# SYNTHETIC APPROACHES TO LEUKOTRIENE ANALOGUES

by

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TO MUM AND DAD.

"Science is the great antidote to the
poison of enthusiasm and superstition."

-Adam Smith.

## SUMMARY

A review of the discovery, biological properties, and synthesis of the leukotrienes is presented. The opening of β-alkylstyrene oxides with nucleophiles is also discussed, with respect to the possible preparation of leukotriene analogues in which an aromatic species replaces the triene system.

The reactions of E-β-methylstyrene oxide (67a) with thiophenol and benzylthiol gave single regioisomers derived from attack at the α-carbon, whereas similar reactions of the Z-isomer (67b) gave mixtures of the two possible regioisomers. Reaction of both E- and Z- 4-methoxy-β-methylstyrene oxides (85) gave only products derived from α-attack. These results are discussed with reference to steric and electronic effects.

A possible route to E- and Z-4-methoxy-β-methylstyrene oxides (85) *via* bromohydrins of the type (89) was investigated. It was found that this sequence gave mainly the E-isomer (85a) irrespective of the geometry of the starting olefin. A mechanistic study was performed and it was concluded that these results were owed to the intermediacy of the benzylic carbocation (92).

Methyl 6-phenyl-5-hexenoate (101) was synthesised *via* three different routes, and was converted to the corresponding epoxide (57) by oxidation with peracid. Reaction of this epoxide with simple thiols gave products derived from attack at the α-carbon (C-6 of the aliphatic chain).

The nor-LTA-analogue, methyl 4,5-epoxy-5-phenylpentanoate (120) was prepared and allowed to react with thiophenol to give a mixture

of the lactone (126) and the hydroxy sulphide (127).

The opening of E-β-methylstyrene oxide (67a) and the LTA-analogue (57) with cysteine was studied and the protected LTE analogue (139) containing a benzene ring in place of the normal acyclic triene system was prepared.

ACKNOWLEDGEMENTS

I would like to record my gratitude to my supervisor - Brian Marples - for his patience and guidance, and to the rest of the organic research personnel for their companionship and intellectual stimulation.

I would also like to thank Mike Harris for running some of the spectra and the rest of the technical staff for all their help.

Finally, I would like to thank the Science and Engineering Research Council for the financial support which made this research possible; and my parents for their faith in my ability.

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## ABBREVIATIONS

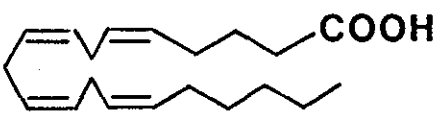
| | |
|---|---|
| BuLi | Butyllithium |
| DME | Dimethoxyethane |
| DMF | Dimethylformamide |
| ETE | Eicosatetraenoic acid |
| H.P.L.C. | High pressure liquid chromatography |
| LT | Leukotriene |
| MCPBA | m-Chloroperoxybenzoic acid |
| PG | Prostaglandin |
| PMNL | Polymorphonuclear leukocytes |
| p.t.l.c. | Preparative thin layer chromatography |
| RBL-1 | Rat basophil leukemia cells |
| SRS | Slow reacting substance |
| SRS-A | Slow reacting substance of anaphylaxis |
| THF | Tetrahydrofuran |
| t.l.c. | Thin layer chromatography |
| Tx | Thromboxane |
| FGI | Functional group interconversion |

The terms E and Z, which are used to designate the configuration of epoxides, are assigned applying the Sequence Rule as for alkenes.

# 1. INTRODUCTION

## 1.1 THE LEUKOTRIENES AND THEIR SYNTHESIS

The leukotrienes are the newest among many important natural products derived from 5,8,11,14-Z-eicosatetraenoic (arachidonic) acid (1). This material has already been shown to be a precursor of the prostaglandins, the thromboxanes, and prostacyclin ($PGI_2$) via the cyclooxygenase pathway, and various hydroxy fatty acids via the lipoxygenase pathway (scheme 1).



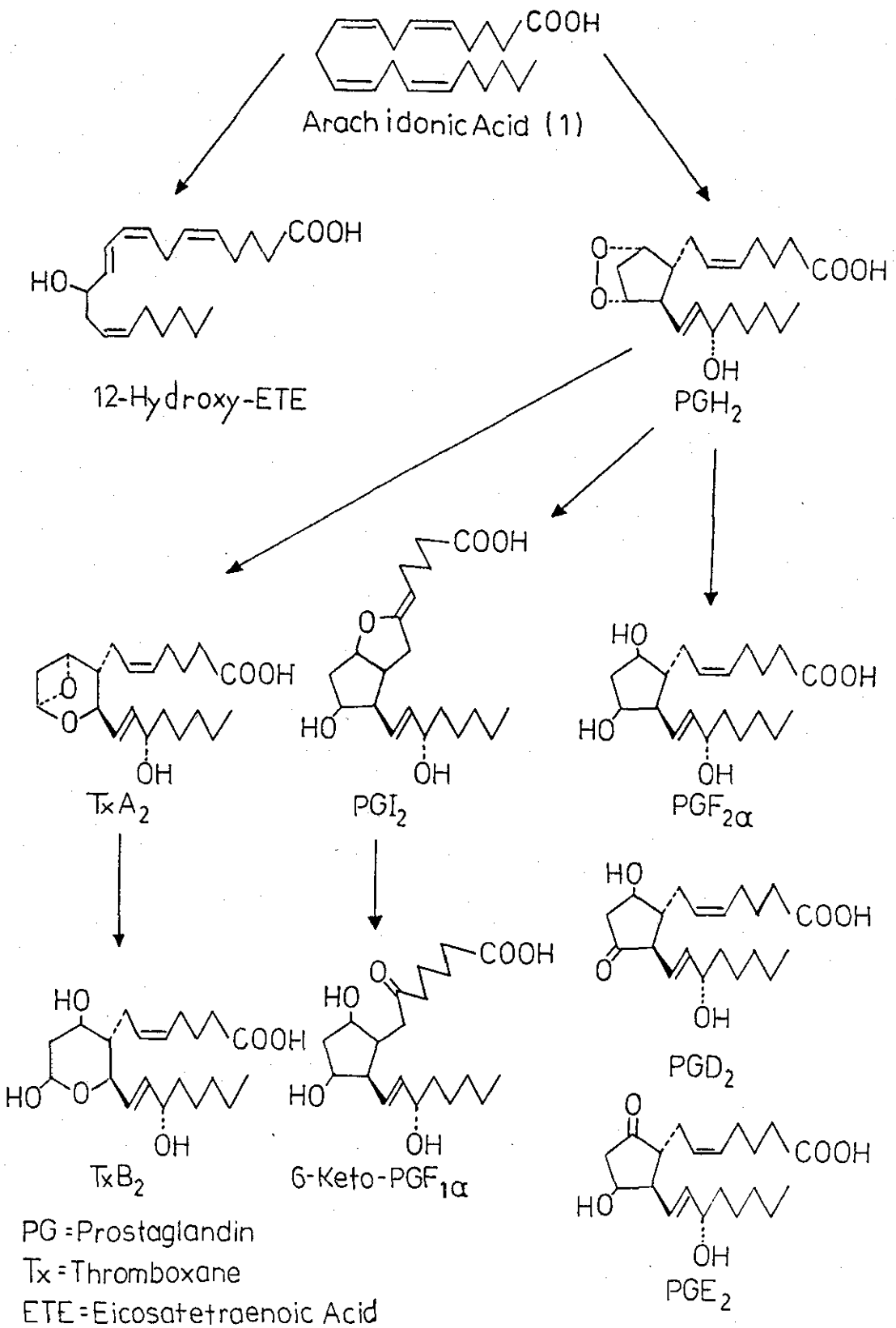

**(1)**

The systems from which the leukotrienes have been isolated are closely related to those involved in immediate hypersensitivity reactions. Slow reacting substance of anaphylaxis (SRS-A), an important mediator in this type of reaction, is thought to be a member of the leukotriene family. Therefore any discussion of the leukotrienes must begin with SRS-A.

### 1.1.1 SLOW REACTING SUBSTANCE OF ANAPHYLAXIS

In 1938, Feldberg and Kellaway[1] demonstrated that perfusates of cat and guinea pig lungs, treated with cobra venom, caused contraction of guinea pig ileum. Kellaway and Trethewie[2] described a muscle contracting substance released from guinea pig lung after anaphylactic challenge, which could account for some of its symptoms. Because of its slow contracting effect on guinea pig jejunum, this entity was called "slow reacting smooth muscle stimulating substance (SRS)."

SCHEME 1.




PG = Prostaglandin
Tx = Thromboxane
ETE = Eicosatetraenoic Acid

Brockelhurst[3,4] coined the term SRS-A to differentiate the substance produced by lungs on immunological challenge by specific antigens, from those generated upon non-immunological stimulation (SRS). Crude preparations of SRS-A were shown to induce long lasting contractions of human bronchioles.[5] Also significant amounts of SRS-A were produced by the lungs of sensitised animals, and from asthmatic human lungs.[4,6,7] This work linked SRS-A with the long lasting bronchoconstriction experienced by asthmatics.

The main physiological effect of SRS-A appears to be the contraction of smooth muscle, although it has been shown to alter skin permeability in guinea pigs, monkeys, and humans.[8] The normal method of bioassay is based on its contracting effect for guinea pig ileum.[5] These contractions are slow in onset, prolonged in duration, and not blocked by inhibitors of histamine,[4] serotonin, bradykinin, or the prostaglandins.[9]

Two reproducible systems for generating SRS-A in human tissues have been developed. The most widely studied is sensitised lung fragments challenged with ragweed antigen.[10] The other is the use of mixed blood leukocytes in response to antigen challenge.[11] These responses would appear to be correlated with the presence of IgE antibodies,[12] the immunoglobulins associated with hypersensitivity.

In addition to the production of SRS-A by specific antigen challenge, a number of other stimuli have been shown to produce SRS activity. The most widely studied is the Lilly compound A23187,[13,14] which is a calcium ionophore also capable of releasing histamine. This has been shown to produce SRS from mouse mast cell tumour,[15] rat basophil leukemia (RBL-1) cells,[16] rat mononuclear cells,[17] and human leukocytes.[18]

Although much of the biology of SRS and SRS-A had been investigated, the exact chemistry of these substances remained elusive. The turning point in the study of the chemical structure of SRS and SRS-A came with the discovery of the leukotrienes.

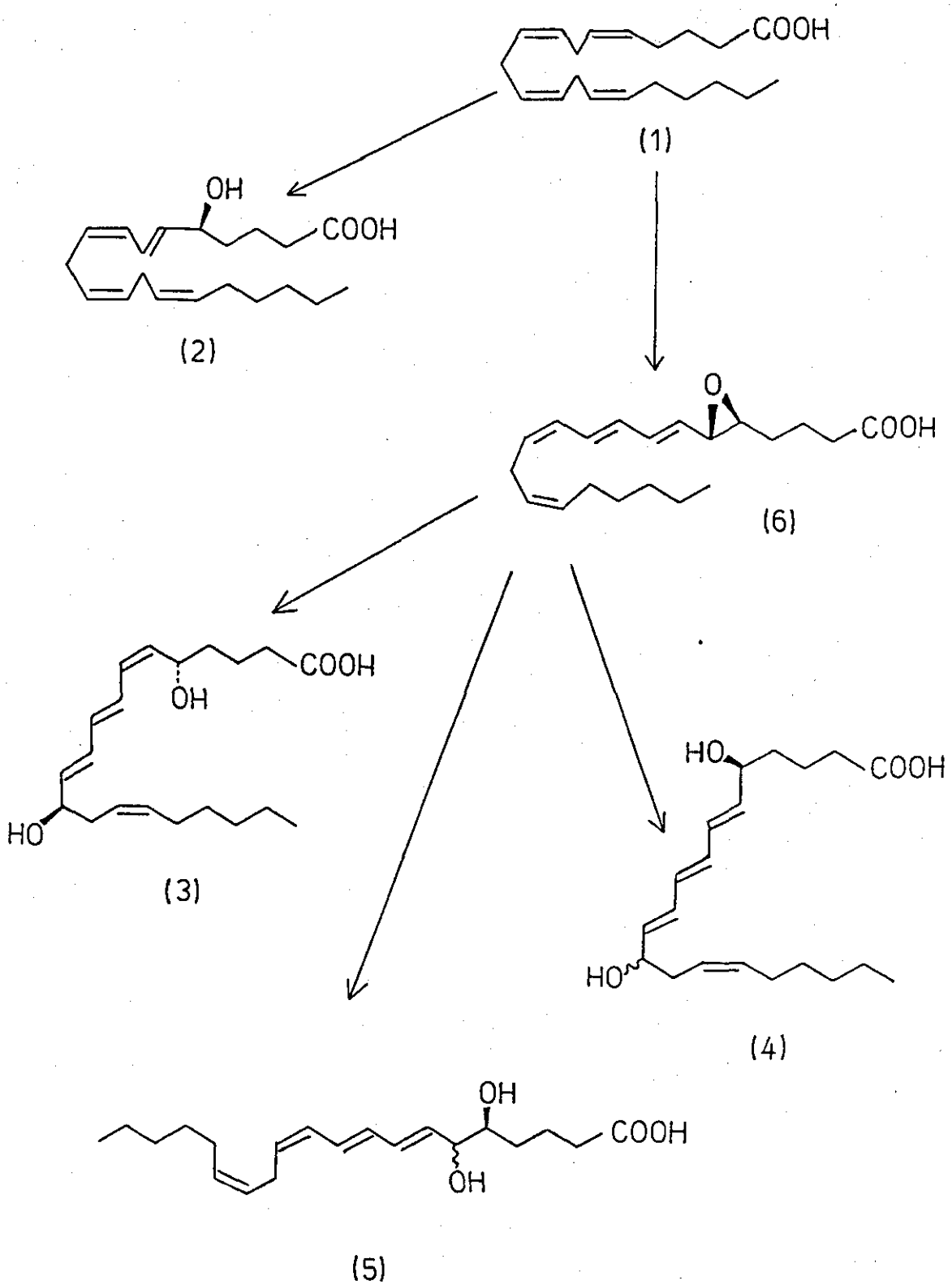
### 1.1.2 LEUKOTRIENE A AND LEUKOTRIENE B

The discovery of the leukotrienes resulted from a study of the metabolism of arachidonic acid in rabbit and human polymorphonuclear leukocytes (PMNL), stimulated with ionophore A23187. The first metabolite characterised was 5(S)-hydroxy-6,8,11,14-eicosatetraenoic acid (2),[19] (scheme 2). The stereospecific formation of the hydroxyl group at C-5 indicated the occurrence of a novel lipoxygenase-type enzyme reaction at the C-5 position of arachidonic acid.

The first leukotriene to be isolated was 5(S), 12(R)-dihydroxy-6,8,10,14-eicosatetraenoic acid (3).[20] Also isolated were minor amounts of an epimeric mixture of the geometric isomer (4) and an epimeric mixture of 5(S), 6-dihydroxy-7,9,11,14-eicosatetraenoic acid (5).[21] These compounds were unique in that they contained a triene system, showing characteristic ultra-violet spectra (maximum absorption at 270 nm and shoulders at 260 and 281 nm ).[21,22] These compounds all showed the stereospecificity at C-5 and therefore appeared to be related to 5(S)-hydroxy-6,8,11,14-eicosatetraenoic acid (2).[20,23]

Studies on the incorporation of isotopic oxygen[24] indicated that the hydroxyl group at C-5, in all metabolites, was derived from oxygen and consequently that the hydroxyl group at either C-6 or C-12 was derived from water. These data strongly suggested a common pathway of formation, involving an unstable intermediate. Trapping experiments

SCHEME 2.



with alcohols[24] proved that an unstable intermediate, which could easily react with weak nucleophiles, was generated in PMNL.

Comparison of the structures of the various metabolites, the results of isotopic oxygen incorporation, and the results of trapping experiments all supported a common unstable intermediate.[25] It was proposed that this intermediate was 5,6-epoxy-7,9,11,14-eicosatetraenoic acid (6),[24,25] which was given the name leukotriene A.[26] The 5(S), 12(R)-dihydroxy-6,8,10,14-eicosatetraenoic acid (3) was given the name leukotriene B.[26] The term leukotriene (LT) derives from the facts that the compounds were isolated from leukocytes and contained a triene system.[27]

The geometry of the double bonds and the configuration of the epoxide were unknown at this time. Corey *et al.*[28] synthesised a racemic mixture of LTA containing 7,9-*E* and 11,14-*Z* double bonds. Hydrolysis of this synthetic material gave products identical to those from natural sources. Later Corey *et al.*[29] reported the total stereospecific synthesis of 5(S), 6-*E*-epoxy-7,9-*E*-11,14-*Z*-eicosatetraenoic acid (6). This was found to be transformed, in leukocytes, into a product indistinguishable from LTB (3).[30] Therefore the detailed structure (6) was assigned to LTA. The stereochemistry and double bond geometry of LTB (3) was also confirmed by comparison with synthesised material.[31]

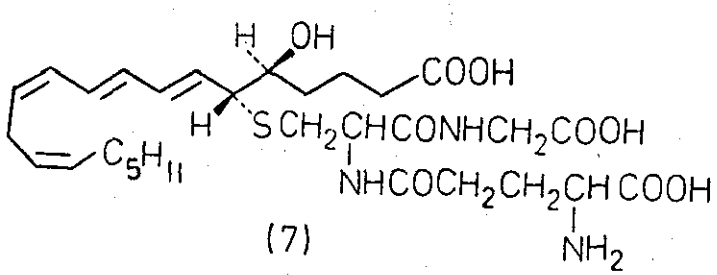
### 1.1.3 LEUKOTRIENE C

Although the dihydroxy fatty acids are devoid of any smooth muscle contracting activity, and therefore cannot account for the actions of SRS-A,[31] certain pieces of evidence suggest a relationship between SRS-A and the leukotrienes. Purified samples of SRS-A gave

ultra-violet spectra similar to LTA and LTB.[32] Cyclooxygenase inhibitors, such as indomethacin, fail to inhibit both SRS-A and leukotriene release.[19,33,34] Radiolabeled arachidonate is incorporated into SRS and SRS-A.[35] The calcium ionophore A23187 stimulates SRS release[13,15-18] and is a powerful stimulus for leukotriene release from PMNL.[20,21,23,24]

Many thiols, and particularly cysteine, are reported to stimulate the formation of SRS and SRS-A.[36] This led to the suggestion that SRS and SRS-A could be sulphur containing compounds and possibly conjugates of cysteine (or a related compound) and LTA. Careful chemical analysis of an SRS released from mouse mastocytoma cells by ionophore A23187 indicated a structure of 5(S)-hydroxy-7,9,11,14-eicosatetraenoic acid containing a thio ether linkage at C-6.[27]

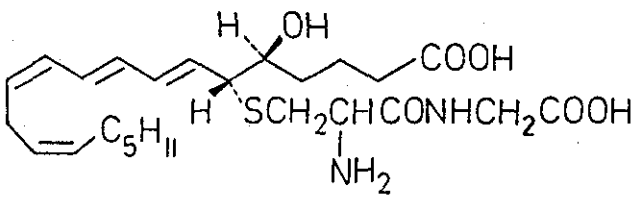
Hammarström *et al.*[37] identified the substituent at C-6 as glutathione and established the stereochemistry of the molecule by comparison of SRS from natural sources and totally synthetic material of known structure.[29] Therefore the SRS from mouse mastocytoma cells was identified as 5(S)-hydroxy-6(R)-glutathionyl-7,9-*E*-11,14-*Z*-eicosatetraenoic acid (7) and was given the name leukotriene C (LTC).[38]




(7)

### 1.1.4 LEUKOTRIENE D AND LEUKOTRIENE E

Morris et al.[39] purified an SRS from RBL-1 cells and found that the biologically active material showed the characteristics of the leukotrienes. However amino acid analysis revealed the presence of a cysteinyl-glycine moiety in the molecule. Örning et al.[40] isolated an SRS from the same source, and assigned 5(S)-hydroxy-6(R)-cysteinyl-glycine-7,9-E-11,14-Z-eicosatetraenoic acid (8) as the structure. This substance was given the name leukotriene D (LTD).[38]



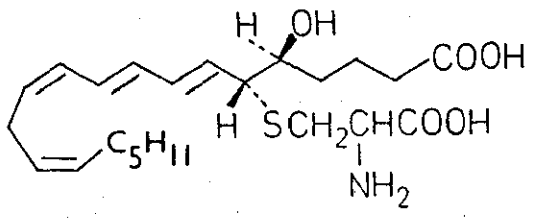
(8)

The same workers also demonstrated that LTD could be generated by the action of γ-glutamyl-transferase on LTC.[40] These data suggested that LTA and LTC were intermediates in the formation of LTD and consequently that the stereochemistry was the same.

Morris et al.[41] have also attributed the structure (8) to an SRS-A released from guinea pig lung on immunological challenge. This was the first report on the structure of an immunologically released SRS-A.

Lewis et al.[42] studied an SRS-A released from rat peritoneal cavity and isolated, along with LTC and LTD, a third biologically active material. This was identified by comparison with synthetic

material[29] as 5(S)-hydroxy-6(R)-cysteinyl-7,9-E-11,14-Z-eicosatetraenoic acid (9) or leukotriene E (LTE)[38].




(9)

## 1.1.5 THE BIOSYNTHESIS OF THE LEUKOTRIENES

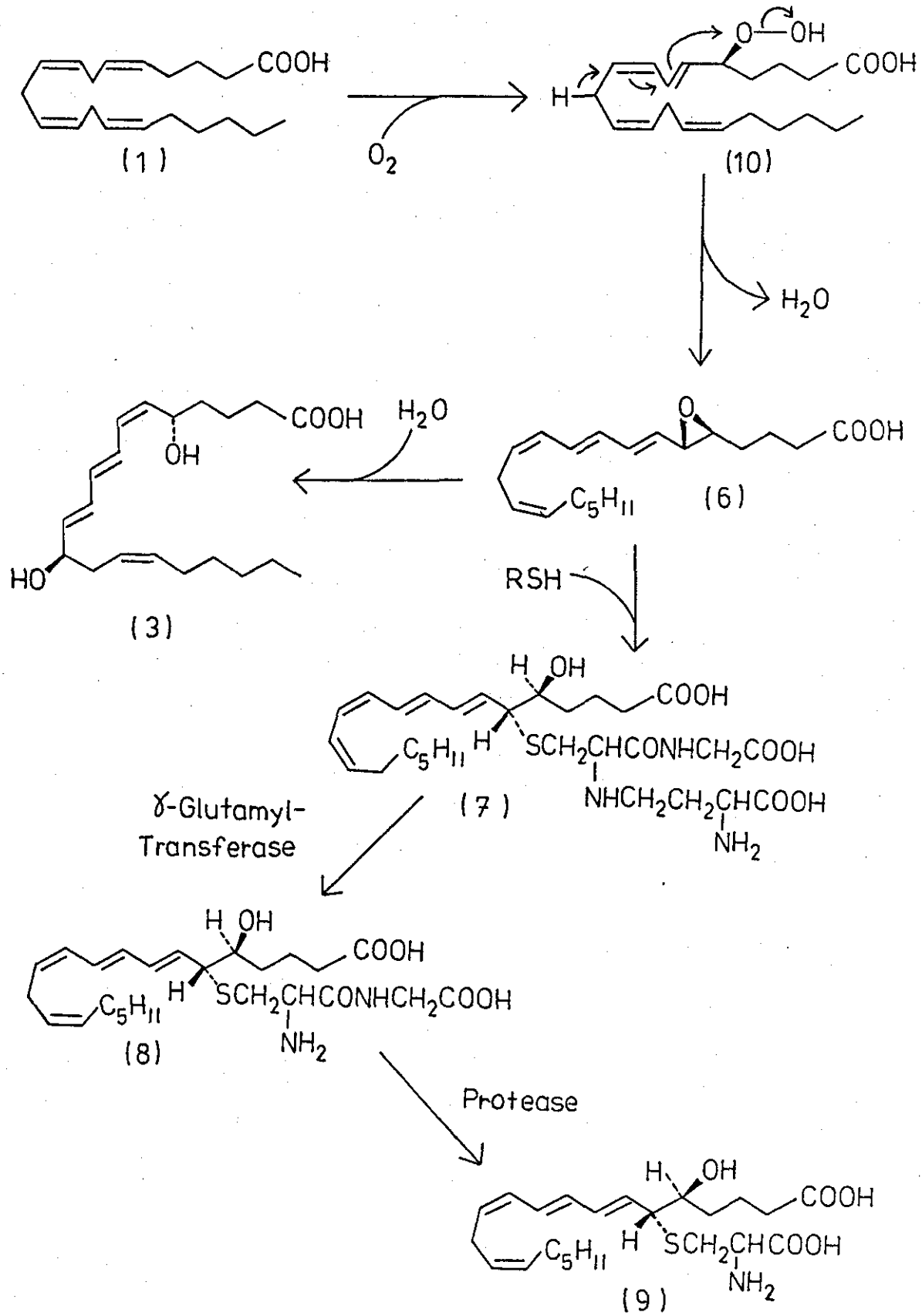
Based on the structural resemblance of LTC with the dihydroxy fatty acids isolated from leukocytes, a biosynthetic pathway involving LTA as a common intermediate has been proposed[15,40] (scheme 3).

Arachidonic acid (1) is transformed by lipoxygenase into 5(S)-hydroperoxy-6,8,11,14-eicosatetraenoic acid (10) dehydration of which leads to LTA (6). Reaction of this unstable intermediate with water and glutathione leads to LTB (3) and LTC (7) respectively. The action of γ-glutamyl-transferase converts LTC (7) to LTD (8) and further metabolism by protease produces LTE (9).[43]

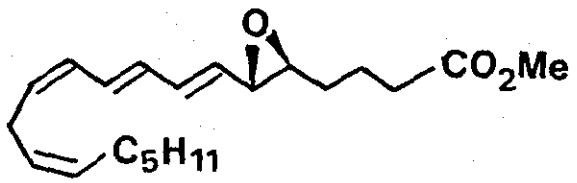
## 1.1.6 THE SYNTHESIS OF THE LEUKOTRIENES

As previously stated, synthetic leukotrienes have proved invaluable in determining the structure, geometry, and the stereochemistry of material isolated from natural sources. Although LTB (3) has been prepared by a chemical route,[31] this section concentrates on the synthesis of leukotriene A methyl ester (11). This compound has proved a useful intermediate in the synthesis of leukotriene C (7),

SCHEME 3.


COOH
(1)
$O_2$
O—OH
H
COOH
(10)
$H_2O$
O
COOH
$C_5H_{11}$
(6)
RSH
$H_2O$
COOH
OH
HO
(3)
H OH
COOH
$C_5H_{11}$ H $SCH_2CHCONHCH_2COOH$
$NHCH_2CH_2CHCOOH$
$NH_2$
(7)
γ-Glutamyl-
Transferase
H OH
COOH
$C_5H_{11}$ H $SCH_2CHCONHCH_2COOH$
$NH_2$
(8)
Protease
H OH
COOH
$C_5H_{11}$ H $SCH_2CHCOOH$
$NH_2$
(9)

leukotriene D (8) and leukotriene E (9).[29]



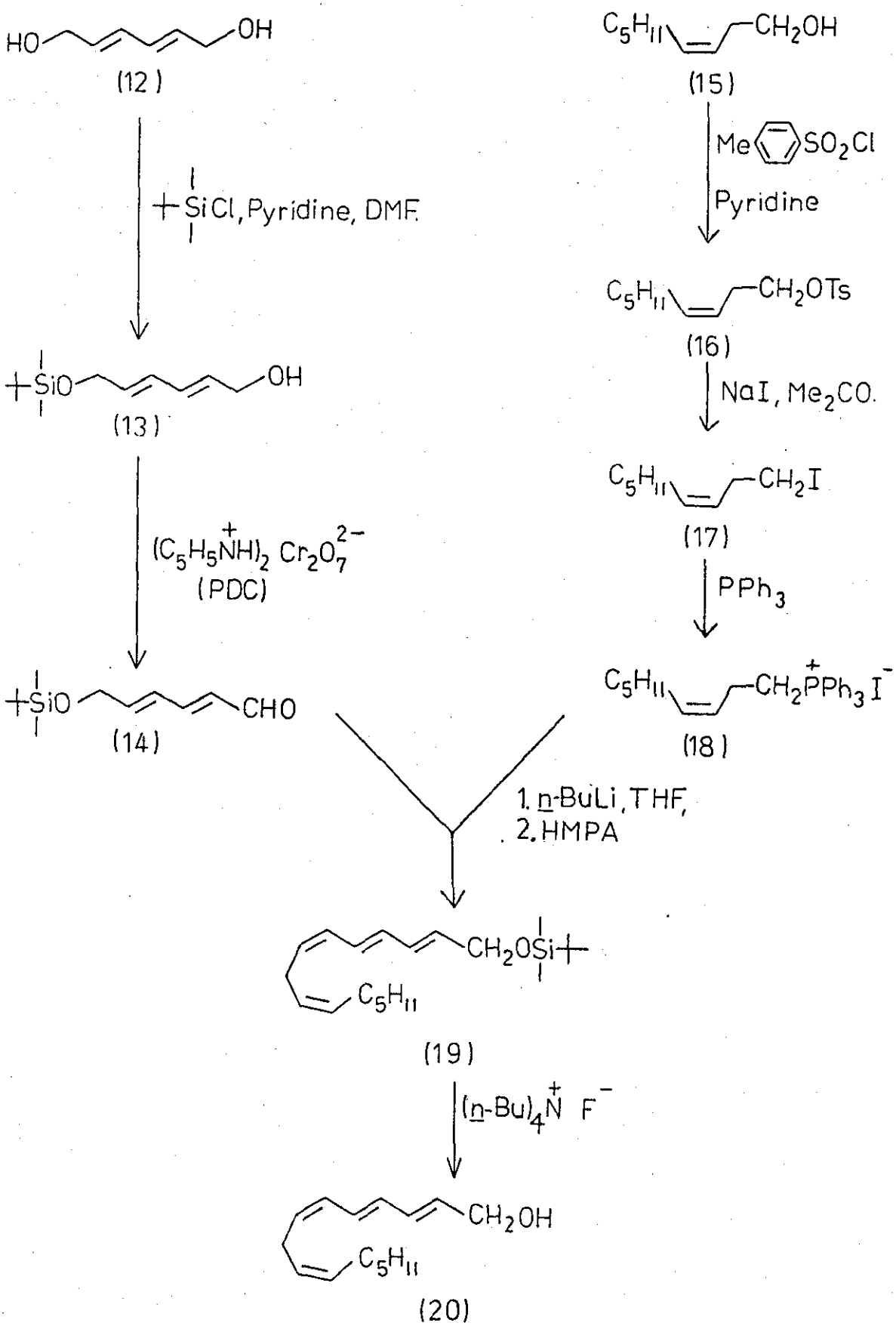

(11)

A route to racemic LTA methyl ester (11), described by Corey and his co-workers,[28] is outlined in scheme 4. The mono-tert.-butyldimethylsilyl ether (13)[44] of E-2,4-hexadiene-1,6-diol (12)[45] was converted to the aldehyde (14) by oxidation with pyridinium dichromate (PDC) in dichloromethane.[46] Z-3-Nonen-1-ol (15)[28,47] was converted to the tosylate (16) with p-toluenesulphonyl chloride and pyridine. Treatment of the tosylate (16) with sodium iodide gave the iodide (17) which on quaternisation with triphenylphosphine afforded the phosphonium salt (18).

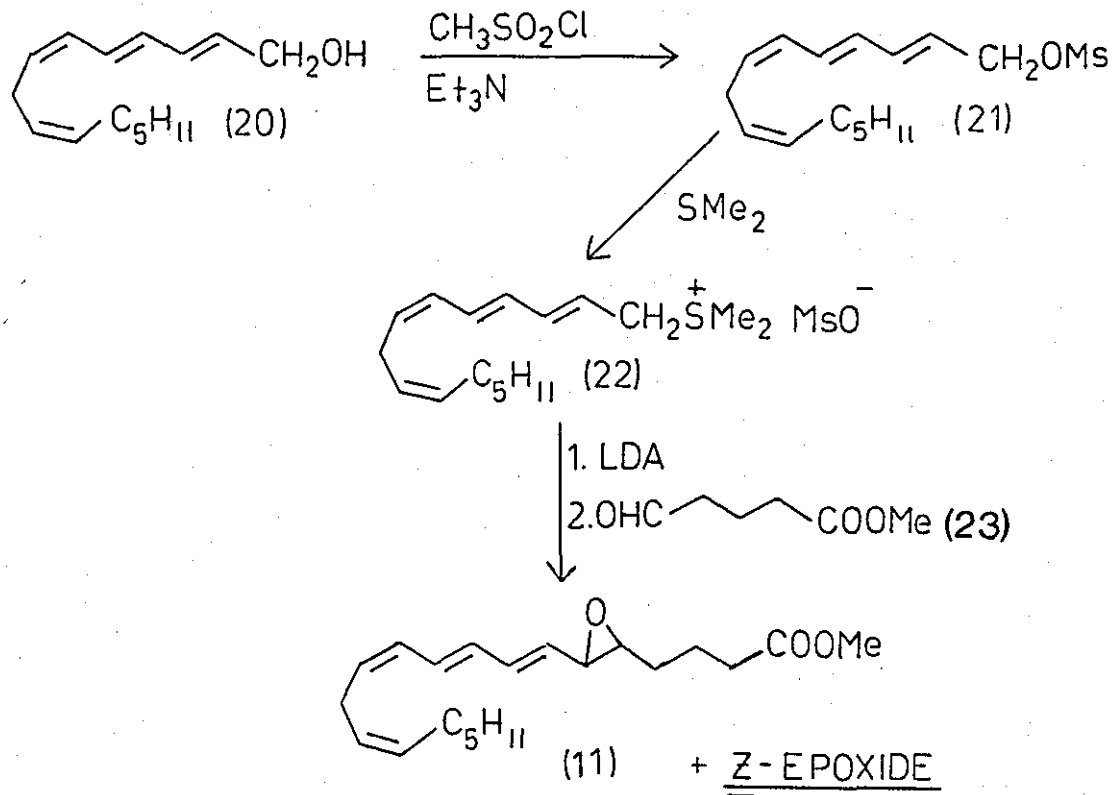
Reaction of the phosphonium salt (18) with n-butyllithium in tetrahydrofuran produced the corresponding ylid which was treated sequentially with hexamethylphosphoramide and the aldehyde (14) to give the tetraene silyl ether (19). Cleavage of the silyl ether with tetra-n-butylammonium fluoride[44] gave the tetraene alcohol (20).

The alcohol (20) was converted to racemic LTA methyl ester (11) by the sequence: a) conversion of the alcohol to the mesylate (21); b) treatment with dimethylsulphide; c) conversion of the resulting sulphonium salt (22) to the ylid with lithium diisopropylamide and d) treatment of the ylid with methyl 4-formylbutyrate (23).[48] Because of the high reactivity of the mesylate (21) and the sulphonium salt (22), these intermediates were not isolated but were prepared

SCHEME 4.


HO
OH
(12)
+SiCl, Pyridine, DMF
+SiO
OH
(13)
(C5H5NH)2 Cr2O7 2-
(PDC)
+SiO
CHO
(14)
C5H11
CH2OH
(15)
Me
SO2Cl
Pyridine
C5H11
CH2OTs
(16)
NaI, Me2CO.
C5H11
CH2I
(17)
PPh3
C5H11
CH2PPh3 I-
(18)
1. n-BuLi, THF,
2. HMPA
CH2OSi+
C5H11
(19)
(n-Bu)4N F-
CH2OH
C5H11
(20)

SCHEME 4 (Cont.).

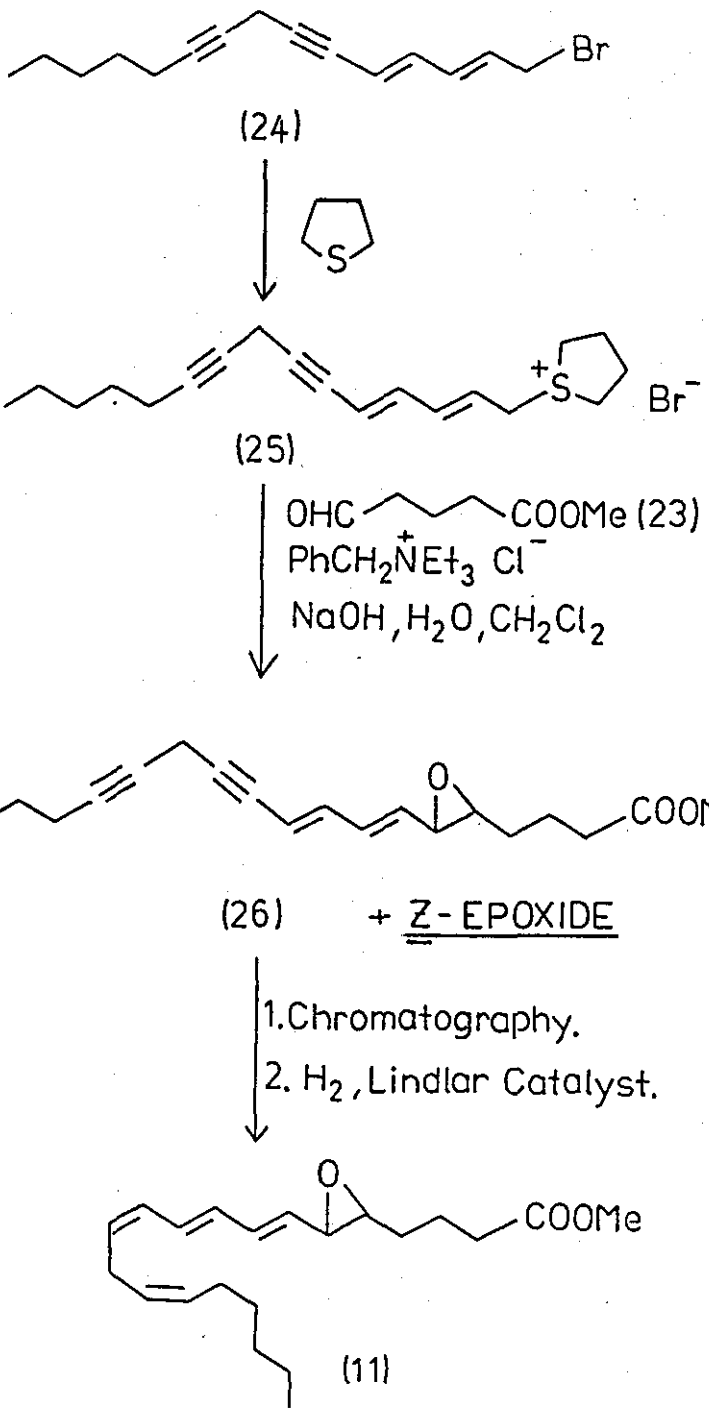



in situ. The epoxide was found (n.m.r. spectroscopy) to contain approximately equal amounts of racemic LTA methyl ester (11) and its 5,6-Z-isomer.[28,49]

Sulphonium ylids have also been employed in other routes to LTA methyl ester (11). Rosenberger and Neukom[50] (scheme 5) have prepared the sulphonium salt (25) of the bromide (24). Subsequent reaction with methyl 4-formylbutyrate (23)[48] in dichloromethane and aqueous sodium hydroxide using benzyltriethylammonium chloride as a phase transfer catalyst, gave the epoxide (26). The E-isomer was isolated by high pressure liquid chromatography (H.P.L.C.) and converted to racemic LTA methyl ester (11) by hydrogenation over Lindlar catalyst.

