Tetrahedron Vol 39, No 10, pp 1687 to 1721, 1983
Printed in Great Britain

0040-4020/83/101687-35$17.50/0
Pergamon Press Ltd

TETRAHEDRON REPORT NUMBER 148

LEUKOTRIENES

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(*Received in the UK 24 August* 1982)

CONTENTS

NOMENCLATURE

The term leukotriene was first introduced by Samuelsson[1] to describe a family of unsaturated C_{20}-carboxylic acids biosynthesised from 5Z,8Z,11Z,14Z-eicosatetrenoic acid (arachidonic acid). This new group of compounds were first identified in leukocytes and the characteristic feature is a conjugated triene unit.

Structurally different leukotrienes (LTs) are distinguished by the letters A to E (Fig. 1). Since LTs can be produced from 5Z,8Z,11Z-, 5Z,8Z,11Z,14Z-, and 5Z,8Z,11Z,14Z,17Z-eicosenoic acids, a subscript is added to denote the number of double bonds in the molecule. The family of LTEs is

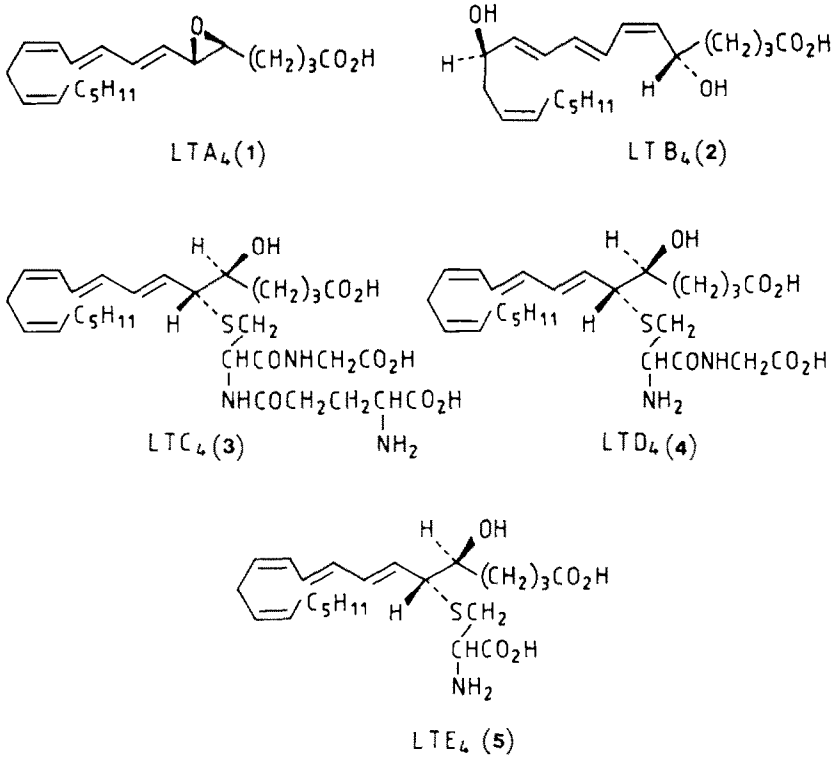


Fig. 1. Structures of leukotrienes A_4–E_4 derived from arachidonic acid.

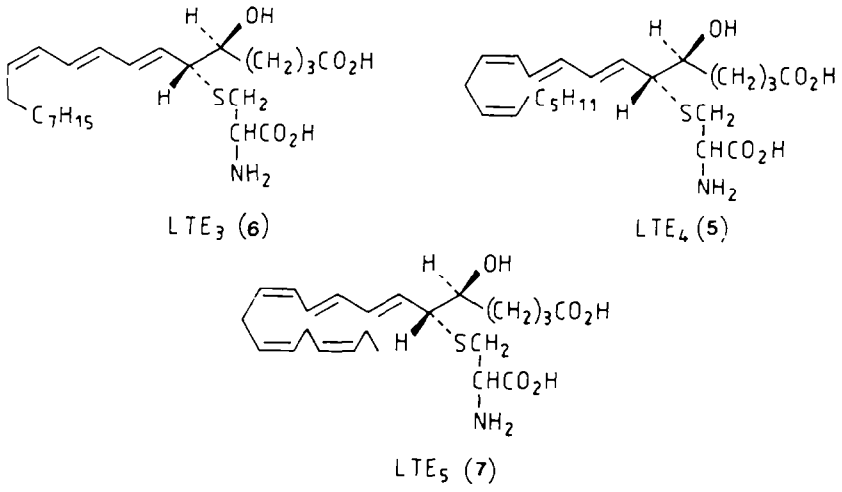


Fig. 2. Structures of leukotrienes E.

described in Fig. 2: the other LTs form similar series. Confusion arises in the literature, and the following points should be noted:-

(i) The first component of a "slow reacting substance" (*vide infra*) to be characterised as a leukotriene—a cysteinyl derivative of 5-hydroxyeicosa-7,9,11,14-tetrenoic acid—was originally referred to as LTC. This compound is now called LTE_4.

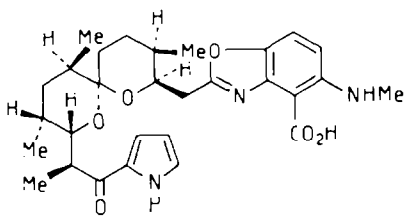
(ii) Early work on the purification of leukotrienes led to the isolation of two C_{11}-double bond isomers of a glutathione derivative of 5-hydroxyeicosa-7,9,11,14-tetrenoic acid. The major component was originally designated LTC-1 and the minor component was called LTC-2. These compounds are now generally referred to as LTC_4 and 11-*trans*-LTC_4 (or 11E-LTC_4) respectively.

HISTORY AND OCCURRENCE

The oxygenation and subsequent metabolism of arachidonic acid in a variety of cell types occurs by two major routes. The cyclo-oxygenase pathway leading to prostaglandins and thromboxanes is well understood and the products of this pathway have been the subject of numerous reviews.[2] An alternative series of transformations *via* the lipoxygenase pathway converts arachidonic acid into a more recently characterised group of compounds, the leukotrienes. These compounds play a major role as biological mediators in immediate hypersensitivity reactions and inflammation.

The first report of a substance possessing the sort of biological activity now associated with leukotrienes came in 1938. Feldberg and Kellaway[3] described a material, obtained from guinea pig lungs on perfusion with cobra venom, which caused a contraction of guinea pig jejunum. This they called "slow reacting substance" (SRS) since the contraction was slow to start and of long duration. Kellaway and Trethewie[4] also described a related substance which was released from lungs during anaphylactic shock. This was called "slow reacting substance of anaphylaxis" (SRS-A) by Brocklehurst[5] to differentiate it from those slow reacting substances produced by non-immunological stimulation.

