, 2 H); 3.7-4.05 (m, 6 H); 4.6 (m, 1 H). $\nu_{max.}$ (liquid film): 2 225 (C≡C stretch) cm^{-1}.

1-t-Butoxy-5-(2-methoxyethoxymethyl)pent-2-yne (102)

2-Methoxyethoxychloromethane (0.40 g, 0.0019 mol) was added to 5-t-butoxypent-3-yn-1-ol (88, 0.20 g, 0.0013 mol) and diisopropylamine (0.25 g, 0.0019 mol) in dichloromethane (5 ml). After stirring at room temperature overnight more 2-methoxyethoxychloromethane (0.080 g, 0.00064 mol) and diisopropylamine (0.083 g, 0.00064 mol) were added. The reaction mixture was added to water (150 ml) after 2.5 days, then ether (100 ml) was added and shaken, together with cold 10% HCl (10 ml). The ether extract was dried with $MgSO_4$ then rotary-evaporated. The product (102) was obtained as a liquid, yield 0.096 g (40%).
$\delta(CDCl_3)$: 1.2(s, 9 H); 2.45(m, 2 H); 3.3 (s, 3 H); 3.6(m, 6 H); 4.05(t, J 2 Hz, 2 H); 4.7 (s, 2 H).
$\nu_{max.}$(liquid film): 2 215 (C≡C stretch) cm^{-1}.

cis-5-t-Butoxypent-3-en-1-ol (103)

5-t-Butoxypent-3-yn-1-ol (88, 1.0 g, 0.0064 mol) in methanol (19 ml) containing 5% palladium on charcoal (0.043 g) was hydrogenated at atmospheric pressure until 144 ml of hydrogen was taken up. The catalyst was removed by filtration through celite and the product was isolated by rotary-evaporation followed by distillation. The product (103) was obtained as a colourless liquid, yield 0.88 g (87%). b.p. 95-96 ^{o}C/6.5 mm Hg. Found: C, 68.17; H, 11.28. $C_9H_{18}O_2$ requires C, 68.35; H, 11.39%.

$\delta(CDCl_3)$: 1.2(s, 9 H); 2.35(m, 2 H); 2.55(br, 1 H, disappears after addition of D_2O); 3.55(m, 2 H); 3.93(d, J 6 Hz, 2 H); 5.65(m, 2 H). $\nu_{max.}$ (liquid film): 3 400 (O-H stretch) and 1 660 (C=C stretch) cm^{-1}.

cis-1-t-Butoxy-5-tetrahydropyranyloxypent-2-ene (104)

1-t-Butoxy-5-tetrahydropyranyloxypent-2-yne (101, 11.91 g, 0.050 mol) in methanol (145 ml) containing 5% palladium on charcoal (0.34 g) and calcium carbonate (1.0 g) was hydrogenated at atmospheric pressure until 1113 ml of hydrogen was taken up. The catalyst was removed by filtration through celite and the product was isolated by rotary-evaporation, followed by distillation at reduced pressure. The product (104) was obtained as a colourless liquid, yield 9.10 g (48%). b.p. 118-120 °C/0.6 mm Hg. Found: C, 69.58; H, 10.76. $C_{14}H_{26}O_3$ requires C, 69.42; H, 10.74%. $\delta(CDCl_3)$: 1.2 (s, 9 H); 1.63(m, 6H); 2.35(m, 2 H); 3.35-4.00(m, 6 H); 4.6(m, 1 H); 5.57(m, 2 H).

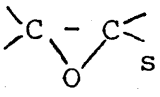
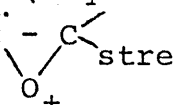
cis-1-t-Butoxy-5-t-butyldimethylsilyloxypent-2-ene (105)

cis-5-t-Butoxypent-3-en-1-ol (103, 0.50 g, 0.0032 mol) was stirred in dry dimethylformamide (4 ml) at room temperature under nitrogen with t-butyldimethylsilyl chloride (0.57 g, 0.0038 mol) and imidazole (0.55 g, 0.0081 mol). After stirring overnight water (10 ml)

was added and the solution was extracted with ether (3 x 15 ml). The combined ether extracts were dried with $MgSO_4$ and rotary-evaporated. The product (105) was obtained as an oil, yield 0.79 g (92%). Found: C, 66.09; H, 11.86. $C_{15}H_{32}SiO_2$ requires C, 66.18; H, 11.76%. $\delta(CDCl_3)$: 0.1 (s, 6 H); 0.97(s, 9 H); 1.27(s, 9 H); 2.35(m, 2 H); 3.66(t, J 7 Hz, 2 H); 4.02(m, 2 H); 5.6(m, 2 H).

1-t-Butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106)

cis-1-t-Butoxy-5-tetrahydropyranyloxypent-2-ene (104, 8.04 g, 0.033 mol) was dissolved in dichloromethane (539 ml) at room temperature and magnetically stirred with m-chloroperbenzoic acid (85%, 10.79 g, 0.053 mol) and sodium hydrogen carbonate (4.19 g, 0.053 mol) under nitrogen. After stirring for 40 h the precipitated m-chlorobenzoic acid was filtered off and the solution was washed well with 10% sodium hydrogen carbonate solution (200 ml). The resulting solution was dried with $MgSO_4$ and rotary-evaporated. The crude product was column chromatographed (silica gel 60-120 mesh) using gradient elution from petroleum ether 60-80 ^{o}C: ether (9:1) to ether. The product (106) was obtained as a colourless liquid, yield 8.90 g (31%). Found: C, 64.66; H, 10.02. $C_{14}H_{26}O_4$ requires C, 65.12; H, 10.08%. $\delta(CDCl_3)$: 1.22 (s, 9 H); 1.65 (m, 6 H); 1.9 (m, 2 H); 3.13 (m, 2 H); 3.5-4.05 (m, 6 H); 4.6 (m, 1 H).

$\nu_{max.}$ (liquid film): 1 260 ( stretch) and 816 ( stretch) cm^{-1}. m/e : 257 (M^+-1); 243 (M^+-CH_3); 200 ($M^+-C_4H_9$); Found: M^+-1, 257.1774. $C_{14}H_{26}O_4$ requires M^+-1, 257.1746.

1-t-Butoxy-5-t-butyldimethylsilyloxy-2,3-epoxypentane (107)

cis-1-t-butoxy-5-t-butyldimethylsilyloxypent-2-ene (105, 0.70 g, 0.0026mol) was dissolved in dichloromethane (42 ml) at room temperature, and was magnetically stirred with m-chloroperbenzoic acid (85%, 0.63 g, 0.0031 mol) and sodium hydrogen carbonate (0.26 g, 0.0031 mol) under nitrogen. After stirring for 2 days the precipitated m-chlorobenzoic acid was filtered off and the filtrate washed well with 10% sodium hydrogen carbonate solution (18 ml). The resulting solution was dried with $MgSO_4$ and rotary-evaporated. The crude mixture was separated by column chromatography (silica gel 60-120 mesh) using petroleum ether 60-80 ^oC: ether (7:1) as eluant. The product (107) was obtained as an oil, yield 0.51 g (69%). Found: C, 62.41; H, 11.02. $C_{15}H_{32}SiO_3$ requires C, 62.50; H, 11.11%. $\delta(CDCl_3)$: 0.06(s, 6 H); 0.85(s, 9 H); 1.16 (s, 9 H); 1.7(m, 2 H); 3.05(m, 2 H); 3.45(d, J 6 Hz, 2 H); 3.73(t, J 7 Hz 2 H).

Attempted synthesis of 1-t-Butoxy-5-tetrahydropyranyloxy-2,3-epithiopentane (108)

(a) Potassium thiocyanate (2.64 g, 0.027 mol) in ice-

water (5 ml) and diethyl ether (10 ml) were shaken with orthophosphoric acid (3.97 g) and the resulting pink thiocyanic acid solution separated and dried with $MgSO_4$. This solution was added to 1-t-butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106, 0.31 g, 0.0012 mol) in dry diethyl ether (10 ml) and stirred for 3 h at room temperature. The solution was extracted with ether (3 x 50 ml), the extracts being washed well with water (100 ml). The combined ether extracts were dried with $MgSO_4$ and rotary-evaporated to give 1-t-butoxy-5-tetrahydropyranyloxy-2-thiocyanatopentan-3-ol (194, 0.29 g, 77%). $\nu_{max.}$ 3 420 (O-H stretch) and 2 140 (SC≡N stretch) cm^{-1}.

Attempts were then made to form (108):

(i) The alcohol (194, 0.26 g, 0.00082 mol) was refluxed in 5% potassium hydroxide: methanol (17 ml) for 30 min. The solution was cooled immediately and extracted with ether (3 x 50 ml). The combined ether extracts were dried with $MgSO_4$ and rotary-evaporated. Tlc (ether: hexane, 1:1) indicated that desulphurisation was occurring and alkene (104) being formed. The product was refluxed for a further hour, and tlc indicated that almost total alkene formation had occurred.