The first stereospecific synthesis of LTA methyl ester (11) was described by Corey et al. (scheme 6). The stereochemical control

SCHEME 5.


Br
(24)
S
+S
Br⁻
(25)
OHC
COOMe (23)
PhCH2N+Et3 Cl⁻
NaOH, H2O, CH2Cl2
O
COOMe
(26)
+ Z-EPOXIDE
1. Chromatography.
2. H2, Lindlar Catalyst.
O
COOMe
(11)

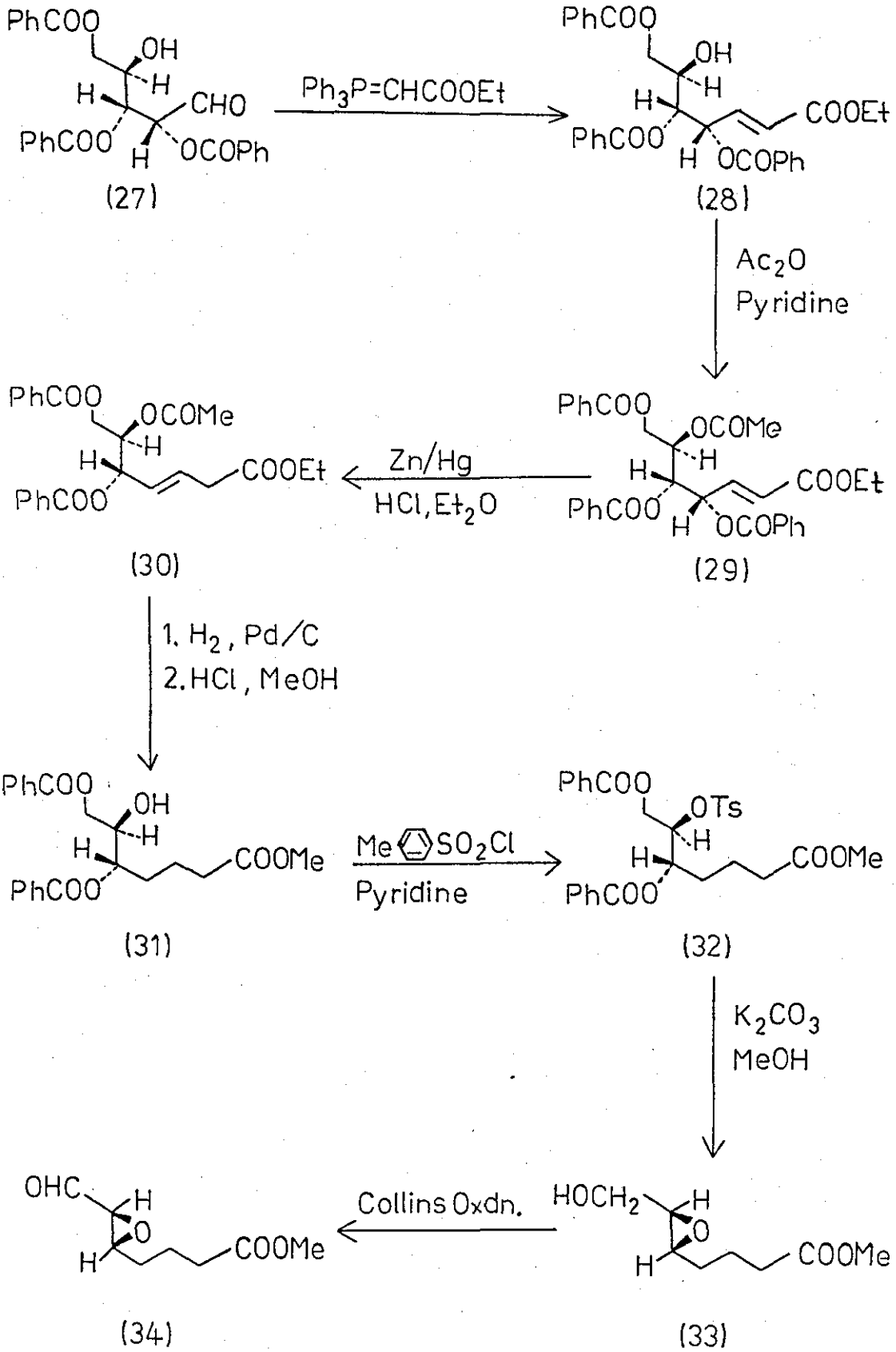
was obtained by the use of a D-(-)-ribose derivative as an optically active starting material.

Reaction of D-(- )-2,3,5-tribenzoylribose (27)[51] with ethoxycarbonylmethylenetriphenyl phosphorane[52] afforded the α,β-unsaturated ester (28) which was acetylated with acetic anhydride and sulphuric acid to give the acetate (29). Treatment of the acetate (29) with excess zinc amalgam and dry ethereal hydrogen chloride[53] gave the β,γ -unsaturated ester (30). The saturated hydroxy ester (31) was prepared by catalytic hydrogenation of the β,γ -unsaturated ester (30) followed by treatment with dry hydrogen chloride in methanol and was converted to the tosylate (32). Treatment of the tosylate (32) with potassium carbonate in methanol gave the 5(S),6(S)-E-epoxy alcohol (33), which was oxidised to the aldehyde (34) with Collins reagent.[54]

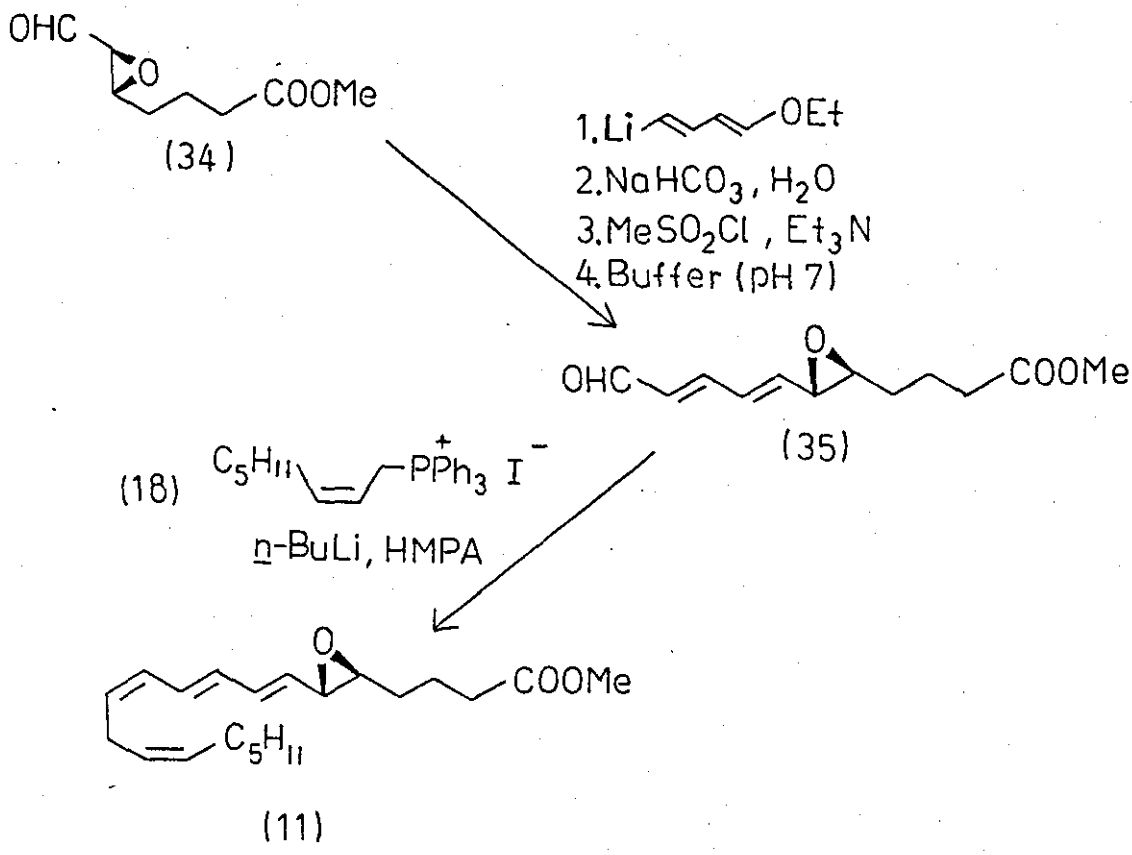
Reaction of the epoxy aldehyde (34) with 1-lithio-4-ethoxybutadiene[55] in tetrahydrofuran gave a secondary alcohol. This was treated, without purification, with methanesulphonyl chloride and triethylamine followed by phosphate buffer (pH 7), affording the dienal ester (35). The phosphorane derived from the phosphonium salt (18)[28] with n-butyllithium, was allowed to react with hexamethylphosphoramide and the aldehyde (35) giving LTA methyl ester (11).

A key intermediate in this synthesis is the 5(S), 6(S)-E-epoxy alcohol (33). This has also been prepared by shorter routes using the asymmetric epoxidation of Katsuki and Sharpless.[56] These workers found that a reagent produced from optically active diethyl tartrate, tert.-butylhydroperoxide, and titanium tetraisopropoxide effects epoxidation of allylic alcohols with a high degree of enantioselectivity.

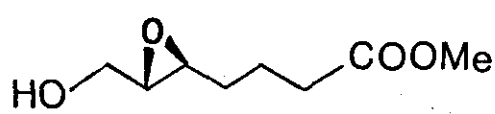
SCHEME 6.


PhCOO
OH
H
CHO
PhCOO
H
OCOPh
(27)
Ph3P=CHCOOEt
COOEt
(28)
Ac2O
Pyridine
OCOMe
(30)
Zn/Hg
HCl, Et2O
(29)
1. H2, Pd/C
2. HCl, MeOH
COOMe
(31)
Me
SO2Cl
Pyridine
OTs
(32)
K2CO3
MeOH
OHC
(34)
Collins Oxdn.
HOCH2
(33)

SCHEME 6 (Cont.)

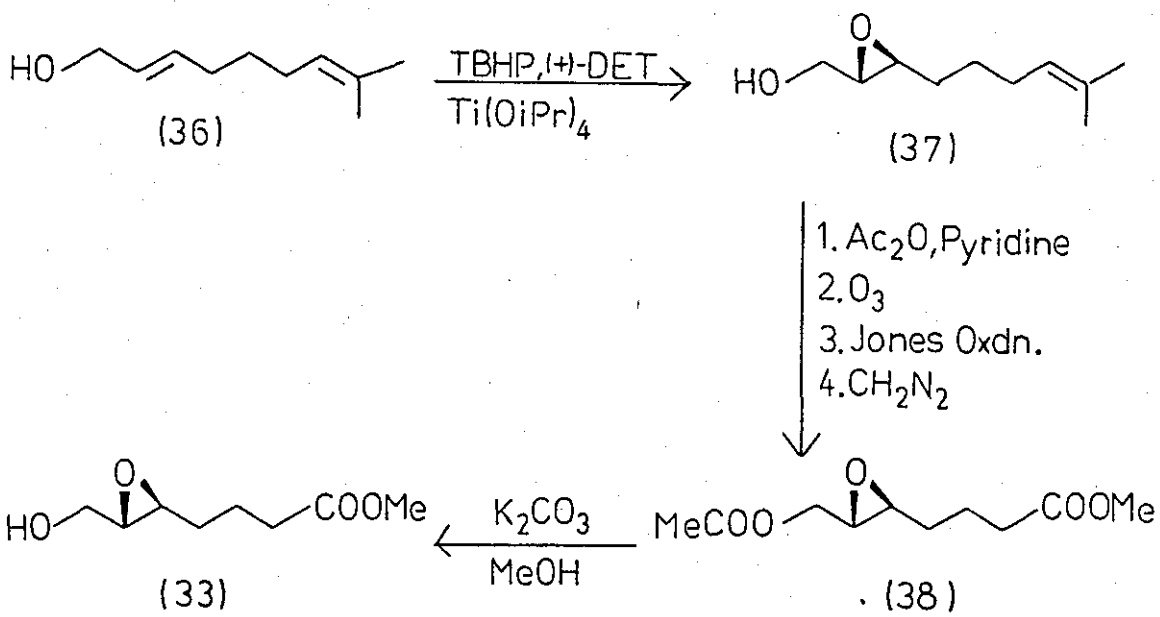



These conditions were used by Corey et al.[57] (Scheme 7) for the conversion of E-8-methyl-2,7-nonadien-1-ol (36) to the epoxide (37). Acetylation of the epoxide (37), ozonolysis of the acetate, Jones oxidation,[58] and esterification gave the epoxy acetate (38). Deacetylation with potassium carbonate in methanol gave the required 5(S), 6(S) -E-epoxy alcohol (33).




(33)

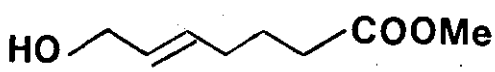
SCHEME 7.




TBHP = Tert.-Butyl hydroperoxide.

DET = **Diethyl tartrate**

Attempts by the same workers[57] to prepare the alcohol (33) directly by asymmetric epoxidation of E-methyl-7-hydroxy-5-heptenoate (39) were unsuccessful. However, Sharpless et al.[59] using (+) - diisopropyltartrate and a modified work up have achieved this conversion.

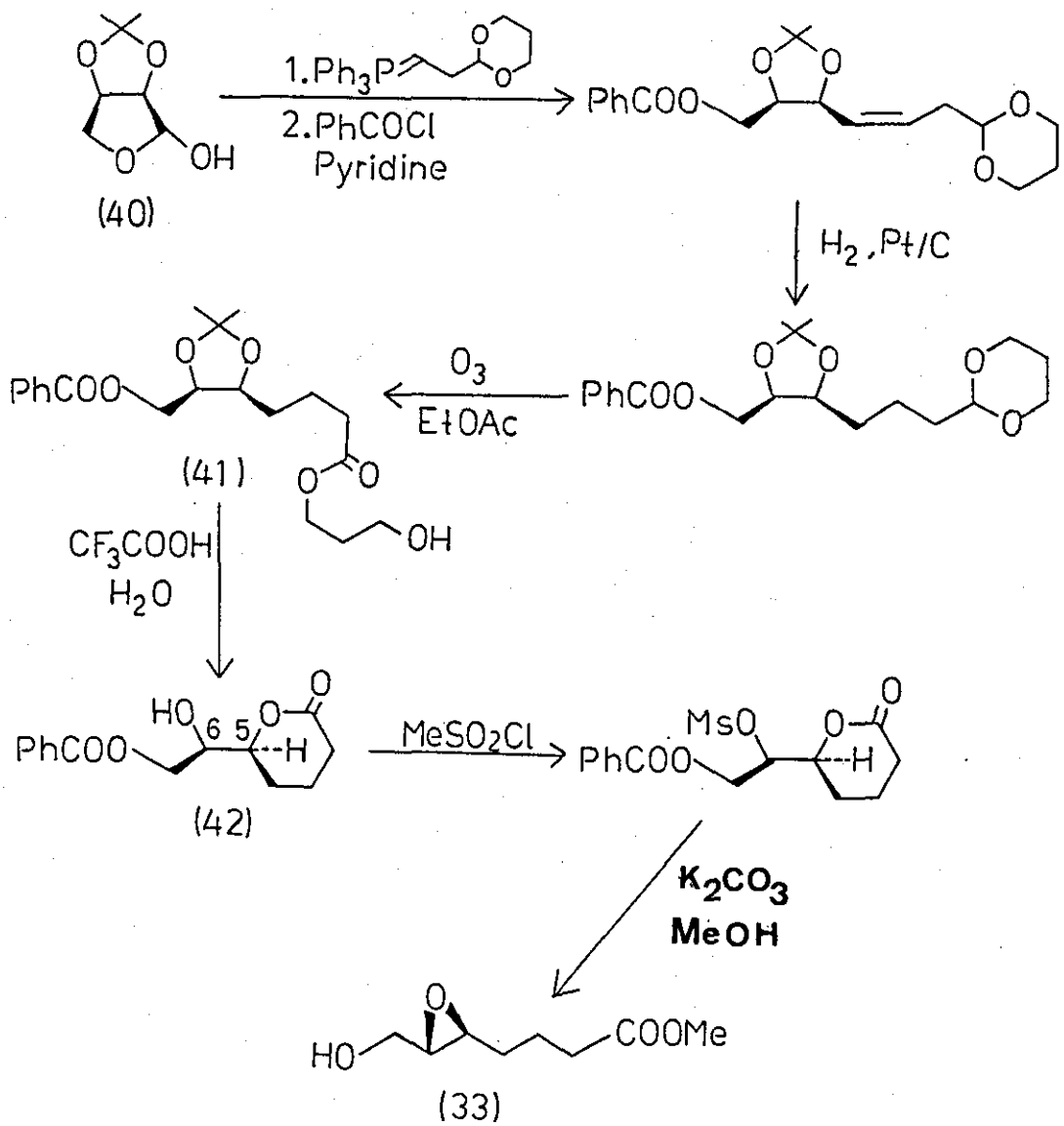



**(39)**

Another important synthesis of the alcohol (33) was described by Cohen et al.[60] (scheme 8). This route involves the use of 2,3-O-isopropylidene erythrose (40)[61] as the starting material. An interesting

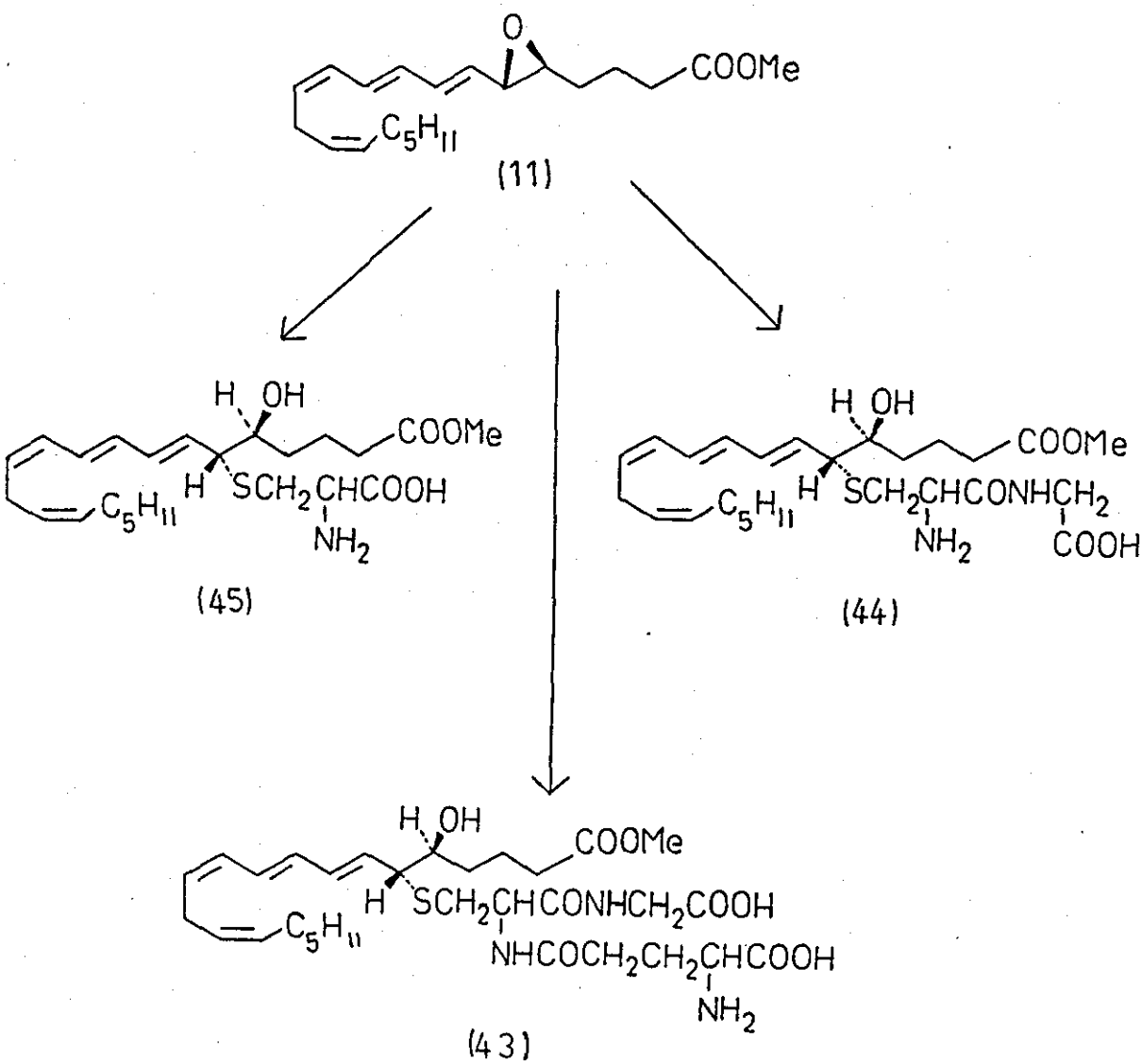
feature of this synthesis is the conversion of the isopropylidene ester (41) to the hydroxy lactone (42). In this process lactone formation differentiates the hydroxyl groups at C-5 and C-6 leaving the 6-hydroxyl free to form a suitable leaving group.

SCHEME 8.

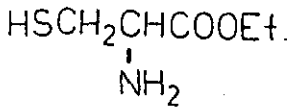


Treatment of LTA methyl ester (11) with cold aqueous base has produced solutions of LTA (6), as the sodium salt, which were reconverted to the methyl ester with dimethylsulphate.[28] Acid hydrolysis,[28] gave similar mixtures of LTB (3) and its isomers (4) and (5), (as the methyl esters) to those obtained from PMNL on stimulation with ionophore A23187.[20,21]

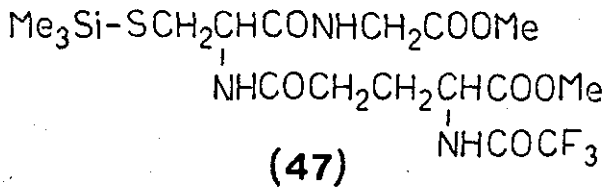
SCHEME 9.



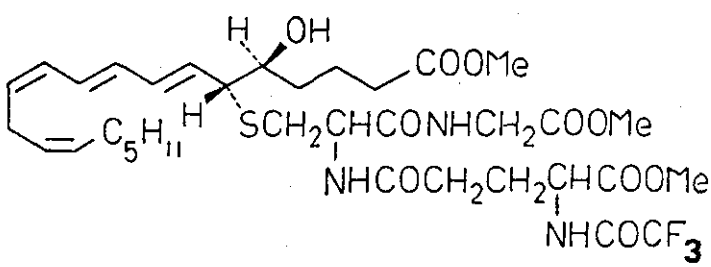
The conversion of LTA methyl ester (11) to the other members of the leukotriene family has been studied by several groups. Corey et al.[29] (scheme 9) prepared the methyl esters of LTC (43), LTD (44) and LTE (45) by treatment of LTA methyl ester (11) with the required amino acid or peptide and triethylamine in a minimum of methanol. Subsequent ester hydrolysis gave the corresponding leukotrienes. Rosenberger et al.[50] have also prepared LTE (9) by a similar procedure using cysteine ethyl ester (46) as the thiol species.



(46)



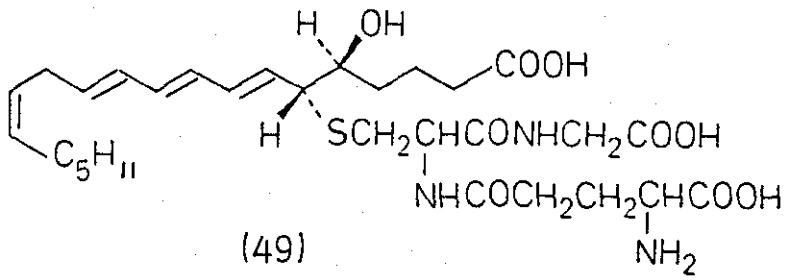
(47)



(48)

An alternative route to LTC (7) was described by Rokach et al.[62]. This involves the use of a trimethylsilylthio ether as a stereoselective reagent for the formation of the β-hydroxy thio ether group.[63]

A mixture of racemic LTA methyl ester (11) and its 5,6-Z isomer was prepared, via a similar route to that described by Corey,[28] and the epoxides separated by H.P.L.C.. Treatment of the E-epoxide with S-trimethylsilyl-N-trifluoroacetyl glutathione dimethyl ester (47) gave a mixture of the two erythro diastereoisomers of the protected LTC derivative (48). Separation of the diastereoisomers by H.P.L.C. followed by basic hydrolysis gave LTC (7).




(49)

LTC (7), LTD (8), and LTE (9), when isolated from natural sources, were found to contain minor amounts of the corresponding 11-E-isomer.[27,41,42] The 11-Z-geometry has been found to be important for biological activity[42] and therefore these isomers probably play little part in the physiological actions of the leukotrienes. The 11-E-isomer of LTC (49) has been prepared,[64] as have various other double bond isomers, by routes analogous to those used for the leukotrienes themselves.[29,65,66]

In summarising the synthetic approaches to the leukotrienes, the synthesis of LTA methyl ester (11) and in particular, the introduction of the 5,6-epoxide function seem to be the key features of the various routes available. The use of sulphonium ylids suffers from the

inherent disadvantage that the products contain racemic mixtures of both E- and Z-epoxides. This leads to the need for separation of the epoxide geometric isomers and the diastereoisomers of products derived from subsequent reactions. The problems of the 5,6-stereochemistry have been overcome by the use of optically active sugars as starting materials. However, these procedures are lengthy and therefore it would appear that asymmetric epoxidation offers the most advantageous routes to the leukotrienes.

The information available on the biological significance of SRS-A, clearly indicates an important role in immediate hypersensitivity reactions (reviewed in ref. 8). This information is based on studies performed before the identification of these agents as leukotrienes. The elucidation of structure and the availability of pure synthetic material should aid the clarification of this information and may provide a clue to the treatment of certain pathological conditions including allergy, anaphylaxis, and asthma.

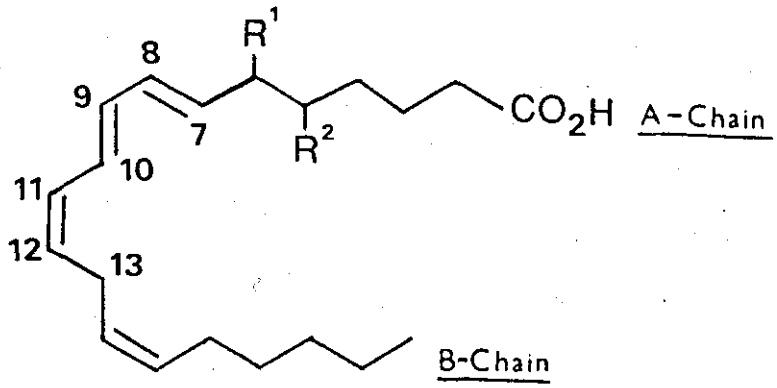
## 1.2 THE OPENING OF β-ALKYLSTYRENE OXIDES IN RELATION TO THE PREPARATION OF LEUKOTRIENE ANALOGUES

The unusual fatty acid-peptide (amino acid) combination in the structure of the leukotrienes involved in SRS-A activity, provides several areas which could be exploited in the preparation of analogues. The triene containing hydrocarbon chain is one of these possibilities and is the one which we chose to investigate. It was our intention to replace this portion of the molecule with a system containing an aromatic species.

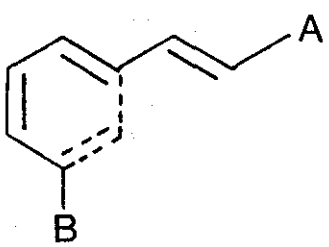
Several aromatic species can be envisaged as possible replacements for the triene system of the leukotrienes. These can be compared by considering the generalised leukotriene structure (50). For the purposes of this comparison, the 7, 9, 11-triene will be considered the nucleus of the molecule with the carbons 1-6 termed the A-chain and the carbons 14-20 the B-chain.

The structure (51) illustrates the possibility of using a 3-substituted styrene system as a replacement for the triene. In analogues of this type, the benzene ring replaces the 9,11-diene with the A-chain being attached to the equivalent of the 7,8-double bond in the leukotrienes. The styrene (52) shows a reversal of this situation with the aromatic nucleus replacing the 7,9-diene. The A-chain is attached to the benzene ring and the B-chain to the external double bond.

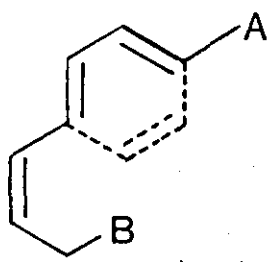
The inclusion of an aromatic nucleus could be extended by the use of a 2,7-disubstituted naphthalene of the type (53). In this case the naphthalene replaces the entire triene system with the A and B chains attached to the 2 and 7 positions respectively. This could be extended



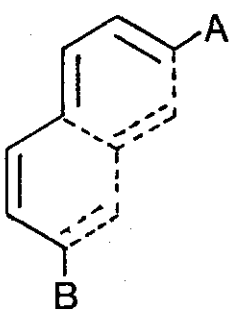

(50)



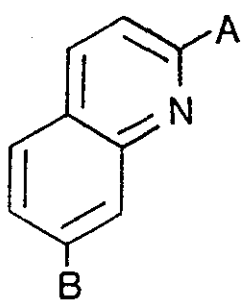

(51)



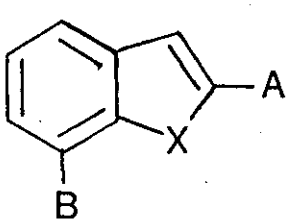

(52)



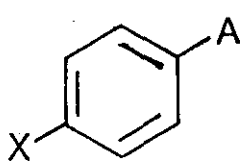

(53)




(54)




(55)

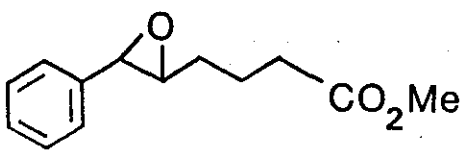



(56)

further by the inclusion of a heterocyclic system. The structures (54) and (55) illustrate some possible examples.

Another possible way of introducing a hetero atom is represented by the 1,4-disubstituted benzene (56). The A-chain would be attached as shown in the styrene (52) but the B-chain and $\Delta^{11}$ bond would be replaced by a group containing a hetero atom. An interesting feature of this possibility is that in the simplest form (56, R = H), the hetero atom could provide a "handle" for the introduction of a wide range of substituents.

The observations of Austen et al.,[67] concerning the deactivation of SRS-A preparations by arylsulphatases, lends some support to this approach. The arylsulphatases are a class of enzymes which cleave sulphoester linkages from benzene and other unsaturated ring systems. The significance of these enzymes in the control of SRS-A activity is not fully understood.[9] Analogues containing an aromatic species may help to clarify the position held by the arylsulphatases in SRS-A and leukotriene metabolism.

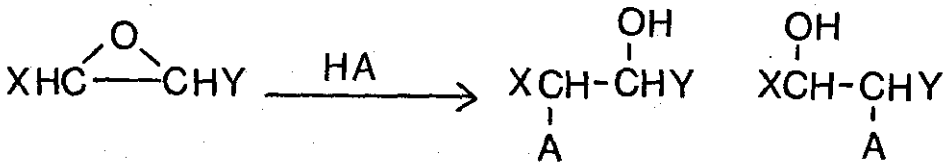



(57)

The simplest aromatic system which could be introduced is a phenyl ring. This seemed an obvious starting point for model studies leading to compounds of the types previously described. Since the synthetic routes to the leukotrienes involve the use of LTA methyl ester (11) as an intermediate (see section 1.1.6), the epoxide (57) could be used in a similar way in the preparation of analogues

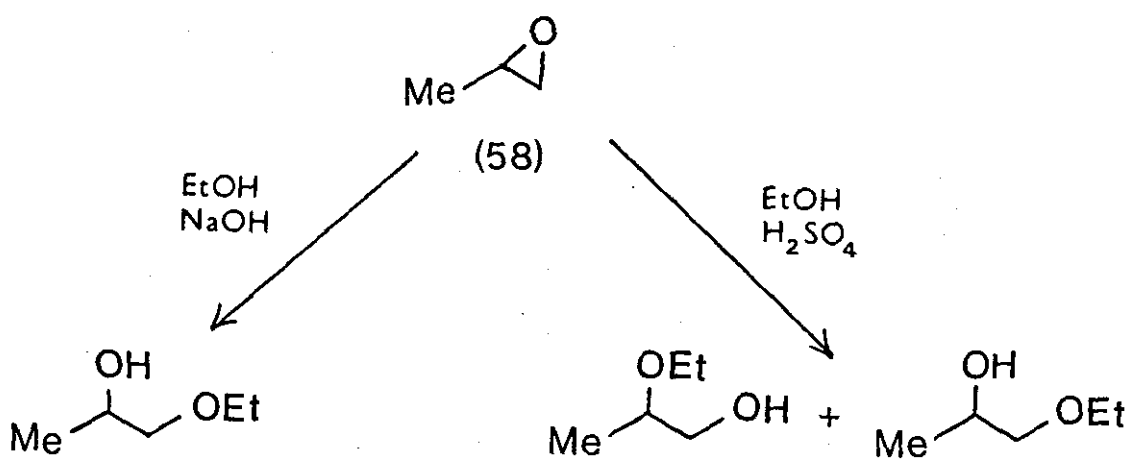
containing a phenyl ring. The conversion of the epoxide (57) to analogues of the sulphur containing leukotrienes (e.g. LTC) would involve the addition of a thiol compound to a β-alkylstyrene oxide. The remainder of this section contains a general discussion of the orientation and mechanism of nucleophilic openings of unsymmetrical epoxides, with special reference to β-alkylstyrene oxides.

SCHEME 10




In general nucleophilic additions to unsymmetrical epoxides can lead to two possible regioisomers derived from attack at either carbon of the epoxide ring (scheme 10). The orientation of ring opening can be related to three main substituent effects: steric, polar, and conjugative.[68]

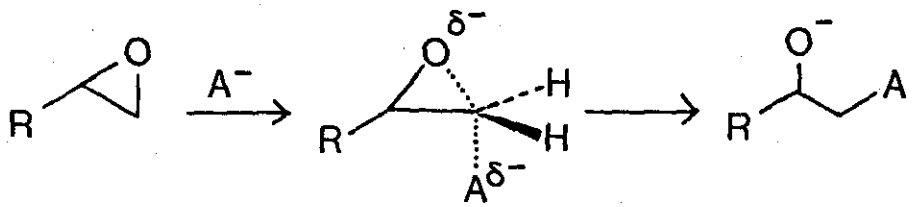
SCHEME 11




The reactions of alkyl substituted epoxides under basic or neutral conditions are mainly governed by steric factors.[68] This is illustrated by the reaction of propylene oxide (58) with ethanol and sodium

hydroxide (scheme 11).[69] This reaction gave only the product derived from attack at the unsubstituted carbon, providing strong evidence for an $S_N2$ type mechanism (scheme 12) involving the transition state (59). These processes are well known to be sensitive to steric hindrance.