During the 1950s and 1960s further sources of SRSs were recognised. They are released from a variety of tissues and cell preparations including the lungs of various species,[6] perfused cat paws,[7] isolated rat mast cells,[8] human leukocytes,[9] rat peritoneal fluid[10] and, perhaps of most significance, from human asthmatic lungs.[11] More recently, SRS release has been shown to be stimulated by the calcium ionophore A 23187[12] and by high concentrations of L-cysteine.[13]



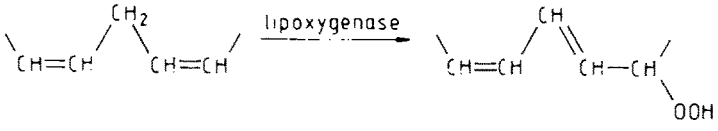
A23187

All the SRSs described above appeared to possess the same type of biological activity. Particularly noticeable was their ability to strongly contract guinea pig ileum, various other types of gastrointestinal smooth muscle, smooth muscle from guinea pig trachea, and human bronchus. Despite considerable efforts by several groups the chemical structure of the SRSs remained elusive. This was principally because pure material was not available until reverse phase high pressure liquid chromatography was used in the isolation procedure.[14] However, evidence from hydrogenation and oxidation experiments, in addition to some physicochemical properties, led Brocklehurst to suggest that SRS-A was an unsaturated fatty acid.[11] The presence of sulphur in the molecule was first indicated by spark source mass spectrometry studies[15] and later substantiated by the incorporation of radioactive sulphur following treatment of sensitised guinea pig lungs with ^{35}S-methionine or radiolabelled sodium sulphate.[16] On the basis of the inactivation of SRS-A by limpet arylsulphatase, it was initially suggested that the mediator contained a sulphate ester group.[15] When cysteine was shown[13] to stimulate the formation of slow reacting substances it seemed more likely that SRS and SRS-A were conjugates of this sulphur-containing amino-acid.[17] Inactivation of SRS-A following treatment with cyanogen bromide, suggested the presence of a thioether linkage.[18] Loss of biological activity following brief exposure of SRS-A to acetylating and esterifying agents indicated the presence of amino- and carboxylic acid functionalities.[18]

That arachidonic acid was a precursor of SRS-A was proposed by a number of groups. Jakschik *et al.*[19] showed that arachidonic acid stimulated the release of slow reacting substance from rat basophilic-leukaemia cells and that eicosa-5,8,11,14-tetraynoic acid (an inhibitor of both the cyclo-oxygenase component of prostaglandin synthetase and of the lipoxygenase enzyme) inhibited the mediator's production. Even more significantly, arachidonic acid radiolabelled with ^{14}C and ^{3}H was incorporated into SRS-A as evidenced by the coincidence of radioactivity and biological activity after purification of the incubation medium. Hence it was suggested that SRS-A was a previously undescribed product of arachidonic acid metabolism. These results were confirmed by other workers on mediators (SRSs) released from a variety of sources.[20]

The ultraviolet spectrum of SRS-A has a characteristic λ_{max}^{MeOH} at 280 nm. This was attributed to a triply conjugated non-aromatic chromophore[21] after inspection of the UV spectra of certain well-characterised hydroxylated lipids.[22]

Degradation of SRS by Raney nickel desulphurisation gave 5-hydroxyarachidonic acid indicating a 5-hydroxy function and confirming the presence of a thioether linkage.[23] The positions of the double bonds were determined in two ways. Firstly reductive ozonolysis of SRS biosynthesised from tritium labelled arachidonic acid yielded ^{3}H-1-hexanol demonstrating retention of the Δ^{14} double bond of the precursor.[23] Secondly, an ingenious enzymic method was employed: inactivation of SRS-A occurred on treatment with soya bean lipoxygenase.[24] This enzyme was known to have extreme specificity for oxygenating C_6 of fatty acids containing a *cis, cis*-1,4-diene system (as contained in linoleic and arachidonic acids) with concomitant isomerisation of the alkene bond.[25] The observed bathochromic shift of 30 nm in the UV spectrum of the product led to the suggestion that oxygenation and isomerisation of a Z-alkene unit at C_{14} had occurred, bringing it into conjugation with a pre-existing triene unit. This indicated the presence of a second *cis* double bond at C_{11} and additional double bonds at C_7 and C_9.



In parallel with studies on the structures and roles of various slow reacting substances, other research groups were investigating the metabolism of arachidonic acid in rabbit peritoneal polymorphonuclear leukocytes (PMNL). Borgeat incubated arachidonic acid with PMNL and characterised the major metabolite as 5(S)-hydroxyeicosa-6,8,11,14-tetrenoic acid (5-HETE; **8**). Similarly, eicosa-8,11,14-trienoic acid was transformed into 8(S)-hydroxy-9,11,14-eicosatrienoic acid.[26] The formation of the two metabolites was not inhibited by indomethacin indicating that the enzymes of the prostaglandin synthetase system were *not* involved. A novel lipoxygenase type reaction was invoked with enzymic reduction of the first-formed hydroperoxide yielding the observed product.

Later the same research group isolated a further metabolite of arachidonic acid from PMNL to which the structure 5(S),12(R)-dihydroxy-6,8,10,14-eicosatetrenoic acid **2** was assigned. The geometry about

the double bonds could not be definitively assigned from the available spectroscopic data.[27] The acid **2** was the first metabolite of arachidonic acid whose structure was shown to contain three conjugated double bonds. It was subsequently named leukotriene B_4 (LTB_4).[1] The configuration of the double bonds was later shown to be 6Z,8E,10E,14Z by an unambiguous chemical synthesis by Corey *et al.*[28] Other minor metabolites, namely two 5,6-dihydroxyeicosa-7,9,11,14-tetrenoic acids [epimers at C_6; **9**] and two geometric isomers of leukotriene B_4 (**10**) were also characterised.[29]

The structural similarities of the metabolites of arachidonic acid isolated from PMNL (i.e. a 5(S)-hydroxy group and a conjugated triene unit) suggested a common synthetic pathway. Studies with isotopic oxygen demonstrated incorporation of the isotope into the hydroxy function at C_5 whereas oxygen from H_2O^{18} was incorporated at C_{12}.[30] The participation of an unstable intermediate which could react with weak nucleophiles such as water was suspected. Trapping experiments with alcohols and the isolation of 5(S)-hydroxy-12-O-alkyl derivatives of arachidonic acid from the reaction media confirmed this suspicion.[30] The intermediate was shown to be very labile at low pH with a short half-life (about 3 min at pH 7.4 at 37°). Studies on the hydrolysis under conditions in which enzymic activities were suppressed showed that LTB_4 was produced enzymically, as suggested by its stereochemical purity. The other metabolites produced from this intermediate were the result of non-enzymic hydrolysis. These results led Samuelsson to propose that the unstable intermediate was 5,6-oxidoeicosa-7,9,11,14-tetrenoic acid, formed from 5-hydroperoxyeicosa-6,8,11,14-tetrenoic acid (5-HPETE; **11**). The latter compound was thought to be produced by a lipoxygenase catalysed oxygenation of arachidonic acid. The structure of the intermediate was confirmed by Corey *et al.* who synthesised 5(S)-*trans*-5,6-oxidoeicosa-7E, 9E, 11Z, 14Z-tetrenoic acid **1**.[31] This epoxide was transformed by neutrophils into a product indistinguishable from leukotriene B_4.[32] The epoxide, now called leukotriene A_4 (LTA_4), has recently been isolated from human polymorphonuclear leukocytes.[33] It has been shown that arachidonic acid can be transformed into 5(S)-HPETE **11** by potato lipoxygenase.[34]

From the above results Samuelsson has proposed that the transformation of arachidonic acid in polymorphonuclear leukocytes occurs as shown in Scheme 1.