(ii) The alcohol (194, 0.10 g, 0.00032 mol) was stirred overnight at room temperature in 5% potassium hydroxide: methanol (6.5 ml). The solution was extracted with ether (3 x 50 ml). The combined ether extracts were dried with

$MgSO_4$ and rotary-evaporated. The product was obtained as an oil (0.10 g) and preparative plate chromatography afforded an oil (0.05 g). Found: C, 65.56; H, 10.58; S, 0.00. $C_{14}H_{26}O_3S$ requires C, 61.31; H, 9.49; S, 11.68%. (106) $C_{14}H_{26}O_4$ requires C, 65.12; H, 10.08; S 0.00%. $\delta(CDCl_3)$ and $\nu_{max.}$ (liquid film) compare exactly with (106). m/e: 257(M^+-1); 243(M^+-CH_3); 200(M^+-C_4H_9) indicating (106).

(b) 1-t-Butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106, 0.10 g, 0.00039 mol) was added to a solution of potassium thiocyanate (0.078 g, 0.0008 mol) in absolute ethanol (5 ml) and water (7 ml), and the solution was magnetically stirred at room temperature overnight. Tlc (hexane: ether, 1:1) indicated that after 1 day, 2 days and 6 days no reaction had occurred. More potassium thiocyanate (0.04 g, 0.00042 mol) was added, and the solution was refluxed overnight. Tlc indicated that desulphurisation had occurred to give the product corresponding to (104).

Reaction of allylmagnesium bromide with ethyl chloroformate

(i) Magnesium turnings (0.51 g, 0.021 mol) and dry diethyl ether (4 ml) were placed in a flask together with a crystal of iodine, under dry nitrogen. Allyl bromide (redistilled, 1.18 g, 0.0097 mol) in dry diethyl ether (20 ml) was added dropwise to the above mixture over 3 h, whilst cooling in an ice-salt bath. After the addition the mixture was

refluxed on a water-bath for 1 h. After cooling, the Grignard solution was decanted from the excess magnesium into another flask under dry nitrogen.

(ii) Ethyl chloroformate (0.30 g, 0.0028 mol) was added dropwise over 1 h to the stirred and cooled (ice-bath) solution of allylmagnesium bromide in dry diethyl ether (5 ml). The solution was refluxed on a water bath for 2 h, then stood overnight at room temperature, followed by a final reflux for 1.5 h. The solution was cooled in an ice-salt bath and decomposed with an ice: 10% H_2SO_4 mixture (20 ml : 20 ml). The solution was given the usual ether extraction (3 x 50 ml) and the combined organic extracts dried with $MgSO_4$ and rotary-evaporated. 4-allylhepta-1,6-dien-4-ol (113) was obtained as an oil, yield 0.25 g (60%) (lit.,[75] 66.6%). $\delta(CDCl_3)$: 2.40(m, 6 H); 4.10(br, 1 H, disappears after addition of D_2O); 4.95-6.05(m, 9 H). $\nu_{max.}$ (liquid film): 3 400 (O-H stretch) and 1 640(C=C stretch) cm^{-1}.

Attempted ring-opening of (106) with allylmagnesium bromide

(i) Magnesium turnings (0.26 g, 0.011 mol) and dry diethyl ether (2 ml) were placed in a flask together with a crystal of iodine, under dry nitrogen. Allyl bromide (redistilled, 0.59 g, 0.0049 mol) in dry diethyl ether (10 ml) was added dropwise to the above mixture over 3 h, whilst cooling in an ice-salt bath. After the addition the mixture was refluxed on a water-bath for 1 h.

After cooling, the Grignard solution was decanted from the excess magnesium into another flask under dry nitrogen.

(ii) To the Grignard solution, cooled in an ice-salt bath, was added 1-t-butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106 , 1.0 g, 0.0039 mol) in dry diethyl ether (5 ml) dropwise over 1 h. The reaction mixture was stirred at room temperature overnight. Hydrolysis was effected by adding 20% NH_4Cl solution (15 ml) to the reaction mixture. The solution was given the usual ether extraction (3 x 50 ml) and the combined organic extracts dried with $MgSO_4$ and rotary-evaporated. Tlc (hexane: ether, 1:1) indicated that (106) was still present together with several other products. Several methods to consume all the starting material were tried, namely (a) lengthening the reaction time, (b) using an excess (10 molar equivalents) of Grignard reagent, (c) refluxing the reaction mixture. However, these methods did not markedly change the product distribution. Refluxing gave rise to a yellow polymeric solid together with a non-polar product (detectable by tlc) which was most probably a polymer of 1,5-hexadiene arising by coupling of the Grignard reagent. Preparative plate chromatography afforded a relatively pure product with $\nu_{max.}$ (liquid film): 1 722 (C=O stretch) cm^{-1}.

Attempted ring-opening of (106) with diallylmagnesium

(i) Allylmagnesium bromide was prepared exactly as above using allyl bromide (0.59 g, 0.0049 mol) and magnesium turnings (0.15 g, 0.0060 mol).

(ii) Whilst the Grignard solution from (i) was refluxing, 1,4-dioxane (1.75 ml, 0.020 mol) was added to the solution over 10 min by syringe. The mixture was refluxed for 15 min. After cooling to room temperature the mixture was filtered under nitrogen into a graduated flask, and the total volume made up to 20 ml with diethyl ether.

(iii) To the diallylmagnesium solution from (ii) (2 ml, 0.00024 mol) 1-t-butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106, 0.050 g, 0.00019 mol) in dry diethyl ether (5 ml) was added at -20 ^{o}C over 10 min. After 1 h the solution was allowed to warm to room temperature and left overnight. Tlc (hexane: ether, 1:1) indicated that little reaction had taken place, and so more diallylmagnesium solution (4 ml, 0.00050 mol) was added and the solution refluxed for 2 h. Tlc again indicated that little reaction had taken place, with one non-polar product.

Attempted ring-opening of (106) with allyllithium

(i) Dry diethyl ether (23 ml) was added to tetrallyltin (0.98 g, 0.0035 mol) at 0 °C. Phenyllithium (0.50 M, 6.8 ml, 0.014 mol) was added dropwise over 5 min and the mixture was stirred under nitrogen for 1 h. The allyllithium reagent was allowed to separate from the precipitated tetraphenyltin, which was removed by centrifugation. The allyllithium solution obtained was standardised using the diphenylacetic acid method.

(ii) Allyllithium (0.20 M, 0.44 ml, 0.00021 mol) was added dropwise to 1-t-butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106, 0.050 g, 0.00019 mol) in dry diethyl ether (10 ml) at -78 °C over 5 min. Tlc (hexane: ether, 1:1) showed no sign of reaction at -78 °C, and so more allyllithium (0.44 ml, 0.00021 mol) was added. Again no reaction was detected, and the mixture was warmed to room temperature and more allyllithium (2.2 ml, 0.0011 mol) was added. Tlc indicated a non-polar product.

Attempted ring-opening of (106) with lithium diallylcuprate

(i) Allyllithium solution was prepared exactly as in (i) above.

(ii) Allyllithium (0.41 M, 5.0 ml, 0.0021 mol) was added by syringe to ultrapure copper(I)iodide (0.20 g, 0.0011 mol) in dry diethyl ether (5 ml) over 15 min, maintained at -15 ^{o}C by means of an ethane-1,2-diol-dry ice bath. A dark brown solution of lithium diallylcuprate was formed. To this solution 1-*t*-butoxy-5-tetrahydropyranyloxy-2,3-epoxypentane (106, 0.050 g, 0.00019 mol) in dry diethyl ether (4 ml) was added by syringe. After stirring for 30 min at -15 ^{o}C the mixture was allowed to warm to room temperature and stood overnight under nitrogen. Tlc (hexane: ether, 1:1) indicated little sign of reaction.

CHAPTER 7

Route to 11a-Thiathromboxane B_2 (71)

Route to 11a-Thiathromboxane B_2 (71)

Methyl 4-t-butoxybut-2-ynoate (120)

To magnesium turnings (21.8 g, 0.9 mol) suspended in dry THF (100 ml) was added bromoethane (over 3A sieves, 98 g, 0.9 mol) in dry THF (550 ml) dropwise over 2.5 h. The flask was cooled in an ice-bath and the reaction carried out under nitrogen. Then 3-t-butoxypropyne (87, 88.0 g, 0.79 mol) in dry THF (350 ml) was added dropwise to the stirred reaction over 2 h and stirred for a further 1 h. The Grignard solution was added dropwise over 2 h to dimethyl carbonate (244 g, 2.7 mol) in dry THF (300 ml), and the reaction mixture stirred at room temperature overnight. Water (300 ml) was added to the stirred solution and the supernatant liquor was decanted off. The yellow residue was washed with benzene (3 x 300 ml) and the organic extracts combined and filtered through celite.

The solvent and excess dimethyl carbonate were distilled off at atmospheric pressure. The residue was distilled at reduced pressure. The product (120) was obtained as a colourless liquid, yield 70.7 g (59%) (lit.,[87] 68%). b.p. 76-78 ^{o}C/1 mmHg. $\delta(CDCl_3)$: 1.26(s, 9 H); 3.78(s, 3 H); 4.20(s, 2 H). $\nu_{max.}$ (liquid film): 2 210(C≡C stretch) and 1 715(C=O stretch) cm^{-1}.