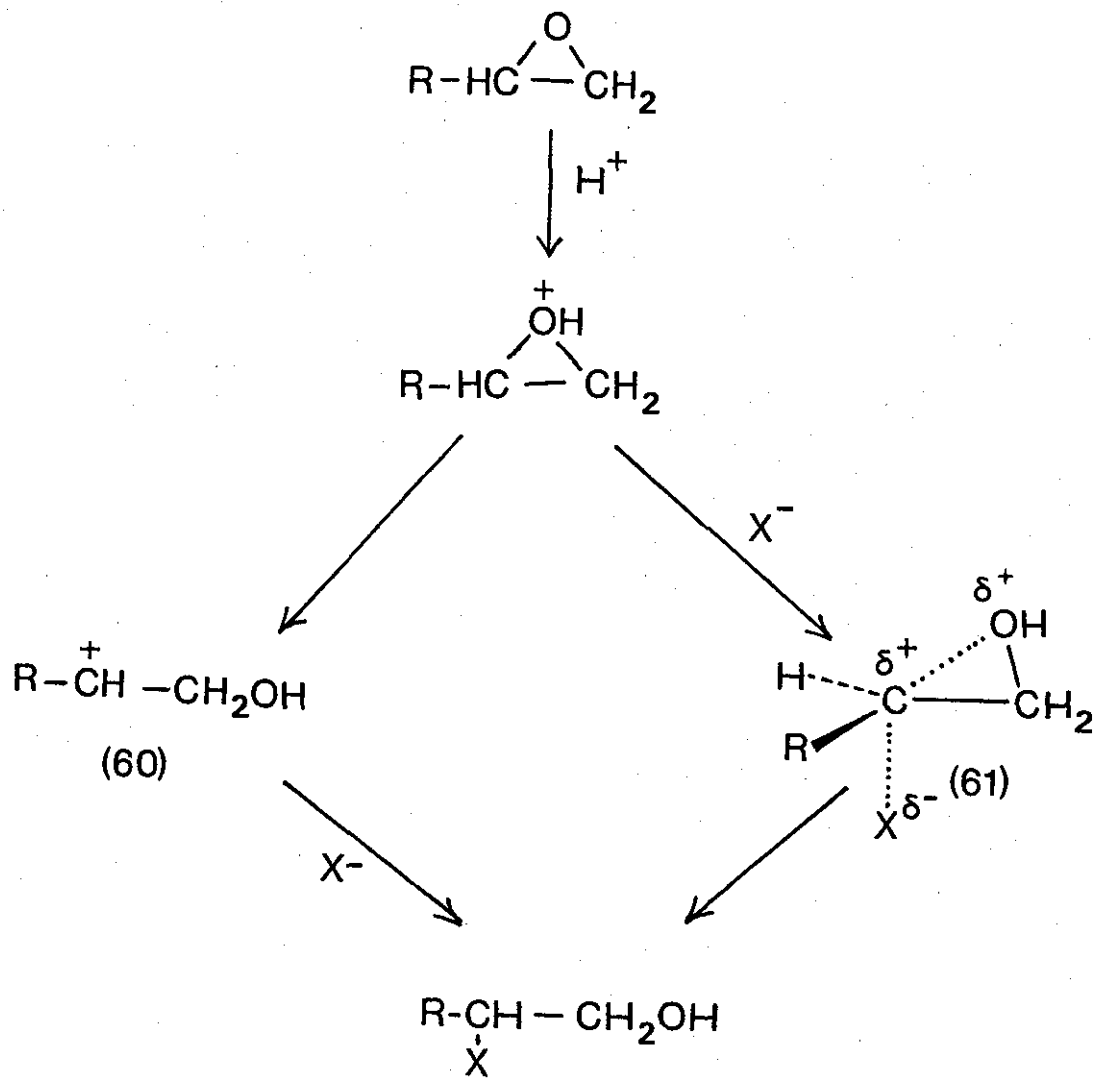
SCHEME 12




(59)

Under acidic conditions, reactions of this type show a marked tendency toward the formation of products derived from attack at the substituted carbon. The reaction of propylene oxide (58) with ethanol and sulphuric acid (scheme 11) was shown to give a mixture of the two possible regioisomers.[69] This observation cannot be explained strictly on steric grounds, and it is necessary to take into account the inductive electron releasing effect of the alkyl group. An effect of this type can stabilise a positive charge on the adjacent carbon. Two possible mechanisms are consistent with the formation of such a charge.[70]

SCHEME 13

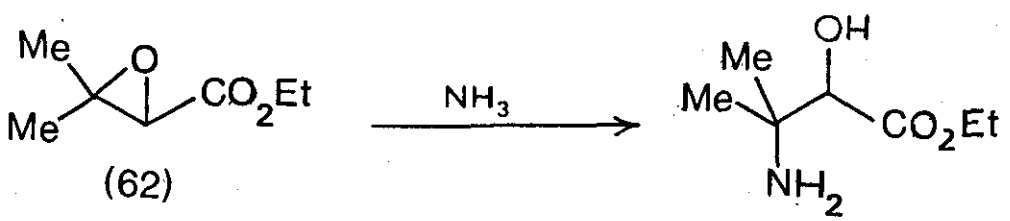



The first is the A1 mechanism (scheme 13) which involves the formation of a carbocation (60). This mechanism is unlikely because the entering nucleophile usually leads to inversion of configuration at the point of attack.[68,70] This inversion provides strong evidence against the formation of a carbocation since an intermediate of this type would be expected to give rise to a mixture of stereoisomers. Also, it can be seen in the addition of ethanol with propylene oxide (58) under acid conditions (scheme 11), that the reaction is still subject to a certain amount of steric hindrance. This observation is also inconsistent with an A1 mechanism.

The second possible mechanism is an A2 type mechanism in which bond breaking is more advanced than bond formation. In this case the partial bonds of the transition state (61) are longer, than in the case of an ordinary $S_N2$ mechanism, and the central carbon possesses a certain amount of carbocation character.[68] This is sometimes referred to as a "borderline" or modified $S_N2$ mechanism.[68,70] The fractional positive charge on carbon can be stabilised by electron release from an alkyl group in the same way as in an A1 process. However, unlike A1 or $S_N1$ reactions, this mechanism will be subject to a certain amount of steric hindrance although to a smaller extent than in an ordinary $S_N2$ process.[68]

The modified $S_N2$ mechanism is supported by evidence from the openings of epoxides containing polar electron withdrawing groups. In these cases addition usually occurs at the carbon remote from the polar group even when this carbon is subject to considerable steric hindrance and the reactions are performed under basic or neutral conditions. The reaction of ethyl 2,3-epoxy-3-methylbutanoate (62) with ammonia (scheme 14)[71] illustrates this type of behaviour.

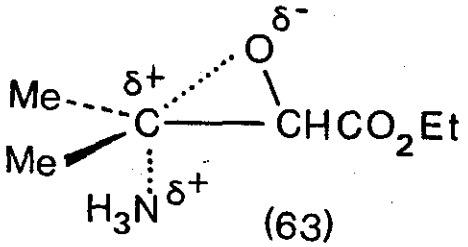
SCHEME 14




(62)

Since an electron withdrawing group facilitates the approach of a nucleophile but inhibits bond breaking, it seems likely that the mechanism involved is an $S_N2$ type in which bond breaking is more important than bond formation (i.e. modified $S_N2$). This process could conceivably proceed via a transition state (63) in which the

central carbon carries a fractional positive charge.[68]



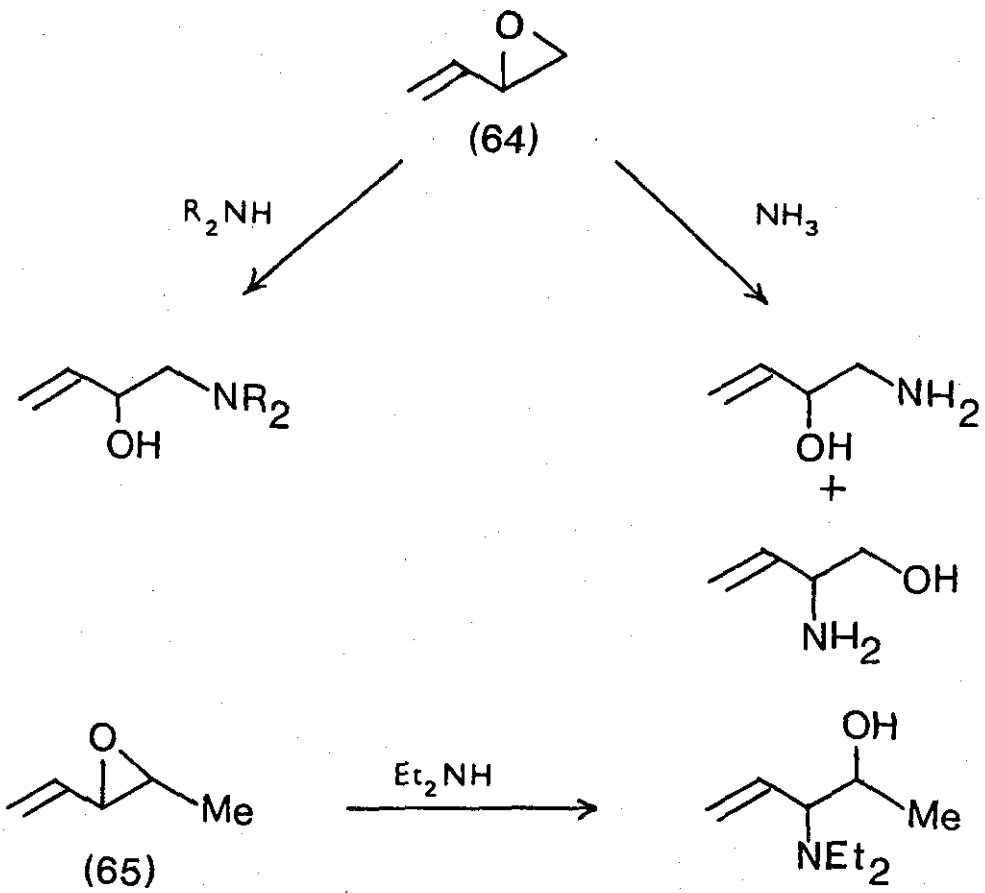

(63)

Substituents which can stabilise a positive charge by conjugated electron release from a π-orbital or an atomic p-orbital have profound effects. These include a carbon-carbon double bond, a carbon-carbon triple bond, a benzene ring, and an alkoxy group. Conjugating groups usually favour attack at the adjacent carbon under both basic and neutral conditions, and even more so under acid conditions. These groups also possess steric effects which will tend to direct attack away from the adjacent carbon. Therefore the orientation of the epoxide opening will depend on a balance of these two opposing effects.

Scheme 15 shows the reaction of 3,4-epoxybutene with secondary amines[72] and ammonia.[73] It can be seen that secondary amines attack only at the unsubstituted carbon whereas ammonia gives products from attack at both carbons. This may be due to the greater steric bulk of the secondary amine.[68]

This situation is reversed in the reaction of 3,4-epoxypentene (65) with diethylamine.[74] This reaction gives only the product derived from attack at the carbon adjacent to the conjugating group. Presumably the added steric effect of the methyl group is responsible for directing the attack away from the carbon adjacent to it. Therefore it appears that when both carbons of the epoxide ring are substituted with groups of approximately the same size, the conjugating effect is decisive.[68] Triple bonds appear to influence epoxide

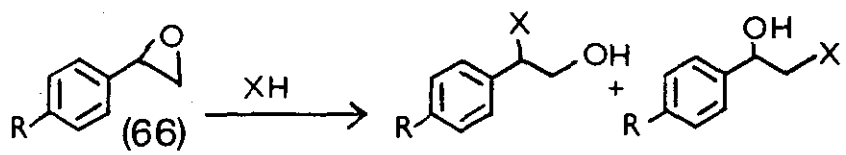
SCHEME 15




openings in a similar manner.[68]

TABLE 1

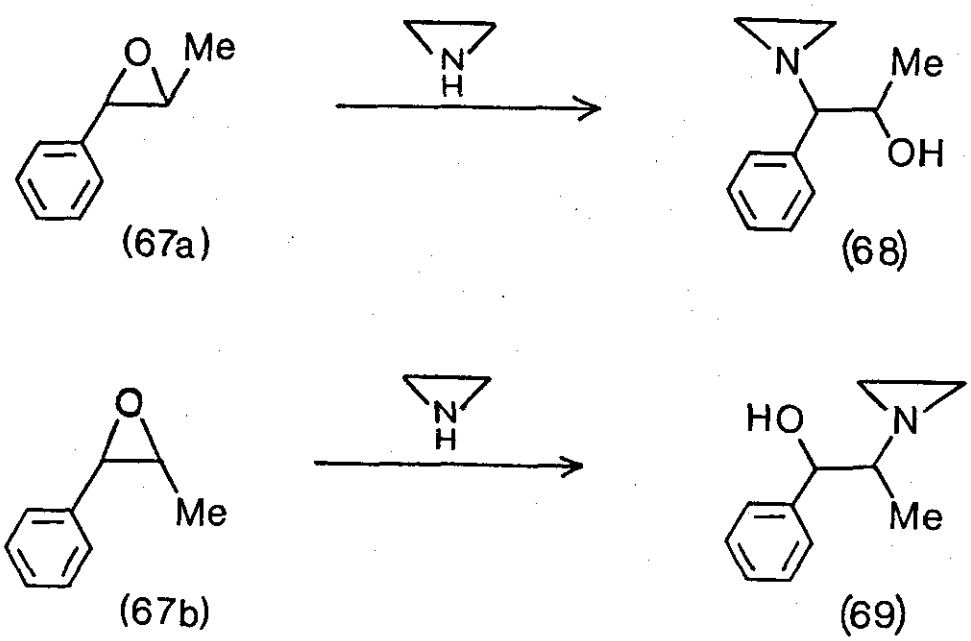
REACTIONS OF NUCLEAR SUBSTITUTED STYRENE OXIDES WITH NUCLEOPHILES




| R | X | % | % | REF. |
|---|---|---|---|---|
| $NO_2$ - | PhO - | 36 | 64 | 75 |
| H - | PhO - | 76 | 24 | 75 |
| MeO | PhO - | 100 | 0 | 76 |
| Br - | $PhCH_2NH$ - | 19 | 81 | 77 |
| H - | $PhCH_2NH$ - | 22 | 78 | 77 |
| Me - | $PhCH_2NH$ - | 55 | 45 | 77 |
| $NO_2$ - | PhS - | 33 | 67 | 78 |
| H - | PhS - | 50 | 50 | 78 |
| MeO - | PhS - | 80 | 20 | 78 |

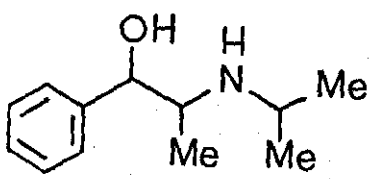
The benzene ring is another example of a conjugating substituent. Table 1 shows the results of the reactions of p-substituted styrene oxides (66) with various nucleophiles. These results indicate that an electron withdrawing group decreases and an electron donating group increases the amount of attack at the carbon adjacent to the benzene ring ( α-carbon). Therefore, it appears that the aryl ring is exerting a specific conjugative effect, which is consistent with a modified $S_N2$ mechanism for attack at the α-carbon. These results also show that the phenyl ring exerts a steric effect which opposes the conjugative effect and, in most cases, leads to mixtures of products.

SCHEME 16

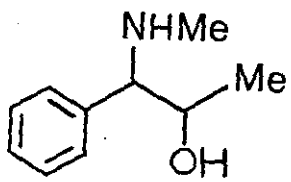



Considering the result obtained for the reaction of 3,4-epoxypentane (65) with diethylamine ( scheme 15) it might be expected that β-alkylstyrene oxides would follow a similar pattern. Funke and Benoit[79] found that the reaction of E-β-methylstyrene oxide (67a) with ethylenimine ( scheme 16) gave the expected regioisomer (68). Fischer and Rönsch[80] observed the same result for the E-epoxide (67a) but found that the Z-epoxide (67b) gave the alternative regioisomer (69).

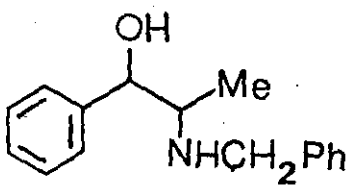
These findings are supported by those in the reactions of E- and Z-β-methylstyrene oxides (67) with other amines. Villa et al.[81] isolated the β-amino alcohol (70), as the major product, from the reaction of the Z-epoxide (67b) with isopropylamine. Also, Bodendorf and Dettke [82] found that the E-epoxide (67a) gave mainly the amino alcohol (71) on treatment with methylamine. An unusual result was obtained by Parker and Rockett.[83] These workers found that reaction of the E-epoxide (67a) with benzylamine gave mainly the amino alcohol (72). Therefore it appears that the electronic and steric effects in the β-methylstyrene oxides (67) are finely balanced and predictions of regioselectivity would seem to be somewhat difficult. However, the general trend of amine addition to β-methylstyrene oxides (67) appears to be that attack on the E-isomer usually occurs preferentially at the α-carbon and the Z-isomer shows a greater tendency towards attack at the β-carbon.




(70)




(71)




(72)

The additions of simple thiols to styrene oxide and some of its nuclear substituted derivatives have been reported (table 1).[78] However, there are no examples of similar additions to β-alkylstyrene oxides and taking into account the results discussed above, it was of obvious interest to investigate the regioselectivity of such reactions.

Therefore the aims of our work were threefold: 1) to investigate the synthesis of the epoxide (57) as an example of an LTA analogue containing a phenyl ring; 2) to study the reactions of β-methylstyrene oxides with thiols as models for similar reactions of the epoxide (57); and 3) to attempt the opening of the epoxide (57) with cysteine (or a derivative) in order to prepare analogues of other leukotrienes.

## 2. DISCUSSION

## 2.1 THE PREPARATION AND THIOL OPENING OF β-METHYLSTYRENE OXIDES

The regiochemistry of the reactions of E and Z-β-methylstyrene oxides and their 4-methoxy derivatives with thiophenol and, in some cases, benzylthiol were investigated. The reactions were performed under similar conditions to those described by Corey[29] in the synthesis of LTC. This involved reaction of the epoxide with thiol (3 equivalents) and triethylamine (4 equivalents) in a minimum of methanol. Products were isolated by preparative thin layer chromatography (p.t.l.c.), and the regioselectivity of epoxide opening determined from the $^1$H n.m.r. and mass spectra.

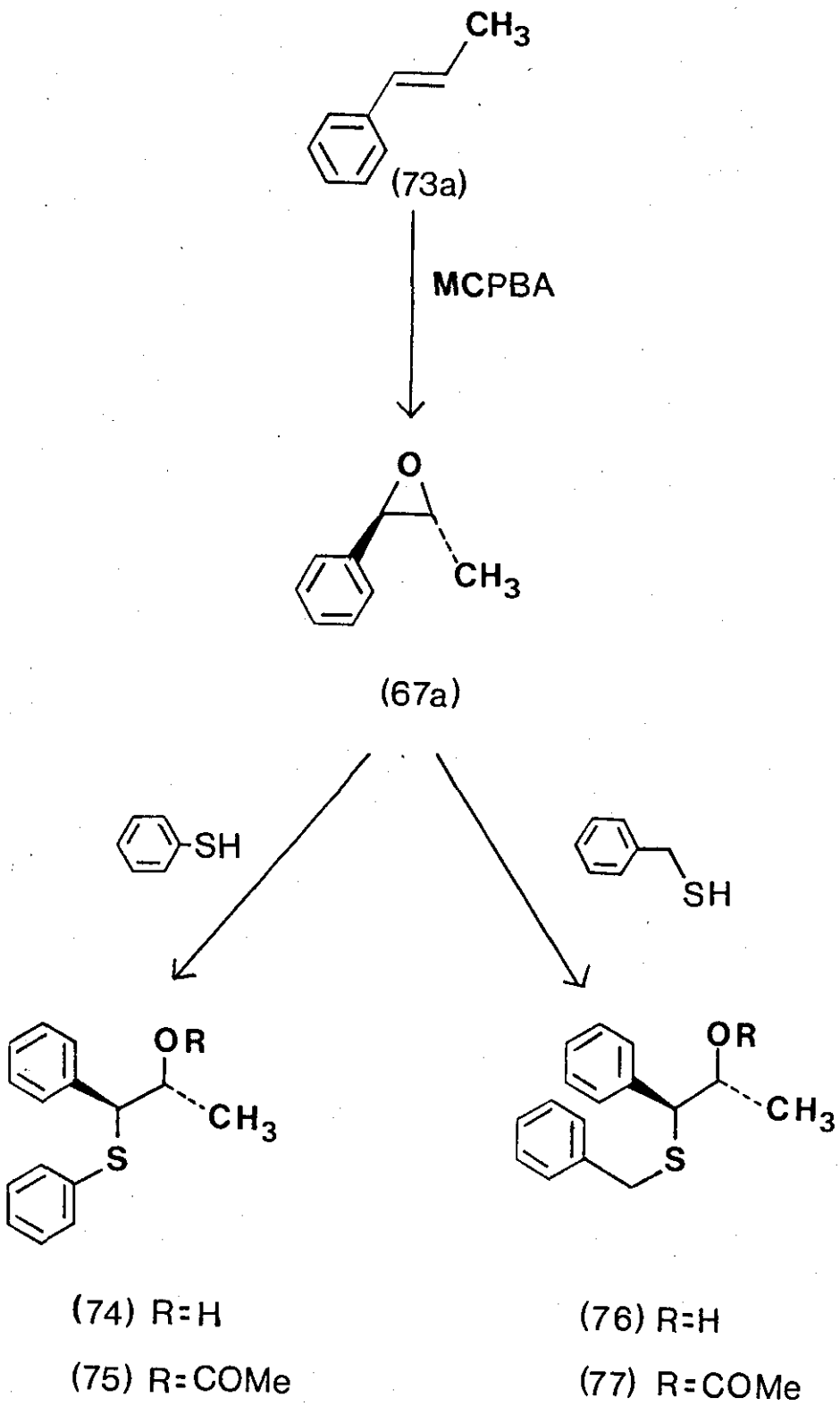
### 2.1.1 E-β-METHYLSTYRENE OXIDE

E-β-Methylstyrene oxide (67a) was prepared from the commercially available E-β-methylstyrene (73a) by a standard procedure using m-chloroperoxybenzoic acid (MCPBA) in dichloromethane[84] (scheme 17).[85] The product gave satisfactory i.r., $^1$H n.m.r., and mass spectra.[86]

Reaction of the E-epoxide (67a) with thiophenol gave a single racemic product after p.t.l.c. on silica. The presence of a hydroxyl group was shown by the i.r. spectrum (3500 $cm^{-1}$).[87] The $^1$H n.m.r. spectrum showed bands at δ 7.45-7.10 (m, 10H), 3.96-4.30 (m, 2H), 2.50 (bs, exchangeable with $D_2O$, -OH), and 1.20 (d, $-CH_3$). The mass spectrum showed a weak molecular ion at m/e 244.0922, a base peak at m/e 200.0664, and a major peak at m/e 199.0593 (85%).

The $^1$H n.m.r. and i.r. spectra indicated that ring opening had taken place, however the regiochemistry of this opening was unclear. The peaks at m/e 200 and 199 in the mass spectrum corresponded to the

SCHEME 17.




(74) R=H

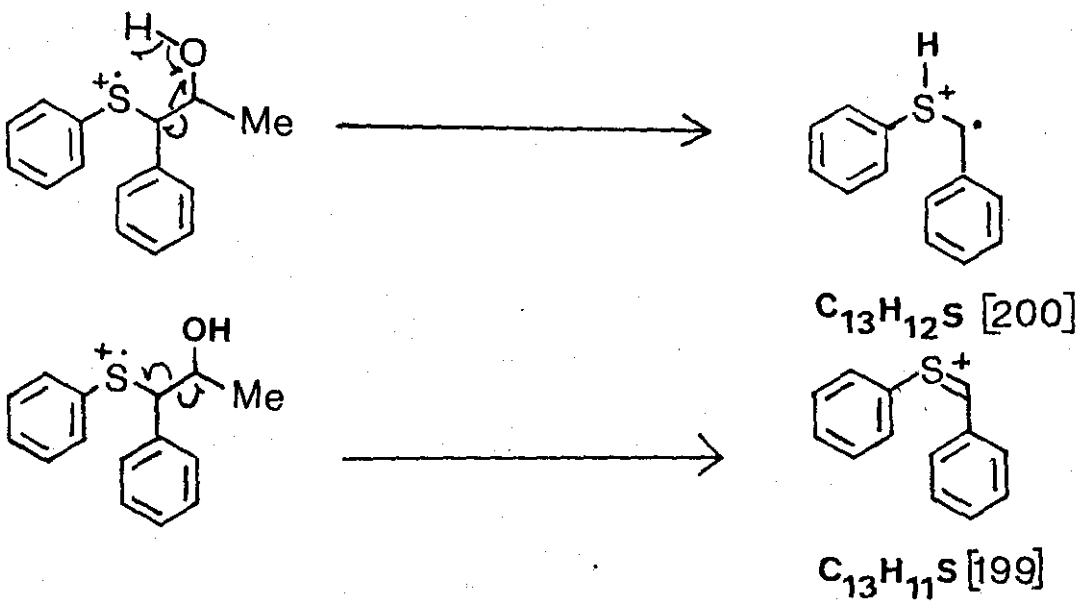
(75) R=COMe

(76) R=H

(77) R=COMe

formulas $C_{13}H_{12}S$ and $C_{13}H_{11}S$ respectively. These peaks were thought to arise from the fragmentations shown in scheme 18[88] and indicated that the sulphur was attached to the α-carbon. Therefore the structure of the single racemate obtained from the reaction of the E-epoxide (67a) with thiophenol was assigned as erythro-2-hydroxy-1-phenyl-1-(phenylthio) propane (74).

SCHEME 18




$C_{13}H_{12}S$ [200]

$C_{13}H_{11}S$ [199]

The assignment of structure was confirmed by comparison of the spectral data obtained for the erythro-α-sulphide (74) and its acetoxy derivative (75) prepared from (74) by treatment with acetic anhydride and pyridine. The i.r. spectrum of the acetate (75) showed characteristic bands (1740, 1240 $cm^{-1}$)[87] and the mass spectrum showed a molecular ion at m/e 286, a major peak at m/e 199, and a base peak at m/e 43. The $^1$Hn.m.r. spectrum showed bands at δ 5.30 (d of q, -CH-Me), 4.26 (d, -CH-Ph) and 1.30 (d, $-CH_3$). Double irradiation of this spectrum at δ 1.30 reduced the doublet of quartets at δ 5.30 to a doublet, confirming the assignment of this signal to the β-CH proton.

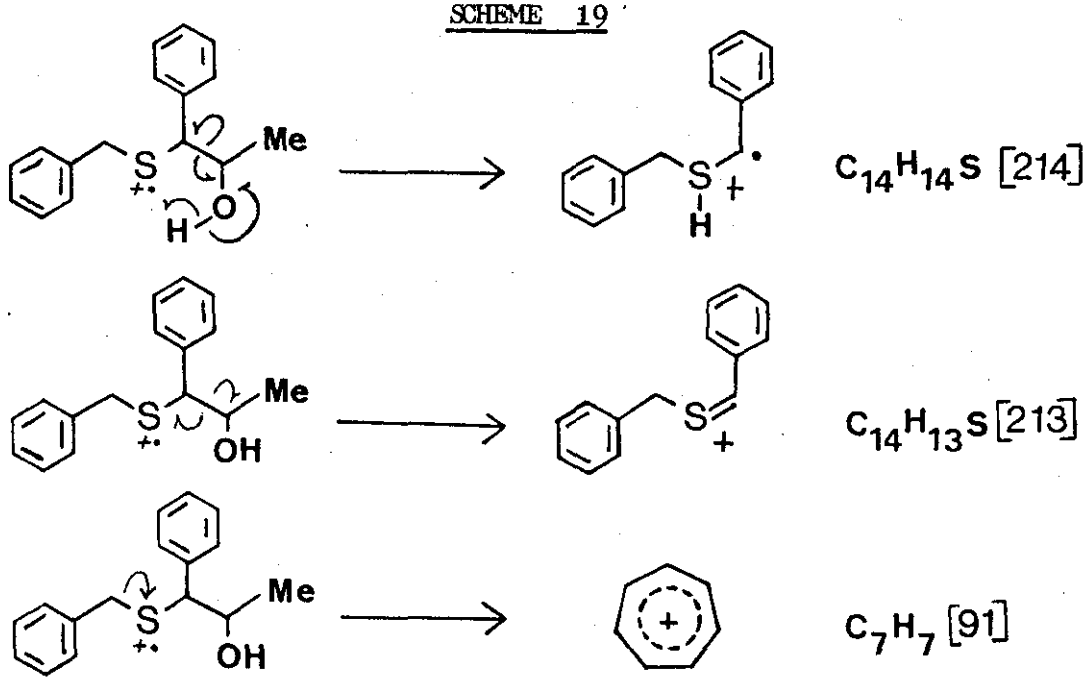
It was apparent from the $^1$Hn.m.r. spectrum of the acetate (75) that only the doublet of quartets due to the β-CH proton was shifted downfield on acetylation. These data implied that the hydroxyl group

formed on epoxide opening was attached to the $\beta$-carbon and confirmed the assignment of structure. The mass spectrum of the acetate (75) did not show the peak at m/e = 200. This lends some support to the proposed fragmentations for the erythro-$\alpha$-sulphide (74), (scheme 18).

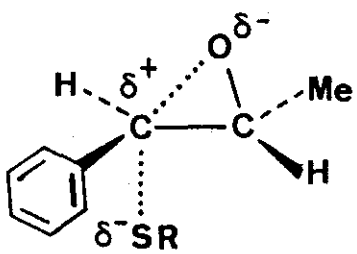
Reaction of the E-epoxide (67a) with benzylthiol gave a similar result to that obtained from the thiophenol reaction. A single racemic product was isolated, and was identified as erythro-2-hydroxy-1-phenyl-1-(phenylmethylthio) propane (76), using a similar procedure to that described for the thiophenol product (74).

The i.r. spectrum showed a band (3380 $cm^{-1}$) consistent with the presence of a hydroxyl group. The $^1$Hn.m.r. spectrum showed bands at $\delta$ 3.98 (d of q, -CH Me), 3.60 (d, -CH Ph), and 1.15 (d, $-CH_3$). Double irradiation at $\delta$ 1.15 reduced the doublet of quartets at $\delta$ 3.98 to a doublet confirming coupling to the methyl group. The mass spectrum did not show a molecular ion but did show characteristic peaks at m/e 214.0881 (44%, $C_{14}H_{14}S$) and 213.0734 (18%, $C_{14}H_{13}S$), and a base peak at m/e 91.0555 (tropylium ion). These peaks were thought to arise from processes of the type shown in scheme 19 [88,89] and indicated that attack of the thiol had taken place at the $\alpha$-carbon.

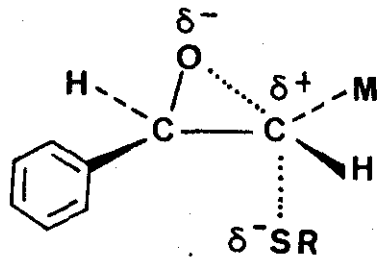
SCHEME 19



The $^1H$ n.m.r. spectrum of the acetate (77) confirmed the assignment of regiochemistry. This spectrum showed a doublet of quartets at $\delta$ 5.25, indicating attachment of hydroxyl in the α-sulphide (76) at the β-carbon. The mass spectrum of the acetate (77) showed a molecular ion at m/e 300 and a major peak at m/e 213. The disappearance of the peak at m/e 214 on acetylation supported the proposed fragmentations shown in scheme 19.




(78)



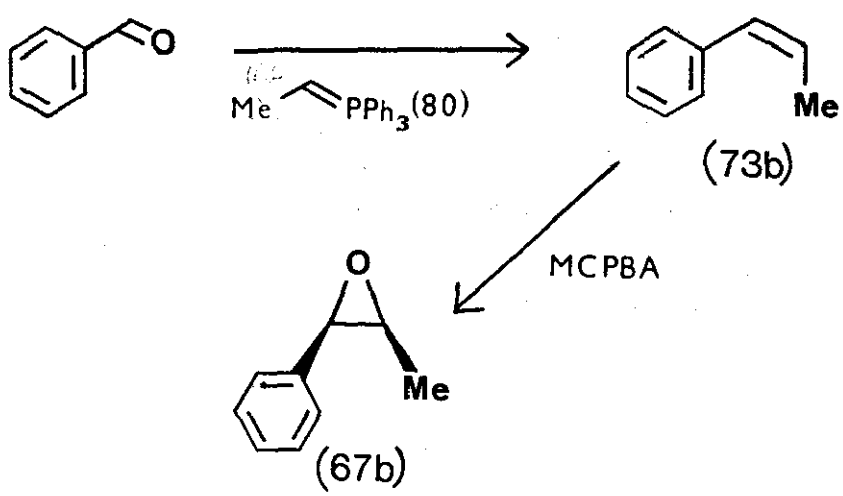

(79)

These results are consistent with steric and electronic effects discussed previously (see section 1.2). In a modified $S_N2$ mechanism,[68] addition to the α-carbon would lead to the transition state (78) in which the central carbon possesses a certain amount of carbocation character. In this transition state there is a possibility of conjugative stabilisation by the phenyl ring. In the alternative transition state (79), the methyl group could also stabilise such a charge by inductive electron release. However, it has been shown[68,69] that under basic conditions additions to alkyl substituted epoxides are mainly governed by steric factors. Therefore, the steric effect of the methyl group and the conjugative effect of the benzene ring direct attack towards the α-carbon and these additive effects appear to overcome the steric hindrance due to the phenyl ring.

## 2.1.2 Z-β-METHYLSTYRENE OXIDE

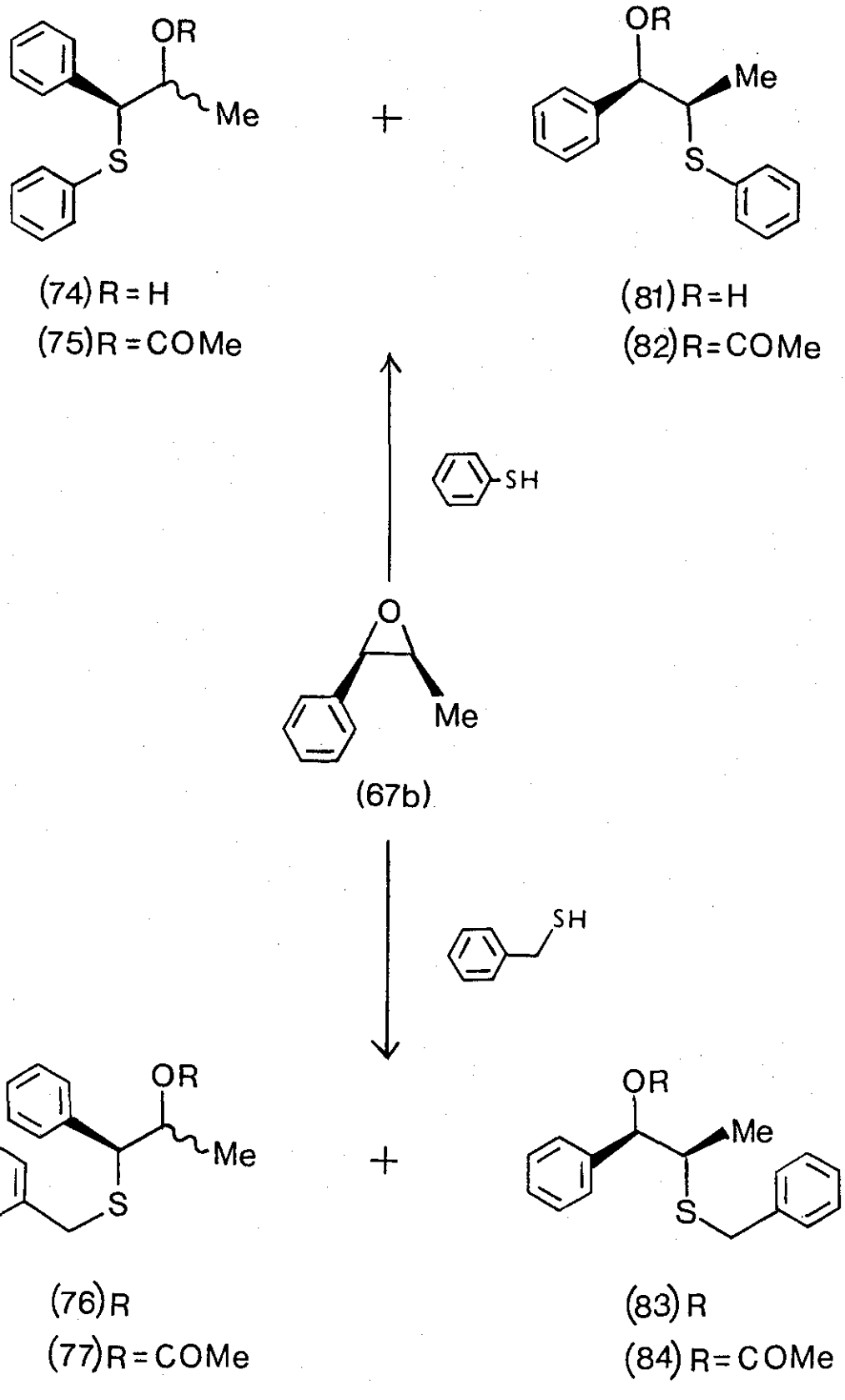
Z-β-Methylstyrene (73b) was prepared (scheme 20) by reaction of benzaldehyde with a solution of the ylid (80), prepared from ethyltriphenylphosphonium bromide and n-butyllithium in benzene. The u.v. spectrum was typical of a styrene ( λmax 247 nm, ε 10,900) and was similar to that of known E-β-methylstyrene (73a) ( λmax 249 nm, ε 14,700).[90] The i.r. and $^1$H n.m.r. were satisfactory and the mass spectrum showed a molecular ion at m/e 118. Analysis by gas liquid chromatography (g.l.c.) showed the presence of both geometric isomers in the proportions: Z 75; E 25%. This was slightly different from that observed by Schlosser[91] (87% Z). A repetition of this reaction using a 3:1 mixture of benzene and hexamethylphosphoramide as the solvent gave an increased proportion of the Z-olefin (85%).

SCHEME 20




The Z-styrene (73b) was converted to Z-β-methylstyrene oxide (67b) by reaction with m-chloroperoxybenzoic acid. The $^1$H n.m.r. spectrum showed a similar pattern to that observed for the E-isomer (67a) and gave important bands at δ 4.05 (d, Ph C<u>H</u>-), 3.2 - 3.45 (d of q, -C<u>H</u> - Me), and 1.10 (d, -C<u>H</u>$_3$).

SCHEME 21.




(74) R = H
(75) R = COMe

(81) R = H
(82) R = COMe

(67b)

(76) R
(77) R = COMe

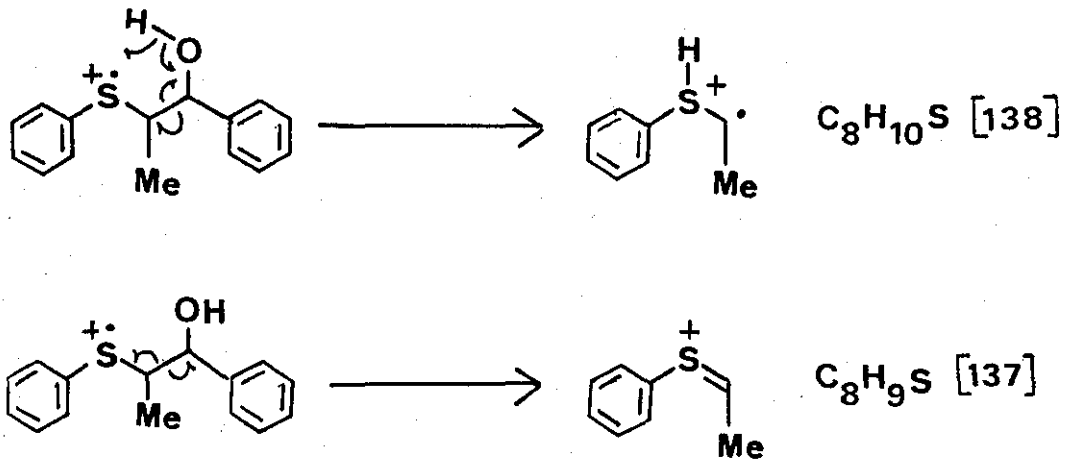
(83) R
(84) R = COMe

The reactions of the Z-epoxide (67b) with thiols showed distinct differences in regioselectivity from those of the E-epoxide (67a). With thiophenol the Z-epoxide (67b), (75% Z by g.l.c.) gave two products which were separated by p.t.l.c. (scheme 21). One of these products was identified from the i.r. and mass spectra as the α-sulphide (74) and was shown to be a mixture of diastereoisomers from the $^1$H n.m.r. spectrum. The signals corresponding to the methyl protons appeared at differing chemical shifts. That of the erythro diastereoisomer appeared at δ 1.20, as seen in the spectrum of the product from the E-epoxide (67a), and that of the threo isomer appeared at δ 1.05. Integration of these signals showed the diastereoisomers to be present in approximately equal amounts. Spectral data obtained for a diastereomeric mixture of acetates (75), prepared as previously described, confirmed these assignments.