Thus several pieces of evidence were emerging which suggested that the various slow reacting substances described earlier in the literature were related to the newly discovered leukotrienes. This evidence can be summarised as follows:

(a) Both species are metabolites of arachidonic acid.[19,27]

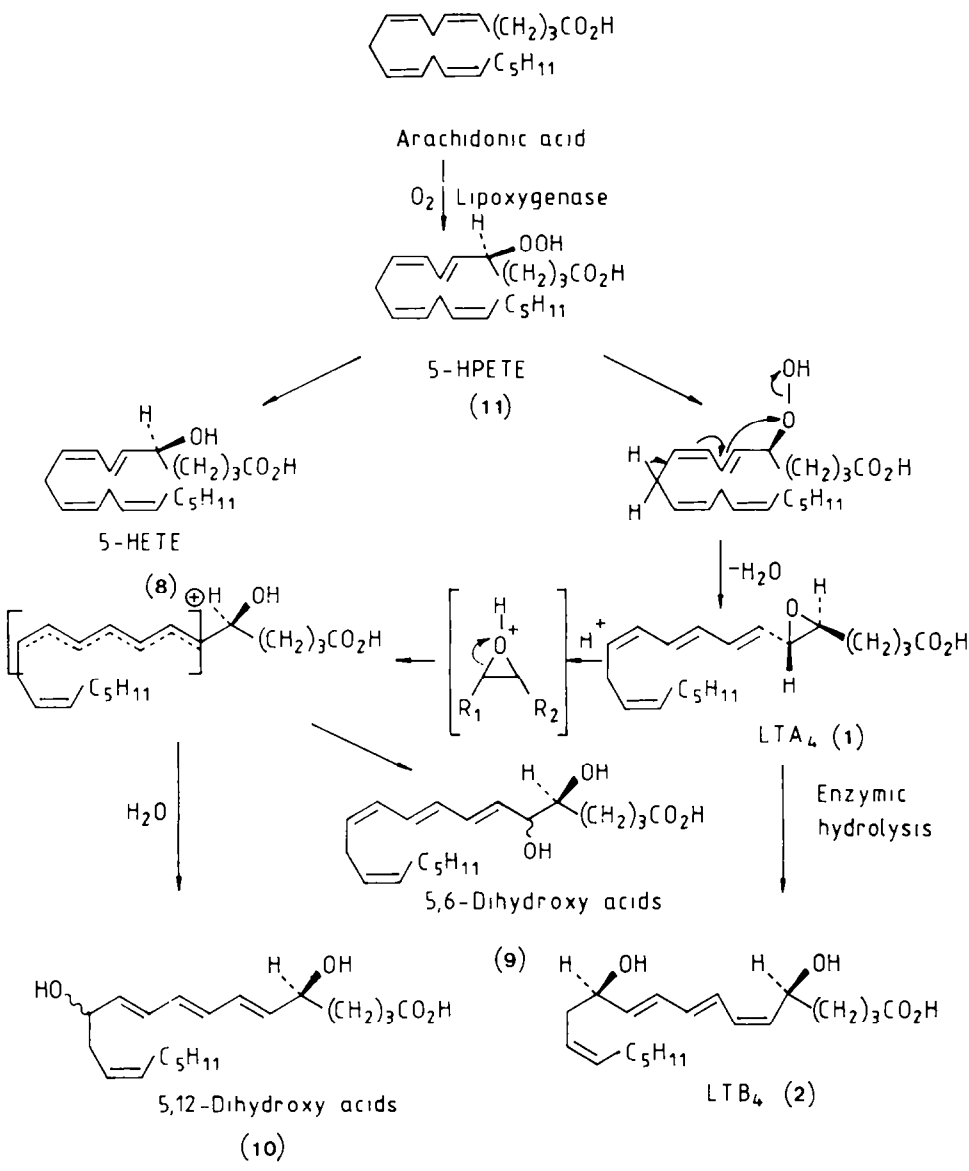
(b) Neither the biosynthesis of 5-HETE[26] nor that of SRS-A[35] is inhibited by indomethacin.

(c) The calcium ionophore A 23187 stimulated the production of both SRS[12] and leukotrienes[36] from arachidonic acid.

These observations coupled with what was known of the structure of SRS and the recently discovered role of leukotriene A_4 in arachidonic acid metabolism led Samuelsson to suggest that SRS might be a conjugate of LTA_4 and a cysteine containing moiety. Incubation of mouse mastocytoma cells with arachidonic acid, cysteine and ionophore A 23187 gave, as the major component, SRS having an UV spectrum characteristic of the leukotrienes.[23] Thus SRS appeared to be a derivative of 5-hydroxyeicosa-7,9,11,14-tetrenoic acid possibly with a cysteine containing substituent: spectroscopic evidence indicated the postulated cysteinyl side-chain was attached by a thioether linkage at C_6.[23] Determination of the substituent by standard amino-acid analysis identified it as a glutathione (γ-glutamylcysteinylglycine) residue.[37] The structure was confirmed and the stereochemistry elucidated by an independant chemical synthesis. Reaction of stereospecifically prepared leukotriene A_4[31] with glutathione yielded a product whose chemical, physical, and biological properties closely resembled SRS isolated from mouse mastocytoma cells.[38] This constituted the first published structural determination of a slow reacting substance, namely 5(S)-hydroxy-6(R)-S-glutathionyleicosa-7E,9E,11Z,14Z-tetrenoic acid (**3**), subsequently named leukotriene C_4 (LTC_4).

The intermediacy of LTA_4 in the metabolism of arachidonic acid has been confirmed by the conversion of LTA_4 into LTC_4 both by mouse mastocytoma cells and by human polymorphonuclear leukocytes.[39] Alternative structures for LTC_4 have been proposed. The presence of a 5-hydroperoxy or peroxyester group was suggested by Parker[40] while Japanese workers concluded that the amino-acid side chain was attached to C_6 by a sulphone group, rather than by a thioether linkage.[41] Both structures were discounted on the basis of a fast atom bombardment mass spectrometry study[42] and, in the case of the sulphone, by chemical synthesis.[43]

In addition to LTC_4, smaller amounts of a different slow reacting substance were obtained from mouse mastocytoma cells.[23] This substance was subsequently shown to be the 11-E isomer of LTC_4(**12**)[44]; whether this compound is formed from LTC_4 or via a separate biological pathway from LTA_4 is not known.