Methyl cis-4-t-butoxybut-2-enoate (121)

Methyl 4-t-butoxybut-2-ynoate (120, 49.39 g, 0.31 mol) in methanol (950 ml) containing 5% palladium on charcoal (2.28 g) was hydrogenated at atmospheric pressure until 3 000 mol of hydrogen was taken up. The catalyst was removed by filtration through celite and the solution rotary-evaporated. The crude product was distilled at reduced pressure to give the product (121) as a colourless liquid, yield 31.90 g (45%). b.p. 64-67 ^{o}C/5 mmHg (lit.,[138] b.p. 32-34 ^{o}C/1 mmHg). $\delta(CDCl_3)$: 1.2(s, 9 H); 3.7(s, 3 H); 4.52(dd, J 2 and 5 Hz, 2 H); 5.75 (dt, J 2 and 12 Hz, 1 H); 6.35(dt, J 5 and 12 Hz, 1H). $\nu_{max.}$ (liquid film): 1 715(C=O stretch) and 1 645 (C=C stretch) cm^{-1}.

Attempted synthesis of 2-(t-butoxymethyl)-3-methoxycarbonylthian-4-one (123)

Sodium hydride (50%, 0.96 g, 0.020 mol) was washed with petroleum ether 40-60 ^{o}C (2 x 15 ml) then dry diethyl ether (2 x 15 ml). Dry diethyl ether (45 ml) was added, followed by methyl 3-mecaptopropanoate (distilled, 0.020 mol, 2.40 g, 2.22 ml) by syringe. The mixture was refluxed under nitrogen for 44 h to give the white precipitate, then cooled in an ice-bath. cis-Methyl 4-t-butoxybut-2-enoate (121, 0.020 mol, 3.40 g) in dry diethyl ether (10 ml) was added over 15 min. The

reaction mixture was stirred overnight at room temperature under nitrogen, a yellow suspension being formed. The mixture was poured into ice-cold 10% v/v H_2SO_4 (50 ml) and extracted with ether (3 x 150 ml). The combined ether extracts were washed with saturated sodium chloride solution (150 ml), dried with $MgSO_4$ and rotary-evaporated to give the crude product. This was purified by column chromatography (silica gel 60-120 mesh) using gradient elution from petroleum ether 60-80 ^{o}C to petroleum ether 60-80 ^{o}C: ether (4:1). The product obtained was further purified by distillation at reduced pressure. S-(2-methoxycarbonyl-ethyl) cis-4-(t-butoxy)but-2-enethioate (125) was obtained as a colourless liquid, yield 2.09 g (40%). b.p. 80-85 ^{o}C/3.2 mmHg. $\delta(CDCl_3)$: 1.17(s, 9 H); 3.04(m, 4 H); 3.68(s, 3 H); 4.05(dd, J 2 and 5 Hz, 2 H); 6.06 (dt, J 2 and 12 Hz, 1 H); 7.00(dt, J 5 and 12 Hz, 1 H). ^{13}C-NMR ($CDCl_3$): 171.7(s, ester C=O); 166.7(s, ester C=O); 147.0(d, =C); 120.6(d, =C); 73.5, 67.1, 61.4, 51.7, 41.0, 28.0, (alkyl carbon atoms) ppm. $\nu_{max.}$ (liquid film): 1 735(C=O stretch, ester); 1 720(C=O stretch, α,β-unsaturated thiol ester) and 1 650(C=C stretch) cm^{-1}.

CHAPTER 8

A General Route to 2,3-Disubstitued Thian-4-ones

Chapter 8

A General Route to 2,3-Disubstituted Thian-4-ones

8.1 The Synthesis of Thianone Substrates

8.1.1 Thian-4-one (83)

Method A 3,3′-thiodipropanoic acid (131, recrystallised from water, 178 g, 1 mol) was mechanically stirred with dry benzene (375 ml) and absolute ethanol (233 ml) at room temperature. Whilst cooling in an ice-bath, concentrated H_2SO_4 (31.6 ml) was added dropwise over 15 min. The mixture was stirred for 2 h at room temperature, then refluxed for 2.75 h. After standing overnight, water (500 ml) was added and the benzene layer separated. After drying with $MgSO_4$ most of the benzene was distilled off at atmospheric pressure, and then the product was distilled at reduced pressure. Ethyl 3,3′-thiodipropanoate (132) was obtained as a straw-coloured liquid, yield 182.7 g (78%) (Lit.,[47] 70%). b.p. 105-107 °C/0.9 mm Hg (Lit.,[47] 174 °C/15 mm Hg). R_f = 0.50, hexane:ether (1:1). $\delta(CDCl_3)$: 1.24 (t, J 7 Hz, 6H); 2.65 (m, 8 H); 4.04 (q, J 7 Hz, 4H).

Sodium ethoxide (97%, 71.4 g, 1.05 mol) and absolute ethanol (3 ml) were mechanically stirred in dry diethyl

ether (470 ml) under nitrogen. Ethyl 3,3′-thiodipropanoate (132, 110.8 g, 0.47 mol) in dry diethyl ether (390 ml) was added dropwise over 1 h whilst cooling in an ice-salt freezing mixture. The mixture was stirred for 6 h in the freezing mixture before more diethyl ether (500 ml) was added. The mixture was then allowed to warm to room temperature and stirred for 1.5 h. Since tlc indicated that about 40% of (132) was still present, the mixture was refluxed for 2.5 h, and stirred at room temperature overnight. A mixture of glacial acetic acid (61 g) and ice-water (200 ml) was added to the reaction mixture whilst stirring rapidly, and the product was extracted with ether (5 x 250 ml). The combined ethereal extracts were washed with 10% sodium hydrogen carbonate solution, dried with $MgSO_4$, and rotary-evaporated. 3-Ethoxycarbonylthian-4-one (133) was obtained as a light-brown liquid, yield 79.1 g (89%) (Lit.,[47] 43%). R_f=0.61, hexane: ether (1:1).

3-Ethoxycarbonylthian-4-one (133, 79.1 g, 0.42 mol) was refluxed with 10% H_2SO_4 (350 ml) for 1 h. After standing overnight tlc indicated that about 25% of product had been formed, so the solution was refluxed for a further 5.5 h. The solution was cooled, and extracted with ether (3 x 500 ml); the combined ethereal extracts were washed with 10% sodium hydrogen carbonate solution (2 x 300 ml). After drying with $MgSO_4$ the combined ethereal extracts were rotary-evaporated to give the crude product

as a yellow semi-solid. The product was recrystallised from petroleum ether 40-60 °C (400 ml), decanting the hot solution from the yellow insoluble oil. After cooling, the recrystallised product was isolated and recrystallised a further twice from the same solvent. Thian-4-one (83) was obtained as a colourless crystalline solid, yield 14.20 g (30%) (Lit.,[47] 85%). M.p.64-65 °C (Lit.,[47] 65-66 °C). R_f = 0.41, hexane : ether (1:1). $\delta(CDCl_3)$: 2.55-3.15 (m).

Method B To a stirred solution of 1-methyl-4-piperidone (134, distilled, 98%, 115.3 g, 1.0 mol) in dry diethyl ether (500 ml), iodomethane (150 g, 1.06 mol) in dry diethyl ether (300 ml) was added dropwise with ice-bath cooling. The addition was complete in 30 min, and the mixture was stirred for a further 1 h at room temperature. The mixture was rotary-evaporated to remove all the ether, and the crude product, 1,1-dimethyl-4-oxopiperidinium iodide (135) was isolated and used without further purification, since it is hygroscopic and liable to decomposition to 1-methyl-4-piperidone. The yield was taken to be the literature yield[49] of 97% (245 g). Water (500 ml) and diethyl ether (1 L) were heated on a water-bath under nitrogen while sodium sulphide (nonahydrate, 240 g, 1.0 mol) in water (500 ml) and 1,1-dimethyl-4-oxopiperidinium iodide (135, 245 g, 0.97 mol) in water (2 L) were added simultaneously to the mixed solvents over a period of 5 h. The reaction mixture was stirred mechanically and diethyl ether was

continuously added to make up for that which escaped through the condensers. After the addition was complete, the mixture was refluxed for a further 2 h. After cooling, the ether layer was separated from the aqueous layer, and the latter was extracted with ether (3 x 500 ml). The combined ethereal extracts were washed with 10% HCl (200 ml), then water (200 ml) and finally dried with $MgSO_4$ before rotary-evaporation. The crude product was obtained as a pale-yellow solid, which was recrystallised three times from petroleum ether 40-60 °C (3 x 500 ml). Thian-4-one (83) was obtained as a colourless crystalline solid, yield 37.1 g (33%) (lit.,[49] 48%). M.p. 65-66 °C (lit.,[49] 65-67 °C). R_f = 0.41, hexane : ether (1:1). $\delta(CDCl_3)$: 2.55-3.15 (m).

8.1.2 2,3-Dihydrothi-in-4-one (84)

Method A To a solution of thian-4-one (4.58 g, 0.039 mol) in dry benzene (54 ml), N-chlorosuccinimide (recrystallised from water, 98%, 5.92 g, 0.043 mol) was added in portions whilst maintaining the temperature of the solution between 10-20 °C with an ice-salt bath. A sudden rise in temperature occurred after 5 min and the total addition took 25 min. After 30 min the precipitated succinimide was filtered off and was washed with dry benzene (15 ml). 1,5-Diazabicyclo [4.3.0] non-5-ene (DBN, 1.34 g, 0.011 mol) in dry benzene (8 ml) was added dropwise

over 10 min to the filtrate, and the solution was stirred for 1.75 h at room temperature. The mixture was poured into 10% H_2SO_4 (100 ml), and the benzene layer was separated; the aqueous layer was extracted with chloroform (3 x 100 ml). The combined organic layers were washed with 10% sodium hydrogen carbonate solution (2 x 300 ml), dried with $MgSO_4$, and rotary-evaporated. The crude product was distilled at reduced pressure to give 2,3-dihydrothi-in-4-one (84) as a colourless liquid (which crystallised on standing), yield 2.50 g (63%) (Lit.,[51] 70%). b.p. 58 °C/0.1 mm Hg (Lit.,[51] 62-66 °C/0.1 mm Hg). R_f = 0.30, hexane : ether (1:1). $\delta(CDCl_3)$: 3.25 (m, 4 H); 6.15 (d, J 10 Hz, 1 H); 7.50 (dd, J 1 and 10 Hz, 1 H).