The second product was identified as the regioisomeric threo-1-hydroxy-1-phenyl-2-(phenylthio) propane (81) on the basis of the following information. The $^1$H n.m.r. spectrum showed bands at δ 4.35 (d, -CH Ph), 3.26 (d of q, -CH Me), and 1.05 (d, $-CH_3$). The mass spectrum showed a molecular ion at m/e 244.0920, a base peak at m/e 138.0491, and a major peak at m/e = 137.0416 (93%). The major fragmentations could arise from similar processes to those suggested for the α-sulphide (74) (scheme 22). These fragmentations indicated that the sulphur was attached to the α-carbon and consequently that the hydroxyl was attached to the β-carbon.

Support for this assignment was obtained from the $^1$H n.m.r. spectrum of the acetate (82). This spectrum showed a doublet (α-CH) at δ 5.80, which is 1.45 p.p.m. further downfield than the corresponding signal in the β-sulphide (81). This also implied that the

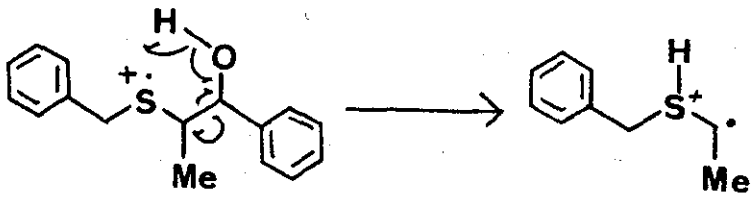
SCHEME 22



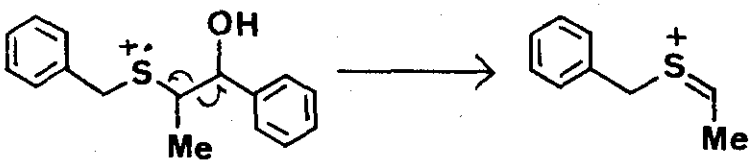

hydroxyl group was attached to the α-carbon.

Two products were also isolated from the reaction of the Z-epoxide (67b) with benzylthiol. These were identified as a diastereoisomeric mixture of the α-sulphide (76) and threo-1-hydroxy-1-phenyl-2-(phenylmethylthio) propane (83). The erythro to threo ratio (1.3:1) of diastereoisomers in the α-sulphide (76) was determined by integration of the methyl signals in the $^1$H n.m.r. spectrum (δ 1.15 and 1.05 respectively). The structure of the β-sulphide (83) was determined mainly on evidence from the mass spectrum. A very weak molecular ion m/e 258.1046 was observed in addition to major peaks at m/e 152.0664 (64%, $C_9H_{12}S$) and 151.0569 (30%, $C_9H_{11}S$), and a base peak at m/e 91.0559 (tropylium ion). These peaks were thought to arise from the fragmentations shown in scheme 23.

SCHEME 23




$C_9H_{12}S$ [152]




$C_9H_{11}S$ [151]

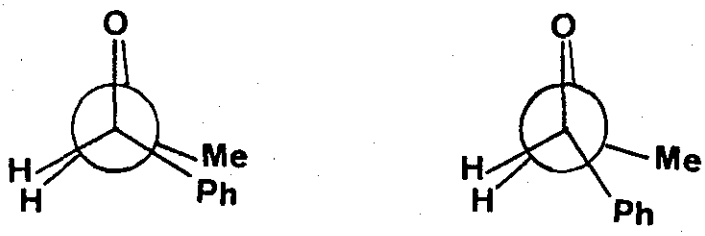
Analysis of the $^1H$ n.m.r. spectrum of the threo-acetoxy-β-sulphide (84) and the mixture of erythro- and threo-diastereoisomers of the acetoxy-α-sulphide (77), derived from the corresponding hydroxy compounds, confirmed the structural and stereochemical assignments.

Since the E-content of the epoxide used for these reactions was known (25%) and was shown to give only the α-sulphides (74,76), the ratio of α to β attack on the Z portion of the epoxide could be estimated. These were found to be approximately 1:2 for thiophenol and 1:3 for benzylthiol. These ratios indicated that the additions of thiols to Z-β-methylstyrene oxide (67b) show selectivity towards attack at the β-carbon. These results are consistent with those obtained for the addition of amines[79-82] (see section 1.2).

Several groups[80,92,93] have explained this type of behaviour by suggesting that steric compression, between the substituent groups in the Z-epoxide (67b), provides a driving force for addition which takes precedence over the electronic effects. Although attack at either

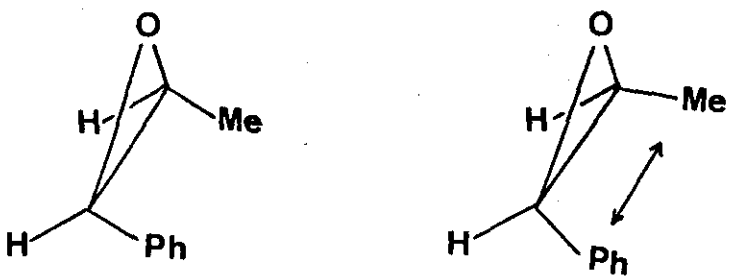
carbon of the epoxide ring would relieve this compression, it is also suggested that the greater hindrance of the phenyl ring causes the nucleophile to attack at the $\beta$-carbon.

FIGURE 1



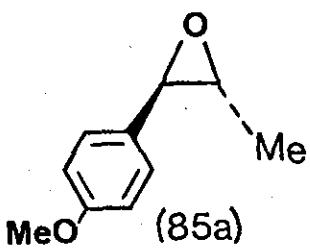

This view is rather simplistic in that it does not fully explain the differences in the steric effect, on approaching nucleophiles, of the individual substituents in the E- and Z-epoxides. It is not obvious why the phenyl ring exerts a greater steric effect in the Z-epoxide. This may be explained, in part, by considering some type of deformation due to the steric compression between the syn-bulky groups. If this compression causes the phenyl group to move more into line with the approaching nucleophile, it might be expected to have a greater steric effect (Figure 1). Simple linear separation of the substituents would not adequately explain the preference for $\beta$-attack, since the difference in steric effect of the phenyl and methyl groups would be expected to remain constant (Figure 2).

FIGURE 2

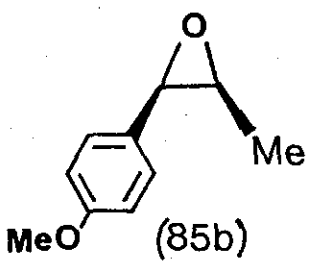


Deformation of the molecule due to steric compression may cause some type of change in the bonding of the ring. If, in this process, the $\alpha$ C–O bond is strengthened or the $\beta$ C–O bond is weakened, then $\beta$–attack may be favoured.

The exact consequences of steric compression in Z-epoxides are unknown. Therefore, any suggested explanations for its effect on regiochemistry are, at this time, only speculative. However, it is obvious that there is a fine steric and electronic balance in the behaviour of $\beta$–methylstyrene oxides towards nucleophiles, which can be markedly affected by the geometry of the substituents.



(85a)



(85b)

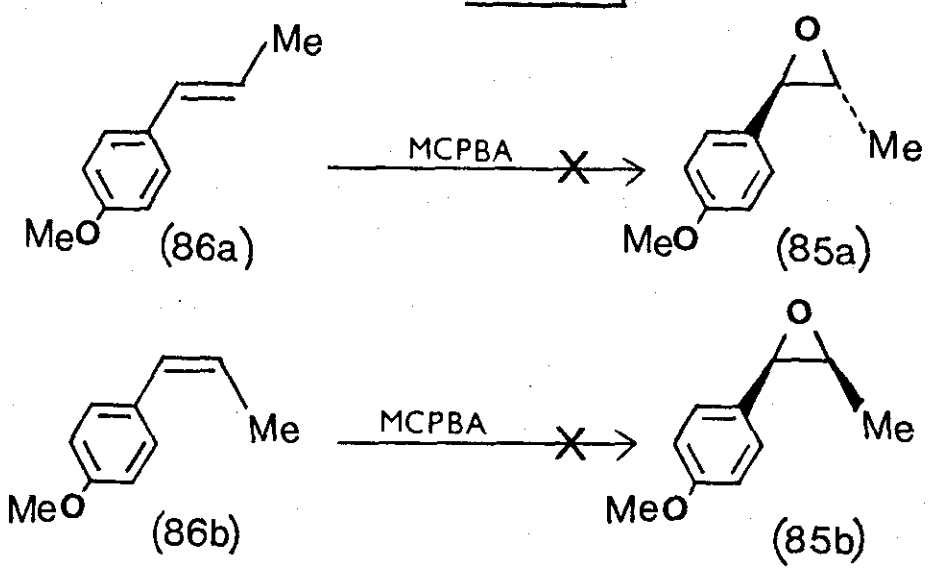
One possible way of obtaining more information concerning the balance of steric and electronic effects would be to perform the same reactions on the 4–methoxy–$\beta$–methylstyrene oxides (85). The 4–methoxy–group in the Z–epoxide (85b) should increase the ability of the benzylic carbon to stabilise a positive charge. This might be expected to produce at least a partial reversion to $\alpha$–attack. Therefore the preparation of these epoxides and their reactions with thiophenol were investigated.

### 2.1.3 4–METHOXY–$\beta$–METHYLSTYRENE OXIDES

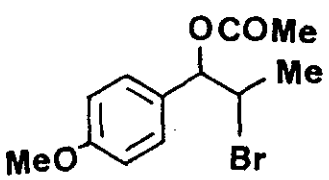
Commercially available Z-4-methoxy-$\beta$–methylstyrene (86a) was treated with m–chloroperoxybenzoic acid in dichloromethane (scheme 24). Analysis of the crude product by t.l.c. showed the presence of at least

three components. The i.r. spectrum showed the presence of a hydroxyl group (3430 $cm^{-1}$) which implied that some sort of epoxide opening had taken place. The $^1H$ n.m.r. spectrum was very complex and gave no indication of possible structures for the components of this mixture.

SCHEME 24




Z-4-Methoxy - β-methylstyrene (86b) was prepared by Wittig reaction of ethylenetriphenylphosphorane (80) and anisaldehyde. Treatment with m-chloroperoxybenzoic acid in dichloromethane gave a similar result to that obtained for the E-styrene (86a).

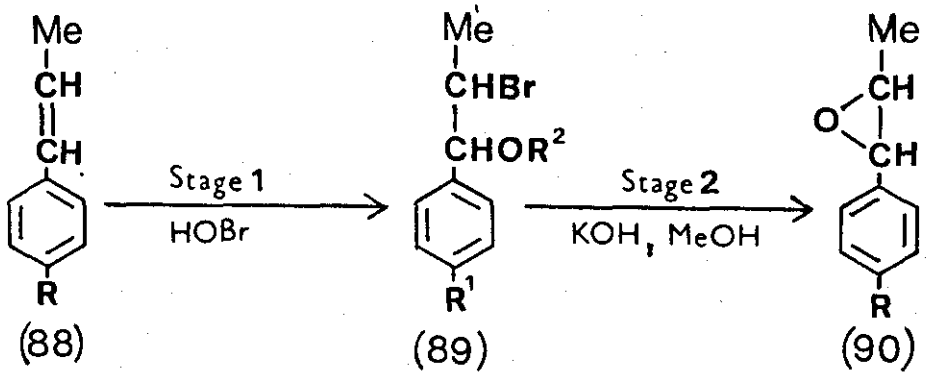



(87)

Benassi et al.[86] prepared E-4-methoxy-β-methylstyrene oxide (85a) from the corresponding styrene via the bromoacetate (87).[94] This led us to investigate a similar route (scheme 25) involving bromohydrins of the type (89, $R^2$= H). Some of the work described below has recently been published.[95] We were particularly interested in the

regioselectivity and stereoselectivity of the reactions of the β-methylstyrenes (88) with hypobromous acid. The stereochemistry of these reactions will determine the geometry of the resulting epoxide (90).

SCHEME 25




The reactions of E- and Z-β-methylstyrene (88, R=H) and their 4-methoxy-derivatives (88, R = O Me) with hypobromous acid, generated from N-bromoacetamide and aqueous perchloric acid. The reactions were performed in dioxane, tetrahydrofuran, and acetone and the bromohydrins formed were converted to the epoxides (90) by treatment with methanolic potassium hydroxide. The results of these reactions are summarised in table 2. The $^1$H n.m.r. spectra of the epoxides (90), the bromohydrins (89, $R^2$= H) and the bromoacetates (89, $R^2$ = COMe), prepared by acetylation of the bromohydrins, were recorded. Tables 3 and 4 show the chemical shifts for the α-CHOH, β-CH Br, and methyl protons of these various products.

The E to Z ratios of the epoxides (90) were determined by integration of the methyl doublets in the $^1$H n.m.r. spectra (E; δ 1.40 and Z; δ 1.10 ppm.) and in the epoxides (90, R = H) the ratios were also determined by g.l.c. Decomposition of the epoxides (90, R = O Me) prevented their similar determination by g.l.c. The erythro to threo

TABLE 2

INFLUENCE OF SOLVENT ON PRODUCT STEREOCHEMISTRY

| (83) R | E | Z | SOLVENT: DIOXANE Yields Stage[f] 1 | DIOXANE Yields Stage[f] 2 | DIOXANE Erythro | DIOXANE Threo | ACETONE Yield Stage[f] 1 | ACETONE Yield Stage[f] 2 | ACETONE Erythro | ACETONE Threo | TETRAHYDROFURAN Yield Stage[f] 1 | TETRAHYDROFURAN Yield Stage[f] 2 | TETRAHYDROFURAN Erythro | TETRAHYDROFURAN Threo |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 98 | 2 | 86 | 86 | 100[a] | — | 100 | 91 | 100[a] | — | 56[e] | 96 | 100[a] | — |
| H | 18 | 12 | 85 | 77 | 69[b] | 31 | 95 | 96 | 26[b] | 74 | — | — | — | — |
| H | 15 | 85 | — | — | — | — | — | — | — | — | 48[e] | 95 | 53[a] | 47 |
| MeO | 100 | 0 | 100 | 78 | 100[c] | | 97 | 93 | 100[d] | | 47[e] | 77 | 100[d] | |
| MeO | | | 84 | 90 | 90[c] | 10 | 100 | 91 | 88[d] | 12 | 92 | 73 | 85[d] | 15 |

a, average determined from g.l.c. and $^1$H n.m.r. on epoxides (90);

b, average determined from g.l.c. and $^1$H n.m.r. of epoxides (90) and from $^1$H n.m.r. of acetates of bromohydrins (89, $R^2 = COCH_3$);

c, average determined from $^1$H n.m.r. of epoxides (90) and of acetates of bromohydrins (89, $R^2 = COCH_3$);

d, determined from $^1$H n.m.r. of epoxides (90); e, after chromatography; f, see Scheme 25.

TABLE 3

$^1$H N.M.R. DATA FOR BROMOHYDRINS (89)

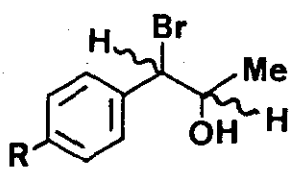
| $R^1$ | $R^2$ | STEREOCHEMISTRY | Chemical Shift (δ) | | |
|---|---|---|---|---|---|
| | | | α - H | β - H | $CH_3$ |
| H | H | Erythro | 4.95 | 4.20 - 4.60 | 1.53 |
| H | $COCH_3$ | Erythro | 5.95 | 4.20 - 4.60 | 1.67 |
| H | H | Threo | 4.58 | 4.00 - 4.60 | 1.53 |
| H | $COCH_3$ | Threo | 5.85 | 4.00 - 4.60 | 1.55 |
| OMe | H | Erythro | 4.92 | 4.15 - 4.60 | 1.58 |
| OMe | $COCH_3$ | Erythro | 5.90 | 4.10 - 4.60 | 1.20 |
| OMe | H | Threo | 4.55 | 4.15 - 4.60 | 1.58 |
| OMe | $COCH_3$ | Threo | 5.75 | 4.10 - 4.60 | 1.60 |

TABLE 4

$^1$H N.M.R. DATA FOR EPOXIDES (90)

| R | Stereochemistry | Chemical Shift (δ) | | |
|---|---|---|---|---|
| | | α - H | β - H | $CH_3$ |
| H | Z | 4.05 | 3.20 - 3.45 | 1.10 |
| H | E | 3.57 | 2.90 - 3.20 | 1.45 |
| OMe | Z | 4.00 | 3.20 - 3.40 | 1.10 |
| OMe | E | 3.50 | 2.90 - 3.20 | 1.40 |

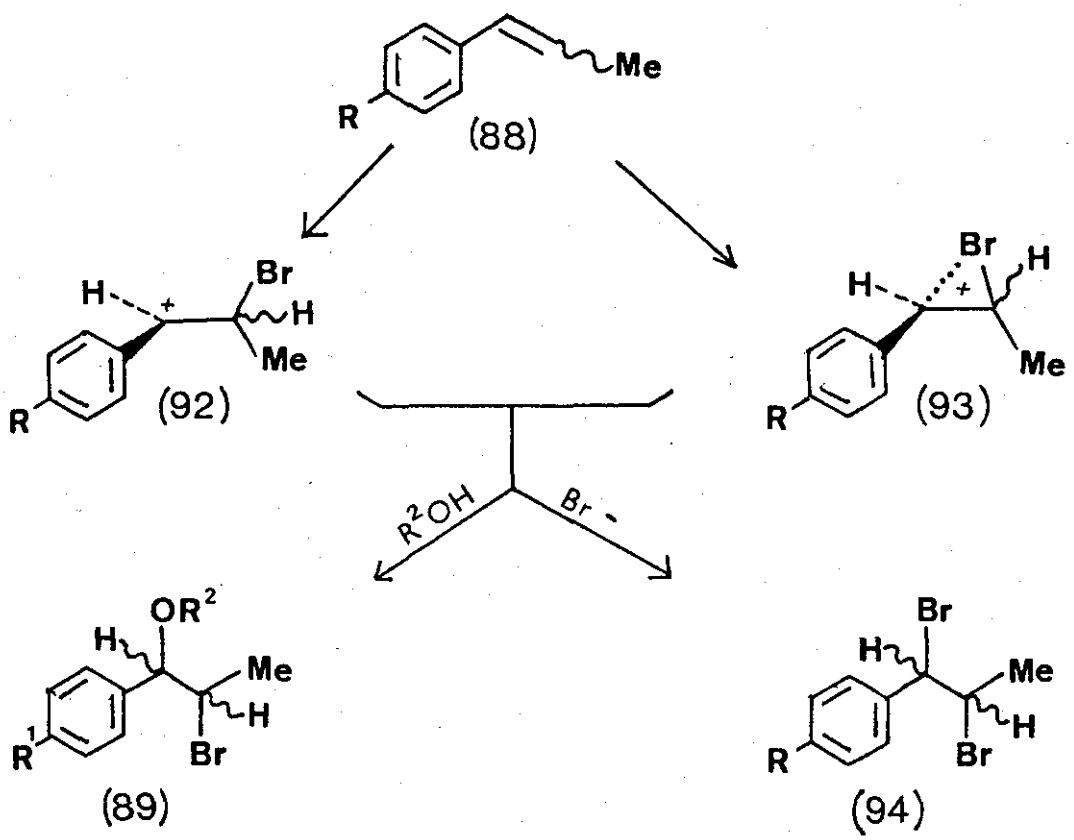
ratios (table 2) of the bromohydrins (89, $R^2$= H) were inferred by the E to Z ratios of the epoxides. This was more satisfactory than attempting to determine the erythro to threo ratios directly from the $^1$H n.m.r. spectra of the mixed bromohydrins (89, $R^2$= H) owing to superimposition of the methyl doublets ( $\delta$ 1.53). Additionally, although the $\alpha$-CH-OH doublet for the erythro-bromohydrins (89, $R^2$= H) was clearly resolved ( $\delta$ 4.95), the threo-$\alpha$-CH-OH doublet and the erythro- and threo- $\beta$-CH-Me multiplets were superimposed ($\delta$ 4.00-4.60). Acetylation of the bromohydrins (89, $R^2$= H) confirmed the above assignments and demonstrated the absence of any significant quantity of the regioisomeric bromohydrins (91) in the products since all and only the $\alpha$-CH doublets were shifted downfield by approximately 1 p.p.m. in the $^1$H n.m.r. spectra. Additionally in the acetylated bromohydrins (89, R = CO Me) it was possible to confirm the erythro to threo ratios since the $\alpha$-CH and methyl doublets were resolved.



(91)

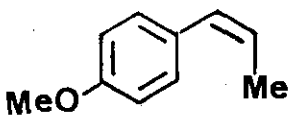
It is well known that the reactions of $\beta$-methylstyrenes (88) with bromine in non-nucleophilic solvents proceed with varying degrees of stereospecificity dependent upon the dielectric constant of the solvent and the electronic properties of the substituents on the aromatic ring.[96-98] It has been suggested that reactions of this type proceed by competitive formation of a benzylic carbocation (92) or an unsymmetrical bromonium ion (93) (scheme 26).[98] Reactions in dioxane are quite unique in that, despite its low dielectric constant, the products appear to be largely derived from benzylic carbocations and the ratio of erythro- to threo-dibromides (94, R = H) is almost independent of the stereochemistry of the starting $\beta$-methylstyrene.[99]

SCHEME 26

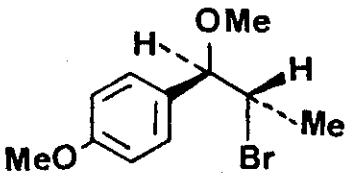



Bromination of β-methylstyrenes (88) in nucleophilic solvents such as acetic acid or methanol give solvent incorporated products (89) which are produced regiospecifically and are formed almost stereospecifically via anti-addition.[96,99-101] The reaction of Z-4-methoxy-β-methylstyrene (86a) with bromine in methanol is exceptional in that complete syn-addition gives only the erythro-methoxy bromide (95).[100] In general, it is assumed that anti-addition of the nucleophilic solvent molecules and $Br^+$ usually occurs owing to the solvent molecules being readily available on the side opposite to that of approach of $Br^+$.[97] Thus they compete effectively with attack by $Br^-$ which has to reorient itself to the opposite side of the cation (92 or 93). The highly stereoselective conversion of the Z-styrene (86b)

to the methoxybromide (95) is interesting since the similar reaction of the E isomer (86a) with bromine in methanol also gives the erythro-compound (95) while its reaction with bromine in carbontetrachloride gives a mixture of erythro- and threo-dibromides (94, R = O Me)[98] in a ratio of 63:37.

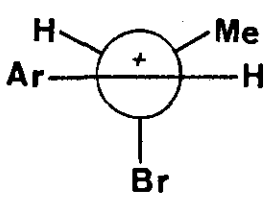



(86b)

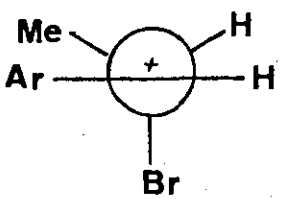



(95)

It is apparent (table 2) that the reactions of β-methylstyrenes (88) with hypobromous acid are markedly effected by the presence of dioxane and by a 4-methoxy group. The effect of dioxane is not quite so marked as in the bromination reactions since the product is less independent of the original configuration of the β-methylstyrene (88, R = H). Introduction of a 4-methoxy group is crucial since the major product is always the erythro- bromohydrin (89, $R^1$ = O Me, $R^2$ = H); the solvent appears to have little effect.




(96)

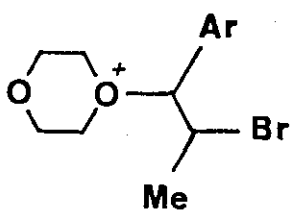



(97)

The implications of these results may be that dioxane and/or the electron releasing 4-methoxy group direct the reaction through the benzylic carbocation (92) in its more stable conformation (96) rather than the less stable conformation (97). Preferential attack by water molecules at the side remote from the attached bromine atom in (96)

would be expected, and would lead to the erythro-bromohydrin. The greater dependence of the product stereochemistry on that of the β-methylstyrenes (88, R = H) than observed for their reactions with bromine in dioxane may be attributed to the ready availability of the water molecules in the solvent matrix. As observed earlier, brominations may require some reorganisation of the originally formed ion pair.

That dioxane has a special influence on these reactions is apparent from a comparison (table 2) of the reactions in aqueous acetone and aqueous tetrahydrofuran, where the stereochemistry of the products is rather more dependent on that of the β-methylstyrene (88, R = H). This may be due to lower stabilisation of the carbocation intermediates and the more rapid attack by water molecules. Simple coordination of dioxane to the carbocation (98)[99] cannot adequately explain its remarkable stabilising effect as tetrahydrofuran is much less effective though apparently more effective than acetone. It seems more likely that owing to its bidentate nature it is able to provide a more highly organised solvating matrix.[99,102]




(98)

The reactions previously reported for β-methylstyrenes (88) with bromine in methanol or acetic acid are similar to those obtained for hypobromous acid. The introduction of the 4-methoxy-group appears to allow equilibration of the carbocations (96) and (97) so that in methanol the erythro-methoxybromide (95) is the only product reported

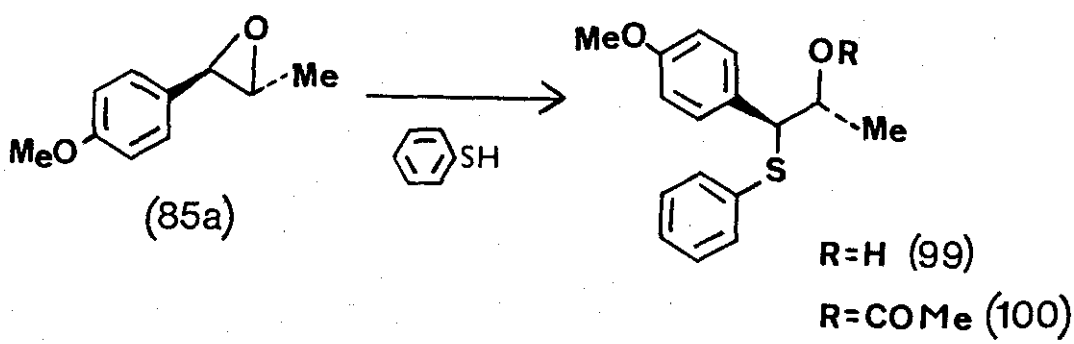
from both the E- and Z-methoxy-β-methylstyrene (88, R = O Me). Since the reactions of Z-4-methoxy-β-methylstyrene (88, R = O Me) involves rather more syn addition than that observed in any of its reactions with hypobromous acid which are not particularly solvent dependent (table 2), it is probable that other factors than the stabilities of the carbocations are also involved. Indeed, in all of the reactions, the relative stabilities of the diastereoisomeric products could have some influence on the relative rate of reaction of the conformers of the carbocation (92). This appears to be confirmed by the observation of Fahey and Schneider[98] that the reaction of E-4-methoxy-β-methylstyrene (88, R = O Me) with bromine in carbontetrachloride to give essentially the equilibrium mixture of erythro- and threo-dibromides (94, R = O Me).

It appears that the stereochemistry and regiochemistry of the reactions of β-methylstyrenes (88) with hypobromous acid may be explained, to a large extent, by considering the intermediacy of the benzylic carbocations (92). In favourable solvents and in 4-methoxy-derivatives the conversion of the carbocation conformer (97) to the more stable conformer (96) competes with the reaction of water which is expected to attack from the side opposite the attached bromine atom. It was not possible in this qualitative study to distinguish between the intermediacy of the carbocations (92) and the equivalent unsymmetrical bromonium ions (93). It may be argued that the stabilisation of the carbocations allows ready interconversion of the unsymmetrical bromonium ions derived from the conformers (96) and (97). That any bromonium ions involved are unsymmetrical was confirmed by the regiospecificity of these reactions. By analogy with the more quantitative study by Dubois et al.[96] on the bromination of β-methyl-

styrenes, it is suggested unsymmetrical bromonium ions could be involved, in part, in the reactions of E- and Z-β-methylstyrene (88, R = H) with hypobromous acid but not in the similar reactions of the 4-methoxy-derivatives.

The above results with 4-methoxy-β-methylstyrenes (88, R = O Me) showed that this route was not applicable to the synthesis of Z-4-methoxy-β-methylstyrene oxide (85b) but did provide a route to the E-isomer (85a). Reaction of this epoxide with thiophenol (scheme 27) gave the expected erythro-2 hydroxy-1-(4-methoxyphenyl)-1-(phenylthio) propane (99).

SCHEME 27




(85a)

R=H (99)

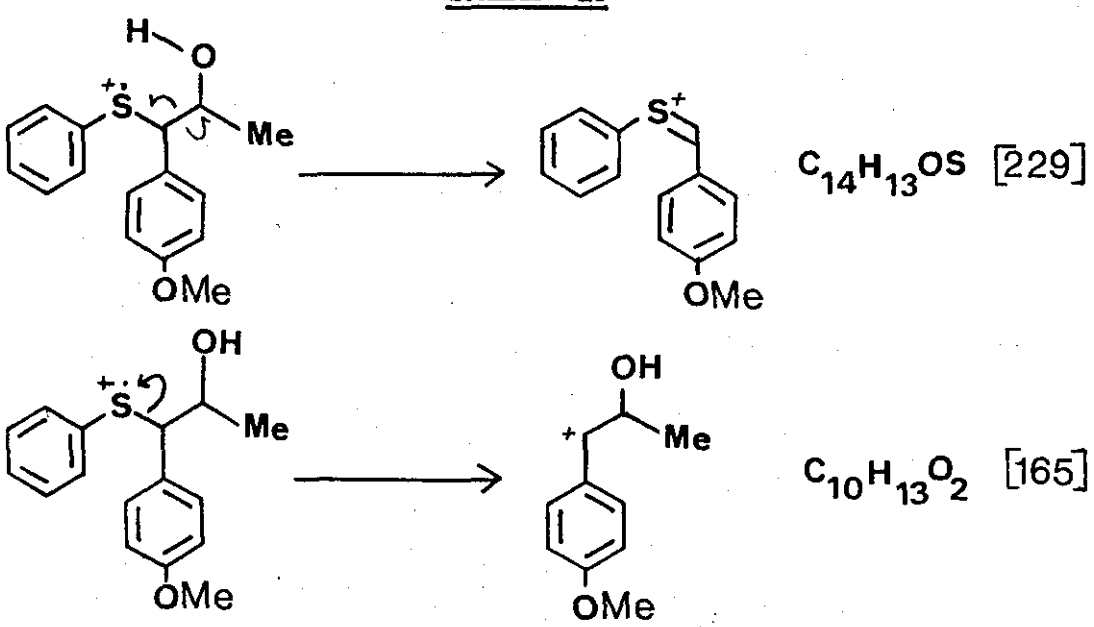
R=COMe (100)

The i.r. spectrum showed bands typical of a hydroxyl group (3420 $cm^{-1}$), an alkyl aryl ether (1260, 1055 $cm^{-1}$), a 1,4-disubstituted benzene ring (815 $cm^{-1}$), and a phenyl ring (745, 690 $cm^{-1}$).[87] The $^1H$ n.m.r. spectrum showed bands at δ 7.45 - 6.70 (m, 9H), 4.25 - 3.90 (m, 2H), 3.75 (s, $-OC\underline{H}_3$), 2.25 (bs, exchangeable with $D_2O$, $-O\underline{H}$), and 1.22 (d, $-C\underline{H}_3$). The mass spectrum showed a molecular ion at m/e 274.1017, a major peak at m/e 229.0663 (26%, $C_{14}H_{13}OS$), and a base peak at m/e 165.0917 ($C_{10}H_{13}O_2$). These peaks were thought to arise from the processes shown in scheme 28. In particular, the base peak at m/e 165 may arise because of stabilisation of the positive charge by the methoxy group. In the absence of the methoxy group, as in the

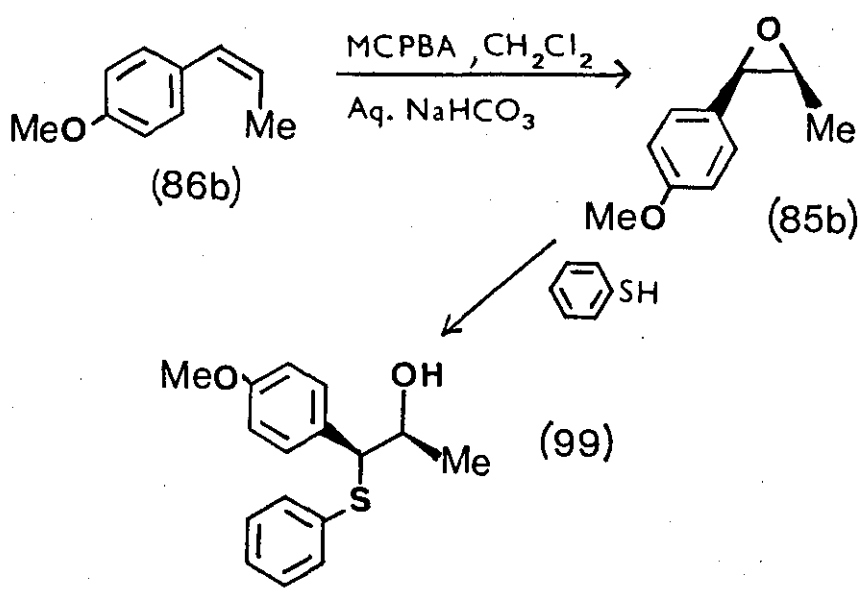
$\alpha$-sulphide (74) the base peak arises from $\beta$-cleavage and hydrogen transfer (scheme 18).

The ion at m/e 229 indicated that the sulphur was attached to the $\alpha$-carbon. This was supported by the $^1$H n.m.r. spectrum of the acetate (100) in which only a doublet of quartets appeared at $\delta$ 5.20 (-C<u>H</u> Me) confirming that the hydroxyl group was attached to the $\beta$-carbon.

SCHEME 28




SCHEME 29



The Z-epoxide (85b) was finally prepared by a modification of the epoxidation procedure described by Paquette.[103] This involved the use of a two-phase system with m-chloroperoxybenzoic acid in dichloromethane and aqueous sodium bicarbonate. The $^1$H n.m.r. spectrum showed bands at $\delta$ 7.45 - 6.55 (m, 4H), 4.00 (d, PhCH-), 3.20 - 3.40 (d of q, -CH Me), and 1.10 (d, $-CH_3$). Also the mass spectrum gave a molecular ion at m/e 164.

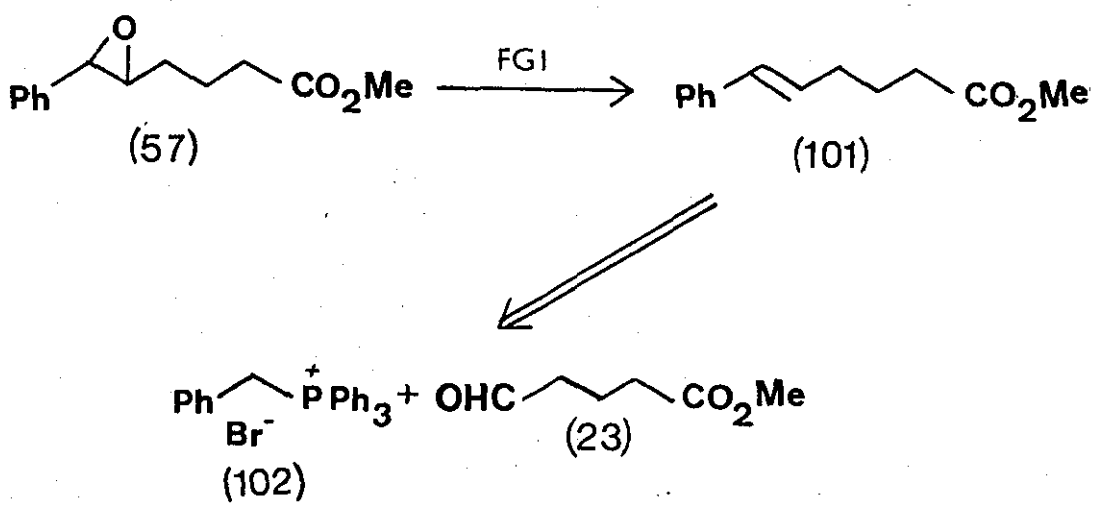
Reaction of the Z-epoxide (85b) with thiophenol gave the threo-$\alpha$--sulphide (99), which gave very similar i.r. and mass spectra to those obtained for the erythro-$\alpha$-sulphide (99). The doublet due to the methyl protons in the $^1$H n.m.r. spectrum appeared at $\delta$ 1.10, but otherwise this spectrum was similar to that of the erythro- isomer. The product analysed correctly for $C_{16}H_{18}O_2S$.

The increased conjugative effect caused by the 4-methoxy-substituent appears to overcome any steric or other electronic effects. (see section 2.12). However, these observations do not give any indication of the exact consequences of steric compression in Z-$\beta$-methylstyrene oxide (67b). The only conclusion which can be drawn is that the electronic effect of a 4-methoxyphenyl-group, "swamps" all other effects and controls the regioselectivity of reactions with thiophenol.

## 2.2 THE SYNTHESIS OF LEUKOTRIENE A ANALOGUES CONTAINING A PHENYL RING AND THEIR REACTIONS WITH SIMPLE THIOLS

The results obtained for the reactions of E-$\beta$-methylstyrene oxide (67a) with thiols (see section 2.1.1) implied that similar reactions of the E-epoxide (57) would proceed regioselectively to give products derived from attack at the $\alpha$-carbon. This would lead to the required regiochemistry for the preparation of leukotriene analogues containing a thio ether group. Therefore, the synthesis of the E-epoxide (57), and its reactions with simple thiols, were investigated.