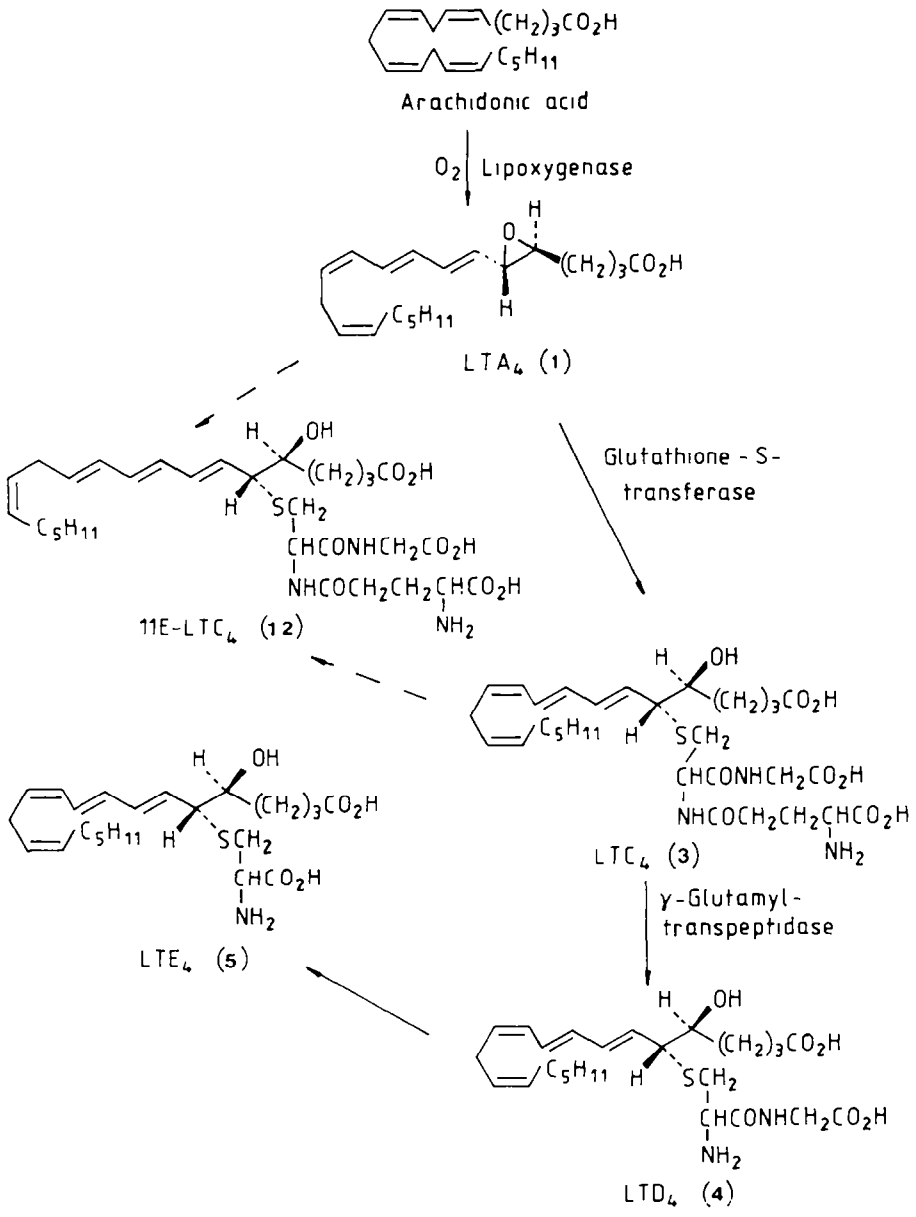
Scheme 1.

More recently, two groups of workers have established the structure of the slow reacting substance released by rat basophil leukaemia cells (RBL-1). Morris *et al.*[45] purified this SRS by a combination of gel chromatography and reverse phase HPLC and showed that the bio-active component had the characteristic UV spectrum of the leukotrienes. On the basis of amino-acid analysis and electron impact mass spectroscopy on the N-acetyl, methyl ester, trimethylsilyl ether derivative (the first such data to be published on an intact SRS molecule) the structure was proposed to be a cysteinylglycinyl conjugate of leukotriene A_4. This was confirmed, and the stereochemistry elucidated, by an independant chemical synthesis from leukotriene A_4 methyl ester and by comparison of the physicochemical and biological properties of the natural and the synthetic materials.[46] RBL-1-SRS, given the trivial name leukotriene D_4 (LTD_4) was shown to be 5(S)-hydroxy-6(R)-cysteinylglycinyleicosa-7E,9E,11Z,14Z-tetrenoic acid (4). Almost simultaneously Orning *et al.*[47] deduced the structure of RBL-1-SRS by a combination of UV spectroscopy, enzymic conversions and chemical degradation. The latter group showed that γ-glutamyl-transpeptidase catalysed the conversion of LTC_4 into LTD_4 suggesting that LTC_4 is an intermediate in the biosynthesis of LTD_4.

The structure of SRS-A was elucidated when Morris showed that the slow reacting substance

isolated from guinea pig lungs sensitised to ovalbumin was identical with LTD_4.[46,48] This contrasted with an earlier report by Samuelsson at the IVth International Prostaglandin Conference in 1979 when the structure of a substance released from murine mastocytoma cells by A 23187 was announced as 5-hydroxy-6-cysteinyleicosa-7,9,11,14-tetrenoic acid and, in error, referred to as SRS-A.[49] To add to the confusion, this compound was initially called leukotriene C, as mentioned earlier. The 6-cysteinyl conjugate has since been identified in SRS-A released from rat peritoneum:[50] the chemical structure and the stereochemistry was confirmed by chemical synthesis.[51] 5(S)-Hydroxy-6(R)-cysteinyleicosa-7E,9E,11Z,14Z-tetrenoic acid (5) has been designated leukotriene E_4 (LTE_4).