Method B To an ice-cold stirred solution of thian-4-one (83, 7.0 g, 0.060 mol) and pyridine (4.8 g, 4.9 ml, 0.061 mol) in dry dichloromethane (128 ml), N-chloro-succinimide (recrystallised from water, 98%, 8.46 g, 0.061 mol) was added in portions over 15 min. The reaction mixture was allowed to reach room temperature (2 h), and left for 2 h at room temperature. Dichloro-methane was removed on a rotary-evaporator with the water-bath maintained at 30-35 °C. Dry diethyl ether (128 ml) was added to the residue, and the precipitated succinimide was broken up, removed by filtration and washed with diethyl ether (250 ml) until colourless. The combined ethereal extracts were dried with $MgSO_4$ and rotary-evaporated. The crude product was distilled at reduced

pressure to give 2,3-dihydrothi-in-4-one (84) as a colourless liquid (which crystallised on standing), yield 5.22 g (76%) (Lit.,[50] 92%). b.p. 61-65 °C/0.3 mm Hg (Lit.,[50] 56-58 °C/0.9 mm Hg). Other characteristics were exactly as 8.1.2 Method A above.

3.1.3 2,3-Dihydrothi-in-4-one 1-oxide (175)

Method A 2,3-Dihydrothi-in-4-one (84, 1.0 g, 0.0088 mol) was stirred in acetonitrile (21 ml) at -10 °C. Sodium metaperiodate solution (0.50 M, 2.1 ml, 0.011 mol) was added dropwise over 20 min whilst stirring at -5 °C. Tlc indicated that starting material was still present after 2 h at -5 °C, so more sodium metaperiodate solution (0.50 M, 50 ml) was added to the reaction mixture. After stirring for 2 days at 0 °C the reaction was only about 40% complete and no further additions were made.

Method B 2,3-Dihydrothi-in-4-one (84, 3.28 g, 0.029 mol) was dissolved in dry chloroform (165 ml) and stirred at -10 °C. m-Chloroperbenzoic acid (85%, 5.84 g, 0.029 mol) was added in portions over 15 min, and after the addition the mixture was stirred at -20 °C for 1.25 h. The precipitated m-chlorobenzoic acid was filtered off and was washed with chloroform (10 ml). The combined chloroform extracts were dried with $MgSO_4$ and rotary-

evaporated to give an oily solid. Attempts at purification by column chromatography and washing with sodium hydrogen carbonate solution resulted in the loss of most of the product. Furthermore, a suitable recrystallisation solvent could not be found. The product was satisfactorily purified by heating with diethyl ether (50 ml) on a hot-water bath and filtering whilst hot. The m-chlorobenzoic acid present as an impurity dissolved in the diethyl ether leaving the required product undissolved. 2,3-Dihydrothi-in-4-one 1-oxide (175) was isolated as a white solid, yield 2.98 g (91%). M.p. 57-58 °C, R_f = 0.33, hexane : acetone (1:2) Found : C, 46.06; H, 4.46; S, 23.50. $C_5H_6O_2S$ requires C, 46.15; H, 4.62; S, 24.62. δ(d_6-acetone) : 2.95 (m, 2 H), 3.62 (m, 2 H); 6.34 (dd, J 1 and 11 Hz, 1 H); 7.74 (dd, J 2 and 11 Hz, 1 H). $\nu_{max.}$ (nujol mull) : 1 692 (C=O stretch) and 1 064 (S=O stretch) cm^{-1}. m/e : 130.0088 (M^+); 102 ($M^+ - C_2H_4$, base peak). $C_5H_6O_2S$ requires 130.0081.

.4 2,3-Dihydrothi-in-4-one 1,1-dioxide (176)

To a stirred solution of 2,3-dihydrothi-in-4-one (84, 1.50 g, 0.013 mol) in dry chloroform (119 ml), m-chloroperbenzoic acid (85%, 5.35 g, 0.026 mol) was added in portions at -30 °C over a 15 min period. The mixture was then stirred for 2.5 h at -15 °C and the precipitated m-chlorobenzoic acid filtered off. The chloroform was

partially evaporated (75%), and dry diethyl ether (25 ml) was added to precipitate the product, which was filtered off and dried under vacuum. At this stage there was still some m-chlorobenzoic acid present and this was removed by either (i) flash chromatography using hexane : acetone (5:3) or (ii) recrystallisation from absolute ethanol (30 ml), the yields being the same by both methods. 2,3-Dihydrothi-in-4-one 1,1-dioxide (176) was isolated as a white solid, yield 1.65 g (68%) (Lit.,[51] 79%). M.p. 150-51 °C (Lit.,[51] 150-51 °C). R_f = 0.33, hexane : ether (1:4). Found : C, 40.99; H, 3.88; S, 21.85. $C_5H_6O_3S$ requires C, 41.10; H, 4.11; S, 21.92. δ(d_6-DMSO) : 3.0 (m, 2 H); 3.8 (m, 2 H); 6.4 (dd, J 1 and 12 Hz, 1 H); 7.7 (dd, J 2 and 12 Hz, 1H).

3.2 The Synthesis of 2-Substituted Thian-4-ones

3.2.1 Reactions of (84) with Lithium Dimethylcuprate (Me_2CuLi)

Bis(5-methyl-3-oxohexyl) disulphide (141)

To a cold (0 °C) slurry of copper(I) iodide (ultrapure, 0.93 g, 0.0049 mol) in dry diethyl ether (21 ml) was added methyllithium (1.50 M, 5.85 ml, 0.0088 mol) over 15 min, followed by dropwise addition of 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in cold, dry diethyl ether (5 ml). After 1 h saturated NH_4Cl solution

(100 ml) was added and air was bubbled through the solution for several hours. Extraction with ether (3 x 100 ml) was followed by rapid washing of the organic layer with cold 5% HCl (100 ml), then 5% sodium hydrogen carbonate (2 x 100 ml) and drying with $MgSO_4$. Rotary-evaporation and flash chromatography using petroleum ether 60-80 ^{o}C : ether (4:1) gave bis(5-methyl-3-oxohexyl) disulphide (141), yield 0.24 g (38%). R_f = 0.77, hexane : ether (1:1). Found : C, 58.36; H, 9.01; S, 21.81. $C_{14}H_{26}O_2S_2$ requires C, 57.93; H, 8.97; S, 22.07. $\delta(CDCl_3)$: 0.93 (d, J 6 Hz, 6 H); 2.29 (m, 3 H); 2.82 (s, 4 H). $\nu_{max.}$ (liquid film) : 1 714 (C=O stretch) cm^{-1}. m/e : 292 ($M^+ + 2$); 291 ($M^+ + 1$); 290.1365 (M^+); 145 ($\frac{M^+}{2}$); 85 ($C_5H_9O^+$, base peak). $C_{14}H_{26}O_2S_2$ requires 290.1368.

1-Mercapto-5-methylhexan-3-ol (142)

Lithium aluminium hydride (0.19 g, 0.0051 mol) was stirred in dry diethyl ether (20 ml) under nitrogen. Bis(5-methyl-3-oxohexyl) disulphide (141, 0.37 g, 0.0013 mol) in dry diethyl ether (10 ml) was added to this mixture by syringe over 10 min, the temperature being maintained at 0 ^{o}C. The mixture was refluxed for 20 min, and then cooled in an ice-bath whilst moist diethyl ether (20 ml) was added in order to destroy excess lithium aluminium hydride. 10% H_2SO_4 (20 ml) was added to the resulting mixture and the layers separated. The aqueous layer was saturated with sodium chloride and extracted

with ether (50 ml). The combined ethereal layers were washed with water (50 ml) and with saturated sodium chloride solution (50 ml), dried with $MgSO_4$ and rotary-evaporated. Preparative plate chromatography using petroleum ether 60-80 °C : ether (1:1) gave 1-mercapto-5-methylhexan-3-ol (142), yield 0.29 g (78%). R_f = 0.53, hexane : ether (1:1). Found : C, 56.59; H, 10.67; S, 22.02. $C_7H_{16}OS$ requires C, 56.76; H, 10.81; S, 21.62. δ($CDCl_3$) : 0.90 (d, J 6 Hz, 6 H); 1.19-1.87 (m, 5 H); 1.99 (s, 1 H, reduced with D_2O); 2.68 (m, 2 H); 3.29 (t, J 7 Hz, 1 H); 3.82 (m, 1 H). $\nu_{max.}$ (liquid film) : 3 360 (O-H stretch) and 2 565 (S-H stretch) cm^{-1}.