SCHEME 30




### 2.2.1 METHYL 6-PHENYL-5-HEXENOATE

The retro-synthetic pathway shown in scheme 30 illustrates a possible direct route to the epoxide (57). It can be seen that the synthesis of the key intermediate, methyl 6-phenyl-5-hexenoate (101), might be possible by a Wittig reaction of the aldehyde (23) and the phosphonium salt (102). The aldehyde (23) has been used in several of the routes to LTA methyl ester (11) (see section 1.1.6). However, we chose initially, a less direct route from 5-hydroxypentanal (103)

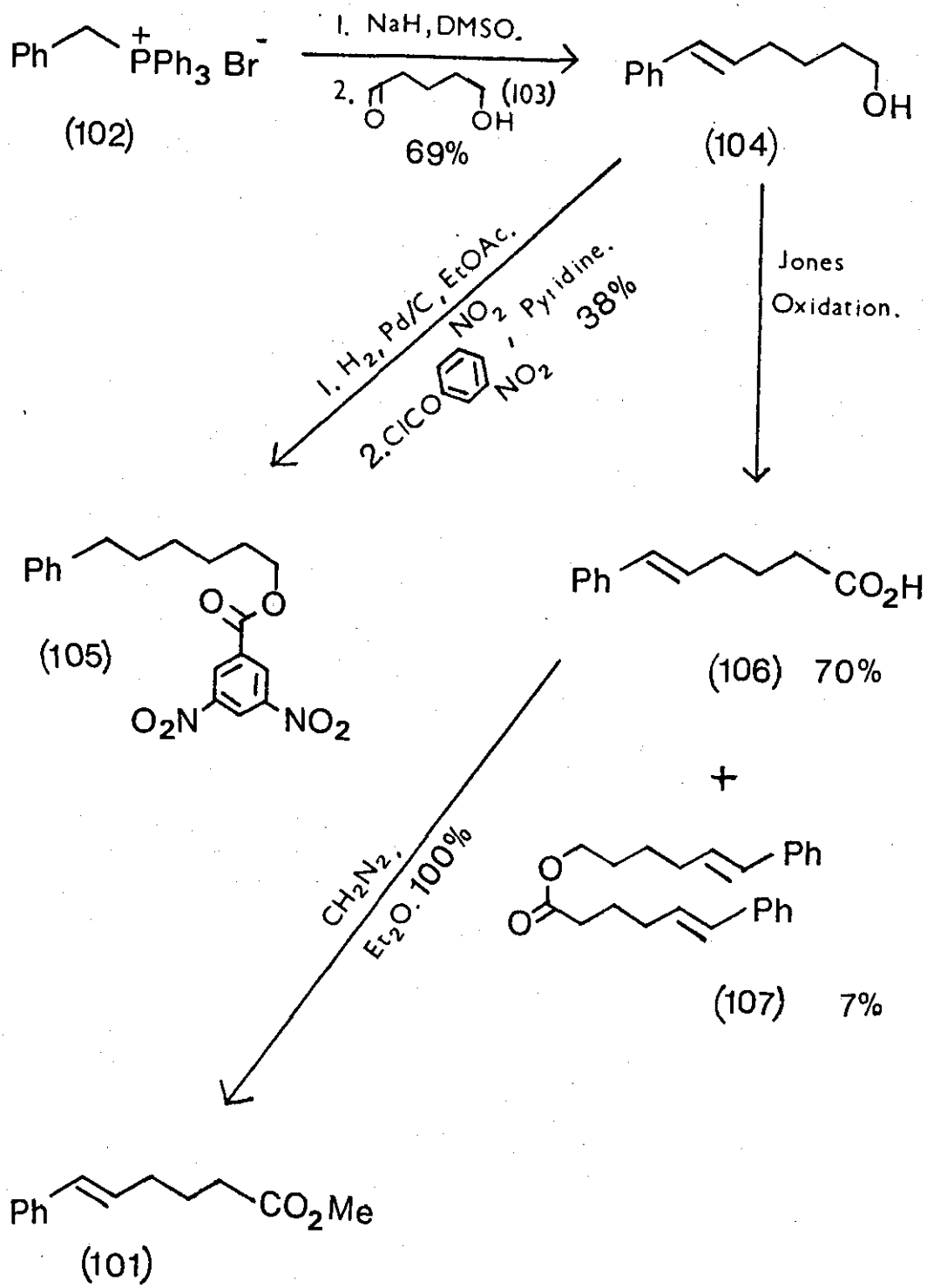
(scheme 31). This material is commercially available, whereas the aldehyde (23) requires preparation from glutaric anhydride.[104]

The phosphonium salt (102) was converted to a solution of the corresponding ylid with dimethylsulphenyl carbanion in dimethylsulphoxide.[105] Treatment of this solution with 5-hydroxypentanal (103) gave the alcohol (104). The i.r. spectrum showed the presence of a hydroxyl group (3400 $cm^{-1}$) and the u.v. spectrum showed a characteristic maximum at 246 nm ($\epsilon$ 6430)[106]. The $^1H$ n.m.r. spectrum showed a band ($\delta$ 5.35-6.60) typical of a $\beta$-alkylstyrene double bond[107] and the mass spectrum showed a molecular ion at m/e 176. Further characterisation was obtained by preparation of the crystalline saturated 3,5-dinitrobenzoate (105).

Jones oxidation[58] of the alcohol (104) gave two products which were isolated by column chromatography. The major product (70%) was identified as the acid (106) on the basis of the following data. The i.r. spectrum showed bands at 2480-3440 (acid hydroxyl) and 1710 (acid carbonyl) $cm^{-1}$. The u.v. spectrum indicated the presence of a styrene double bond ($\lambda_{max}$ 248 nm, $\epsilon$ 9100). The $^1H$ n.m.r. spectrum showed a broad singlet at $\delta$ 11.00 (exchangeable with $D_2O$), which indicated the presence of an acid hydroxyl group, and a signal ($\delta$ 5.30 - 6.60) corresponding to the olefinic protons. The mass spectrum showed a molecular ion at m/e 190.0995.

The minor product (7%) showed a band (1740 $cm^{-1}$) in the i.r. spectrum which indicated the presence of an ester. The $^1H$ n.m.r. spectrum was similar to that obtained for the acid (106) except for the absence of an acid proton ($\delta$ 11.0) and the presence of a multiplet at $\delta$ 3.80-4.20. The structure (107) was proposed and was confirmed by the mass spectrum which showed a molecular ion at m/e 348. The

SCHEME 31

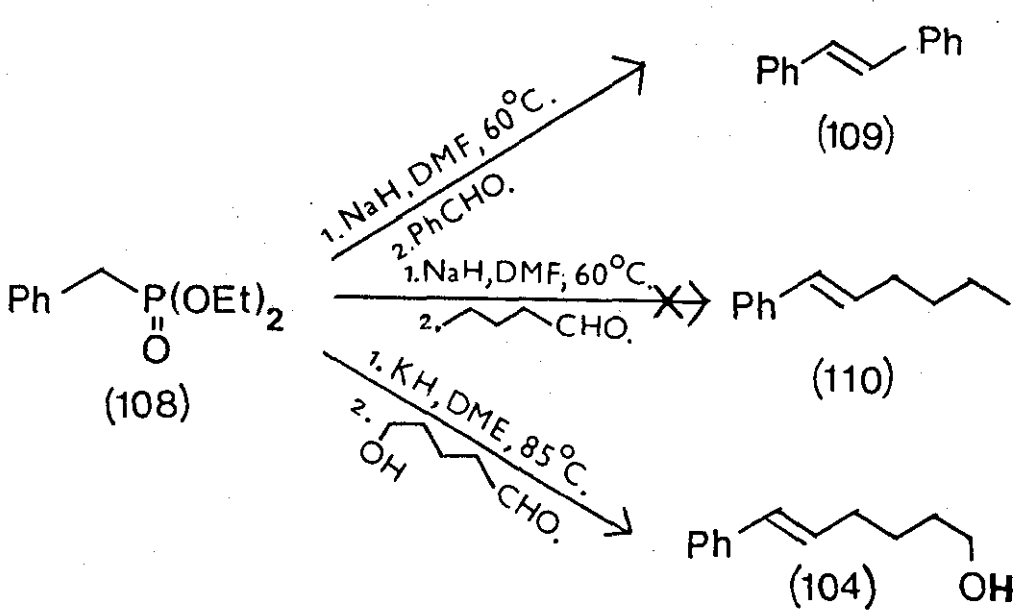

Ph
PPh3 Br
(102)
1. NaH, DMSO.
2.
(103)
OH
69%
Ph
OH
(104)
1. H2, Pd/C, EtOAc.
2. ClCO
NO2
NO2
Pyridine.
38%
Jones
Oxidation.
Ph
(105)
O2N
NO2
Ph
CO2H
(106) 70%
+
Ph
Ph
(107) 7%
CH2N2,
Et2O. 100%
Ph
CO2Me
(101)

multiplet ($\delta$ 3.80–4.20) in the $^1$H n.m.r. spectrum was assigned to the protons adjacent to oxygen. It was assumed that this minor product arose from acid catalysed esterification of newly formed acid with remaining alcohol.

The acid (106) was converted to the methyl ester (101) by treatment with diazomethane.[108] The i.r. spectrum showed a carbonyl stretching frequency characteristic of an ester (1740 $cm^{-1}$). The $^1$H n.m.r. spectrum showed the appearance of two singlets at $\delta$ 3.52 and 3.55. These were assigned to the ester methyl protons of the Z- and E-isomers respectively.

Analysis of the ester (101) by g.l.c. confirmed the presence of both geometric isomers and showed the E to Z ratio to be approximately 80:20. This information confirmed the assignments of the methyl signals in the $^1$H n.m.r. spectrum, and suggested that the Wittig reaction leading to the alcohol (104) gave mainly the E-isomer. However, repetition of the sequence (scheme 31) showed that this isomer ratio was not consistent. In most cases, the proportion of the E-isomer ranged from 40 - 60 %. Since the required geometry is E, this route was not ideal for the preparation of the intermediate ester (101).

SCHEME 32



In an attempt to find an alternative preparation of the alcohol (104), the reactions of the anion, derived from the phosphonate (108),[109] with aldehydes were investigated[110] (scheme 32). Reaction of the phosphonate (108) with sodium hydride in dimethylformamide followed by treatment with benzaldehyde gave a good yield (62%) of 95% E-stilbene (109).[111] However, reaction of this anion, under similar conditions, with pentanal did not give the styrene (110). Therefore, various other reaction conditions were investigated in an attempt to bring about this reaction (table 5).

TABLE 5

REACTIONS OF DIETHYL BENZYLPHOSPHONATE (108) WITH PENTANAL

| BASE | SOLVENT | TEMP. °C | PROCEDURE[a] | YIELD OF (110) %[b] | E % | Z[c] % | REF. |
|---|---|---|---|---|---|---|---|
| NaH | DMF | 60 | A | 0 | | | 111 |
| NaH | DME | 23 | B | 20 | | | 112 |
| KH | DME | 85 | C | 48 | 87 | 13 | — |
| $NaNH_2$ | DME | 23 | B | 21 | | | — |
| $NaNH_2$ | DMF | 23 | B | 5 | | | 113 |
| $NaNH_2$ | PhH | 23 | B | 0 | | | 114 |
| $Bu^tOK$ | THF | 23 | B | 40 | | | 115 |
| $Bu^tOK$ | THF | 80 | C | 39 | 85 | 15 | 115 |
| NaOMe | DMF | 23 | B | 0 | | | 116 |
| n-BuLi | THF | -78 | D | 5 | | | 117 |

a. See section 3.

b. After chromatography.

c. Determined by g.l.c.

DME Dimethoxyethane.

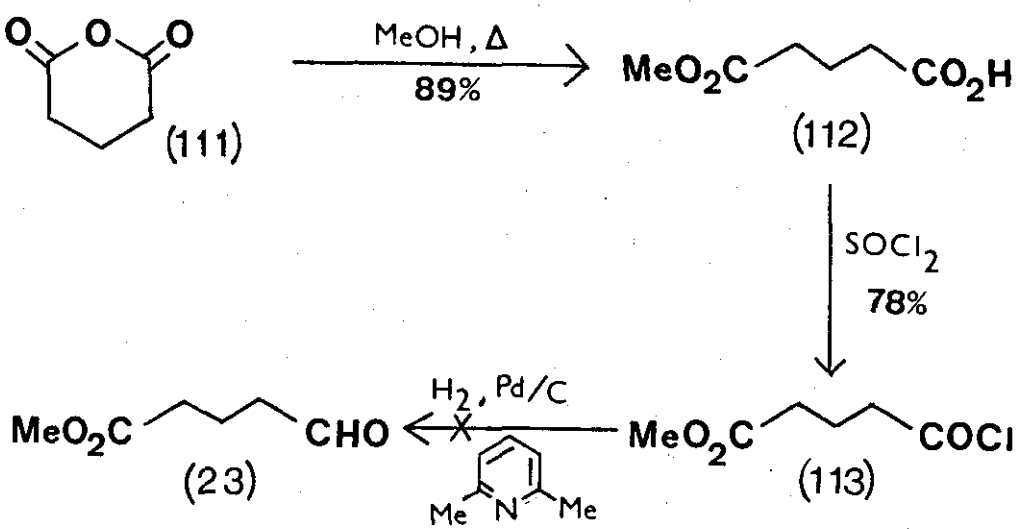
DMF Dimethylformamide.

THF Tetrahydrofuran.

It was apparent (table 5) that the most favourable condition for this reaction were potassium hydride in dimethoxyethane (DME) or potassium tert.-butoxide in tetrahydrofuran (THF). These two sets of conditions were used in attempts to prepare samples of the alcohol (104) containing a higher proportion of the E-isomer.

Reaction of the phosphonate (108) with potassium tert.-butoxide in THF gave only a low yield (25%) of the alcohol (104), but potassium hydride in DME gave a reasonable yield (45%). This was similar to that obtained for the reaction with pentanal (48%). This sample of the alcohol (104) was converted to the ester (101) using the procedure illustrated in scheme 31. Analysis of the ester (101) by g.l.c. showed the E to Z-isomer ratio to be approximately 85:15.

SCHEME 33

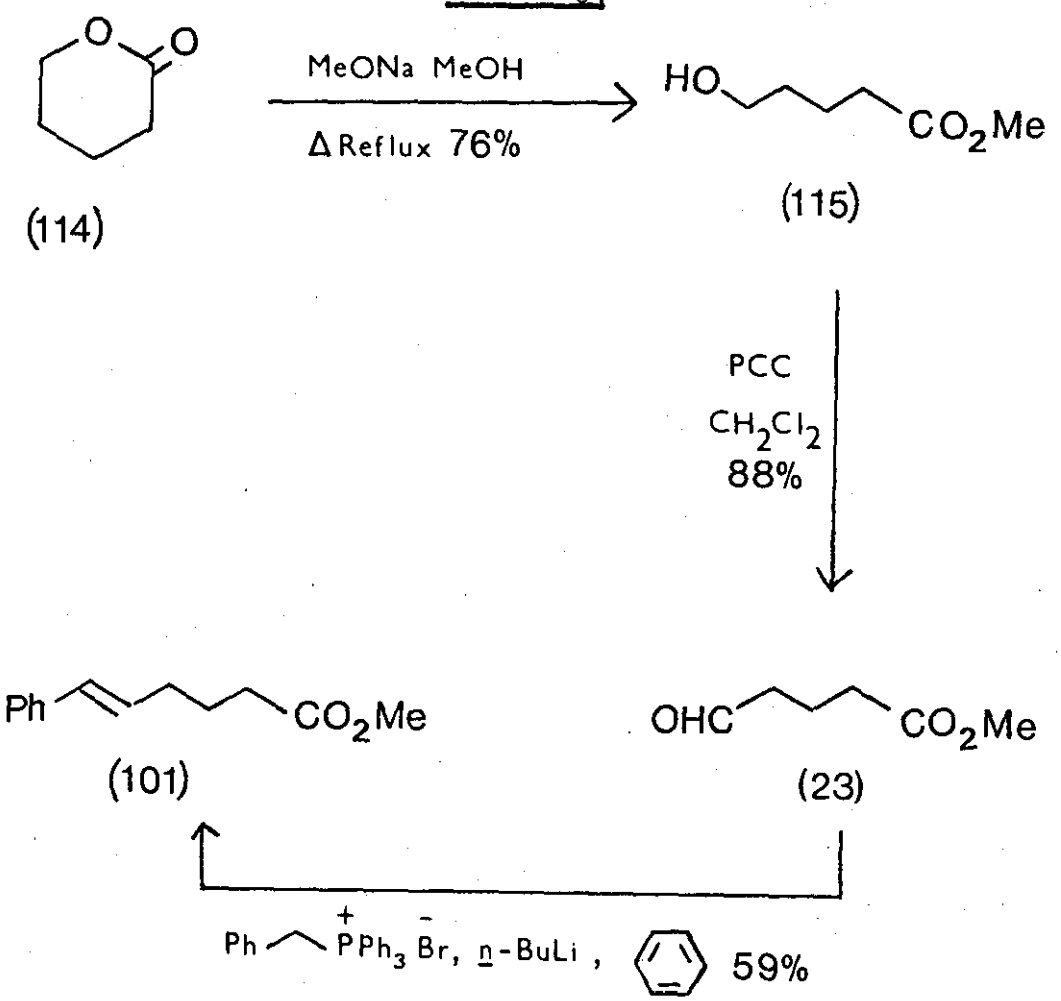



We were not entirely satisfied with the overall efficiency of this route through the alcohol (104) to the unsaturated ester (101) owing to the relatively poor yield of the Horner-Emmons reaction. Accordingly we sought to investigate the route from methyl-4-formyl-butyrate (23) originally outlined in the retro-synthetic analysis in scheme 30. The aldehyde (23) has previously been prepared from

glutaric anhydride[48,104] and we attempted to repeat this preparation (scheme 33).

Glutaric anhydride (111) was converted to the half ester (112), by heating under reflux in methanol, and when treated with thionyl chloride gave the acid chloride (113). Rosenmund reduction of the acid chloride (113) is reported to give the aldehyde (23)[48,104b]. However, in our hands, this reaction was unsuccessful. The only isolatable product was the half ester (112).

SCHEME 34




This result led us to investigate an alternative route to the aldehyde (23) (scheme 34). $\delta$-Valerolactone (114) was heated under reflux in methanol containing 0.2 equivalents of sodium methoxide, and gave the ester alcohol (115). The i.r. spectrum of the alcohol (115)

showed bands at 3480 (hydroxyl group) and 1740 (ester carbonyl) $cm^{-1}$. The $^1H$ n.m.r. spectrum showed bands at $\delta$ 3.67 (S, $-OCH_3$), 3.20 - 3.75 (m, $HOCH_2-$), 2.36 (bs, exchangeable with $D_2O$, -OH), 2.05 - 2.60 (m, 2H), and 1.25 - 2.00 (m, 4H). Oxidation of the alcohol (115) with pyridinium chlorochromate[118] gave the required aldehyde (23).

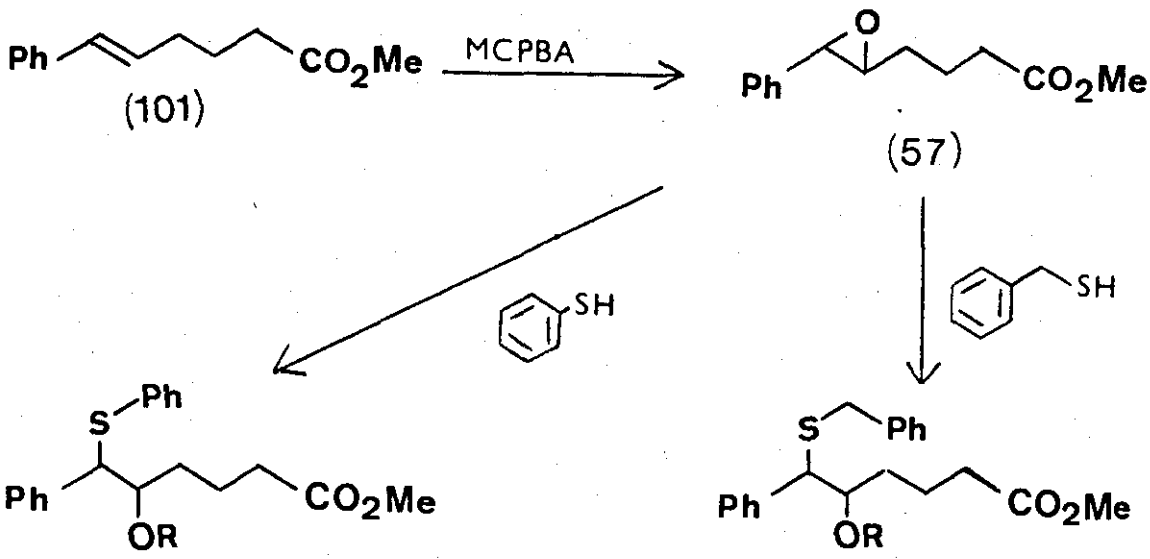
The phosphonium salt (102) was converted to the corresponding ylid by treatment with n-butyllithium in benzene and allowed to react with the aldehyde (23). Column chromatography gave the unsaturated ester (101), which was shown to contain 75% of the E-isomer.

In summary, Wittig reaction of 5-hydroxypentanal (103) gave good yields of the alcohol (104), and subsequently, the ester (101), but gave variable E to Z-isomer ratios. The use of a Horner-Emmons reaction with the phosphonate (108) gave the required E to Z ratio but gave only modest yields of the alcohol (104). Therefore the most advantageous route appeared to be the use of a Wittig reaction between the aldehyde (23) and the phosphonium salt (102) in benzene. The standard procedure for the preparation of the aldehyde (23) was unsuccessful, and a shorter, alternative route was developed.

### 2.2.2 METHYL 5,6-EPOXY-6-PHENYLHEXANOATE

A sample of the unsaturated ester (101), containing 80% of the E isomer, was oxidised with m-chloroperoxybenzoic acid to methyl 5,6-epoxy-6-phenylhexanoate (57) (scheme 35). The $^1H$ n.m.r. spectrum showed the presence of both geometric isomers. The E-isomer showed bands at $\delta$ 3.55 (s, $-OCH_3$), 3.48 (d, $PhCH-$), and 2.70 - 3.00 (m, $-CH$ $CH_2-$) and the Z-isomer bands at $\delta$ 4.00 (d, $PhCH-$), 3.52 (S, $-OCH_3$) and 3.05 - 3.35 (m, $-CH-CH_2-$). The mass spectrum showed a molecular ion at m/e 220.1099 ($C_{13}H_{16}O$).

SCHEME 35




(116) R=H

(117) R=COMe

(118) R=H

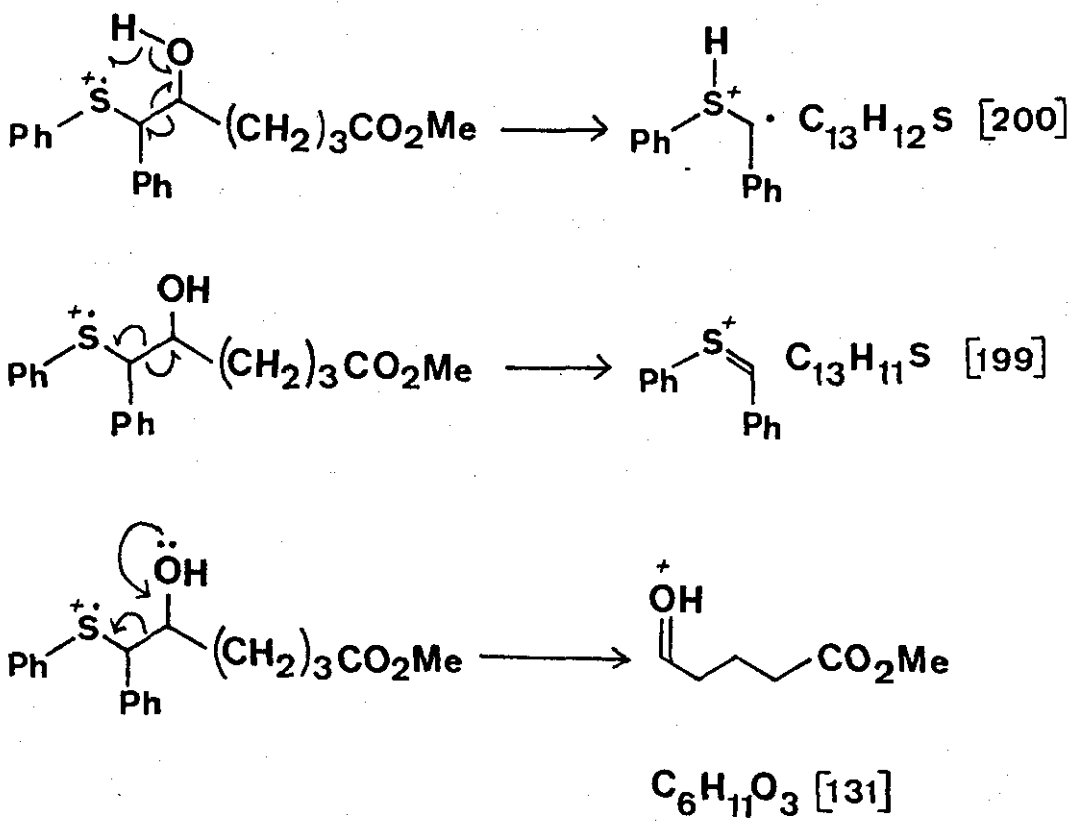
(119) R=COMe

Reaction of the epoxide (57) with thiophenol under the usual conditions (see p.36), gave methyl-5-hydroxy-6-phenyl-6-(phenylthio) hexanoate (116) which was purified by p.t.l.c. This assignment of structure was possible from the following information. The i.r. spectrum showed bands at 3500 (hydroxyl group) and 1730 (ester carbonyl) $cm^{-1}$. The $^1H$ n.m.r. spectrum showed bands at $\delta$ 6.90 - 7.50 (m, 10H), 4.20 (d, PhC<u>H</u>-), 3.75 - 4.05 (m, -C<u>H</u>-$CH_2$-), 3.58 (S, -OC<u>H</u>$_3$), 2.55 (bs, exchangeable with $D_2O$, -O<u>H</u>), 2.00 - 2.40 (m, 2M), and 1.10 - 1.95 (m, 4H). The mass spectrum did not show a molecular ion but did show characteristic peaks at m/e 200.0659 (34%, $C_{13}H_{12}S$), 199.0599 (base peak, $C_{13}H_{11}S$), and 131.0704 (38%, $C_6H_{11}O_3$). The compound analysed correctly for $C_{19}H_{22}O_3S$.

The fragment ions observed in the mass spectrum were thought to arise from the processes shown in scheme 36. The ions at m/e 200 and 199 were also observed in the spectrum of the $\alpha$-sulphide (74), (see scheme 18), which had been obtained by reaction of <u>E</u>-$\beta$-methyl styrene

oxide (67a) with thiophenol. These ions suggested that the sulphur was attached to the $\alpha$-carbon (C-6 of aliphatic chain).

SCHEME 36




The assignment of structure was confirmed by the $^1$H n.m.r. spectrum obtained for the acetate (117). This spectrum showed a multiplet at $\delta$ 5.15 - 5.40 (-C<u>H</u>CH$_2$-) and a doublet at $\delta$ 4.30 (PhC<u>H</u>-) which indicated that the hydroxyl group formed on epoxide opening was attached to the $\beta$-carbon (C5 of the aliphatic chain). The mass spectrum of the acetate (117) showed a molecular ion at m/e 372.

Reaction of the epoxide (57) with benzylthiol gave the expected methyl-5-hydroxy-6-phenyl-6-(phenylmethylthio) hexanoate (118). The i.r. spectrum showed bands characteristic of a hydroxyl group (3500 cm$^{-1}$) and an ester carbonyl (1730 cm$^{-1}$). The $^1$H n.m.r. spectrum showed bands

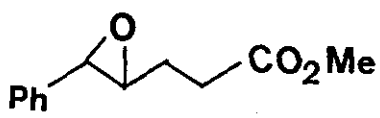
at $\delta$ 3.70 - 3.95 (m, -C<u>H</u>CH$_2$-), 3.65 (d, PhC<u>H</u>-), 3.58 (S, -OC<u>H</u>$_3$), 3.5 (q, PhC<u>H</u>$_2$S-), 2.05 - 2.40 (m, 2H), and 1.00 - 1.95 (m, 4H). The mass spectrum showed characteristic peaks at m/e 214.0811 (12% $C_{14}H_{14}S$) and 213.0741 (35%, $C_{14}H_{13}S$) and a base peak at m/e 91.0558 (see scheme 19). Although the mass spectrum did not show a molecular ion, the elemental analysis of the compound confirmed the molecular formula to be $C_{20}H_{24}O_3S$.

Spectra obtained for the acetate (119) confirmed the assignment of structure. The $^1$H n.m.r. spectrum showed a multiplet at $\delta$ 5.10 - 5.32 (-C<u>H</u>CH$_2$-) and the mass spectrum showed a weak molecular ion at m/e 386.

These results indicated that the predicted regioselectivity was correct, and openings with cysteine or other thiol-amino acids or peptides should lead to the target leukotriene analogues containing a phenyl ring.

### 2.2.3 METHYL 4,5-EPOXY-5-PHENYLPENTANOATE

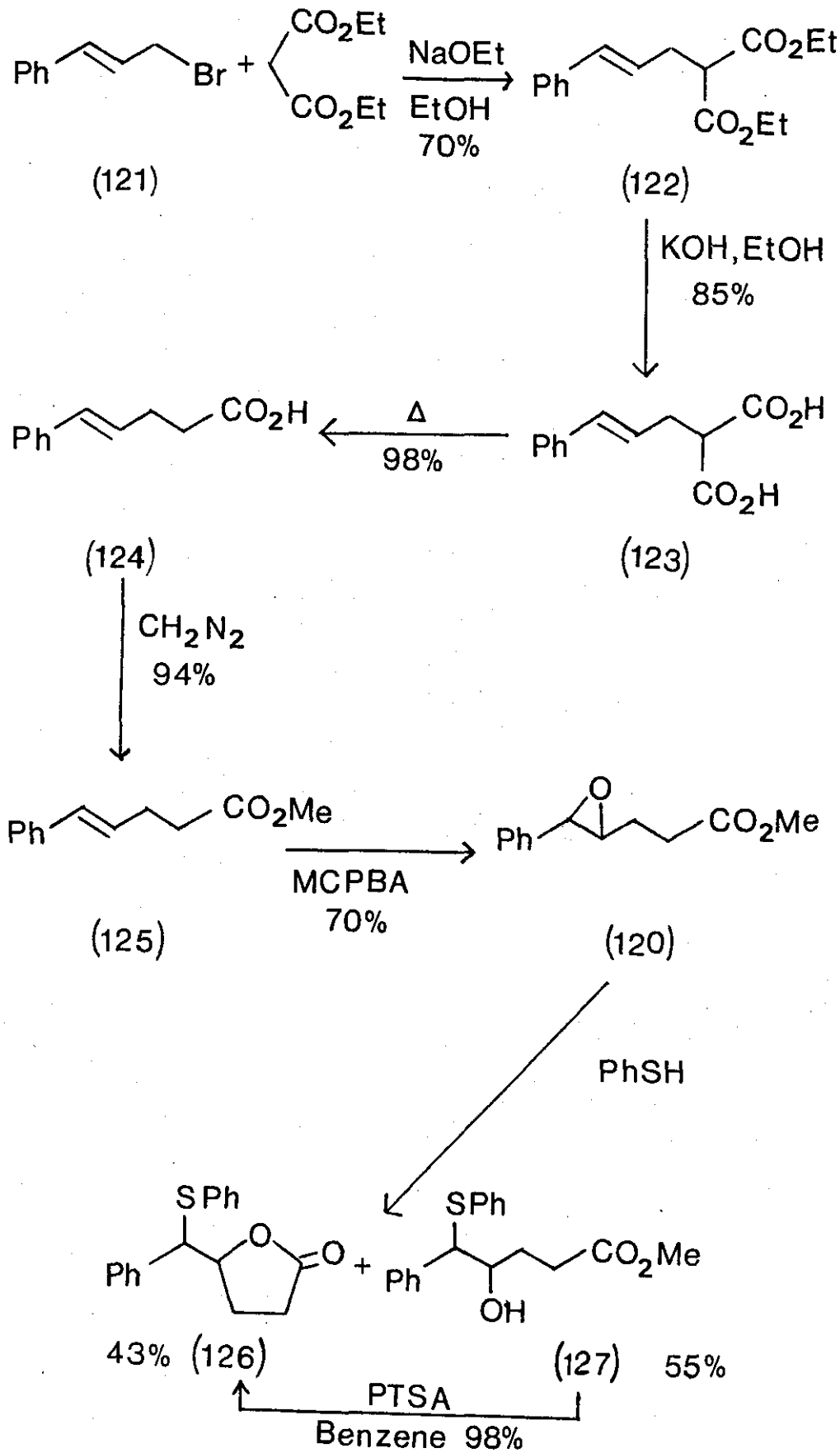
The synthesis of methyl 4,5-epoxy-5-phenylpentanoate (120) was investigated with a view to preparing a nor-LTA analogue and studying its reactions with simple thiols.




(120)

The synthesis of the epoxide (120) was achieved by a simple route (scheme 37). Using the procedures described by Farmer and Hose[119] the acid (124) was prepared by the following sequence. A solution of sodium ethoxide in ethanol was treated sequentially with diethyl-malonate and cinnamyl bromide (121). The crude product was distilled,

SCHEME 37


Ph
Br
+
CO2Et
CO2Et
NaOEt
EtOH
70%
(121)
Ph
CO2Et
CO2Et
(122)
KOH, EtOH
85%
Ph
CO2H
Δ
98%
Ph
CO2H
CO2H
(124)
(123)
CH2N2
94%
Ph
CO2Me
MCPBA
70%
Ph
O
CO2Me
(125)
(120)
PhSH
SPh
Ph
O
O
+
SPh
Ph
CO2Me
OH
43%
(126)
(127)
55%
PTSA
Benzene 98%

yielding diethyl cinnamylmalonate (122). Basic hydrolysis gave a good yield of the diacid (123) which, when heated to 140°C, decarboxylated to give the unsaturated acid (124).

Esterification of the acid (124) with diazomethane, gave the methyl ester (125) which was treated with m-chloroperoxybenzoic acid in dichloromethane. The i.r. spectrum of the product showed the presence of an ester carbonyl (1740 $cm^{-1}$). The $^1H$ n.m.r. spectrum showed bands at $\delta$ 7.25 (S, Ph), 3.68 (S, 3H), 3.60 (d, 1H), 2.90 - 3.10 (d of t, 1H), 2.50 (t, 2H), 1.80 - 2.20 (m, 2H). These data indicated the structure to be that of the epoxide (120) and this was confirmed by the mass spectrum which showed a molecular ion at m/e 206.

Reaction of the epoxide (120) with thiophenol gave two products which were isolated by p.t.l.c. The minor product (43%) was identified as 4-(1'-phenylthiobenzyl)butyrolactone (126) on the basis of the following information. The i.r. spectrum showed a carbonyl stretching frequency, characteristic of a $\gamma$-lactone (1770 $cm^{-1}$). The $^1H$ n.m.r. spectrum showed bands at $\delta$ 4.70 - 5.05 (m, -O-C<u>H</u>-$CH_2$-) and 4.30 (d, PhC<u>H</u>-). The mass spectrum showed a molecular ion at m/e 284.0872 and elemental analysis confirmed the molecular formula to be $C_{17}H_{16}O_2S$.

The major product (55%) appeared to be the expected $\beta$-hydroxy sulphide (127) from the following spectral data. The i.r. spectrum showed bands at 3500 (hydroxyl group) and 1735 (ester carbonyl) $cm^{-1}$. The $^1H$ n.m.r. spectrum showed bands at $\delta$ 4.15 (d, PhC<u>H</u>-), 3.66 - 4.02 (m, -C<u>H</u>$CH_2$-), 3.55 (S, -OC<u>H</u>$_3$), 2.06 (bs, exchangeable with $D_2O$, -O<u>H</u>) and 1.15 - 2.40 (m, 4H). Further characterisation was impossible because, on standing, the product reverted to a mixture of the $\beta$-hydroxy-sulphide (127) and the $\gamma$-lactone (126) (from i.r. and t.l.c. evidence).

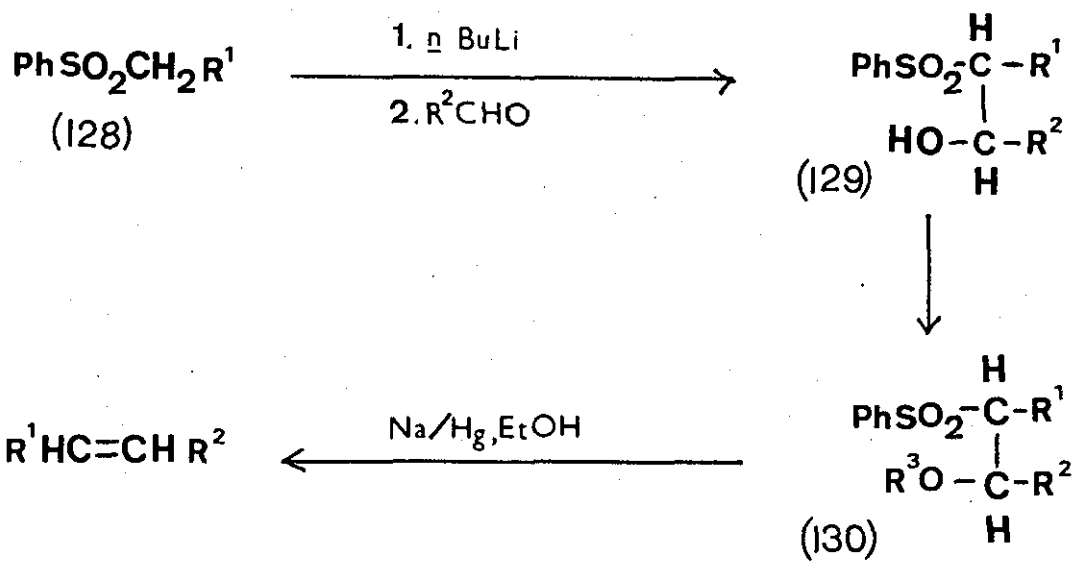
Complete conversion of this mixture to the γ-lactone (126) was achieved by heating under reflux in benzene with a trace of p-toluene sulphonic acid.

It would be expected that reactions of the epoxide (120) with cysteine and other thiol amino acids would lead to analogues of the γ-lactone (126) or the β-hydroxy sulphide (127). A comparison of the biological properties of these compounds with those obtained from the epoxide (57) may be of interest.