Scheme 2 shows a possible pathway for the formation and further metabolism of leukotrienes C_4, D_4 and E_4. A considerable amount of evidence in support of this postulate has been accrued. Bioconversion of LTA_4 into LTC_4 has been observed[39] as has the enzyme catalysed removal of the γ-glutamyl residue from LTC_4 to form LTD_4.[47] In addition Sih *et al.* have realised the conversion of LTD_4 into LTE_4 using an aminopeptidase component of a particular arylsulphatase.[52] The sequential conversion of the glutathionyl side chain of SRS released from rat basophilic leukaemia cells into



Scheme 2.

cysteinylglycyl and cysteinyl conjugates related to LTD_4 and LTE_4 has been described.[53] Finally, Bach *et al.*[54] studied the kinetics of the formation of LTC_4 and LTD_4 in rat peritoneal mononuclear cells and showed that LTC_4 is formed more rapidly than LTD_4. This indicated that the glutathione moiety is added first and is followed by the removal of the glutamate residue. However it should be noted that no change in the ratio of LTC_4 to LTD_4 was observed when the experiment was repeated in the presence of γ-glutamyltranspeptidase inhibitors, suggesting the possibility that LTD_4 could be formed directly from LTA_4 and glycinylcysteine.

SRS isolated from rat peritoneal cells stimulated with A 23187 and L-cysteine has been separated chromatographically into two components, I and II. Fraction I was similar chromatographically and biologically to SRS-A immunologically released from human lungs and characterised as LTD_4.[55] Fraction II was subsequently characterised as a mixture of LTC_4 and 11E-LTC_4.[56] LTC_4, LTD_4 and LTE_4 have been identified in SRS-A from rat peritoneal nuclear cells[50,51] and the same workers found LTC_4 in addition to LTD_4 in SRS-A released from human lung.[50] As previously described the mediator released immunologically from guinea pig lungs is LTD_4[48] and SRS from perfused cat paws has been shown by a combination of chemical, spectroscopic and enzymic methods to consist of a mixture of LTD_4 and LTE_4.[52] Since the leukotrienes are transformed $LTC_4 \rightarrow LTD_4 \rightarrow LTE_4$ in a metabolic cascade, it is not surprising that the composition of any SRS will depend upon the source of the material and the isolation procedure employed.

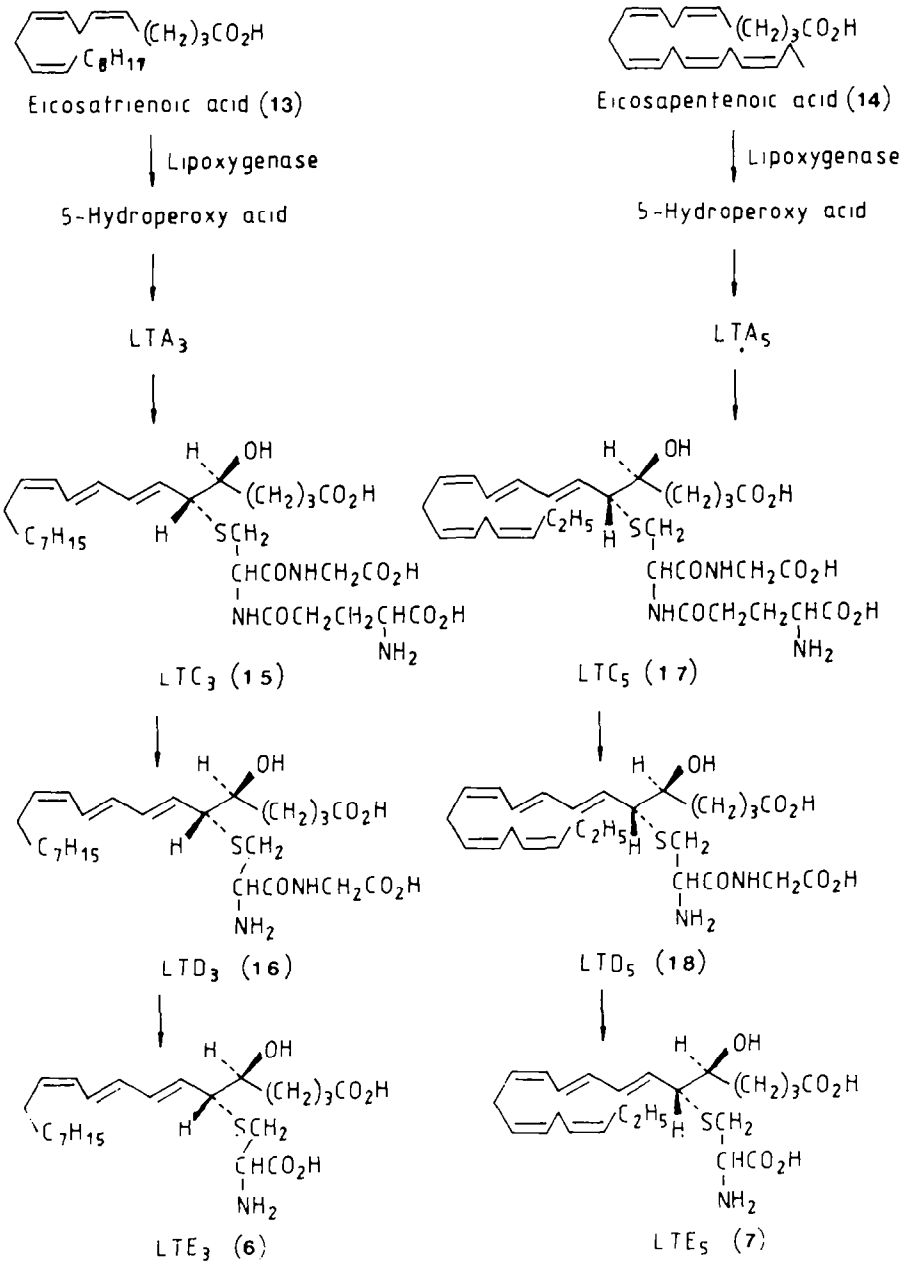
Samuelsson has proposed that single defined compounds be known as the relevant leukotriene and that the term SRS be used to describe biologically derived material where the relative amounts of leukotrienes present are not known.

Leukotrienes derived from eicosa-5,8,11-trienoic acid (**13**) and eicosa-5,8,11,14,17-pentenoic acid (**14**) have been described. Hammarström incubated the acid (**13**) with mouse mastocytoma cells stimulated with A 23187 and isolated 5(R)-hydroxy-6(S)-glutathionyleicosa-7E,9E,11Z-trienoic acid (LTC_3) (**15**) and the corresponding 11E-isomer. Both compounds were converted into the corresponding cysteinylglycine conjugates LTD_3 (**16**) and 11E-LTD_3 by kidney γ-glutamyltranspeptidase.[57] In a similar manner, the acid (**14**) was converted into 5(R)-hydroxy-6(S)-glutathionyleicosa-7E,9E,11Z,14Z,17Z-pentenoic acid (LTC_5) (**17**) and its 11E-isomer. LTC_5 could be converted into LTD_5 (**18**) by γ-glutamyltranspeptidase.[58] Hammarström also showed that rat basophilic leukaemia cells converted the trienoic acid (**13**) into LTC_3 and LTD_3, and transformed the pentenoic acid (**14**) into LTC_5 and LTD_5. The corresponding cysteinyl conjugates LTE_3 (**6**) and LTE_5 (**7**) were also isolated from the incubation medium. Time-course experiments with ^{3}H-labelled LTC_3 and use of an inhibitor of γ-glutamyltranspeptidase indicated that LTD_3 was transiently formed during the conversion into LTE_3.[59] Scheme 3 shows the biosynthetic pathway for leukotrienes of the 3- and 5-series. The 5-hydroperoxy-compounds, and LTA_3 and LTA_5, are assumed to be formed initially by analogy with the more thoroughly investigated pathway from arachidonic acid.