2-Methylthian-4-one (146)

To a cold (0 °C) slurry of copper(I) iodide (ultrapure, 1.86 g, 0.0098 mol) in dry diethyl ether (41 ml) was added methyllithium (1.50 M, 11.70 ml, 0.018 mol) over 15 min, followed by dropwise addition of 2,3-dihydrothiin-4-one (84, 1.0 g, 0.0088 mol) in cold, dry diethyl ether (10 ml), with the temperature of the reaction mixture being maintained at -78 °C. After 45 min saturated NH_4Cl solution (200 ml) was added and the mixture was shaken well. Extraction with ether (3 x 200 ml) was followed by rapid washing of the organic layer with cold 5% HCl (200 ml), then 5% sodium hydrogen carbonate (2 x 200 ml) and drying with $MgSO_4$. Rotary-evaporation and preparative plate chromatography using

petroleum ether 60-80°C : ether (1:1) gave 2-methylthian-4-one (146), yield 0.26 g (23%). R_f = 0.58, hexane : ether (1:1). $\delta(CDCl_3)$: 1.3 (d, J 7 Hz, 3 H); 2.16-3.46 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 711 (C=O stretch) cm^{-1}.

2.2 Reactions of (84) with Heterocuprates

Preparation of Lithium Alkylpent-1-ynylcuprates

$LiCu(R)C{\equiv}CPr$

(a) R = Me, Bu, Ph, t-Bu

A slurry of dry pent-1-ynylcopper[105] (0.69 g, 0.0053 mol) in dry diethyl ether (12 ml) was treated with dry hexamethylphosphorus triamide (90%, 1.90 g, 2.11 ml, 0.011 mol), and the mixture was stirred at room temperature under a nitrogen atmosphere until a clear solution was obtained (10 min). To the cooled (-78 °C) solution was added alkyllithium (R Li, 0.0053 mol) over 5 min, and the resulting mixed-cuprate solution was stirred for 20 min at -78 °C.

(b) R = trans-3-(t-butyldimethylsilyloxy)oct-1-enyl

To trans-3-(t-butyldimethylsilyloxy)-1-iodooct-1-ene[102] (152, 1.61 g, 0.0044 mol) in dry diethyl ether (10 ml) at -78 °C was added butyllithium (1.20 M, 4.0 ml, 0.0048

mol) over 5 min, and the mixture was stirrred for 1 h. A clear solution of pent-1-ynylcopper (0.63 g, 0.0048 mol) and dry hexamethylphosphorus triamide (90%, 1.74 g, 1.94 ml, 0.0096 mol) in dry diethyl ether (10 ml) was prepared, and this was added dropwise over a period of 15 min to the lithium reagent maintained at -78 °C. The resulting mixed-cuprate solution (153, green-yellow) was stirred for a further 1 h at -78 °C.

Reaction of (84) with Lithium Methylpent-1-ynylcuprate-representative procedure

To lithium methylpent-1-ynylcuprate at -78 °C was added 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in dry diethyl ether (10 ml) over a period of 15 min. The mixture was kept at -78 °C under nitrogen for 2 h, and then ice-cold 10% ammonium sulphate solution (100 ml) was added with vigorous stirring. After allowing the mixture to warm up, it was extracted with ether (3 x 100 ml), the ether extracts were washed with ice-cold 2% H_2SO_4 (2 x 100 ml), and the precipitated copper salts were filtered off using celite. The filtrate was washed with 5% sodium hydrogen carbonate solution (200 ml), the solution dried with $MgSO_4$, and the solvent rotary-evaporated. Flash chromatography using petroleum ether 60-80 °C : ether (3:1) gave 2-methylthian-4-one (146), yield 0.21 g (37%). (Lit., 30%,[90] 24.6%[48]). R_f = 0.58,

hexane : ether (1:1). Found : C, 55.47; H, 7.62; S, 24.78. $C_6H_{10}OS$ requires C, 55.38; H, 7.69; S, 24.62. $\delta(CDCl_3)$: 1.3 (d, J 7 Hz, 3 H); 2.16 - 3.46 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 711 (C=O stretch) cm^{-1}. m/e : 130.0449 (M^+, base peak); 115 (M^+-CH_3). $C_6H_{10}OS$ requires 130.0450.

Reaction of (84) with Lithium Butylpent-1-ynylcuprate

The procedure was followed as for the methylpent-1-ynylcuprate, except that the reaction mixture was quenched after 1.75 h at -78 °C. Flash chromatography using hexane : ether (7:2) gave 2-butylthian-4-one (149), yield 0.39 g, (52%). R_f = 0.73, hexane : ether (1:1). Found : C, 62.86; H, 9.30; S, 18.38. $C_9H_{16}OS$ requires C, 62.79; H, 9.30; S, 18.60. δ ($CDCl_3$) : 0.89 (s, 3 H); 1.44 (m, 6 H); 2.22 - 3.52 (m, 7 H). ^{13}C-NMR ($CDCl_3$) : 209.2 (C=O); 50.8, 44.9, 43.5, 35.4, 29.1, 28.2, 22.4, 13.9 (8 alkyl carbon atoms) ppm. $\nu_{max.}$ (liquid film) : 1 714 (C=O stretch) cm^{-1}. m/e : 172.0926 (M^+); 115 ($M^+ - C_4H_9$, base peak); 57 ($C_4H_9^+$). $C_9H_{16}OS$ requires 172.0918.

Reaction of (84) with Lithium Phenylpent-1-ynylcuprate

The procedure was followed as for the methylpent-1-ynylcuprate, the reaction mixture being quenched after

1.75 h at -78 °C. Flash chromatography using petroleum ether 60-80 °C : ether (3:1) gave 2-phenylthian-4-one (150), yield 0.37 g (44%). The product was recrystallised from petroleum ether 40-60 °C, m.p. 67-68 °C (Lit.,[90] 72-74 °C). R_f = 0.50, hexane : ether (1:1). Found : C, 68.89; H, 6.33; S, 16.46. $C_{11}H_{12}OS$ requires C, 68.75; H, 6.25; S, 16.67. $\delta(CDCl_3)$: 2.7 - 3.1 (m, 6 H); 4.2 (m, 1 H); 7.3 (s, 5 H). $\nu_{max.}$ (nujol mull) : 1 710 (C=O stretch) cm^{-1}. m/e : 192.0612 (M^+); 104 ($C_8H_8^+$, base peak). $C_{11}H_{12}OS$ requires 192.0606.

Reaction of (84) with Lithium t-Butylpent-1-ynylcuprate

The procedure was followed as for the methylpent-1-ynylcuprate. Preparative plate chromatography using petroleum ether 40-60 °C : ether (1:1) gave 2-t-butylthian-4-one (151), yield 0.52 g (70%) as a semi-solid, m.p. approximately 25 °C. The solid was sublimed at 25 °C/1 mm Hg. Found : C, 61.53; H, 9.05; S, 19.16. $C_9H_{16}OS$ requires C, 62.79; H, 9.30; S, 18.60. $\delta(CDCl_3)$: 1.0 (s, 9 H); 2.40-3.48 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 709 (C=O stretch) cm^{-1}. m/e : 172.0919 (M^+); 115 (M^+ - C_4H_9); 57 ($C_4H_9^+$, base peak). $C_9H_{16}OS$ requires 172.0918.

Reaction of (84) with Lithium [trans-3-(t-butyldimethylsilyoxy)oct-1-enyl]pent-1-ynylcuprate (153)

To lithium [trans-3-(t-butyldimethylsilyloxy)oct-1-enyl] pent-1-ynylcuprate (153) at -78 °C, 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in dry diethyl ether (10 ml) was added rapidly from a precooled (-78 °C) dropping funnel. After standing for 15 min at -78 °C, powdered ammonium chloride (10 g) was added, followed by a little ice. The mixture was allowed to warm up, and was extracted with ether (3 x 100 ml). The ethereal extracts were washed with ice-cold 2% H_2SO_4 (2 x 100 ml), and the precipitated copper salts were filtered off using celite. The filtrate was washed with 10% sodium hydrogen carbonate solution (200 ml), the solution was dried with $MgSO_4$, and the solvent was rotary-evaporated. Flash chromatography using petroleum ether 60-80 °C : ether (5:1) gave 2-[trans-(3-t-butyldimethylsilyloxy) oct-1-enyl] thian-4-one (155), yield 0.43 g (28%). R_f = 0.77, hexane : ether (1:1). Found : C, 63.93, H, 10.19; S, 8.77. $C_{19}H_{36}O_2SiS$ requires C, 64.04; H, 10.11; S, 8.99. $\delta(CDCl_3)$: 0.06 (s, 6 H); 0.89 (s, 12 H); 1.3 (m, 8 H); 2.76 (m, 6 H); 3.75 (m, 1 H); 4.1 (m, 1 H); 5.62 (m, 2 H). $\nu_{max.}$ (liquid film) : 1 714 (C=O stretch) cm^{-1}. m/e : 356.2184 (M^+); 299 ($M^+ - C_4H_9$); 285 ($M^+ - C_5H_{11}$); 75 (Me_2SiOH^+, base peak). $C_{19}H_{36}O_2SiS$ requires 356.2203.