## 2.2.4 ALTERNATIVE ROUTES TO OLEFINS AND EPOXIDES

Two alternative routes to the epoxide (57) were envisaged. The first involved the preparation of an olefin, via the Julia method[120], and hence to the epoxide (57); and the second involved the direct synthesis of the epoxide (57) by a sulphur ylid reaction.[121]

SCHEME 38

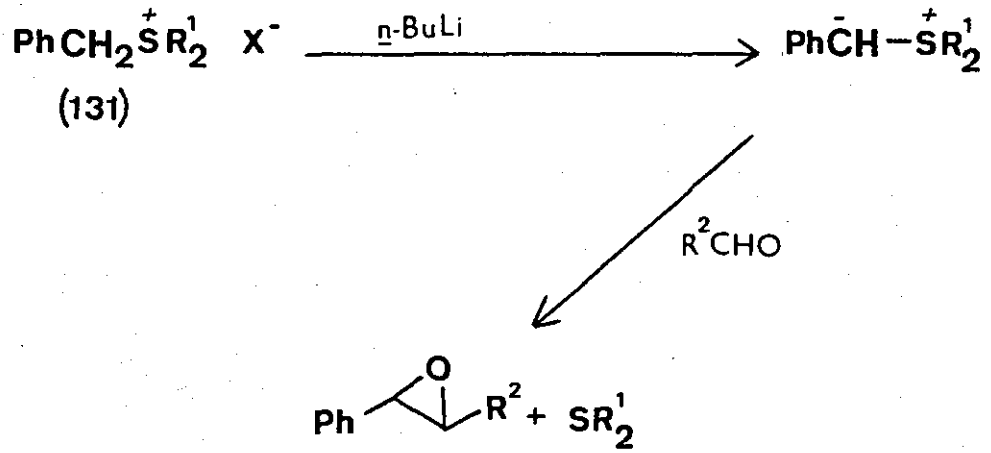



The Julia method of olefin synthesis involves the preparation of a β-hydroxy sulphone (129), conversion to the acetate (130, $R^3$ = Ac),

the methanesulphonate (130, $R^3$= $SO_2Me$), or the tosylate (130, $R^3$= Ts), and treatment with sodium amalgam in ethanol. This method is known to produce mainly E - olefins,[122] and therefore appeared to be applicable to the synthesis of the unsaturated ester (101) and thus providing an alternative route to the epoxide (57).

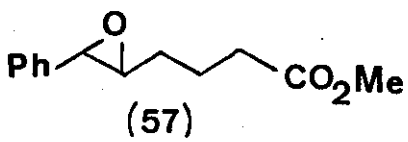
The reactions of sulphonium ylids with aldehydes are known to give epoxides[121] (also see section 1.1.6). It was thought that a sequence of the type shown in scheme 39 might provide a direct route to the epoxide(57).

SCHEME 39

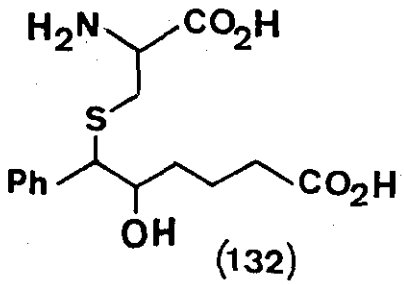



Although initially, both these routes seemed applicable to our needs, the results of preliminary experiments with pentanal were not encouraging. Therefore, the routes via Wittig or Horner-Emmons reactions appeared to be the most promising.

## 2.3 SYNTHETIC APPROACHES TO LEUKOTRIENE E ANALOGUES CONTAINING A PHENYL RING



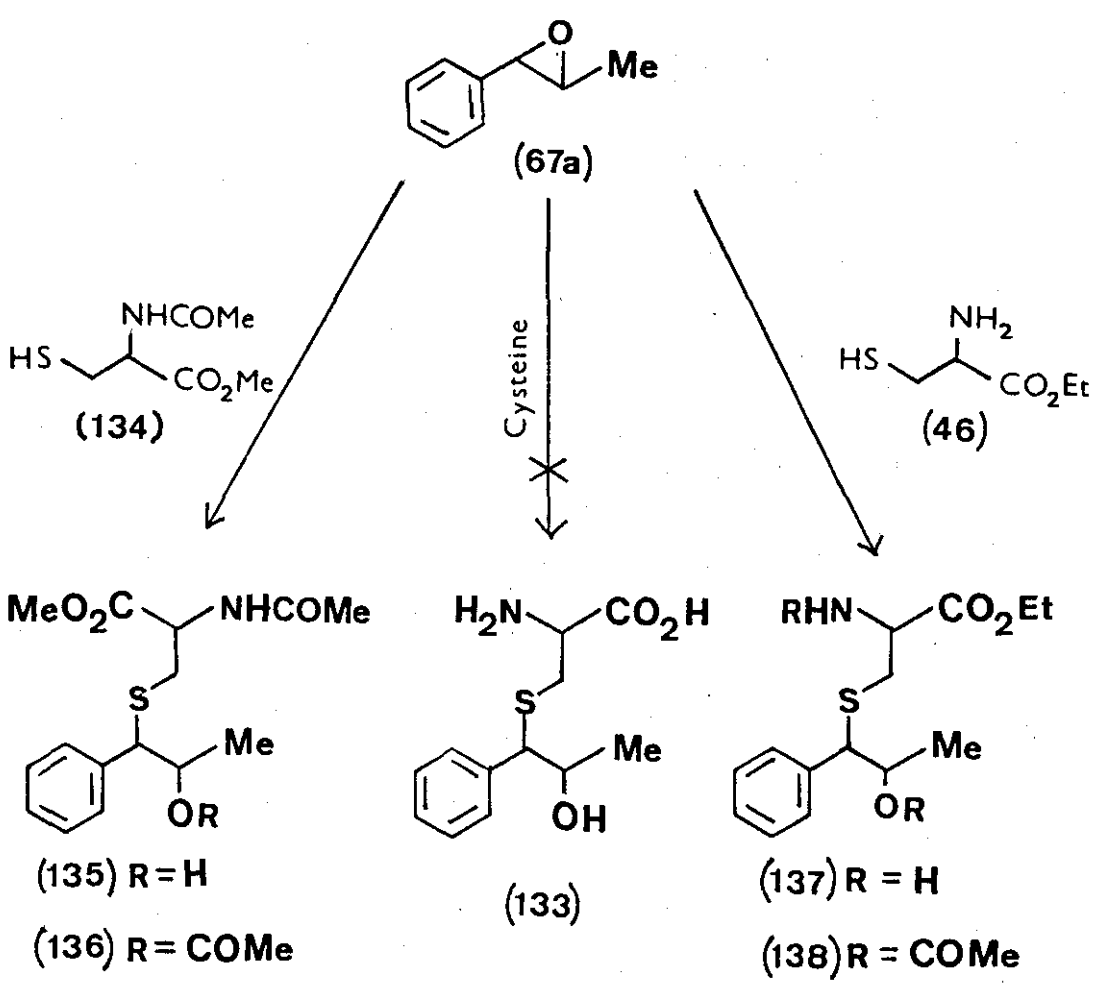
(57)



(132)

As previously stated, it was our aim to prepare leukotriene analogues containing a phenyl ring. The main target compound was the LTE analogue (132) and its synthesis was thought possible via a thiol opening of the epoxide (57). Therefore, some approaches to this conversion were investigated.

SCHEME 40

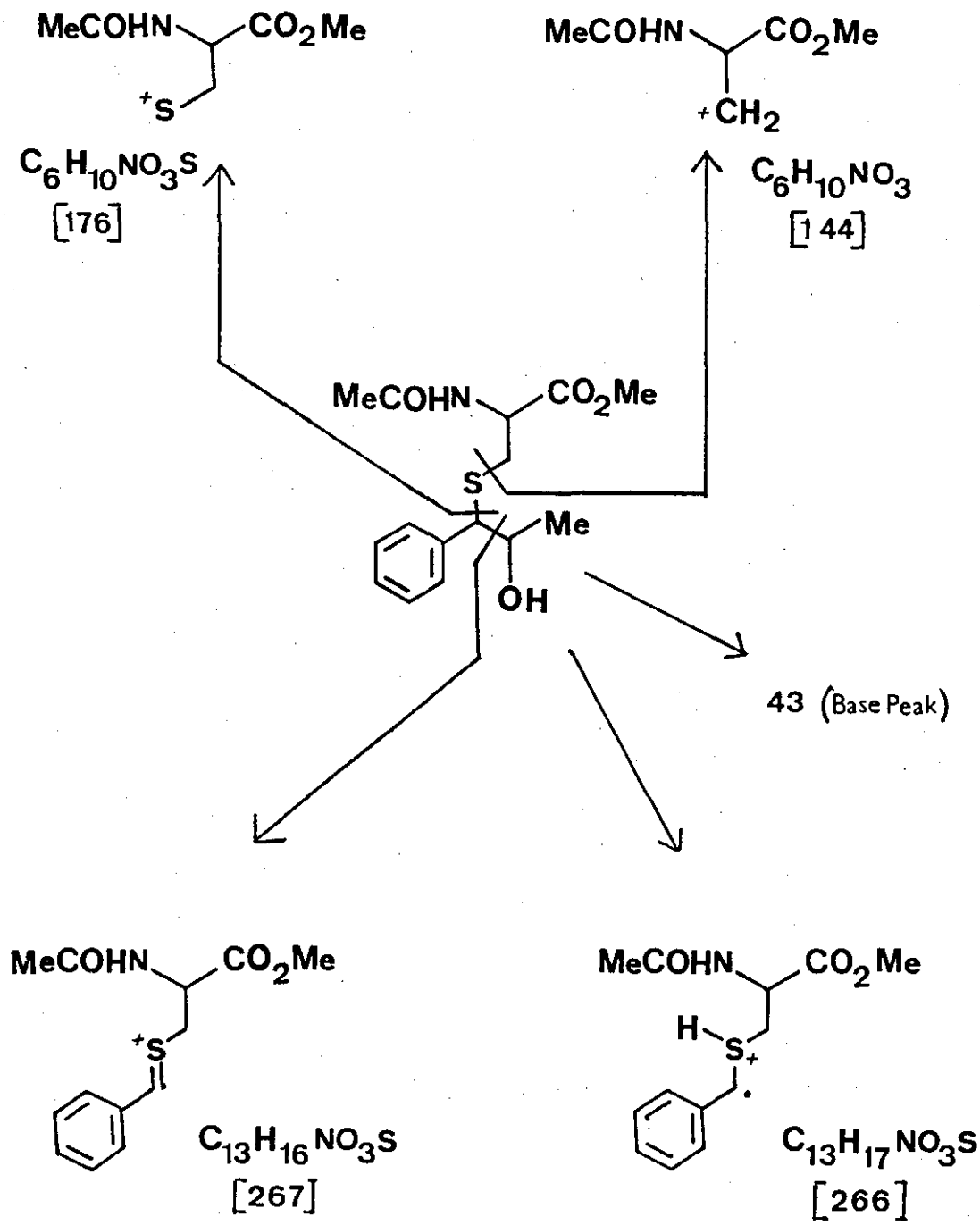


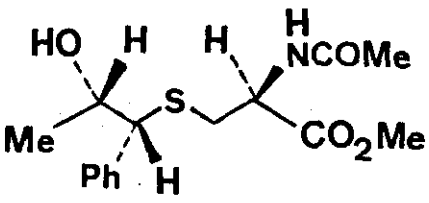
As a model system, the reactions of E-$\beta$-methylstyrene oxide (67a) with cysteine and some of its derivatives were studied (scheme 40). Reaction of the E-epoxide (67a) with cysteine, under the conditions described by Corey *et al.*[29] in their synthesis of LTE, did not give the expected cysteine conjugate (133). A proportion of the starting material (40%) was the only isolatable product.

Treatment of the E-epoxide (67a) with N-acetylcysteine methyl ester (134),[123] under the same conditions, gave the hydroxy sulphide (135). This structure was assigned on the basis of the following data. The i.r. spectrum showed bands at 3200-3400 (hydroxyl group and amide NH), 1745 (ester carbonyl), 1540 and 1660 (amide carbonyl) $cm^{-1}$.[87] The $^1H$ n.m.r. spectrum showed bands at $\delta$ 6.50-7.00 (bm,-NH-), 3.95-4.25 (m,-CHMe), 3.82 and 3.88 (2xd,PhCH-), 3.62 and 3.73 (2xs-$OCH_3$), 2.58 (bs, exchangeable with $D_2O$,-OH), 1.88 and 2.00 (2xs,-$COCH_3$), and 1.20(d,-$CH_3$). The mass spectrum did not show a molecular ion but did show characteristic peaks at m/e 267.0920 (41%), 2.66.0828 (5%), 176.0365 (72%), and 144.0659 (65%). These ions were thought to arise as shown in scheme 41. The ions at m/e 267 and 266 implied that the sulphur was attached to the $\alpha$-carbon.

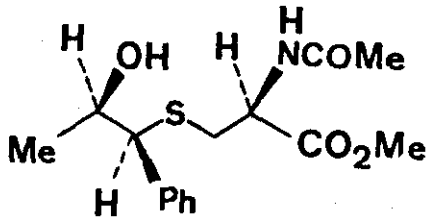
The duplicity of signals in the $^1H$ n.m.r. spectrum suggested that two isomers were present. This would be expected since the nucleophile which is added to the epoxide contains an asymmetric carbon. The two possible diastereoisomers (135a) and (135b) might be expected to show different chemical shifts for some of the signals in the $^1H$ n.m.r. spectra. Attempts to separate these diastereoisomers by t.l.c. were unsuccessful.

SCHEME 41


MeCOHN
CO2Me
+S
C6H10NO3S
[176]
MeCOHN
CO2Me
+CH2
C6H10NO3
[144]
MeCOHN
CO2Me
S
Me
OH
43 (Base Peak)
MeCOHN
CO2Me
+S
C13H16NO3S
[267]
MeCOHN
CO2Me
H
S+
C13H17NO3S
[266]




(135a)




(135b)

The structure of the diastereoisomeric mixture of (135) was confirmed from spectral data obtained for the acetate (136). The $^1$H n.m.r. spectrum showed a doublet of quartets at $\delta$ 5.10-5.40. This indicated attachment of the hydroxyl group at the $\beta$-carbon. The mass spectrum showed a molecular ion at m/e 353 and major peaks at m/e 266 and 43 (base peak).

The synthesis of the hydroxy sulphide (135) showed that the addition of a cysteine derivative to a $\beta$-alkylstyrene oxide was possible and gave a single regioisomer derived from attack at the $\alpha$-carbon. However, similar adducts of the epoxide (57) may not provide an intermediate to the target compound (132). This is due to the presence of an acetamido group in the molecule. Conversion of these groups to the free amines is known to be difficult.[124]

Rosenberger and Neukom[50] achieved the synthesis of LTE (9) using cysteine ethyl ester (46). This involved the reaction of an epoxide (LTA methyl ester in their case) and cysteine ethyl ester (46) in aqueous methanol and triethylamine (to pH 8.5). The use of cysteine ethyl ester, for reactions of the type described above, would remove the problem of amine deprotection.

Reaction of E-$\beta$-methylstyrene oxide (67a) with cysteine ethyl ester (64) under these conditions gave, after p.t.l.c., a diastereoisomeric mixture of the hydroxy sulphides (137). The i.r. spectrum showed bands at 3250-3500 (hydroxyl and amino groups) and 1740 (ester carbonyl) cm$^{-1}$. The $^1$H n.m.r. spectrum showed bands at $\delta$ 4.00-4.45

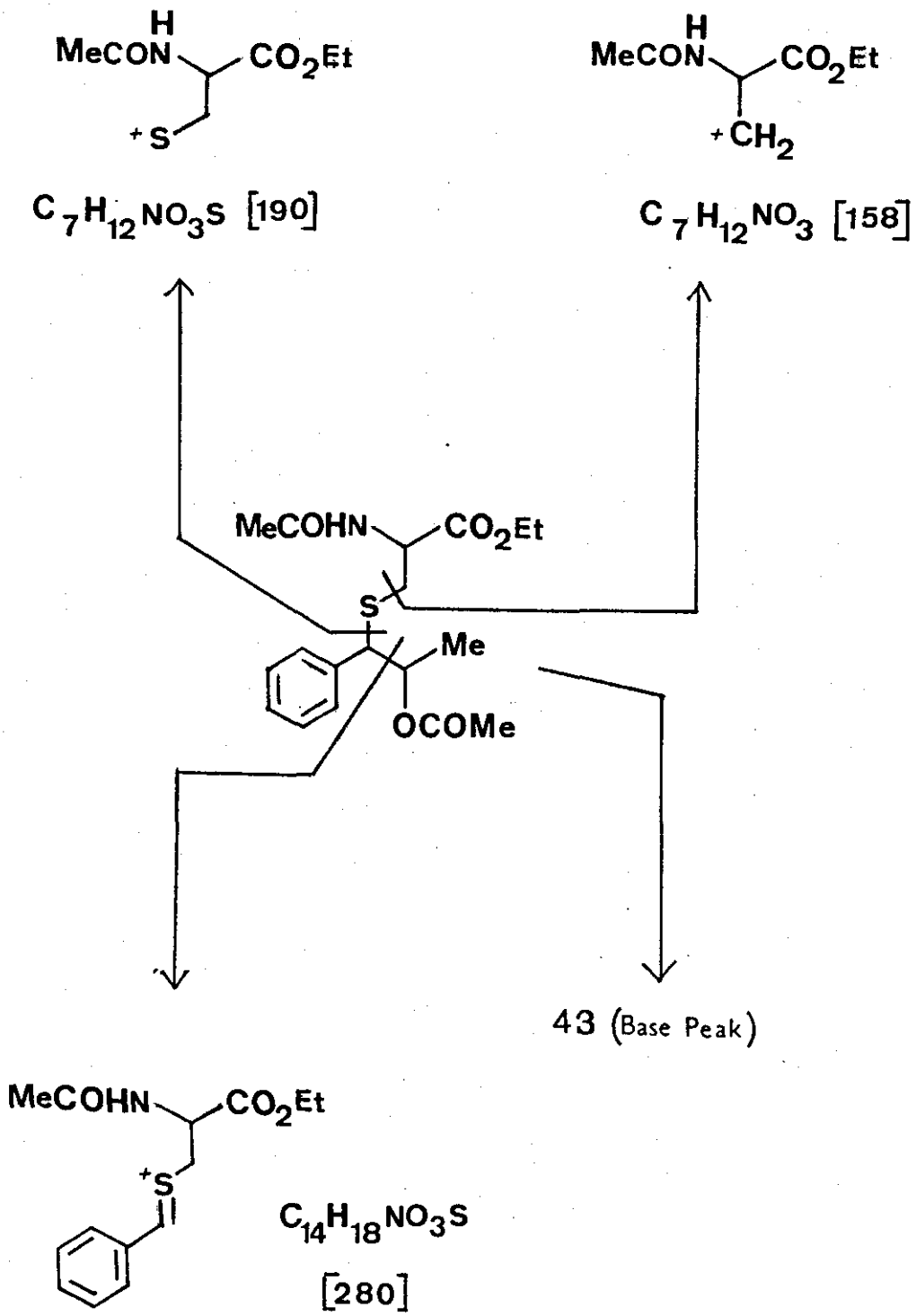
(m, -CHMe and $-CO_2CH_2-$), 3.96 (2xd,PhCH-), 2.10 (bs, exchangeable with $D_2O$,$-NH_2$) and 1.10-1.40 (m,$-CH_3$ and $-CO_2CH_2CH_3$). The mass spectrum showed a molecular ion at m/e 283, major peaks at m/e 239 and 238, and a base peak at m/e 43. The crystalline diacetyl-derivative (138) gave a correct elemental analysis.

Preparative t.l.c. of the diastereoisomeric mixture of hydroxy sulphides (137) on silica gel, eluting with benzene and ethylacetate (3:2) containing 1% triethylamine, allowed the separation of the diastereoisomers (Rf 0.3 and 0.4). The isomer at higher Rf value (0.4) was termed isomer 1 and that at lower Rf value (0.3) was termed isomer 2. Both diastereoisomers gave similar $^1H$ n.m.r. spectra except for the ester methyl triplets. The spectrum of isomer 1 showed this signal at $\delta$ 1.25 and in that of isomer 2 it appeared at $\delta$ 1.3.

Both diastereoisomers were converted to their corresponding diacetates. The 400 MHz. $^1H$ n.m.r. spectra[125] of both diacetates[f] were recorded. The spectrum of the diacetate of isomer 1 showed bands at $\delta$ 7.25-7.38 (m, Ph), 6.19(bd,-NH-), 5.19-5.28 (d of g,-CHMe), 4.70-4.77 (d of t,-NHCHCO-), 4.17-4.26 (d of q,$-CO_2CH_2CH_3$), 3.91 (d, PhCH-), 2.81-2.96 (d of q,$-S\,CH_2-$), 1.96 (s,$-OCOCH_3$), 1.91 (s,$-NHCOCH_3$), 1.30 (t,$-CO_2CH_2CH_3$) and 1.25 (d $-CH_3$). The spectrum of the diacetate of isomer 2 showed bands at $\delta$ 7.24-7.36 (m,Ph-), 6.20(bd,-NH-), 5.21-5.29 (d of q,-CHMe), 4.70-4.76 (d of t,-NHCHCO-), 4.06-4.20 (m,$-CO_2CH_2$ $CH_3$), 3.97 (d, PhCH-), 2.70-2.89 (d of q, $-S\,CH_2-$), 2.04 (s,$-OCO\,CH_3$), 1.94 (s $-NHCOCH_3$), 1.25 (d, $-CH_3$), and 2.12 (t, $-CO_2CH_2CH_3$). Both diacetates gave similar mass spectra showing peaks at m/e 280.0992 (9%) and 280.1023 (7%), 190.0532 (10%) and 190.0515 (12%), 153.0807 (33%) and 158.0817 (29%) respectively, and a base peak at m/e 43. These

[f] From the 400 MHz. $^1H$ n.m.r. spectrum,[125] isomer 1 appeared to be contaminated (< 4% ) with isomer 2.

SCHEME 42


MeCON H CO2Et
+S
C7H12NO3S [190]
MeCON H CO2Et
+CH2
C7H12NO3 [158]
MeCOHN CO2Et
S
Me
OCOMe
43 (Base Peak)
MeCOHN CO2Et
+S
C14H18NO3S
[280]

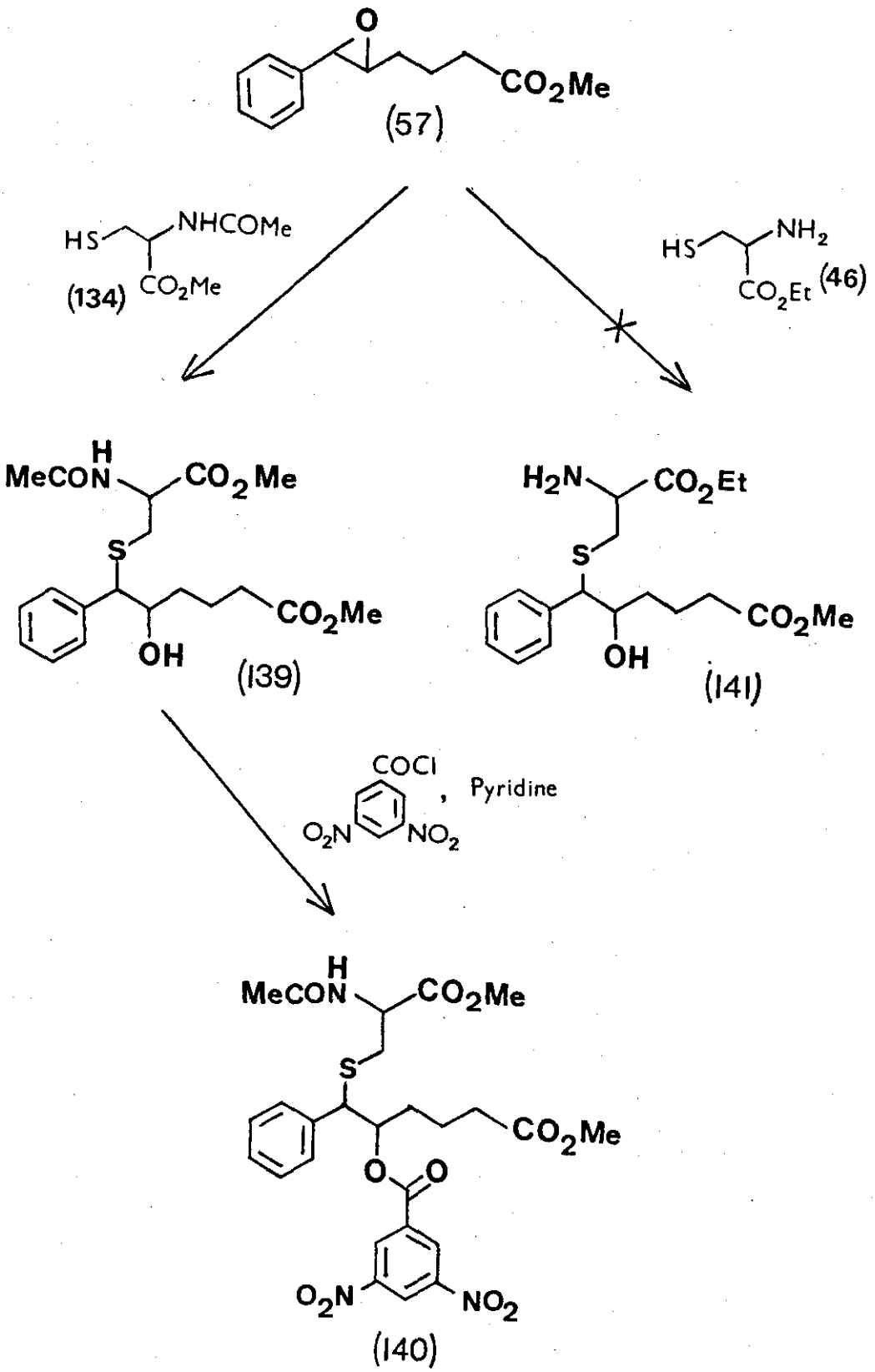
peaks were thought to arise from fragmentations (scheme 42) similar to those shown in scheme 41.

Although these data showed that the expected hydroxy sulphide (137) had been formed, they did not allow the assignment of absolute configuration to the two diastereoisomers. They did, however, show that the addition of cysteine ethyl ester to a $\beta$-alkylstyrene oxide was possible. This in turn implied that similar additions to the epoxide (57) might provide a route to the target compound (132).

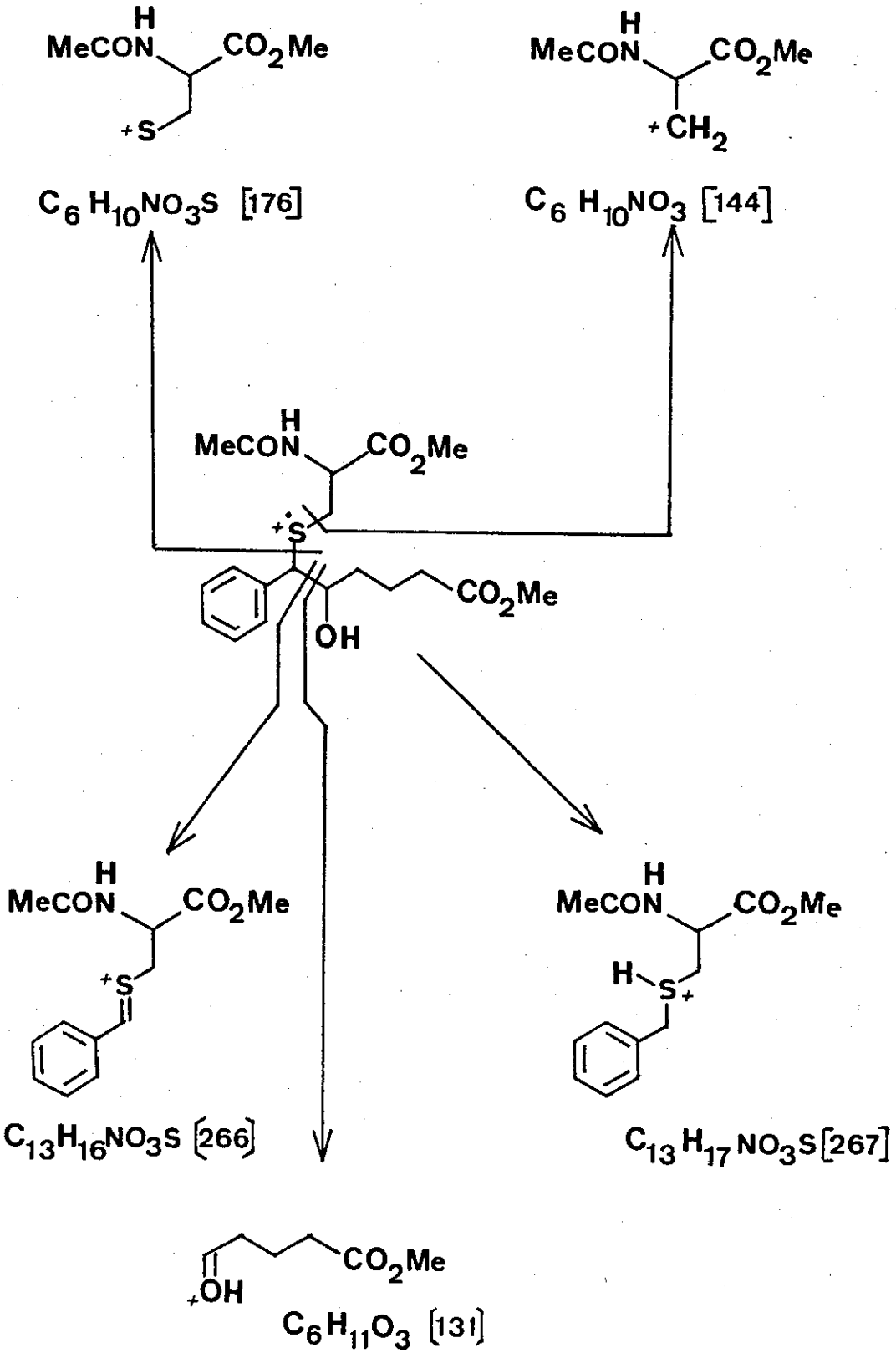
Notwithstanding the deprotection problems associated with the use of N-acetylcysteine derivatives, the reaction of N-acetylcysteine methyl ester (134) with the epoxide (57) was investigated preparatory to the use of more suitably protected cysteine derivatives. Reaction of the epoxide (57) with N-acetyl cysteine methyl ester (134) (scheme 43) gave the expected diastereoisomeric mixture of 5-hydroxy-6-(N-acetylmethylcysteinyl)-6-phenylhexanoate (139). The i.r. spectrum showed a band at 3160-3700 $cm^{-1}$, which was assigned to the hydroxyl and amide -NH groups, and carbonyl stretching frequencies at 1740 (ester), 1660, and 1540 (amide) $cm^{-1}$. The $^1H$ n.m.r. spectrum showed bands at $\delta$ 7.30 (bs,Ph-), 6.30-6.80 (bm,-NH-), 4.50-4.95 (m,NH-CHCO-), 3.80-4.10 m (PhCH- and -CHOH), 3.65 and 3.75(2 x s, amino acid ester $-CH_3$), 3.62 (s,$-CO_2CH_3$), 2.66-3.00 (m, $-CH_2S-$), 2.13-2.40 (m,$-CH_2CO_2Me$), 1.90 and 2.02 (2 x s,$-NHCOCH_3$), and 1.20-2.00 (m, 4H). The mass spectrum did not show a molecular ion but did show characteristic peaks at m/e 267.0928 (30%), 266.0867 (10%), 176.0372 (98%), 144.0653 (76%), and 131.0734 (5%). These peaks were thought to arise from the fragmentations shown in scheme 44.

The regioselectivity of ring opening was confirmed by the $^1H$ n.m.r. spectrum of the 3,5-dinitrobenzoate derivative (140). This spectrum

SCHEME 43


O
CO2Me
(57)
HS
NHCOMe
CO2Me
(134)
HS
NH2
CO2Et
(46)
MeCON
H
CO2Me
S
OH
CO2Me
(139)
H2N
CO2Et
S
OH
CO2Me
(141)
COCl
O2N
NO2
, Pyridine
MeCON
H
CO2Me
S
CO2Me
O
O
O2N
NO2
(140)

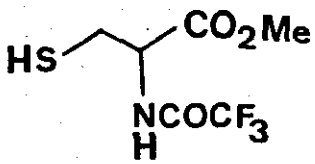
SCHEME 44


MeCON H CO2Me
+S
C6 H10NO3S [176]
MeCON H CO2Me
+CH2
C6 H10NO3 [144]
MeCON H CO2Me
+S
CO2Me
OH
MeCON H CO2Me
+S
C13H16NO3S [266]
MeCON H CO2Me
H
S+
C13 H17 NO3S [267]
CO2Me
+OH
C6H11O3 [131]

showed bands at $\delta$ 5.28–5.62 (m,-$CH_2$-C<u>H</u> O-) and 4.15 and 4.26 (2xd, PhC<u>H</u>-). These bands indicated that the hydroxyl group formed on ring opening was attached to the $\beta$-carbon.

Reaction of the epoxide (57) with cysteine ethyl ester (scheme 43) did not give the required hydroxy sulphide (141). The $^1$H n.m.r. spectra obtained for the crude products implied that epoxide opening had taken place, but attempts to purify these crude mixtures by various techniques (p.t.l.c., column chromatography, H.P.L.C.) did not provide any of the expected product.

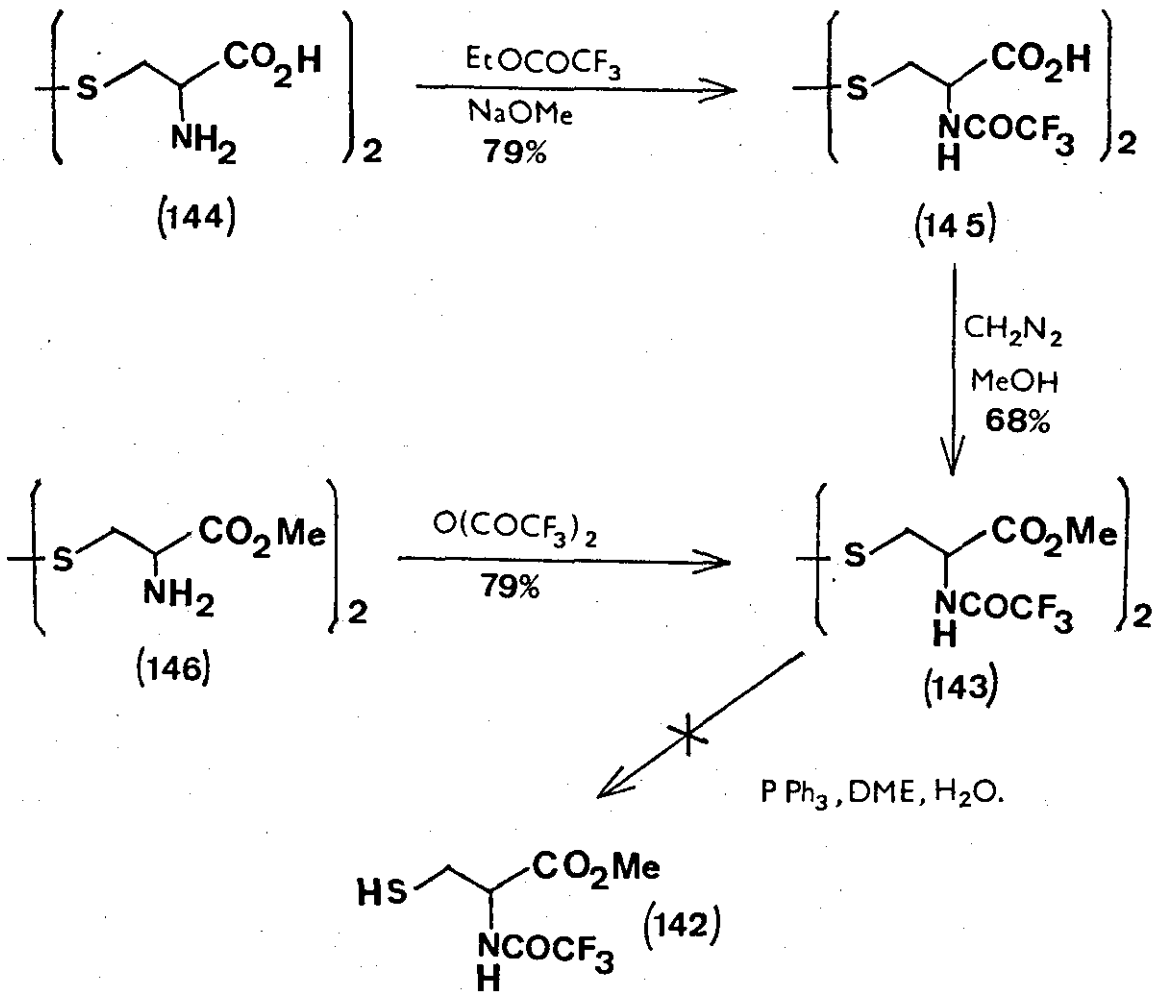
Owing to this result, the preparation of N-trifluoroacetylcysteine methyl ester (142) was investigated (scheme 45). Since trifluoroacetamides are easily converted to the free amine,[29] it was thought that if a conjugate of this cysteine derivative and the epoxide (57) could be prepared, this might provide a route to the target compound (132).



(142)

Bis-N-trifluoroacetylcystine dimethyl ester (143) was prepared by two different routes. The first involved the reaction of cystine (144) with ethyl trifluoroacetate[126] which gave bis-N-trifluoroacetylcystine (145). Treatment of this product with diazomethane[123] afforded the fully protected cystine derivative (143). The second route involved the trifluoroacetylation of cystine dimethylester (146) with trifluoroacetic anhydride and sodium carbonate.[127] Both routes provided pure samples of the required cystine derivative (143).

SCHEME 45




(144) (145) (146) (143) (142)

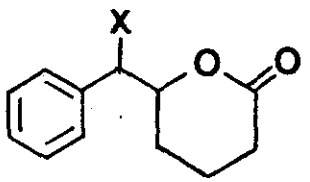
The reduction of the cystine derivative (143) with triphenylphosphine in aqueous dimethoxyethane is reported to give the required amino acid derivative (142).[42,127] However, in our hands only crude samples of this amino acid could be obtained. Attempted purification by column chromatography on silica gel (dichloromethane, hexane) and H.P.L.C.,[127] under the same conditions, proved unsuccessful.

The results described above were disappointing and further investigation is required. Particularly frustrating was our inability to obtain pure samples of N-trifluoroacetylcysteine methyl ester (142). Taking into account the result obtained for the opening of the

epoxide (57) with N-acetylcysteine methyl ester (134), the proposed route to the target compound using the trifluoroacetylcysteine derivative (142) seemed very promising.

Another surprising result was that obtained for the reaction of cysteine ethyl ester (46) and the epoxide (57). Similar reaction with E-$\beta$-methylstyrene oxide (67a) gave the expected product and implied that this was a viable route to the target compound (132).