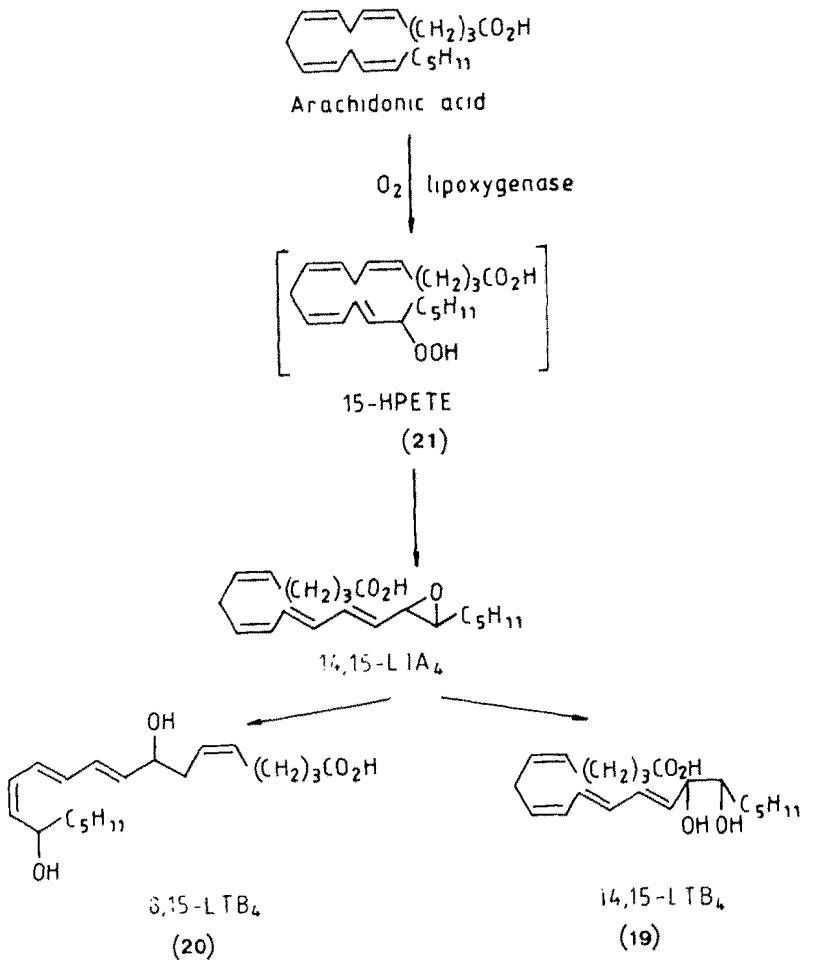
Leukotriene formation is not restricted to products derived from 5-HPETE. Incubation of arachidonic acid with human leukocytes gave, in addition to LTB_4, two isomers of 14,15-dihydroxyeicosa-5,8,10,12-tetrenoic acid (14,15-LTB_4) (**19**) and two isomers of 8,15-dihydroxyeicosa-5,9,11,13-tetrenoic acid (8,15-LTB_4) (**20**). The detailed stereochemistry of these products was not determined. They were assumed to be formed by initial oxygenation at C_{15} followed by epoxide formation and attack by water at C_{14} and C_8 (Scheme 4)[60] in an analogous manner to the process of LTB_4 biosynthesis. The same products were obtained from the incubation of 15-HPETE (**21**) with human leukocytes.[61]

Maas *et al.*[62] demonstrated a similar metabolism of arachidonic acid by leukocytes. Arachidonic acid 15-lipoxygenase from rabbit PMNL has recently been isolated and shown to catalyse the formation of 15-HPETE.[63] Sih *et al.*[64] confirmed the formation of the diols (**19**) and (**20**) from 15(S)-HPETE by incubation of the latter compound with human leukocytes but assigned a different configuration about the 14,15-double bond (**20a**). Sih's group also isolated a new metabilite, 5(S), 15(S)-dihydroxyeicosa-6E,8Z,11Z,13E-tetrenoic acid (**22**). The intermediacy of 14,15-LTA_4 (**23**) was suspected. This was synthesized and shown to be converted non-enzymatically into (**19**) and (**20a**). The same paper also describes the conversion of the epoxide (**23**) into 15(S)-hydroxy-14(R)-S-glutathionyleicosa-5Z, 8Z, 10E, 12E-tetrenoic acid (14-LTC_4) (**24**) and 15(S)-hydroxy-14(R)-S-cysteinylglycyleicosa-5Z,8Z,10E,12E-tetrenoic acid (14-LTD_4) (**25**) by rat basophilic leukaemia cells. These transformations are summarized in Scheme 5.

The diol (**22**) has also been isolated from a double oxygenation of arachidonic acid by soya bean lipoxygenase.[65] Products arising from the initial oxygenation of arachidonic acid at C_9 after incubation