Reaction of (84) with Lithium Alkyl(phenylthio)cuprates LiCu(R)SPh

(a) Lithium Methyl(phenylthio)cuprate (147, R=CH_3)

To phenylthiocopper(I) (1.51 g, 0.0088 mol) in dry THF (38 ml) was added methyllithium (1.50 M, 3.50 ml, 0.0053 mol) at -20 °C. After stirring for 30 min a clear pink solution was formed. This solution was cooled to -78 °C, and 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in dry THF (3 ml) was added dropwise at -78 °C over 25 min. After stirring for 1.75 h at -78 °C tlc indicated that only a trace of starting material was present. After stirring at -78 °C for a further 15 min, the mixture was warmed to 0 °C and stirred for 1.25 h at 0 °C. The reaction mixture was quenched with saturated ammonium chloride solution (150 ml), stirred for 15 min and the precipitated copper salts were filtered off. The filtrate was extracted with ether (3 x 100 ml), and the combined extracts were dried with $MgSO_4$ and rotary-evaporated. The crude oily product was shown by tlc to be a mixture of components, and the pmr spectrum showed signals for aromatic protons but little else. The product was most probably derived from thiophenol only.

(b) Lithium Butyl(phenylthio)cuprate (147, R=Bu)

When the reaction was repeated using butyllithium (R=Bu, 1.53 M, 3.44 ml, 0.0053 mol) and hence butyl(phenylthio) cuprate as the organocuprate, the same result was obtained.

Reaction of (84) with Bromomagnesium Butylpent-1-ynylcuprate (158)

Butylmagnesium bromide was formed by adding bromobutane (1.23 g, 0.0088 mol) in dry diethyl ether (5 ml) to magnesium turnings (0.21 g, 0.0088 mol) in dry diethyl ether (10 ml) with one crystal of iodine. A slurry of dry pent-1-ynylcopper (1.14 g, 0.0088 mol) in dry diethyl ether (10 ml) was prepared, and to it was added the butylmagnesium bromide solution at -20 °C over 10 min. Dry hexamethylphosphorus triamide (90%, 3.17 g, 3.53 ml, 0.018 mol) was added to the mixture, which was warmed to room temperature and stirred for 1 h. The resulting yellow solution (158) was cooled to -40 °C and 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in dry diethyl ether (10 ml) added over 10 min. After warming to -20 °C and stirring for 30 min, then warming to 0 °C and stirring for 1 h, ice-cold 10% ammonium sulphate solution (100 ml) was added with vigorous stirring. The mixture was extracted

with ether (3 x 100 ml), the ethereal extracts were washed with ice-cold 2% H_2SO_4 (2 x 100 ml), and the precipitated copper salts were filtered off using celite. The filtrate was washed with 5% sodium hydrogen carbonate solution (200 ml), the solution dried with $MgSO_4$, and the solvent rotary-evaporated. Flash chromatography using hexane : ether (7:2) gave 2-butylthian-4-one (149), yield 0.15 g (20%). R_f = 0.73, hexane : ether (1:1). $\delta(CDCl_3)$: 0.89 (s, 3 H); 1.44 (m, 6 H); 2.22- 3.52 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 714 (C=O stretch) cm^{-1}.

8.2.3 Copper-catalysed Reaction of (84) with a Grignard Reagent

Reaction of (84) with Methylmagnesium iodide and Copper (II) acetate

Methylmagnesium iodide was formed by adding iodomethane (1.24 g, 0.55 ml, 0.0088 mol) in dry diethyl ether (5 ml) to magnesium turnings (0.21 g, 0.0088 mol) in dry diethyl ether (10 ml) with one crystal of iodine. After stirring for 30 min at room temperature the Grignard solution was cooled to -10 ^{o}C and a solution of copper(II) acetate monohydrate (0.22 g, 0.0011 mol) and 2,3-dihydrothi-in-4-one (0.50 g, 0.0044 mol) in dry THF (10 ml) was added dropwise over 20 min. After 30 min at -10^{o}C the solution was refluxed for 15 min. After cooling to room temperature 10% ammonium chloride

solution (100 ml) was added and the mixture extracted with ether (3 x 100 ml). The combined ethereal extracts were washed with 10% sodium thiosulphate solution (50 ml), dried with $MgSO_4$ and rotary-evaporated. Flash chromatography using petroleum ether 60-80 °C : ether (3:1) gave 2-methylthian-4-one (146), yield 0.11 g (19%). R_f = 0.58, hexane : ether (1:1). $\delta(CDCl_3)$: 1.3 (d, J 7 Hz, 3 H); 2.16 - 3.46 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 713 (C=O stretch) cm^{-1}.

8.3 The Attempted Synthesis of 2,3-Disubstituted Thian-4-ones

8.3.1 Allyl bromide Trapping of Lithium enolates

A slurry of dry pent-1-ynylcopper (0.69 g, 0.0053 mol) in dry THF (12 ml) was treated with dry hexamethylphosphorus triamide (90%, 1.90 g, 2.11 ml, 0.011 mol), and the mixture was stirred at room temperature under a nitrogen atmosphere until a clear solution was obtained (10 min). To the cooled (-78 °C) solution was then added butyllithium (1.53 M, 3.44 ml, 0.0053 mol) over 5 min, and the resulting mixed-cuprate solution was stirred for 20 min at -78 °C. To this butylpent-1-ynylcuprate at -78 °C was added 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in dry THF (10 ml) over 15 min. The mixture was kept at -78 °C under nitrogen for 2 h, then after warming to -30 °C a

mixture of dry hexamethylphosphoramide (5 ml) and dry allyl bromide (redistilled, 2.65 g, 1.90 ml, 0.022 mol), precooled to -20 °C, was added rapidly by syringe. After stirring for 30 min at -20 °C and 30 min at 0 °C, ice-cold ammonium sulphate solution (100 ml) was added with vigorous stirring. After allowing the mixture to warm up, it was extracted with ether (3 x 100 ml), the ethereal extracts were washed with ice-cold 2% H_2SO_4 (2 x 100 ml), and the precipitated copper salts were filtered off using celite. The filtrate was washed with 5% sodium hydrogen carbonate solution (200 ml), the solution dried with $MgSO_4$, and the solvent rotary-evaporated. Flash chromatography using petroleum ether 60-80 °C : ether (10:1) gave trans-1-allylthionon-4-en-3-one (167), yield 0.35 g (38%). R_f = 0.40, hexane : ether (9:1). Found : C, 68.27; H, 9.48; S, 16.11. $C_{12}H_{20}OS$ requires C, 67.92; H, 9.43; S, 15.09. $\delta(CDCl_3)$: 0.90 (m, 3 H); 1.30 (m, 4 H); 2.17 (m, 2 H); 2.71 (s, 4 H); 3.12 (d, J 7 Hz, 2 H); 4.9 - 5.1 (m, 2 H); 5.4 - 6.1 (m, 3 H). ^{13}C-NMR ($CDCl_3$) : 198.3 (C=O); 148.1, 134.2, 130.0, 117.1 (alkene carbon atoms); 39.9, 35.1, 32.2, 30.1, 24.9, 22.2, 13.8 (alkyl carbon atoms) ppm. $\nu_{max.}$ (liquid film) : 1 670 (C=O stretch), 1 630 (C=C stretch) and 950 (C-H bend, trans) cm^{-1}. m/e : 212.1235 (M^+), 155 (M^+ - C_4H_9); 111 (M^+ - C_5H_9S, base peak); 83 (M^+ - C_6H_9OS);

73 ($C_3H_5S^+$); 57 ($C_4H_9^+$). $C_{12}H_{20}OS$ requires 212.1230.

.3.2 Trimethylchlorosilane Trapping of Lithium enolates

To copper(I) iodide (ultrapure, 1.08 g, 0.0057 mol) was added dry diethyl ether (20 ml) and the slurry was cooled to -40 °C under a dry nitrogen atmosphere. Butyllithium (1.53 M, 7.44 ml, 0.011 mol) was added to the slurry over 15 min, and the mixture was stirred for 30 min until a dark-brown solution was obtained. The lithium dibutylcuprate solution was cooled to -78 °C and 2,3-dihydrothi-in-4-one (84, 0.50 g, 0.0044 mol) in dry diethyl ether (10 ml) was added over 15 min. The mixture was kept at -78 °C for 1.75 h, then a mixture of trimethylchlorosilane (distilled, 3.33 g, 3.89 ml, 0.0307 mol) and triethylamine (distilled, 3.10 g, 4.27 ml, 0.0307 mol) was added rapidly by pressure-equalising dropping funnel. After stirring for 30 min at -78 °C, the mixture was warmed to room temperature and stirred for 3.5 h. Ammonium hydroxide solution ('880', 7 ml) and ice-cold saturated sodium hydrogen carbonate solution (70 ml) were added with vigorous stirring. The mixture was extracted with ether (3 x 100 ml), the ethereal extracts were washed with water (100 ml) and dried with $MgSO_4$, and the solvent was rotary-evaporated. Flash chromatography (Florisil) using

hexane : dichloromethane (19:1) gave bis(5-butyl-3-trimethylsilyloxynon-3-enyl)disulphide (172, 2 isomers), yield 0.42 g (40%). Two spots by tlc, R_f = 0.18 and 0.25, hexane : dichloromethane (19.:1). Found : C, 64.34; H, 11.01; S, 10.67. $C_{32}H_{66}O_2Si_2S_2$ requires C, 63.79; H. 10.96; S, 10.63. $\delta(CDCl_3)$: 0.24 (s, 18 H); 0.94 (m, 12 H); 1.30 (m, 24 H); 2.00 (m, 2 H); 2.66 (m, 8 H); 4.42 (d, J 9 Hz, 2 H). $\nu_{max.}$ (liquid film) : 1 664 (C=C stretch) cm^{-1}. m/e : 301.2011 ($\frac{M^+}{2}$, base peak); 269 ($\frac{M^+}{2}$ - S); 243 ($\frac{M^+}{2}$ - C_4H_{10}); 211 ($\frac{M^+}{2}$ - $C_3H_{10}Si$); 175 ($\frac{M^+}{2}$ - C_9H_{18}); 57 ($C_4H_9^+$). $C_{16}H_{33}OSiS$ requires 301.2013.