Although the target compound (132) was not obtained, the preparation of its fully, though not ideally, protected analogue (135) was encouraging and it seemed likely that further investigation of the routes discussed will probably provide this LTE analogue.

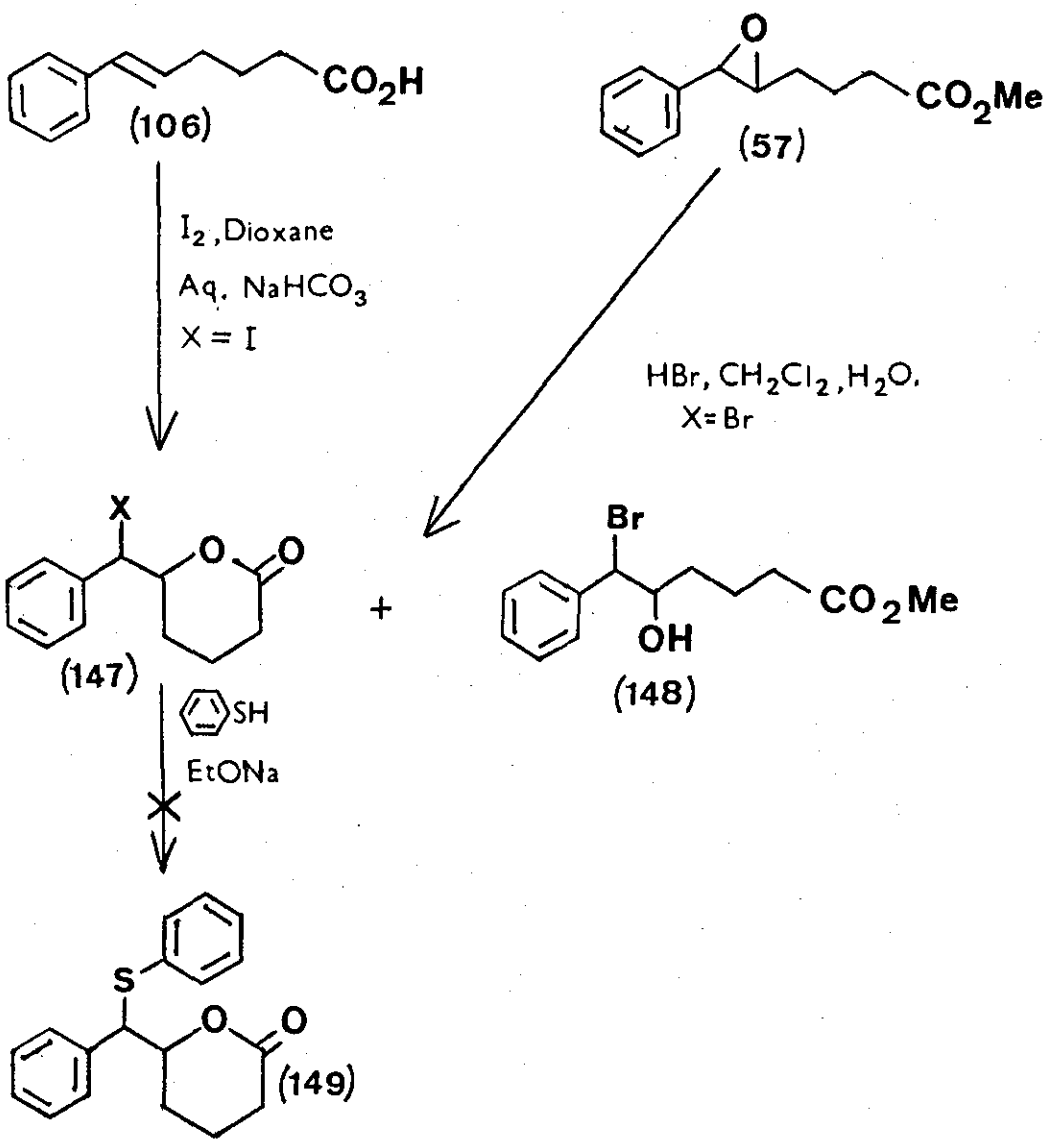



(147)

Alternative routes to the target compound (132) via a halolactone of the type (147) were also investigated. The use of lactones of this type would eliminate any problems of regiochemistry and also provide internal protection for the carboxylic acid group.

The iodolactone (147, X = I) was prepared in poor yield (25%) by treatment of the acid (*106*) with iodine and sodium bicarbonate in aqueous dioxane (scheme 46). This lactone was characterised from the following information. The $^{1}$H.n.m.r. spectrum showed bands at $\delta$ 5.12 (d, -CHI) and 4.20-4.58 (m, -COOC<u>H</u>CH$_2$). The i.r. spectrum showed a band at 1730 cm$^{-1}$. The mass spectrum did not show a molecular ion but did show a characteristic base peak at m/e 189 (M-I). The structure was confirmed by the $^{13}$C n.m.r. spectrum which showed bands

SCHEME 46




at $\delta$ 170.5 (s, C = o), 139.9 (s), 123.9 (d), 123.6 (d), 82.9 (d, O-CH), 34.5 (d, CHI), 29.4 (t, $-CH_2$ CO-), 27.0 (t, -O CH $CH_2$-), and 18.1 (t, $-CH_2CH_2CH_2-$).

Treatment of the epoxide (57) with aqueous hydrogen bromide gave a mixture of the halolactone (147, X= Br) and the bromohydrin (148), in 47 and 41% yield respectively. The bromohydrin (148) was converted to the bromolactone (147, X=Br) by heating under reflux in benzene and p-toluene sulphonic acid. The i.r. spectrum of the bromolactone (147, X=Br) showed a carbonyl stretching frequency at

1740 $cm^{-1}$. The $^1H$ n.m.r. spectrum showed bands at $\delta$ 5.00 (d,-C<u>H</u>Br) and 4.45-4.88 (m, COOC<u>H</u> $CH_2$), and the mass spectrum showed a doublet at m/e 268 and 270.

Reactions of both the halolactones with thiophenol and sodium ethoxide in ethanol did not give the expected lactone (149) and a complex mixture of products was obtained. These preliminary experiments suggested that this approach to the target compound (132) via a halolactone may require considerable further investigation and it was not pursued in view of the more promising results obtained from the alternative, epoxide approach.

# 3. EXPERIMENTAL

## EXPERIMENTAL

All solvents were routinely distilled before use and aprotic solvents were stored over sodium wire. Dimethylsulphoxide, N,N-dimethylformamide, and hexamethylphosphoramide were dried by standing over calcium hydride, vacuum distilled, and stored over molecular sieve. Tetrahydrofuran and dimethoxy ethane were distilled from lithium aluminium hydride as required. Methanol and ethanol were distilled after reaction with magnesium and a catalytic amount of iodine. Pyridine and triethylamine were distilled and stored over potassium hydroxide pellets. Unless otherwise stated, all solutions of products in organic solvents were dried over anhydrous magnesium sulphate.

Analytical thin layer chromatography (t.l.c.) was carried out on either silica gel (Merck Art. 7747) or alumina (Merck Art. 1103) with layers 0.75 mm thick. Products were detected by iodine vapour, ultra violet light, and 5% chlorosulphonic acid in acetic acid followed by heating to 250°C for 10 minutes. Preparative t.l.c. was performed on silica gel or alumina (as described above) spread on 1 m plates at a thickness of 0.75 mm. Column chromatography was carried out using silica gel (Hopkins and Williams 7555/75-150 $\mu$m) or alumina (Hopkin and Williams "Camag") with a stationary phase to product ratio of 30:1.

Analytical gas liquid chromatography (g.l.c.) was run using a Pye 104 series chromatograph with a hydrogen flame ionization detector. A five foot column of 3% SE30 on Chromasorb W was used for all determinations.

$^{1}H$ Nuclear magnetic resonance (n.m.r.) spectra were recorded for 20% w/v solutions in deuteriochloroform or 10% $[^{2}H]_{6}$ dimethyl-

sulphoxide in deuteriochloroform, with tetramethylsilane as internal standard. The spectra were recorded at 90 MHz using a Perkin-Elmer R32 spectrometer. $^{13}C$ n.m.r. spectra were recorded using a Brucker WP80 spectrometer. Multiplicity of $^{13}C$ n.m.r. signals were obtained from the off-resonance spectra.

Infra-red (i.r.) spectra were recorded for thin films or nujol mulls, using a Perkin-Elmer 257 spectrometer. Ultra-violet (u.v.) spectra were obtained for ethanolic solutions using a Pye-Unicam SP8-100 spectrophotometer. Mass spectra (m.s.) were recorded on an A.E.I. M.S. 12 or a Kratos M.S. 80 spectrometer. High resolution mass spectrometry were carried out on a Kratos M.S. 50 spectrometer at the Physio-chemical Measurements Unit (P.C.M.U.), courtesy of the Science and Engineering Research Council (S.E.R.C.).

Melting points were determined on a Kofler hot stage apparatus and are uncorrected.

1. General Procedure for Epoxidation of Olefins[84]

A solution of the olefin (ca. 5 g) in dichloromethane (100 ml) was cooled in an ice bath, treated with 85% m-chloroperoxybenzoic acid (1.1 equivalents), and stirred for 4 hours at room temperature. The reaction mixture was diluted with dichloromethane (100 ml), washed with saturated sodium sulphite (50 ml), and 5% sodium bicarbonate (3 x 50 ml), and evaporated. Column chromatography on silica gel, eluting with ether, gave the epoxide.

2. General Procedure for Thiol Openings of Epoxides[29]

The epoxide (200 mg), triethylamine (4 equivalents), the thiol (3 equivalents), and methanol (1 ml) were stirred under nitrogen until

t.l.c. indicated complete reaction. The reaction mixture was diluted with ether (30 ml), washed with 5% sodium bicarbonate (3 x 20 ml) and dilute hydrochloric acid (3 x 20 ml), and evaporated. P.t.l.c. on silica, eluting with benzene and ethyl acetate (10:1), gave the hydroxy sulphide(s).

3. General Procedure for Acetylation of Alcohols

The alcohol (ca. 100 mg) was dissolved in a mixture of pyridine (2 ml) and acetic anhydride (1 ml) and was left to stand at room temperature for 24 hours. The reaction mixture was poured into ether (30 ml), washed with 5% sodium bicarbonate (3 x 10 ml) and dilute hydrochloric acid (3 x 10 ml), and evaporated. Preparative t.l.c. on silica gel, eluting with benzene, gave the acetate.

4. Preparation of E-β-Methylstyrene Oxide (67a)

E-β-Methylstyrene (5 g) was converted to E-β-methylstyrene oxide (5.1 g, 80%) using the procedure outlined in experiment 1.

IR:- $\nu_{max}$ 750, 705 $cm^{-1}$.

$^1$H N.M.R.:- $\delta$ 7.25 (s, 5H), 3.50 (d, 1H), 2.90 - 3.20 (dq, 1H), 1.45 (d, 3H).

MS:- m/e 134 ($M^+$).

5. Reaction of E-β-Methylstyrene Oxide (67a) with Thiophenol

E-β-Methylstyrene oxide was allowed to react with thiophenol, under the conditions described in experiment 2, yielding erythro-2-hydroxy-1-phenyl-1-(phenylthio) propane (74) as a yellow oil. (319 mg, 87%).

IR:- $\nu_{max}$ 3500, 750, 700 $cm^{-1}$.

$^1$HNMR:- δ 7.10 - 7.45 (m, 10 H), 3.96 - 4.30 (m, 2H), 2.5 (bs, $D_2O$ exchangeable, 1H), 1.20 (d, 3H).

MS:- m/e 244.0922 ($M^+$); $C_{15}H_{16}OS$ requires 244.0922, 200.0664 (100%);

$C_{13}H_{12}S$ requires 200.0660, 199.0593 (85%);

$C_{13}H_{11}S$ requires 199.0581.

Erythro-2-hydroxy-1-phenyl-1-(phenylthio)propane was acetylated using the procedure described in experiment 3. Erythro-2-acetoxy-1-phenyl-1-(phenylthio)propane (75) was isolated as a yellow oil (93%).

IR:- $\nu_{max}$ 1740, 1240 $cm^{-1}$.

$^1$HNMR:- δ 7.05 - 7.40 (m, 10H), 5.30 (dq , 1H), 4.26 (d, 1H), 1.88 (s, 3H), 1.30 (d, 3H).

MS:- 286 ($M^+$), 199, 43 (base peak).

6. Reaction of E-β-Methylstyrene Oxide (67a) with Benzylthiol

Reaction of E-β-Methylstyrene oxide (67a) with benzylthiol under the conditions described in experiment 2 gave erythro-2-hydroxy-1-phenyl-1-(phenylmethylthio)propane (76) as a yellow oil (293 mg, 76%).

IR:- $\nu_{max}$ 3430, 755, 700 $cm^{-1}$

$^1$HNMR:- δ 7.00 - 7.45 (m, 10 H), 3.98 (dq, 1 H), 3.6 (d, 1 H), 3.46 (q, 2 H), 2.40-2.80 (bs, $D_2O$ exchangeable, 1 H), 1.15 (d, 3 H).

MS:- m/e 214.0808 (26%); $C_{14}H_{14}S$ requires 214.0800, 213.0737 (8%); $C_{14}H_{13}S$ requires 213.0738, 91.0560 (100%); $C_7H_7$ requires 91.0573.

Erythro-2-hydroxy-1-phenyl-1-(phenylmethylthio)propane was acetylated using the procedure described in experiment 3. Erythro-2-acetoxy-1-phenyl-2-(phenylthio)propane (77) was isolated as a yellow oil (79%).

IR:- $\nu_{max}$ 1735, 1235 $cm^{-1}$.

$^1$HNMR:- δ 7.05 - 7.40 (m, 10 H), 5.25 (dq, 1 H), 3.75 (d, 1 H), 3.50 (q, 2 H), 1.86 (s, 3 H), 1.20 (s, 3 H).

MS:- m/e300 ($M^+$), 213, 91, 43 (base, peak).

7. Preparation of Ethyltriphenylphosphonium Bromide (80)

Triphenylphosphine (26 g) and ethyl bromide (10 g) were placed in a sealed tube and heated in an oven (100°C) for 4 hours. The solid was removed, ground to a fine powder and washed with benzene. Recrystallisation from water gave ethyltriphenylphosphonium bromide (34 g, 98%), m.p. 205 - 208°C (Lit.[128] 206.5 - 207.5 °C).

8. Preparation of Z-β-Methylstyrene (73b)

A suspension of ethyltriphenylphosphonium bromide (16 g) in dry benzene (100 ml) was stirred under nitrogen and treated with a solution of 1.5 M n-butyllithium in hexane (28 ml). After 30 min., a solution of benzaldehyde (2.3 g) in benzene (20 ml) was added dropwise over 10 min. and the stirring was continued for a further 6 hours.

The reaction mixture was poured into petroleum ether (200 ml), filtered, washed with water (3 x 100 ml), and evaporated. Column chromatography on silica gel (hexane) and distillation gave Z-β-methylstyrene (2.3 g, 90%), b.p.$_{20}$ 65-70°C (Lit[129] b.p.$_{20}$ 64.5°C).

IR:- $\nu_{max}$ 755, 700 $cm^{-1}$.

UV:- $\lambda_{max}$ 247 nm ($\varepsilon$ 10,900).

$^1$HNMR:- $\delta$ 7.30 (s, 5 H), 5.60-6.50 (m, 2 H), 1.90 (d, 3 H).

MS:- m/e 118 ($M^+$).

GLC:- E: Z ratio; 25:75.

9. Alternative Preparation of Z-β-Methylstyrene (78b)

A suspension of ethyltriphenylphosphonium bromide (3.7 g) in benzene (30 ml) and hexamethylphosphoramide (10 ml) was stirred under nitrogen and treated with a 1.5 M solution of n-butyllithium in hexane (6.7 ml). After stirring at room temperature for 30 min., a solution of benzaldehyde (1 g) in benzene (5 ml) was added dropwise over 10 mm., and the stirring was continued for a further 6 hours. The reaction mixture was poured into petroleum ether (100 ml), filtered washed with water (3 x 30 ml) and evaporated. Column chromatography on silica gel (hexane) and distillation gave Z-β-methylstyrene (1.05 g, 94%), b.p.$_{20}$ 64-68°C (Lit.$^{129}_{20}$ 64.5°C).

GLC:- E : Z ratio; 15 : 85.

10. Preparation of Z-β-Methylstyrene Oxide (67b)

Z-β-Methylstyrene (5.0 g, 75% Z by g.l.c.) was converted to Z-β-methylstyrene oxide (4.05, 59%) using the procedure outlined in experiment 1.

IR:- $\nu_{max}$ 750, 705 $cm^{-1}$.

$^1$HNMR:- δ 7.25 (m, 5 H), 4.05 (d, 1 H), 3.20 - 3.45 (dq, 1 H), 1.10 (d, 3 H).

MS:- m/e 134 ($M^+$).

11. Reaction of Z-β-Methylstyrene Oxide (67b) with Thiophenol

Z-β-Methylstyrene Oxide (75% E by g.l.c.) was treated with thiophenol as described in experiment 2. Preparative t.l.c. gave:

(1) 2-Hydroxy-1-phenyl-1-(phenylthio)propane (74) as a mixture of diastereoisomers (178 mg, 48%).

IR:- $\nu_{max}$ 3500, 750, 700 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.10 - 7.50 (m, 10 H), 3.95 - 4.30 (m, 2 H), 2.45 (bs, $D_2O$ exchangeable, 1 H), 1.20, 1.05 (2 x d, 3 H). Integration of peaks ($\delta$ 1.20, 1.05) gave erythro : threo ratio as 1 : 1.

MS:- m/e 244.0925 ($M^+$); $C_{15}H_{16}S\,O$ requires 244.0922.

(2) Threo-1-hydroxy-1-phenyl-2-(phenylthio)propane (81) (170 mg, 46%).

IR:- $\nu_{max}$ 3440, 750, 700 $cm^{-1}$

$^1$HNMR:- $\delta$ 7.00-7.55 (m, 10 H), 4.35 (d, 1 H) 3.26 (dq, 1 H), 1.05 (d, 3 H).

MS:-m/e 244.0920 ($M^+$); $C_{15}H_{16}OS$ requires 244.0922, 138.0491 (100%); $C_8H_{10}S$ requires 138.0503, 137.0416 (93%); $C_8H_9S$ requires 137.0425.

The diastereoisomeric mixture of 2-hydroxy-1-phenyl-1-(phenylthio) propane was acetylated using the procedure described in experiment 3. 2-Acetoxy-1-phenyl-1-(phenylthio) propane (75) was isolated as a yellow oil (92%).

IR:- $\nu_{max}$ 1730, 1230 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.20-7.40 (m, 10 H), 5.35 (m, 1 H),4.30, 4.35 (2 x d, 1 H), 1.90, 1.98 (2 x s, 3 H) 1.20, 1.30 (2 x d, 3 H).

MS:- m/e 286 ($M^+$), 199, 73 (base peak).

Threo-1-hydroxy-1-phenyl-2-(phenylthio)propane was also acetylated using the procedure described in experiment 3. Threo-1-acetoxy-1-phenyl-2-(phenylthio)propane (82) was isolated as a clear oil (91%).

IR:- $\nu_{max}$ 1740, 1230, 750, 700 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.05-7.55 (m, 10 H), 5.80 (d, 1 H) 3.62 (dq, 1 H), 1.96 (s, 3 H), 1.15 (d, 3 H).

MS:- m/e 286 ($M^+$), 137, 43 (base peak).

12. Reaction of Z-$\beta$-Methylstyrene Oxide (67b) with Benzylthiol

Z-$\beta$-Methylstyrene Oxide (75% E by g.l.c.) was treated with benzylthiol as described in experiment 2. Preparation t.l.c. gave:

(1) 2-Hydroxy-1-phenyl-1-(phenylmethylthio)propane (76) as a mixture of diastereoisomers (120 mg, 31%).

IR:- $\nu_{max}$ 3430, 755, 705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.05-7.40 (m, 10 H), 4.05 (m, 1 H), 3.70 (d, 1 H), 3.53 (q, 2 H), 2.20 (bs, $D_2O$ exchangeable, 1 H), 1.15, 1.05 (2 x d, 3 H). Integration of peaks ($\delta$ 1.15, 1.05) gave erythro : threo ratio as 1.3 : 1.

MS:- m/e 214.0811 (44%); $C_{14}H_{14}S$ requires 214.0817, 213.0734 (18%); $C_{14}H_{13}S$ requires 213.0738, 91.0555 (100%); $C_7H_7$ requires 91.0547.

(2) Threo-1-hydroxy-1-phenyl-2-(phenylmethylthio)propane (83) (90 mg, 23%).

IR:- $\nu_{max}$ 3440, 760, 705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.20-7.50 (m, 10 H), 4.43 (d, 1 H), 3.70 (s, 2 H) 3.25-2.60 (bs, $D_2O$ exchangeable, 1 H), 2.93 (dq, 1 H) 1.05 (d, 3 H).

MS:- m/e 258.1046 ($M^+$); $C_{16}H_{18}OS$ requires 258.1015, 152.0664 (64%); $C_9H_{12}S$ requires 152.0660, 151.0569 (30%); $C_9H_{11}S$ requires 151.0582.

The diastereoisomeric mixture of 2-hydroxy-1-phenyl-1-(phenyl methylthio) propane was acetylated using the procedure described in experiment 3. 2-Acetoxy-1-phenyl-1-(phenylmethylthio) propane (77) was isolated as a yellow oil (91%).

IR:- $\nu_{max}$ 1740, 1235, 760, 705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.15-7.45 (m, 10 H), 5.23 (dq, 1 H), 3.75, 3.78 (2 x d, 1 H), 3.50 (g, 2 H), 1.88, 2.05 ( 2 x s, 3 H), 1.10, 1.20 (2 x d, 3 H).

MS:- m/e 300 ($M^+$), 213, 91, 43 (base peak).

Threo-1-hydroxy-1-phenyl-2-(phenylmethylthio)propane was also acetylated using the procedure described in experiment 3. Threo- 1-acetoxy-1-phenyl-2-(phenylmethylthio) propane (84) was isolated as a yellow oil (85%).

IR:- $\nu_{max}$ 1740, 1235, 760, 705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.18-7.50 (m, 10 H) 5.80 (d, 1 H), 3.70 (s, 2 H) 3.00 (dq, 1 H), 2.05 (s, 3 H), 1.10 (d, 3 H).

MS:- m/e 300 ($M^+$), 151, 91, 43 (base peak).

13. Preparation of Z-4-Methoxy-$\beta$-Methylstyrene (86b)

A suspension of ethyltriphenylphosphonium bromide (37a) in dry tetrahydrofuran (200 ml) and hexamethylphosphoramide (65 ml) was stirred under nitrogen and treated with a solution of 1.5 M n-butyl-lithium (66 ml). After 30 min., a solution of anisaldehyde (10 g) in dry tetrahydrofuran was added dropwise and the resulting mixture stirred for 2 hours.

The reaction mixture was poured into ether (2000 ml), filtered, washed with water (3 x 200 ml), and evaporated. Column chromatography

silica gel (hexane) followed by distillation gave pure 4-methoxy-β-methylstyrene (9.2 g, 85%), $bp_{15}$ 100-112°C (Lit.[130] $b.p._{16}$ 106-112°C).

IR:- $\nu_{max}$ 1250, 1035, 840 $cm^{-1}$.

UV:- $\lambda_{max}$ 257 nm (ε 15, 700).

$^1$HNMR:- δ 6.85-7.40 (m, 4 H), 5.48-6.60 (m, 2H), 3.80 (s, 3 H) 1.88 (d, 3 H).

MS:- m/e 148 ($M^+$).

GLC:- E : Z ratio; 15 : 85.

14. General Procedure for Preparation of Bromohydrins (89, $R^2$= H)

A solution of the olefin (1 g) in the appropriate solvent (30 ml) and water (2 ml) was cooled in an ice bath and treated with 14% aqueous perchloric acid (2.5 ml). Solid N-bromoacetamide (1.4 g) was added portionwise ensuring that the temperature remained below 20°C. The ice bath was removed and the solution was stirred for 30 minutes after which it was returned to the ice bath and treated with 1% sodium dithionite (20 ml). The reaction mixture was poured into water (50 ml) and extracted with ether (3 x 30 ml). The extracts were combined, washed with 5% sodium bicarbonate (3 x 30 ml) and brine (20 ml), and evaporated. The bromohydrins were obtained as yellow oils. Silica gel was used for chromatography, where necessary, eluting in toluene. Yields are recorded in table 2 (see p. 50).

Acetylated bromohydrins (89 $R^2$ = COMe) were obtained using the procedure described in experiment 3. $^1$H.n.m.r. spectra were recorded for all products and data obtained from these spectra are given in table 3 (see p. 51).

15. Conversion of the Bromohydrins (89) to the Epoxides (90)

A cold ( $< 5^{\circ}C$), stirred solution of potassium hydroxide (0.1 g) in methanol (5 ml) was treated with a solution of the bromohydrin (0.2 g) in methanol (5 ml). After 15 minutes, the reaction mixture was poured into water (20 ml) and extracted with ether (3 x 10 ml). The extracts were combined, washed with water (3 x 10 ml); and evaporated.

Yields are recorded in table 2 (see p. 50) and $^1$H n.m.r. data are shown in table 4 (see p. 51).

16. Preparation of Z-4-Methoxy-β-methylstyrene Oxide (85b)

85% m-Chloroperoxybenzoic acid (7.5 g) was dissolved in dichloromethane (100 ml) and treated sequentially with 5% aqueous sodium bicarbonate (30 ml) and a solution of Z-4-methoxy-β-methylstyrene (5.0 g)* in dichloromethane (10 ml). After vigorous stirring for 2 hours, the reaction mixture was poured into ether (100 ml) and the layers separated. The organic layer was washed with 5% sodium bicarbonate (3 x 50 ml) and evaporated. Column chromatography on basic alumina (ether) gave Z-4-methoxy-β-methylstyrene oxide (5.7 g, 86%).

IR:- $\nu_{max}$ 1250, 1035, 830 $cm^{-1}$.

$^1$HNMR:- δ 6.85-7.40 (m, 5 H), 4.00 (d, 1 H), 3.20-3.40 (dq, 1H), 1.10 (d, 3 H).

MS:- m/e 164 ($M^+$).

*85% Z by $^1$H n.m.r.

17. Reaction of E-4-Methoxy-$\beta$-Methylstyrene Oxide (85b) with Thiophenol

E-4-Methoxy-$\beta$-methylstyrene oxide (90% E by $^1$H n.m.r.) was allowed to react with thiophenol under the conditions described in experiment 2. Erythro-2-hydroxy-1-(4-methoxyphenyl)-1-(phenylthio) propane (99) was isolated as a yellow oil (300 mg, 90%).

IR:- $\nu_{max}$ 3420, 1495, 1260, 1055, 815, 745, 690 cm$^{-1}$.

$^1$HNMR:- $\delta$ 6.70-7.35 (m, 9 H), 3.90-4.25 (m, 2 H), 3.75 (s, 3 H), 2.25 (bs, $D_2O$ exchangeable, 1 H), 1.22 (d, 3 H).

MS:- m/e 274.1017 ($M^+$); $C_{16}H_{18}O_2S$ requires 274.1028, 229.0663 (26%); $C_{14}H_{13}OS$ requires 229.0687, 165.0917 (100%); $C_{10}H_{13}O_2$ requires 165.0916.

Erythro-2-hydroxy-1-(4-methoxyphenyl)-1-(phenylthio)propane was acetylated using the procedure outlined in experiment 3. Erythro-2-acetoxy-1-(4-methoxyphenyl)-1-(phenylthio)propane (100) was isolated as a yellow oil (82%).

IR:- $\nu_{max}$ 1740, 1240 cm$^{-1}$.

$^1$HNMR:- $\delta$ 6.52-7.56 (m, 9 H), 5.20 (dq, 1 H), 4.20 (d, 1 H), 3.70 (s, 3H), 1.90 (s, 3 H), 1.22 (d, 3 H).

MS:- m/e 316 ($M^+$).

18. Reaction of Z-4-Methoxy-β-methylstyrene Oxide (85b) with Thiophenol

Z-4-Methoxy-β-methylstyrene oxide (85% Z by $^1$H n.m.r.) was allowed to react with thiophenol under the conditions described in experiment 2. Threo-2-hydroxy-1-(4-methoxyphenyl)-1-(phenylthio)propane (99) was isolated, after crystallisation, as colourless needles, m.p. 60-62°C, (213 mg, 64%).

IR:- $\nu_{max}$ 3420, 1495, 1260, 1055, 815, 745, 690 $cm^{-1}$.

$^1$HNMR:- $\delta$ 6.70-7.35 (m, 9 H), 3.85-4.20 (m, 2 H), 3.72 (s, 3 H), 2.80 (bs, $D_2O$ exchangeable, 1 H), 1.10 (d, 3 H).

MS:- m/e 274.1025 ($M^+$); $C_{16}H_{18}O_2S$ requires 274.1028, 229.0686 (33%); $C_{14}H_{13}OS$ requires 229.0687, 165.0918 (100%); $C_{10}H_{13}O_2$ requires 165.0916.

Elemental Analysis:- C; 70.0, H; 6.7, S; 11.5%.

$C_{16}H_{18}O_2S$ requires; C; 70.07, H; 6.56, S; 11.68%.

19. Preparation of Benzyltriphenylphosphonium Bromide (102)

A solution of triphenylphosphine (9.0 g) in benzene (100 ml) was refluxed with benzyl bromide (5.7 g) for 3.5 hours. The resulting solid was filtered, washed with benzene (20 ml) and ether (2 x 10 ml), and recrystallised from dimethylformamide yielding benzyltriphenylphosphonium bromide as colourless needles (12.4 g, 85%), m. p. 284-285 °C (Lit.[131] m.p. 280.5 °C).

20. Preparation of 6-Phenyl-5-hexen-1-ol (104)

Dimethylsulphoxide (400 ml) was stirred under a flow of nitrogen and treated with sodium hydride (60% suspension in paraffin, 7.15 g). The suspension was heated on a water bath (75-80°C) until all the sodium hydride had disappeared. After cooling to room temperature, the solution was treated with solid benzyltriphenylphosphonium bromide (75.5 g) and stirred for 30 mins. A solution of 5-hydroxypentanal (10 g) was added and the stirring continued for 18 hours. The reaction mixture was poured into ether (250 ml), filtered, washed with water (3 x 200 ml), and evaporated. Chromatography on silica gel (cyclohexane: ethyl acetate; 10 : 1) gave pure 6-phenyl-5-hexen-1-ol (9.6 g, 69%).

IR:- $\nu_{max}$ 3400, 963 $cm^{-1}$.

UV:- $\lambda_{max}$ 246 nm ( $\varepsilon$ *6430*)

$^1$HNMR:- $\delta$ 7.28 (s, 5 H), 5.35-6.60 (m, 2 H), 3.20-3.83 (m, 2 H), 2.50 (s, $D_2O$ exchangeable, 1 H), 2.00-2.60 (m, 2 H), 1.05-1.95 (m, 4 H).

MS:- m/e 176 ($M^+$).

21. Preparation of 6-Phenylhexan-1-yl-3,5-dinitrobenzoate (105)

A solution of 6-phenyl-5-hexen-1-ol (126 mg) in ethyl acetate (5 ml) was added to a pre-hydrogenated suspension of 10% palladium on charcoal (15 mg) in ethyl acetate (20 ml). After stirring under an atmosphere of hydrogen for 18 hours the suspension was filtered through "Hyflo" and evaporated.

The crude product (160 mg) was dissolved in pyridine (7 ml) and treated with 3,5-dinitrobenzoyl chloride (160 mg). After standing at room temperature for 18 hours, the reaction mixture was poured into chloroform (10 ml), washed with 2 N hydrochloric acid (2 x 15 ml) and

evaporated leaving a brown solid (249 mg). Preparative t.l.c. on silica gel (ether:petrol; 1:1) and crystallisation from methanol gave 6-phenylhexan-1-yl-3,5-dinitrobenzoate, m.p. 58-60 °C (102 mg, 38%).

IR:- $\nu_{max}$ 1735, 1550, 1350, 1285 $cm^{-1}$.

$^1$HNMR:- $\delta$ 9.22 (m, 3 H), 7.30 (s, 5 H), 4.52 (t, 2 H), 2.50-2.90 (m, 2 H), 1.22-2.35 (m, 8 H).

MS:- m/e 372.1324 ($M^+$); $C_{19}H_{20}N_2O_6$ requires 372.1321.

Elemental Analysis:- C; 61.3, H; 5.5, N; 7.5 %.

$C_{19}H_{20}N_2O_6$ requires C; 61.28, H; 5.41, N; 7.52 %.

22. Jones Oxidation of 6-Phenyl-5-hexen-1-ol (104)

Jones reagent (3 M) was prepared by adding concentrated sulphuric acid (61 ml) to a solution of chromium trioxide (70 g) in water (500 ml).

A solution of 6-phenyl-5-hexen-1-ol (9.6 g) in acetone (150 ml) was cooled in an ice bath and treated with Jones reagent (50 ml) and stirred for 45 mins. The reaction mixture was diluted with water (200 ml) and extracted with ether (3 x 200 ml). The extracts were combined, washed with 5% sodium bicarbonate (100 ml), dried ($MgSO_4$) and evaporated. Column chromatography on silica gel eluting with cyclohexane and ethyl acetate (10 : 1) gave:

(1) 6-Phenyl-5-hexenoic acid (7.5 g, 70%).

IR:- $\nu_{max}$ 2480-3440, 1710 $cm^{-1}$.

UV:- $\lambda_{max}$ 248 nm ( $\varepsilon$ 9100).

$^1$HNMR:- $\delta$ 11.00 (bs, $D_2O$ exchangeable, 1 H), 7.32 (s, 5 H), 5.30-6.60 (m, 2 H), 1.46-2.12 (m, 2 H), 2.15-2.76 (m, 4 H).

MS:- m/e 190.0995 ($M^+$); $C_{12}H_{14}O_2$ requires 190.0993.

(2) 6-Phenyl-5-hexen-1-yl-6-phenyl-5-hexenoate (0.67 g, 7%).

IR:- $\nu_{max}$ 1740, 1250, 750, 700 $cm^{-1}$.

UV:- $\lambda_{max}$ 248 nm ( $\varepsilon$ 10,100).

NMR:- $\delta$ 7.35 (m, 10 H), 5.38-6.60 (m, 4 H), 3.80-4.20 (m, 2 H), 1.05-2.50 (m, 12 H).

MS:- m/e 348 ($M^+$).

23. Preparation of Diazomethane

N-Methyl-N-nitrosotoluene-p-sulphonamide (21.4 g) was dissolved in ether (300 ml) and treated with potassium hydroxide (4.0 g) in 96% ethanol (100 ml). After 5 min., a solution of diazomethane in ether was distilled from a water bath. (60-65 °C).

24. Preparation of Methyl 6-phenyl-5-hexenoate (101)

A cold (0°C), stirred solution of 6-phenyl-5-hexenoic acid (5.2 g) in ether (50 ml) was treated with diazomethane until a yellow colour persisted. Evaporation of the solvent gave the product (5.6 g, 100%).

IR:- $\nu_{max}$ 1740, 1250, 750, 700 $cm^{-1}$.

UV:- $\lambda_{max}$ 248 nm ( $\varepsilon$ 7570).

$^1$HNMR:- $\delta$ 7.25 (s, 5 H), 5.25-6.58 (m, 2 H), 3.25 and 3.55 (2 x s, 3 H), 2.00-2.55 (m, 4 H), 1.35-2.00 (m, 2 H).

MS:- m/e 204 ($M^+$).

GLC:- E : Z ratio; 80 : 20.

25. Preparation of Diethyl benzylphosphonate (108).[109]

Triethylphosphite (16.6 g) and benzyl bromide (17.1 g) were heated under reflux for 4 hours. Vacuum distillation gave diethyl benzylphosphonate (20.5g, 89%), b.p.$_{15}$ 150-156°C (Lit.[109] b.p.$_{14}$ 155°C).

26. Reaction of Diethyl benzylphosphonate (108) with Benzaldehyde.

A suspension of sodium hydride (0.24 g) in dry dimethylformamide (30 ml) was stirred under nitrogen, treated with diethyl benzylphosphonate (2.28 g), and heated to 60°C on a water bath for 1 hour. A solution of benzaldehyde (1 g) in dry dimethylformamide (5 ml) was added and was heated for a further 3 hours. The reaction mixture was poured into 2 N hydrochloric acid (100 ml), extracted with ether (3 x 50 ml), and evaporated, leaving the crude product (1.5 g). Recrystallisation from ethanol gave E-stilbene (1.13 g, 62%), m.p. 122-124°C (Lit[132] m.p. 124-125°C).

GLC:- E : Z ratio; 95 : 5.

27. Reactions of Diethyl benzylphosphonate (108) with Pentanal.

Procedure A.

A stirred suspension of sodium hydride (0.24 g) in dry dimethylformamide (20 ml), under nitrogen, was treated with a solution of diethyl benzylphosphonate (2.3 g) in dimethylformamide (5 ml) and heated in a water bath at 60°C until the evolution of hydrogen had ceased. A solution of pentanal (0.8 g) in dimethylformamide (5 ml) was added and the heating was continued for a further 2 hours. The reaction mixture was poured into 2 N hydrochloric acid (100 ml) and extracted with ether (3 x 50 ml). The extracts were combined and evaporated leaving a crude product. $^1$H n.m.r., t.l.c. on silica gel (hexane), and g.l.c. showed no olefin present.

Procedure B.

A suspension of the base (1 equivalent) in the appropriate solvent (20 ml) was stirred at room temperature under nitrogen. A solution of diethyl benzylphosphonate (2.3 g) was added and was stirred until all the base had dissolved. The resulting solution was treated with pentanal (0.8 g) and was stirred for a further 2 hours. The reaction mixture was poured into 2 N hydrochloric acid (100 ml), extracted with ether (3 x 50 ml), and evaporated leaving a yellow oil. Column chromatography on silica gel (hexane) gave pure β-butylstyrene (110). Yields are recorded in table 5 (p. *64*).

IR:- $\nu_{max}$ 1603, 760, 710 $cm^{-1}$.

UV:- $\lambda_{max}$ 248 nm ($\epsilon$ 12, 800).

$^1$HNMR:- $\delta$ 6.75–7.48 (m, 5 H), 5.22–6.66 (m, 2 H), 1.95–2.50 (m, 2 H), 1.12–1.75 (m, 4 H), 0.75–1.10 (m, 3 H).

Procedure C.