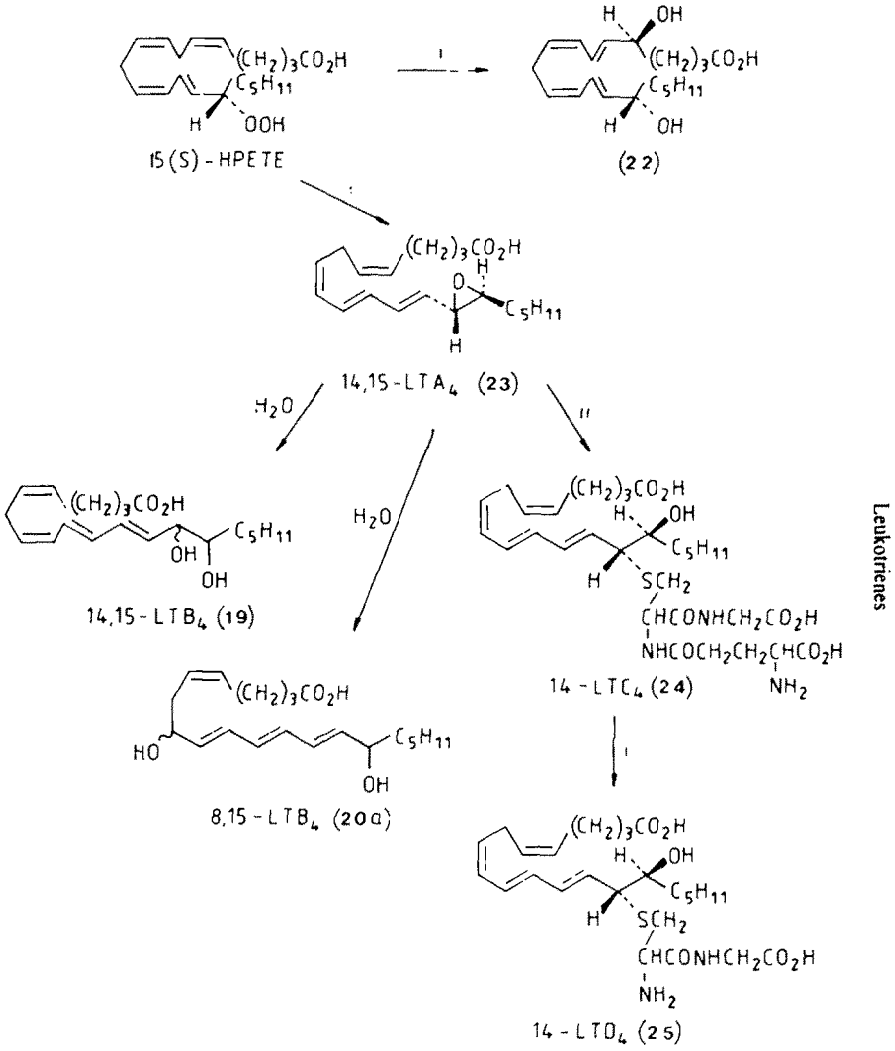

Eicosatrienoic acid (13)
Lipoxygenase
5-Hydroperoxy acid
LTA3
LTC3 (15)
LTD3 (16)
LTE3 (6)
Eicosapentenoic acid (14)
Lipoxygenase
5-Hydroperoxy acid
LTA5
LTC5 (17)
LTD5 (18)
LTE5 (7)

Scheme 3.



The stereochemistry is based on the assumption that the 5- and 15-lipoxygenase pathways are analogous.

Scheme 4.



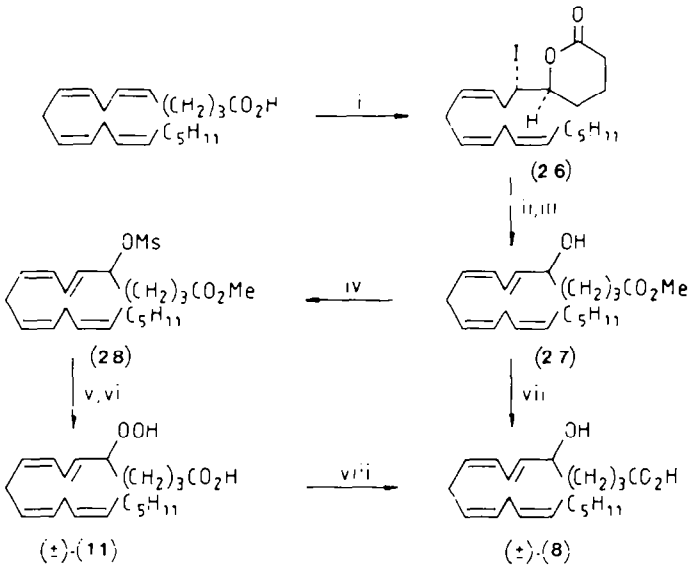
Reagents: i, human leukocytes; ii, rat basophilic leukaemia cells.

Scheme 5.

with cytochrome P-450,[66] and at C_9 and C_{15} after treatment with rabbit renal cortical supernatant fluid, have been described.[67]

CHEMICAL SYNTHESIS

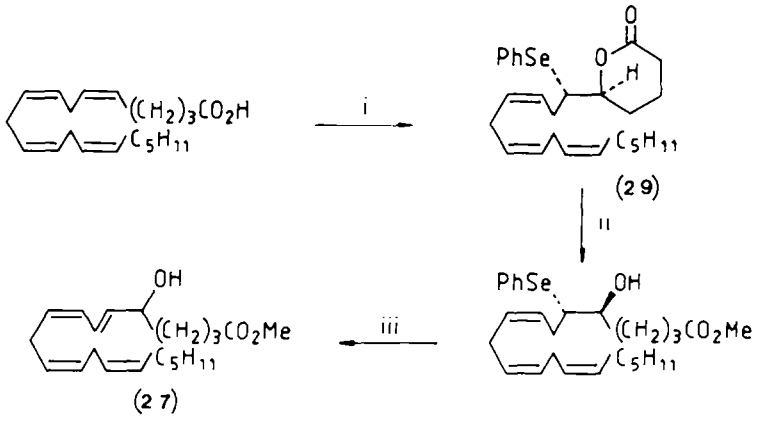
5-Hydroxy-(HETE) and 5-hydroperoxyeicosatetrenoic acids (HPETE). Singlet oxygen oxidation of arachidonic acid,[68] or aerial oxidation followed by reduction,[69] indiscriminately produces mixtures of HPETEs and HETEs and is rarely used as a preparative method.[70] Selective substitution at the 5-position was achieved by iodo-lactonisation of arachidonic acid which furnished the iodo-lactone (**26**) (Scheme 6).[34] Dehydroiodination and methanolic cleavage of the lactone ring gave the methyl ester of



Reagents: i, KI, $KHCO_3$, THF, H_2O, 0°; ii, DBU, PhH; iii, Et_3N, MeOH; iv, CH_3SO_2Cl, Et_3N, CH_2Cl_2, −65°; v, H_2O_2, Et_2O, −110°; vi, LiOH, H_2O_2, DME, H_2O; vii, LiOH, DME, H_2O; viii, $NaBH_4$, H_2O, pH9.

Scheme 6.

(±)5-HETE (**27**) which was converted into (±)-5-HPETE (**11**) by way of the mesylate (**28**). (±)-HETE (**8**) can be prepared by borohydride reduction of (**11**) or by hydrolysis of the ester (**27**). A conceptually similar preparation of (±)-5-HETE involved the phenylselenylation of arachidonic acid to give the seleno-lactone (**29**) (Scheme 7).[71] Hydrolysis, esterification, and oxidative removal of the phenylselenyl

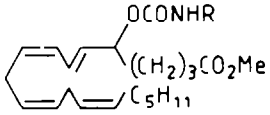


Reagents: i, PhSeCl, CH_2Cl_2, −78°; ii, LiOH, THF, H_2O; then CH_2N_2; iii, oxidation.

Scheme 7.