Hydrolysis of Bis(5-butyl-3-trimethylsilyloxynon-3-enyl)disulphide (172)

Method A Bis(5-butyl-3-trimethylsilyloxynon-3-enyl) disulphide (172, 0.32 g, 0.00053 mol) was passed down a silica gel column (230-400 mesh) using hexane : dichloromethane (9:1) as eluant. However, tlc indicated that only partial deprotection had occurred, so the product was recovered by rotary-evaporation.

Method B Bis(5-butyl-3-trimethylsilyloxynon-3-enyl) disulphide (172, 0.32 g, 0.00053 mol) was stirred with THF (20 ml) with ice-bath cooling. 10% HCl (7 drops) was added and the mixture stirred for 2 h at 0 °C. The mixture was extracted with ether (3 x

15 ml), the ethereal extracts were washed with saturated sodium chloride solution (20 ml) and dried with $MgSO_4$, and the solvent was rotary-evaporated. Flash chromatography using hexane : ether (11:1) gave bis(5-butyl-3-oxononyl)disulphide (173), yield 0.16 g (67%). R_f = 0.55, hexane : ether (6:1). Found : C, 68.18; H, 11.27; S, 13.71. $C_{26}H_{50}O_2S_2$ requires C, 68.12; H, 10.98; S, 13.97. $\delta(CDCl_3)$: 0.88 (m, 12 H); 1.25 (m, 24 H); 2.04 (m, 2 H); 2.38 (d, J 7 Hz, 4 H); 2.85 (s, 8 H). $\nu_{max.}$ (liquid film) : 1 716 (C=O stretch) cm^{-1}. m/e : 458.3256 (M^+); 229 ($\frac{M^+}{2}$); 197 ($\frac{M^+}{2}$ - S); 173 ($\frac{M^+}{2}$ - C_4H_8); 169 ($\frac{M^+}{2}$ - C_2H_4S, base peak); 57 ($C_4H_9^+$). $C_{26}H_{50}O_2S_2$ requires 458.3240.

.4 The Synthesis of 2-Substituted Thian-4-one 1-oxides

.4.1 Reaction of Sulphoxide (175) with Lithium Butylpent-1-ynylcuprate

A slurry of dry pent-1-ynylcopper (0.52 g, 0.0040 mol) in dry THF (10 ml) was treated with dry hexamethylphosphorus triamide (90%, 1.44 g, 1.60 ml, 0.0074 mol), and the mixture was stirred at room temperature under a nitrogen atmosphere until a clear solution was obtained (10 min). To the cooled (-78 °C) solution was added butyllithium (1.53 M, 2.50 ml, 0.0038 mol) over 5 min,

and the resulting mixed-cuprate solution was stirred for 20 min at -78 °C. To this butylpent-1-ynylcuprate at -78 °C was added 2,3-dihydrothi-in-4-one 1-oxide (175, 0.43 g, 0.0033 mol) in dry THF (15 ml) over 15 min. The mixture was kept at -78 °C under nitrogen for 1 h, and then ice-cold 10% ammonium sulphate solution (100 ml) was added with vigorous stirring. After allowing the mixture to warm up, it was extracted with chloroform (3 x 100 ml), the extracts being dried with $MgSO_4$ and rotary-evaporated. The product obtained was mainly hexamethylphosphoramide, and attempts to remove this by flash chromatography proved to be unsuccessful. The aqueous extract from the chloroform extraction was continuously extracted with chloroform for 12 h but no further product was recovered.

.4.2 Reaction of Sulphoxide (175) with Lithium Dialkylcuprates (R_2CuLi)

(a) Reaction of (175) with Lithium Dibutylcuprate

To copper(I) iodide (ultrapure, 0.95 g, 0.005 mol) was added dry THF (20 ml), and the mixture was cooled to -40 °C under a nitrogen atmosphere. Butyllithium (1.53 M, 6.54 ml, 0.01 mol) was added over 10 min, and the mixture was stirred for 30 min until a dark-brown solution was obtained. The lithium dibutylcuprate

solution was cooled to -78 °C and 2,3-dihydrothi-in-4-one 1-oxide (175, 0.50 g, 0.0038 mol) in dry THF (15 ml) was added over 15 min. The mixture was kept at -78 °C for 1.75 h, then ice-cold saturated ammonium sulphate solution (50 ml) was added with vigorous stirring. After allowing the mixture to warm up, it was extracted with ether (3 x 100 ml), and the precipitated copper salts were filtered off using celite. The combined ethereal extracts were dried with $MgSO_4$ and rotary-evaporated. Flash chromatography using hexane : acetone (3:4) gave 2-butylthian-4-one 1-oxide (181), yield 0.36 g (51%). Two spots by tlc, R_f = 0.51 and 0.58, hexane : acetone (1:2). δ(d_6-acetone) : 0.91 (m, 3 H); 1.46 (m, 6 H); 2.33 - 3.41 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 725 (C=O stretch) and 1 041 (S=O stretch) cm^{-1}. Preparative plate chromatography using hexane : acetone (1:2) separated the two components, and the m.s. of each was obtained. m/e (less polar) : 188.0870 (M^+); 139 (M^+ -HOS); 104 (M^+ -C_6H_{12}); 57 ($C_4H_9^+$), 55 ($C_3H_3O^+$, base peak). $C_9H_{16}O_2S$ requires 188.0867. m/e (more polar) : 188.0865 (M^+); 139 (M^+ - HOS); 104 (M^+ - C_6H_{12}); 57 ($C_4H_9^+$); 55 ($C_3H_3O^+$, base peak).

(b) Reaction of (175) with Lithium Dimethylcuprate

The same procedure as for R=Bu (8.4.2 (a) above) was followed. Flash chromatography using hexane : acetone

(1:3) gave 2-methylthian-4-one 1-oxide (182), yield 0.07g (12.5%). Two spots by tlc, R_f = 0.29 and 0.37, hexane : acetone (1:3). δ(d_6-acetone) : 1.26 (d, J 6 Hz, 3 H); 2.38 - 3.39 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 720 (C=O stretch) and 1 039 (S=O stretch) cm^{-1}. m/e : 146.0394 (M^+); 104 ($M^+ - C_3H_6$); 97 (M^+ - HOS); 55 ($C_3H_3O^+$, base peak). $C_6H_{10}O_2S$ requires 146.0399.

.4.3 Oxidation of 2-Butylthian-4-one (149) with m-Chloroperbenzoic acid.

2-Butylthian-4-one (149, 0.19 g, 0.0011 mol) was dissolved in dry chloroform (10 ml) and stirred at -10 °C. m-Chloroperbenzoic acid (85%, 0.23 g, 0.0011 mol) was added in portions over 15 min, and after the addition the mixture was stirred at -20 °C for 1 h. The precipitated m-chlorobenzoic acid was filtered off and was washed with chloroform (5 ml). The combined chloroform extracts were washed with 10% sodium hydrogen carbonate solution (100 ml), then dried with $MgSO_4$ and rotary-evaporated to give 2-butylthian-4-one 1-oxide (181), yield 0.18 g (85%). Two spots by tlc, R_f = 0.51 and 0.58, hexane : acetone (1:2). δ(d_6-acetone) : 0.91 (s, 3 H); 1.46 (m, 6 H); 2.33 - 3.41 (m, 7 H). $\nu_{max.}$ (liquid film) : 1 725 (C=O stretch) and 1 041 (S=O stretch) cm^{-1}. m/e : 188.0875 (M^+); 139 (M^+ - HOS); 104 ($M^+ - C_6H_{12}$); 55 ($C_3H_3O^+$, base peak).

$C_9H_{16}O_2S$ requires 188.0867.

8.5 The Attempted Synthesis of 2,3-Disubstituted Thian-4-one 1-oxides

8.5.1 Allyl bromide Trapping of Lithium enolates

To copper(I) iodide (ultrapure, 0.95 g, 0.005 mol) was added dry THF (20 ml) and the slurry was cooled to -40 °C under a nitrogen atmosphere. Butyllithium (1.56 M, 6.42 ml, 0.010 mol) was added to the slurry over 15 min, and the mixture was stirred for 30 min until a dark-brown solution was obtained. The lithium dibutylcuprate solution was cooled to -78 °C and 2,3-dihydrothi-in-4-one 1-oxide (175, 0.50 g, 0.0038 mol) in dry THF (15 ml) was added over 15 min. The mixture was kept at -78 °C for 2 h, and allyl bromide (distilled, 0.56 g, 0.40 ml, 0.0046 mol) in dry THF (5 ml) was then added rapidly by syringe. After stirring for 1.25 h at -78 °C the mixture was warmed to room temperature and stirred for 1 h, when ice-cold saturated ammonium sulphate solution (100 ml) was added with vigorous stirring. The mixture was extracted with ether (3 x 100 ml), the ethereal extracts were washed with ice-cold 2% H_2SO_4 (2 x 100 ml), and the precipitated copper salts were filtered off using celite. The filtrate was washed with 5% sodium hydrogen

carbonate solution (200 ml), the solution dried with $MgSO_4$ and the solvent rotary-evaporated. Flash chromatography using hexane : acetone (2:1) followed by preparative plate chromatography gave a brown oil, yield 0.045 g. Tlc showed a major product spot, R_f = 0.48, hexane : acetone (2:1) with some streaking. $\delta(CDCl_3)$: 0.88 (s, 3 H); 1.25 (m, 6 H); 2.30 - 3.54 (m, 8 H); 5.19 (m, 3 H). $\nu_{max.}$ (liquid film) : 1 710 (C=O stretch) cm^{-1}. m/e : No M^+ corresponding to $C_{12}H_{20}O_2S$.