A mixture of the base (1 equivalent), diethyl benzylphosphonate (2.28 g), and a suitable solvent were heated under reflux for 1 hour under nitrogen. The resulting solution was treated with pentanal (0.8 g) and heated for a further 2 hours. The reaction mixture was poured into 2 N hydrochloric acid (100 ml), extracted with ether (3 x 50 ml), and evaporated. Column chromatography on silica-gel (hexane) gave pure β-butylstyrene (110). Yields are recorded in table 5 (p. *64*). Isomer ratios were determined by g.l.c. and are also recorded in table 5.

Procedure D.

A solution of diethyl benzylphosphonate(2.28 g) in tetrahydrofuran was stirred under nitrogen and was cooled to -78°C. A 1.5 M solution of n-butyllithium in hexane (7 ml) was added and the resulting solution was treated with pentanal (0.8 g), stirred at -78°C for 2 hours, poured into 2 N hydrochloric acid (100 ml), extracted with ether (3 x 50 ml) and evaporated. Column chromatography on silica-gel (hexane) gave β-butylstyrene (80 mg, 5%).

28. Reactions of Diethyl benzylphosphonate (108) with 5-Hydroxypentanal (103)

Procedure A.

A suspension of potassium tert.- butoxide (2.5 g) in dry tetrahydrofuran (30 ml) was treated with diethyl benzylphosphonate (2.28g) and stirred under nitrogen, at room temperature, for 1 hour. The resulting solution was treated with 5 hydroxypentanal (0.5 g) and stirred for a further 2 hours. The reaction mixture was poured into

water (100 ml), extracted with ether (100 ml) and evaporated. Column chromatography on silica gel (benzene:ethyl acetate) gave 6-phenyl-5-hexen-1-ol (220 mg, 25%).

Procedure B.

A suspension of potassium hydride (0.4 g) in dry dimethoxyethane (20 ml) was stirred under nitrogen, treated with diethyl benzylphosphonate (2.28 g), and stirred for a further 1 hour. The resulting solution was treated with 5-hydroxypentanal (0.5 g) and stirred for a further 2 hours. The reaction mixture was poured into water (100 ml), extracted with ether (3 x 30 ml), and evaporated. Column chromatography on silica-gel (benzene:ethyl acetate) gave 6-phenyl-5-hexen-1-ol (390 mg, 45%).

29. Preparation of Methyl Hydrogen Glutarate (112)[104a]

A mixture of glutaric anhydride (41.2 g) and methanol (25 g) was heated for 2 hours on a steam bath. The excess methanol was removed by evaporation and the residue distilled, yielding methyl hydrogen glutarate (47.1 g, 89%), b.p.$_{15}$ 152-160°C (Lit.[104a] b.p.$_{23}$ 158-165°C).

IR:- $\nu_{max}$ 1740, 1710 cm$^{-1}$.

$^1$HNMR:- $\delta$ 11.25 (bs, $D_2O$ exchangeable, 1 H), 3.70 (s, 3 H), 1.8-3.0 (m, 6 H).

30. Preparation of 4-Carbomethoxybutyryl Chloride (113)[104a]

Methyl hydrogen glutarate (40 g) and thionyl chloride (25 ml) were heated together on a steam bath until the evolution gas was complete (approximately 1 hour). Distillation of the residue gave 4-carbo-

methoxybutyryl chloride (35.4 g, 78%), b.p.$_{10}$ 92-100°C (Lit.[104a] b.p.$_{23}$ 110-113°C).

IR:- $\nu_{max}$ 1800, 1740 $cm^{-1}$.

$^1$HNMR:- $\delta$ 3.70 (s, 3 H), 2.80-3.20 (m, 2 H), 1.60-2.63 (m, 4 H).

31. Attempted Preparation of Methyl 4-formylbutyrate (23)[48,104b]

A solution of 4-carbomethoxybutyryl chloride (5 g) in dry tetrahydrofuran (10 ml) was added dropwise to a pre-hydrogenated suspension of 5% palladium on charcoal in dry tetrahydrofuran (150 ml) containing 2,6-lutidine (3.75 g). After 12 hours, the solvent was removed by evaporation and the residue taken up in ether (100 ml), filtered, washed with 2 N hydrochloric acid (3 x 30 ml), and evaporated. Analytical t.l.c. indicated that no aldehyde was present. Column chromatography gave methyl hydrogen glutarate (2.1 g, 39%).

32. Preparation of Methyl 5-hydroxypentanoate (115)

A solution of sodium methoxide was prepared from sodium (1 g) added to methanol (50 ml), and treated with $\delta$-valerolactone (20 g). After heating at reflux for 3 hours, the reaction mixture was poured into water (30 ml) and extracted with ether (3 x 50 ml) and chloroform (3 x 30 ml). The organic extracts were combined and evaporated leaving methyl 5-hydroxypentanoate as a yellow oil (22 g, 83%).

IR:- $\nu_{max}$ 3480, 1740 $cm^{-1}$.

$^1$HNMR:- $\delta$ 3.67 (s, 3 H), 3.20-3.75 (m, 2 H), 2.36 (bs, $D_2O$ exchangeable, 1 H), 2.05-2.60 (m, 2 H), 1.25-2.00 (m, 4 H).

33. Preparation of Pyridinium Chlorochromate[118a]

Chromium trioxide (100 g) was rapidly added, with stirring, to 6 N hydrochloric acid (184 ml). After 5 min. the homogeneous solution was cooled to 0°C, and pyridine ( 79 g) was added carefully, over 10 min. Recooling to 0°C gave pyridinium chlorochromate (178.5 g, 83%).

34. Preparation of Methyl 4-formylbutyrate (23)

A solution of methyl 5-hydroxypentanoate (14 g) in dry dichloromethane (10 ml) was added to a stirred suspension of pyridinium chlorochromate (23 g) in dry dichloromethane (200 ml). After 2 hours, dry ether (500 ml) was added, and the supernatant liquid was decanted from a black gum. This insoluble residue was washed with ether (3 x 100 ml). The combined organic solutions were filtered through "Hyflo" and evaporated. Distillation gave methyl 4-formylbutyrate (12.1 g, 88%) b.p.$_{1.5}$ 52-60°C (Lit.[104a] b.p.$_{23}$ 100-103°C).

IR:- $\nu_{max}$ 2740, 1735 $cm^{-1}$.

$^1$HNMR:- $\delta$ 9.60 (s, 1 H), 3.70 (s, 3 H), 2.12-2.78 (m, 4 H), 1.50-2.12 (m, 2 H).

35. Alternative Preparation of Methyl 6-phenyl-5-hexenoate (101)

A suspension of benzyltriphenylphosphonium bromide (17.7 g) in dry benzene (100 ml) was stirred under nitrogen, treated with a 1.5 M solution of n-butyllithium in hexane (26.6 ml), and stirred for 30 min. The resulting deep-red solution was treated with methyl 4-formylbutyrate (5.2 g) and stirred at room temperature for 3 hours.

The reaction mixture was poured into dry hexane (500 ml), filtered, and evaporated. Column chromatography gave methyl 6-phenyl-5-hexenoate (4.8 g, 59%).

GLC:- E : Z ratio; 75 : 25.

36. Preparation of Methyl 5,6-epoxy-6-phenyl hexanoate (57)

Methyl 6-phenyl-5-hexenoate (80% E by g.l.c.) (5 g) was converted to methyl 5,6-epoxy-6-phenyl hexanoate (3.7 g, 65%) using the procedure described in experiment 1.

IR:- $\nu_{max}$ 1735 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.22 (s, 5 H), 3.55 (s, 3 H), 3.48 and 4.00 (2 x d, 2 H), 3.05-3.35 and 2.70-3.00 (2 x m, 1 H), 2.05-2.62 (m, 2 H), 1.55-2.00 (m, 4 H).

MS:- m/e 220.1099 ($M^+$); $C_{13}H_{16}O_3$ requires 220.1100.

37. Reaction of Methyl 5,6-epoxy-6-phenylhexanoate (57) with Thiophenol

Methyl 5,6-epoxy-6-phenylhexanoate (80% E) was treated with thiophenol as described in experiment 2. Methyl 5-hydroxy-6-phenyl-6-(phenylthio) hexanoate (116) was isolated as colourless needles, m.p. 84-86°C (272 mg, 90%), after recrystallisation from aqueous methanol.

IR:- $\nu_{max}$ 3500, 1730 $cm^{-1}$.

$^1$HNMR:- $\delta$ 6.90-7.50 (m, 10 H), 4.20 (d, 1 H), 3.75-4.05 (m, 1 H), 3.58 (s, 3 H), 2.55 (bs, $D_2O$ exchangeable, 1 H), 2.00-2.40 (m, 2 H), 1.10-1.95 (m, 4 H).

MS:- m/e 200.0659 (34%); $C_{13}H_{12}S$ requires 200.0660, 199.0599 (100%); $C_{13}H_{11}S$ requires 199.0581, 131.0704 (38%); $C_6H_{11}O_3$ requires 131.0708.

Elemental Analysis:- C; 69.1, H; 6.95, S; 9.6 %.

$C_{19}H_{22}O_3S$ requires C; 69.06, H; 6.71, S; 9.7 %.

Methyl 5-hydroxy-6-phenyl-6-(phenylthio) hexanoate was acetylated using the procedure outlined in experiment *3*. Methyl 5-acetoxy-6-phenyl-6-(phenylthio) hexanoate (117) was isolated as a colourless oil. (84%).

IR:- $\nu_{max}$ 1740, 1235 $cm^{-1}$.

$^1$HNMR:- $\delta$ 6.9-7.40 (m, 10 H), 5.15-5.40 (m, 1 H), 4.30 (d, 1 H), 3.60 (s, 3 H), 2.05-2.36 (m, 2 H), 1.90 (s, 3 H), 1.38-1.78 (m, 4 H).

MS:- m/e 372 ($M^+$).

38. Reaction of Methyl 5,6-epoxy-6-phenyl-hexanoate (57) with Benzylthiol.

Methyl 5,6-epoxy-6-phenylhexanoate (*80%* E by g.l.c.) was treated with benzylthiol as described in experiment *2*. Methyl 5-hydroxy-6-phenyl-6-(phenylmethylthio) hexanoate (118) was isolated as colourless needles, m.p. 76-77.5%, (219 mg, 70%) after recrystallisation from aqueous methanol.

IR:- $\nu_{max}$ 3500, 1730 $cm^{-1}$.

$^1$HNMR:- $\delta$ 6.90-7.40 (m, 10 H), 3.70-3.95 (m, 1 H), 3.65 (d, 1 H), 3.58 (s, 3 H), 3.5 (g, 2 H), 2.05-2.40 (m, 2 H), 1.00-1.95 (m, 4 H).

MS:- m/e 214.0811 (12%); $C_{14}H_{14}S$ requires 214.0800, 213.0741 (35%); $C_{14}H_{13}S$ requires 213.0738, 91.0558 (100%); $C_7H_7$ requires 91.0573.

Elemental Analysis:- C; 69.3, H; 7.0, S; 9.6%.

$C_{20}H_{24}O_3S$ requires C; 69.7, H; 7.0, S; 9.3%.

Methyl 5-hydroxy-6-phenyl-6-(phenylmethylthio)hexanoate was acetylated using the procedure described in experiment 3. Methyl 5-acetoxy-6-phenyl-6-(phenylmethylthio)hexanoate (119) was isolated as a yellow oil (63%).

IR:- $\nu_{max}$ 1745, 1240 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.03-7.42 (m, 10 H), 5.10-5.32 (m, 1 H), 3.76 (d, 1 H), 3.62 (s, 3 H), 3.52 (q, 2 H), 2.00-2.35 (m, 2 H), 1.88 (s, 3 H), 1.30-1.80 (m, 4 H).

MS:- m/e 386 ($M^+$).

39. Preparation of Diethyl cinnamylmalonate (122).[119]

Freshly cut sodium (1.84 g) was added to dry ethanol (100 ml) and cooled in an ice bath under nitrogen. When all the sodium had dissolved, diethyl malonate (12.8 g), and after 30 min., cinnamyl bromide (14.5 g) were added. After stirring at room temperature for 5 hours, the reaction mixture was poured into water (200 ml), extracted with ether (3 x 100 ml), and evaporated leaving a brown oil (18.5 g). Distillation gave diethyl cinnamylmalonate (13.9g, 70%), b.p.$_{15}$ 190-195°C (Lit.[117] b.p.$_{13}$ 180-200°C).

IR:- $\nu_{max}$ 1740 $cm^{-1}$.

$^1$HNMR:- $\delta$ 6.95-7.40 (m, 5 H), 5.65-6.60 (m, 2 H), 4.10 (q, 4 H), 3.45 (t, 1 H), 2.50-2.95 (m, 2 H), 1.25 (t, 6 H).

40. Preparation of Cinnamylmalonic Acid (123)[119]

Diethyl cinnamylmalonate (5 g) was heated under reflux in a solution of potassium hydroxide (0·5 g) in methanol (50 ml). After 2 hours, the reaction mixture was poured into 2 N hydrochloric acid (200 ml), extracted with ether (3 x 100 ml), and evaporated. Recrystallisation from benzene gave cinnamylmalonic acid (3.5 g, 85%), m.p. 129-130°C (Lit.[119] m.p. 131°C), as colourless prisms.

IR:- $\nu_{max}$ 3100-3800, 1730 $cm^{-1}$.

$^1$HNMR:- $\delta$ 10.65 (bs, $D_2O$ exchangeable, 2 H), 7.15-7.40 (m, 5 H), 5.90-6.60 (m, 2 H), 3.45 (t, 1 H), 2.50-2.90 (m, 2 H).

41. Decarboxylation of Cinnamylmalonic Acid (123)[119]

Cinnamylmalonic acid (2.5 g) was heated for 1 hour at 140°C on an oil bath. Carbon dioxide evolution was observed. After cooling, the resulting brown solid was recrystallised from hexane and gave 5-phenyl-4-pentenoic acid (123) as colourless cubes (2.08 g, 98%), m.p. 90-92°C (Lit.[119] m.p. 90°C).

IR:- $\nu_{max}$ 3150-3680, 1695 $cm^{-1}$.

$^1$HNMR:- $\delta$ 11.2 (bs, $D_2O$ exchangeable, 1 H), 7.05-7.45 (m, 5 H), 5.90-6.60 (m, 2 H), 2.55 (m, 4 H).

42. Preparation of Methyl 5-phenyl-4-pentenoate (125)

A solution of 5-phenyl-4-pentenoic acid (1.7 g) in ether (25 ml) was treated with diazomethane until a yellow colour persisted. Evaporation gave methyl 5-phenyl-4-pentanoate (1.7 g, 94%).

IR:- $\nu_{max}$ 1745 $cm^{-1}$.

$^1$HNMR:- δ 7.10-7.45 (m, 5 H), 5.90-6.60 (m, 2 H), 3.70 (s, 3 H), 2.45-2.65 (m, 4 H).

UV:- $\lambda_{max}$ 249 nm (ε 11, 400).

MS:- m/e 190.0995 ($M^+$); $C_{12}H_{14}O_2$ requires 190.0994.

43. Preparation of Methyl 4,5-epoxy-5-phenylpentanoate (120)

Methyl 5-phenyl-4-pentanoate (5 g) was converted to methyl 4,5-epoxy-5-phenylpentanoate (3.8 g, 70%), using the procedure outlined in experiment 1.

IR:- $\nu_{max}$ 1740 $cm^{-1}$.

$^1$HNMR:- δ 7.30 (s, 5 H), 3.70 (s, 3 H), 3.66 (d, 1 H), 1.90-3.10 (dt, 1 H), 2.50 (t, 2 H), 1.80-2.20 (m, 2 H).

MS:- m/e 206 ($M^+$).

44. Reaction of Methyl 4,5-epoxy-5-phenylpentanoate (120) with Thiophenol

Methyl 4,5-epoxy-5-phenylpentanoate was treated with thiophenol under the conditions described in experiment 2. Preparative t.l.c. gave:

(1) 4-(1'-phenylthiobenzyl)butyrolactone (126), after recrystallisation from hexane and ethyl acetate, as colourless needles, m.p. 80-82.5 °C (124 mg, 43%).

IR:- $\nu_{max}$ 1770 $cm^{-1}$.

$^1$HNMR:- δ 7.00-7.40 (m, 10 H), 4.7-5.05 (m, 1 H), 4.30 (d, 1 H), 1.60-2.20 (m, 4 H).

MS:- m/e 284.0872 ($M^+$); $C_{17}H_{16}O_2S$ requires 284.0871.

Elemental Analysis:- C; 71.6, H; 5.8, S; 11.0 %.

$C_{17}H_{16}O_2S$ requires C; 71.8 H; 5.67, S; 11.25 %.

(2) Methyl-4-hydroxy-5-phenyl-5-(phenylthio)pentanoate (127) as a yellow oil (170 mg, 55%).

IR:- $\nu_{max}$ 1735 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.05-7.52 (m, 10 H), 4.15 (d, 1 H), 3.66-4.02 (m, 1 H), 3.55 (s, 3 H), 2.06 (bs, $D_2O$ exchangeable, 1 H), 1.15 - 2.40 (m, 4 H).

Methyl-4-hydroxy-5-phenyl-5-(phenylthio)pentanoate (170 mg) was dissolved in benzene (10 ml), treated with p-toluenesulphonic acid (20 mg) and heated under reflux for 2 hours. The reaction mixture was diluted with benzene (50 ml), washed with water (10 ml) and evaporated, leaving a yellow solid (201 mg). Recrystallisation from hexane and ethyl acetate gave 4-(1'-phenylthiobenzyl)butyrolactone (126) as colourless needles, m.p. 81-82°C, (149 mg, 98%).

45. Preparation of Benzylphenylsulphone (128, $R^1$= Ph)

Sodium (1.06 g) was dissolved in stirred dry ethanol (60 ml) under nitrogen, and the resulting solution was treated with thiophenol (4.3 ml). After 10 mm., benzyl bromide (5 ml) was added and stirred for 1.5 hours. The reaction mixture was poured into 5% aqueous sodium bicarbonate (150 ml) and extracted with chloroform (3 x 100 ml). The extracts were combined and evaporated leaving a yellow solid (10 g). Recrystallisation from ethanol gave benzylphenyl sulphide as colourless plates (4.4 g, 55%), m.p. 40.5-42 °C (Lit.[135] m.p. 39-40.5 °C).

Benzylphenylsulphide (2 g) was added to a stirred solution of 85% m-chloroperoxybenzoic acid (4 g) in dichloromethane (50 ml). The

reaction mixture was stirred at room temperature for 16 hours after which time a white precipitate had formed. This suspension was washed with 5% aqueous bicarbonate (3 x 30 ml) and evaporated. Recrystallisation from ethanol gave benzylphenylsulphone (1.79 g, 77%), m.p. 147-149°C (Lit[135] m.p. 147-149°C).

46. Reaction of Benzylphenylsulphone (128, $R^1$= Ph) with Pentanal[122]

A cold (-78°C), stirred solution of benzylphenylsulphone (2.3 g) in dry tetrahydrofuran (50 ml) under nitrogen was treated with 2 M n-butyllithium in hexane (4.5 ml)., After 30 min., a solution of pentanal (0.8 g) in dry tetrahydrofuran (5 ml) was added dropwise and, after a further 10 min., this was followed by the addition of acetic anhydride (0.8 ml). The reaction mixture was stirred at -78°C for 4 hours, poured into saturated ammonium chloride (100 ml), extracted with chloroform (3 x 50 ml), and evaporated leaving a crude product. Analysis by t.l.c. on silica gel (benzene:ethyl acetate; 10:1) indicated the presence of a complex mixture.

47. Preparation of Benzyldimethylsulphonium Bromide (131, $R^1$= Me, x = Br)

Benzylbromide (17.1 g) and dimethylsulphide (6.8 g) were mixed together and allowed to stand at room temperature for 2 days. The resulting sticky brown solid was dissolved in ethanol (10 ml) and precipitated with ether (100 ml). The solvent was decanted, leaving enough to cover the crystals,* which were washed with ether (20 ml) and decanted again. The remaining solvent was removed in vacuo, leaving colourless needles (15.1 g, 63%) m.p. 99-100.5°C (Lit[134] 100.5-101.5°C).

*The compound was very hygroscopic.

48. Preparation of Benzyldiphenylsulphonium Tetrafluoroborate (131, $R^1$= Ph, x = $BF_4$)

A mixture of diphenylsulphide (8.8 g) and benzyl bromide (8.5 g) was treated portionwise with solid silver tetrafluoroborate (9.7 g) and stirred for 2 hours. The resulting yellow mass was allowed to stand in the dark for 18 hours. Trituration with dichloromethane (3 x 50 ml) and filtration gave a solution of the product which was reduced to a small volume ( < 20 ml) by evaporation and was treated with ether (100 ml). Filtration and further washing with ether gave benzyldiphenylsulphonium tetrafluoroborate (10.1 g, 58%) m.p. 99-101.5°C (Lit[133] m.p. 102.5°C), as colourless cubes.

49. Reaction of Benzyldimethylsulphonium Bromide (131, $R^1$= Me, x = Br) with pentanal

A stirred suspension of benzyldimethylsulphonium bromide (2.3 g) in dry tetrahydrofuran (50 ml) was cooled to -78°C and treated with a 1.5 M solution of n-butyllithium in hexane (6.7 ml). A solution of pentanal (0.8 g) in tetrahydrofuran (10 ml) was added slowly (10 min.). After stirring at -78°C for 1 hour, the reaction mixture was warmed to room temperature and stirred for a further 2 hours. Dilution with water (100 ml), extraction with ether (3 x 50 ml), and evaporation gave a crude product. Analytical t.l.c. on silica gel (hexane) and alumina (cyclohexane ethylacetate; 10 : 1) showed this crude product to be a complex mixture.

50. Reaction of Benzyldiphenylsulphonium Tetrafluoroborate (131, $R^1$= Ph, x = $BF_4$) with Pentanal

Benzyldiphenylsulphonium tetrafluoroborate (3.6 g) was treated with pentanal (0.8 g) under the conditions described in experiment *49*. This reaction gave a crude product which appeared to be a complex mixture by analytical t.l.c. on alumina (cyclohexane:ethylacetate; 10 : 1).

51. Preparation of N-Acetylcysteine Methyl Ester (134)[123]

A solution of N-acetylcysteine (10 g) in methanol (50 ml) was treated with a solution of diazomethane in ether until t.l.c. indicated complete reaction. Evaporation left a white powder (11.0 g). Column chromatography on silica gel (ether : methanol) and recrystallisation from ether and petroleum ether gave N-acetylcysteine methyl ester as colourless needles (8.25 g, 76%), m.p. 78-80°C (Lit[136] m.p. 79-80°C).

IR:- $\nu_{max}$ 1740, 1660, 1535 $cm^{-1}$.

NMR:- $\delta$ 6.1-6.66 (bs, 1 H), 4.70-5.00 (dt, 1 H), 3.82 (s, 3 H), 2.80-3.10 (m, 2 H), 2.00 (s, 3 H), 1.3 (t, 1 H).

52. Reaction of E-β-Methylstyrene Oxide (67a) with N-Acetylcysteine Methyl Ester (134)

E-β-Methylstyrene oxide was allowed to react with N-acetylcysteine methyl ester under the conditions described in experiment 2. 2-Hydroxy-1-(N-acetylmethylcysteinyl)-1-phenylpropane (135) as a yellow oil (206 mg, 44%).

IR:- $\nu_{max}$ 3380, 3300, 1745, 1660, 1540, 750, 705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.33 (bs, 5 H), 6.50-7.00 (bm, 1 H), 4.50-5.00 (m, 1 H), 3.95-4.25 (m, 1 H), 3.82, 3.88 (2 x d, 1 H), 3.73, 3.62 (2 x s, 3 H), 2.70-2.96 (m, 2 H), 2.58 (bs, $D_2O$ exchangeable, 1 H), 1.88, 2.00 (2 x s, 3 H).

MS:- m/e 267.0920 (41%); $C_{13}H_{17}NO_3S$ requires 267.0929, 266.0828 (5%); $C_{13}H_{16}NO_3S$ requires 266.0851, 176.0365 (73%); $C_6H_{10}NO_3S$ requires 176.0381, 144.0659 (65%); $C_6H_{10}NO_3$ requires 144.0660, 43 (100%).

$^{13}$CNMR:- $\delta$ 171.6 (s), 170.1 (s), 139.1 (s), 129.3 (d), 129.1 (d), 128.3 (d), 70.5 (d), 59.35 (d), 52.8 (q), 52.0 (d), 34.1 (t), 23.0 (q), 20.4 (q).

Acetylation of the product, using the procedure described in experiment 3, gave 2-acetoxy-1-(N-acetylmethylcysteinyl)-1-phenylpropane (136) as a yellow oil (73%).

IR:- $\nu_{max}$ 3340, 1740, 1665, 1540, 1240, 755, 705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.35 (s, 5 H), 5.95-6.40 (bm, 1 H), 5.10-5.40 (dq, 1 H), 4.60-4.85 (m, 1 H), 3.95, 3.98 (2 x d, 1 H), 3.65, 3.75 (2 x s, 3 H), 2.95-3.70 (m, 2 H), 1.88, 2.05 (2 x s, 3 H), 1.95 (s, 3 H), 1.25 (d, 3 H).

MS:- m/e 353 ($M^+$), 266, 43 (base peak).

53. Reaction of E-β-Methylstyrene Oxide (67a) with Cysteine Ethyl Ester (46)

A solution of E-β- methylstyrene oxide (200 mg) in methanol and water (10:1, 1 ml) was treated with cysteine ethyl ester (300 mg). The pH of the solution was adjusted to 8.5 with triethylamine and the reaction mixture was stirred under nitrogen for 24 hours. Dilution with water (20 ml), extraction with ether (3 x 10 ml) and evaporation gave the crude hydroxy sulphide. Preparative t.l.c. on silica-gel (cyclohexane : ethylacetate) gave 2-hydroxy-1-(ethylcysteinyl)-1-phenylpropane (137) as a clear oil (257 mg, 60%).

IR:- $\nu_{max}$ 3250-3500, 1740, 755, 705 $cm^{-1}$.

$^1$HNMR:- δ 7.20-7.50 (s, 5 H), 4.00-4.45 (m, 3 H), 3.96 (2 x d, 1 H), 3.40-3.60 (m, 1 H), 2.60-2.80 (m, 2 H), 2.10 (bs, $D_2O$ exchangeable, 2 H), 1.10-1.40 (m, 6 H).

MS:- m/e 283 ($M^+$), 239, 238, 43 (base peak).

Acetylation of the product, using the procedure described in experiment 3, gave 2-acetoxy-1-(N-acetylethylcysteinyl)-1-phenylpropane (138) as colourless needles, m.p. 78-82°C (67%).

IR:- $\nu_{max}$ 3340, 1740, 1660, 1540, 1235, 750, 705 $cm^{-1}$.

$^1$HNMR:- δ 7.18-7.52 (m, 5 H), 6.05-6.36 (bm, 1 H), 5.12-5.42 (m, 1 H), 4.60-4.86 (m, 1 H), 3.88-4.36 (m, 3 H), 2.72-2.95 (m, 2 H), 1.8-2.10 (m, 6 H), 1.10-1.32 (m, 6 H).

MS:- m/e 307, 280, 190, 158, 43 (base peak).

Elemental Analysis:- C; 58.3, H; 7.0, N; 3.7, S; 8.45%.

$C_{18}H_{25}NO_5S$ requires C; 58.8, H; 6.8, N; 3.8, S; 8.7 %.

Preparative t.l.c. on silica gel (benzene : ethyl acetate : triethylamine; 66 : 33 : 1) on a sample of the hydroxysulphide (137, 250 mg) gave:

(1) Isomer 1. (40%), Rf 0.4.

$^1$HNMR:- $\delta$ 7.25-7.55 (m, 5 H), 4.05-4.35 (m, 3 H), 3.98 (d, 1 H), 3.40-3.60 (m, 1 H), 285 (s, $D_2O$ exchangeable, 2 H), 2.60-2.80 (m, 2 H), 1.25 (t, 3 H), 1.20 (d, 3 H).

Acetylation of isomer 1 using the usual conditions (experiment 3) gave the diacetate, m.p. 89-91°C (82%).

$^1$HNMR:- $\delta$ 7.25-7.38 (m, 5 H), 6.19 (bd, 1 H), 5.19-5.18 (dq, 1 H), 4.70-4.77 (dt, 1 H), 4.17-4.26 (dq, 2 H), 3.91 (d, 1 H), 2.81-2.96 (dq, 2 H), 1.96 (s, 3 H), 1.91 (s, 3 H), 1.3 (t, 3 H), 1.25 (d, 3 H).

MS:- m/e 307.1243 (15%); $C_{16}H_{21}NO_3S$ requires 307.1242, 280.0992 (9%); $C_{14}H_{18}NO_3S$ requires 280.1007, 190.0532 (10%); $C_7H_{12}NO_3S$ requires 190.0537, 158.0807 (33%); $C_7H_{12}NO_3$ requires 158.0817, 43 (100%).

$[\alpha]_D^{25}$ $CHCl_3$: + 62.4°.

(2) Isomer 2. (35%), Rf 0.3.

$^1$HNMR:- $\delta$ 7.25-7.55 (m, 5 H), 4.05-4.35 (m, 3 H), 3.98 (d, 1 H), 3.40-3.60 (m, 1 H), 2.90 (s, $D_2O$ exchangeable, 2 H), 2.60-2.90 (m, 2 H), 1.30 (t, 3 H), 1.20 (d, 3 H).

Acetylation of isomer 2 using the usual procedure (experiment 3) gave the diacetate, m.p. 102-105°C (90%).

$^1$HNMR:- $\delta$ 7.24-7.36 (m, 5 H), 6.20 (bd, 1 H), 5.21-5.29 (dq, 1 H), 4.70-4.76 (m, 1 H), 4.06-4.20 (m, 2 H), 3.97 (d, 1 H), 2.70-2.89 (dq, 2 H), 2.04 (s, 3 H), 1.94 (s, 3 H), 1.25 (d, 3 H), 1.21 (t, 3 H).

MS:- m/e 307.1038 (12%); $C_{16}H_{21}NO_3S$ requires 307.1242, 280.1023 (7%), $C_{14}H_{18}NO_3S$ requires 280.1007, 190.0515 (12%) $C_7H_{12}NO_3S$ requires 190.0537, 158.0817 (29%) $C_7H_{12}NO_3$ requires 158.0817, 43 (100%).

$[\alpha]_D^{25}{}_{CHCl_3}$: -79.2°.

54. Reaction of Methyl 5,6-epoxy-6-phenylhexanoate (57) with N-acetylcysteine methyl ester (130)

Reaction of methyl 5,6-epoxy-6-phenylhexanoate with N-acetylcysteine methyl ester under the conditions described in experiment 2 gave a diastereoisomeric mixture of 5-hydroxy-6-(N-acetylmethylcysteinyl)-6-phenylhexanoate (139 ) was isolated as a yellow oil (232 mg, 64%).

IR:- $\nu_{max}$ 3370 - 3500, 1740, 1665, 1540 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.30 (bs, 5 H), 6.30-6.80 (bm, 1 H), 4.50-4.95 (m, 1 H), 3.80-4.10 (m, 2 H), 4.65, 7.75 (2 x s, 3 H), 3.62 (s, 3 H), 2.66-3.0 (m, 2 H), 2.13-2.40 (m, 2 H), 2.02, 1.90 (2 x s, 3 H), 1.10-2.00 (m, 4 H).

MS:- m/e 267.0928 (30%); $C_{13}H_{17}NO_3S$ requires 267.0929, 266.0867 (10%); $C_{13}H_6NO_3S$ requires 266.0851, 176.0372 (98%); $C_6H_{10}NO_3S$ requires 176.0381, 144.0653 (76%); $C_6H_{10}NO_3$ requires 144.0660, 91.0549 (100%); $C_7H_7$ requires 91.0547.

5-Hydroxy-6-(N-acetylmethylcysteinyl)-6-phenylhexanoate (100 mg) was dissolved in dry pyridine (1 ml), treated with 3,5-dinitrobenzoyl chloride (125 mg), and stood under nitrogen and at room temperature for 24 hours. The reaction mixture was poured into ice (50 g), acidified with 2 N hydrochloric acid (20 ml), extracted with ether (3 x 30 ml) and

evaporated. Preparative t.l.c. on silica gel (benzene) gave 5-(3,5-dinitrobenzoyloxy)-6-(N-acetylmethylcysteinyl)-6-phenylhexanoate (140) as a yellow oil (127 mg, 85%).

IR:- $\nu_{max}$ 1740, 1670, 1540 $cm^{-1}$.

$^1$HNMR:- $\delta$ 9.15 (m, 1 H), 8.95 (m, 2 H), 7.15-7.50 (m, 5 H), 6.00- (bm, 1 H), 5.28-5.62 (m, 1 H), 4.50-4.90 (m, 1 H), 4.15, 4.26 (2 x d, 1 H), 3.70, 3.75 (2 x s, 3 H), 3.65 (s, 3 H), 2.72-3.00 (m, 2 H), 2.20-2.50 (m, 2 H), 1.95, 2.03 (2 x s, 3 H), 1.55-2.15 (m, 4 H).

MS:- m/e 591 ($M^+$).

55. Preparation of Bis-N-trifluoroacetylcystine (145)

A solution of sodium methoxide, prepared from sodium (2.3 g) and methanol (100 ml), was treated with cystine (24 g) and stirred under nitrogen at room temperature. Ethyl trifluoroacetate (30 ml) was added and the stirring continued until all the cystine had dissolved (approx. 1 hour). The reaction mixture was diluted with methanol (100 ml), treated with "Dowex" 50 (8 x) $M^+$ resin (80 g), and stirred for a further 10 min. Filtration through a pad of "Hyflo" and evaporation gave a pink solid (44 g). Column chromatography on silica gel (ether:acetic acid) afforded bis-N-trifluoroacetylcystine (34.5 g, 79%), m.p. 165-170°C (Lit.[64] m.p. 166-167°C).

56. Preparation of Bis-N-trifluoroacetylcystine dimethyl ester (143)

(1) A solution of Bis-N-trifluoroacetylcystine (20 g) in methanol (250 ml) was treated portionwise with diazomethane in ether until a yellow colour persisted. Evaporation gave the crude product (21 g). Column chromatography on silica gel (ether) afforded bis-N-trifluoroacetylcystine dimethyl ester (15.2 g, 68%), m.p. 148-150°C (Lit.[127] m.p. 152-154 °C).

IR:- $\nu_{max}$ 3300, 1740, 1705 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.05-7.90 (bs, 1 H), 4.60-4.92 (m, 1 H)
3.75 (s, 3 H), 2.00-2.45 (m, 2 H).

$^{19}$FNMR:- $\delta$ -75.7 (s).

(2) Cystine dimethyl ester dihydrochloride (10 g) was dissolved in water (400 ml) and 1 N $Na_2CO_3$ (50 ml) and stirred with chloroform (100 ml). The chloroform layer was separated, washed with brine and concentrated to provide the free amine (6.8 g, 87%) which was taken up in $CH_2Cl_2$ (750 ml) and stirred with solid anhydrous $Na_2CO_3$ (32 g) at 0° under nitrogen, during dropwise addition of trifluoroacetic anhydride (35 ml). After 1 hour the mixture was diluted to 2000 ml with $CH_2Cl_2$, washed with water (3 x 100 ml), brine (100 ml) and evaporated to yield a solid which was triturated with hexane. The resulting solid was filtered to provide bis-N-trifluoroacetylcystine dimethyl ester (10 g, 79%), m.p. 148-150°C (Lit.[127] m.p. 152-154°C).

57. Preparation of 5-(1'-Idobenzyl)valerolactone (147, X=I).

A solution of 6-phenyl-5-hexanoic acid (200 mg) in dioxane (10 ml) and 5% aqueous sodium bicarbonate (1 ml) was treated with iodine (290 mg) and stirred for 18 hours at room temperature. The excess iodine was removed by titration with 1 M sodium thiosulphate and the reaction mixture was poured into water (20 ml), extracted with ether (3 x 25 ml) and evaporated, leaving a brown solid (171 mg). Recrystallisation from aqueous methanol gave 5-(1'-idobenzyl)valerolactone as colourless cubes, m.p. 95-97°C (84 mg, 25%).

IR:- $\nu_{max}$ 1730 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.30 (s, 5 H), 5.12 (d, 1 H), 4.20-4.58 (m, 1 H), 2.23-2.70 (m, 2 H), 1.35-2.08 (m, 4 H).

$^{13}$CNMR:- $\delta$ 170.5 (s), 139.9 (s), 128.9 (d), 128.6 (d), 82.9 (d), 34.5 (d), 29.4 (t), 27.0 (t), 18.1 (t).

MS:- m/e 189 (M-I), 127 ($I^+$).

58. Reaction of Methyl 5,6-epoxy-6-phenylhexanoate (57) with Hydrobromic acid

A solution of methyl 5,6-epoxy-6-phenylhexanoate (230 mg) in dichloromethane (25 ml) was stirred vigorously with 48% aqueous hydrogen bromide (1 ml) for 3 hours. The reaction mixture was poured into chloroform (50 ml) and washed with water (50 ml) and 5% sodium bicarbonate (20 ml). Evaporation gave a yellow oil (805 mg). Preparative t.l.c. on silica gel, eluting with benzene and chloroform (2:1), gave:

(1) 5-(1'-bromobenzyl)valerolactone (147, X=Br) as colourless cubes, m.p. 134-136°C (140 mg, 47%) after recrystallisation from ethylacetate.

IR:- $\nu_{max}$ 1740 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.40 (s, 5 H), 5.00 (d, 1 H), 4.45-4.88 (m, 1 H), 2.40-2.80 (m, 2 H), 1.55-2.20 (m, 4 H).

MS:- m/e 268, 270 ($M^+$).

(2) Methyl 6-bromo-5-hydroxy-6-phenylhexanoate (148) as a yellow oil (130 mg, 41%).

IR:- $\nu_{max}$ 1735 $cm^{-1}$.

$^1$HNMR:- $\delta$ 7.40 (s, 5 H), 4.90 (d, 1 H), 3.80-4.30 (m, 1 H), 3.60 (s, 3 H), 2.08-2.70 (m, 2 H), 1.08-1.98 (m, 4 H).

Methyl 6-bromo-5-hydroxy-6-phenylhexanoate (100 mg) was heated under reflux with benzene (50 ml) and p-toluene sulphonic acid (10 mg) for 6 hours. After cooling, the reaction mixture was washed with 5% sodium bicarbonate (50 ml) and evaporated. Recrystallisation from ethyl acetate gave 5-(1'-bromobenzyl)valerolactone m.p. 134-139°C, (68 mg, 76%).

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