3.5.2 Trimethylchlorosilane Trapping of Lithium enolates

To copper(I) iodide (ultrapure, 0.95 g, 0.0050 mol) was added dry THF (20 ml) and the slurry was cooled to -40 °C under a nitrogen atmosphere. Butyllithium (1.56 M, 6.42 ml, 0.010 mol) was added to the slurry over 15 min, and the mixture was stirred for 30 min until a dark-brown solution was obtained. The lithium dibutylcuprate solution was cooled to -78 °C and 2,3-dihydrothi-in-4-one 1-oxide (175, 0.50 g, 0.0038 mol) in dry THF (15 ml) was added over 15 min. The mixture was kept at -78 °C for 2 h, then trimethylchlorosilane (distilled, 0.84 g, 0.98 ml, 0.0077 mol) was added rapidly. After 30 min at -78 °C, the mixture was warmed to room temperature and stirred for 2 h. Ammonium hydroxide solution ('880', 7 ml)

and ice-cold saturated sodium hydrogen carbonate solution (70 ml) were added with vigorous stirring. The mixture was extracted with ether (3 x 100 ml), the ether extracts washed with water (100 ml) and dried with $MgSO_4$, and the solvent was rotary-evaporated. The crude product was flash chromatographed (Florisil) using hexane : ether (24:1); but a complex mixture was obtained, as evidenced by tlc and nmr.

8.6 The Synthesis of 2-Substituted Thian-4-one 1,1-dioxides

8.6.1 Reaction of Sulphone (176) with Lithium Dialkylcuprates (R_2CuLi)

Reaction of (176) with Lithium Dibutylcuprate

To copper(I) iodide (ultrapure, 0.85 g, 0.0045 mol) was added dry THF (20 ml) and the mixture was cooled to -40 °C under a nitrogen atmosphere. Butyllithium (1.56 M, 5.7 ml, 0.0089 mol) was added over 15 min, and the mixture was stirred for 30 min until a dark-brown solution was given. The lithium dibutylcuprate solution was cooled to -78 °C and 2,3-dihydrothi-in-4-one 1,1-dioxide (176, 0.50 g, 0.0034 mol) in dry THF (11 ml) was added over 15 min. The mixture was kept at -78 °C for 1.75 h, then ice-cold saturated ammonium sulphate solution (50 ml)

was added with vigorous stirring. After allowing the mixture to warm up, it was extracted with ether (3 x 100 ml), and the precipitated copper salts were filtered off using celite. The combined ethereal extracts were dried with $MgSO_4$ and rotary-evaporated. The aqueous extracts were submitted to continuous extraction with chloroform for 12 h and the material obtained was added to the main product from ether extraction. Flash chromatography using hexane : acetone (2:1) gave 2-butylthian-4-one 1,1-dioxide (183), yield 0.09 g (13%). M.p. 66-68 °C. R_f = 0.50, hexane : acetone (1:1). δ(d_6-acetone) : 0.90 (m, 3 H); 1.52 (m, 6 H); 2.74 (m, 3 H); 3.40 (m, 4 H). $\nu_{max.}$ (nujol mull) : 1 727 (C=O stretch) and 1 320 (SO_2 asymmetric stretch) cm^{-1}. Flash chromatography also gave 2-butylthian-4-one 1-oxide (181), yield 0.01 g (1.5%). Two spots by tlc, Rf = 0.51 and 0.58, hexane : acetone (1:2). m/e : 188.0873 (M^+); 139 (M^+ - HOS); 104 (M^+ - C_6H_{12}); 55 ($C_3H_3O^+$, base peak). $C_9H_{16}O_2S$ requires 188.0867.

Reaction of (176) with Lithium Dimethylcuprate

To copper(I) iodide (ultrapure, 1.20 g, 0.0063 mol) was added dry THF (20 ml) and was cooled to -40 °C under a nitrogen atmosphere. Methyllithium (1.50 M, 8.4 ml, 0.013 mol) was added over 15 min, and the

mixture was stirred for 30 min until a solution was obtained. The lithium dimethylcuprate solution was cooled to -78 °C and 2,3-dihydrothi-in-4-one 1,1-dioxide (176, 0.46 g, 0.0032 mol) in dry THF (11 ml) was added over 15 min. The mixture was kept at -78 °C for 3 h, and ice-cold saturated ammonium sulphate solution (50 ml) was then added with vigorous stirring. After allowing the mixture to warm up, it was extracted with ether (3 x 100 ml), and the precipitated copper salts were filtered off using celite. The combined ethereal extracts were dried with $MgSO_4$ and rotary-evaporated. However, this gave very little product, so the aqueous extract was submitted to continuous extraction with chloroform for 16 h, yielding a significant amount of product. Flash chromatography using hexane : acetone (1:2), followed by passage through a short silica gel column (400-230 mesh) gave 2-methylthian-4-one 1,1-dioxide (188), yield 0.11 g (22%). M.p. 129-131 °C. R_f = 0.70, hexane : acetone (1:2). Found : C, 43.06; H, 5.98; S, 19.91. $C_6H_{10}O_3S$ requires, C, 44.44; H, 6.17; S, 19.75. $\delta(CDCl_3)$: 1.31 (d, J 6 Hz, 3 H); 2.95 (m, 4 H); 3.27 (m, 3 H). $\nu_{max.}$ (nujol mull) : 1 730 (C=O stretch) and 1 130 (SO_2, symmetric stretch) cm^{-1}. m/e : 162.0353 (M^+); 148 ($M^+ - CH_2$); 121 ($M^+ - C_3H_5$); 56 ($C_3H_4O^+$, base peak). $C_6H_{10}O_3S$ requires 162.0348.

8.6.2 Oxidation of 2-Butylthian-4-one (149) with m-Chloroperbenzoic acid

2-Butylthian-4-one (149, 0.19 g, 0.0011 mol) was dissolved in dry chloroform (10 ml) and stirred at -30 °C. m-Chloroperbenzoic acid (85%, 0.45 g, 0.0022 mol) was added in portions over 15 min, and after the addition the mixture was stirred at -15 °C for 2 h, then at 0 °C for 1 h. The precipitated m-chlorobenzoic acid was filtered off and was washed with chloroform (5 ml). The combined chloroform extracts were washed with 10% sodium hydrogen carbonate solution (100 ml), dried with $MgSO_4$, and rotary-evaporated to give a semi-solid. Flash chromatography using hexane : acetone (2:1) gave 2-butylthian-4-one 1,1-dioxide (183), yield 0.16 g (69%). M.p. 66-68 °C. R_f = 0.50, hexane : acetone (1:1). Found : C, 53.00, H, 8.16; S, 15.41. $C_9H_{16}O_3S$ requires C, 52.94; H, 7.84; S, 15.69. δ(d_6—acetone) : 0.90 (m, 3 H); 1.52 (m, 6 H); 2.74 (m, 3 H); 3.40 (m, 4 H). $\nu_{max.}$ (nujol mull) : 1 727 (C=O stretch) and 1 320 (SO_2 asymmetric stretch) cm^{-1}. m/e : 204.0812 (M^+); 140($M^+ - SO_2$); 121 ($M^+ - C_6H_{11}$); 84 ($C_6H_{12}^+$); 56 ($C_3H_4O^+$, base peak). $C_9H_{16}O_3S$ requires 204.0816.

8.6.3 Oxidation of Sulphoxide (181) with m-Chloroperbenzoic acid

2-Butylthian-4-one 1-oxide (181, 0.13 g, 0.00069 mol) was dissolved in dry chloroform (8 ml) and stirred at 0 °C. m-Chloroperbenzoic acid (85%, 0.21 g, 0.0010 mol) was added in portions over 5 min, and after the addition the mixture was stirred at 0 °C for 3 h. The precipitated m-chlorobenzoic acid was filtered off and was washed with chloroform (4 ml). The combined chloroform extracts were washed with 10% sodium hydrogen carbonate solution (80 ml), dried with $MgSO_4$ and rotary-evaporated to give a solid. Flash chromatography using hexane : acetone (2:1) gave 2-butylthian-4-one 1,1-dioxide (183), yield 0.10 g (71%). M.p. 66-68 °C. R_f = 0.50, hexane : acetone (1:1). Found : C, 52.50; H, 7.84; S, 15.15. $C_9H_{16}O_3S$ requires C, 52.94; H, 7.84; S, 15.69. δ(d_6-acetone) : 0.90 (m, 3 H); 1.52 (m, 6 H); 2.74 (m, 3 H); 3.40 (m, 4 H). $\nu_{max.}$ (nujol mull) : 1 727 (C=O stretch) and 1320 (SO_2 asymmetric stretch) cm^{-1}.

CHAPTER 9

References

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