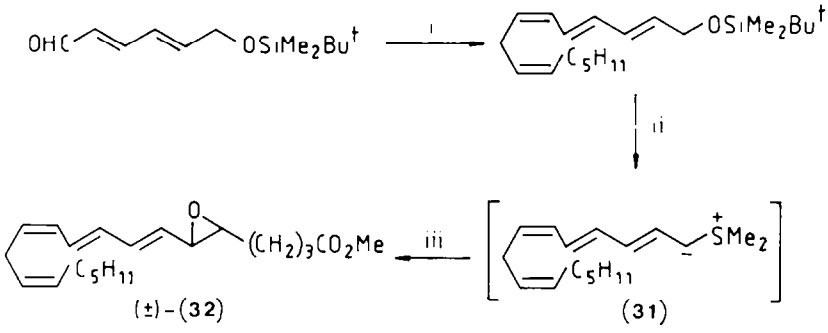
group gave (±)5-HETE methyl ester (**27**) and the 8E isomer in ratios varying from 4:1 to 1:9 depending on the precise experimental conditions utilised.

The naturally occurring (S)-enantiomer of 5-HPETE has been prepared by oxygenation of arachidonic acid with lipoxygenase derived from potato tubers or tomatoes.[34] 5(S)-HETE was prepared by borohydride reduction of 5(S)-HPETE[34] or by chromatographic separation of the diastereomeric urethanes (**30**) followed by hydrolysis.[72]



(30) R = DEHYDROABIETYL AMINE

Preparation of leukotriene A_4. The preparation of (±)LTA_4 was first described in 1979 by Corey (Scheme 8).[78] Experimental conditions for the preparation and use of the sulphonium ylid (**31**) were

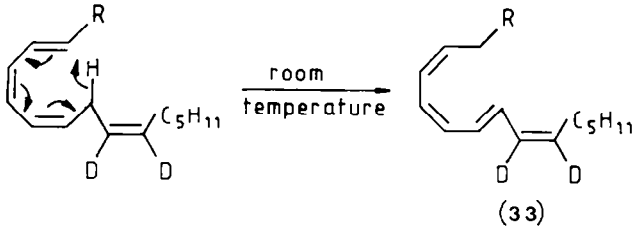


Reagents: i, $Ph_3P{=}CHCH_2{\cdot}CH{=}CH{\cdot}C_5H_{11}$, THF, HMPA, −78°→0°; ii, several steps; iii, $OHC(CH_2)_3CO_2Me$, THF, −78°→0°.

Scheme 8.

reported to be very critical; nevertheless the LTA_4 methyl ester (**32**), which was produced as a 1:1 mixture of *cis* and the natural *trans* epoxides, could be isolated in 35% yield. Hydrolysis of the epoxy-ester (±)(**32**) with cold aqueous base gave aqueous solutions of the salt of (±)LTA_4.

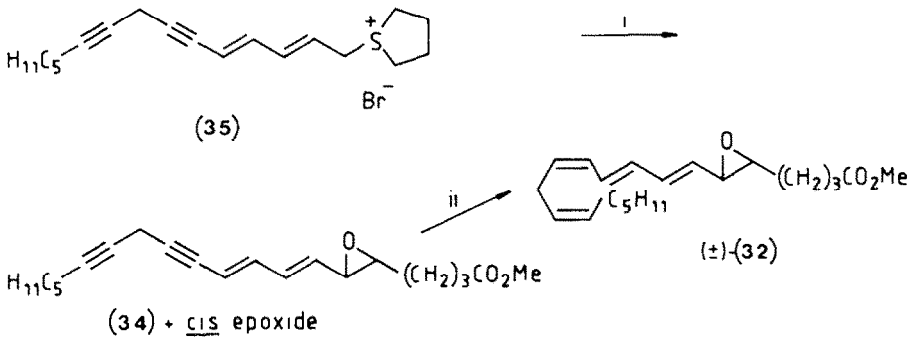
Rokach *et al.* also used the sulphonium ylid (**31**) in a preparation of (±)LTA_4 methyl ester (**32**) and they succeeded in separating the resulting mixture of *cis*- and *trans*-epoxides.[74] This research group also attempted a preparation of 9Z-LTA_4 because the geometry of the 9,10-double bond in the natural material was uncertain at that time. However, the requisite tetraene intermediate underwent a remarkably facile [1, 7]-hydrogen migration to give the isomer (33) (Scheme 9).



(33)

R = CO_2Et or CH_2OH

Scheme 9.

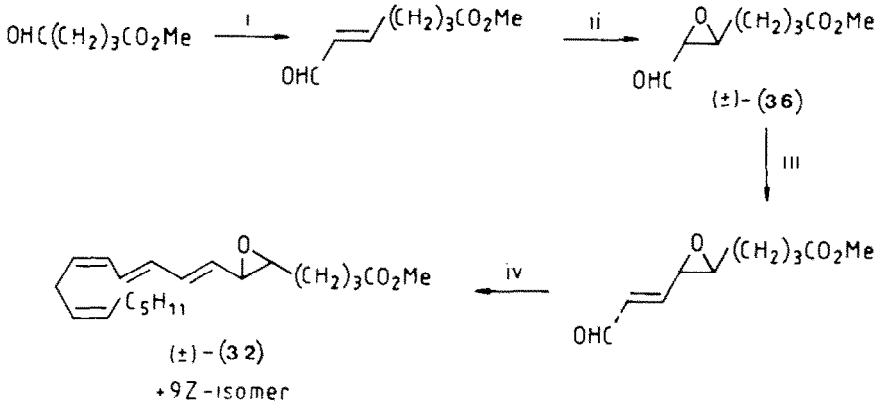


Reagents: i, OHC·$(CH_2)_3CO_2Me$, $PhCH_2\overset{+}{N}Et_3\cdot Cl^-$, NaOH, H_2O, CH_2Cl_2, −30°; ii, H_2, C_6H_{14}, Lindlar catalyst.

Scheme 10.

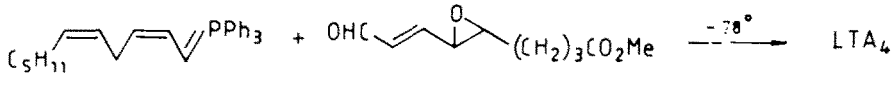
Rosenberger and Neukom[75] have prepared (±)LTA_4 methyl ester (**32**) by partial hydrogenation of the diyne (**34**), which is derived from the salt (**35**) (Scheme 10).

As the early approaches to LTA_4 constructed the epoxide group by ylid addition to an aldehyde unit, they were not capable of selectively preparing the natural enantiomer. For this reason all further non-biomimetic syntheses have utilised the epoxy-ester (**36**) as a key synthon. An example of this strategy is shown in Scheme 11 where (±)LTA_4 methyl ester was prepared in four steps from methyl



Reagents: i, $Ph_3P{=}CH\cdot CHO$, $PhCH_3$, Δ; ii, H_2O_2, $NaHCO_3$; iii, $Ph_3P{=}CH\cdot CHO$; iv, BuLi, 2,5,Z, $Ph_3P=CH\cdot CH=CH\cdot CH_2CH=CH\cdot C_5H_{11}$, −78°.

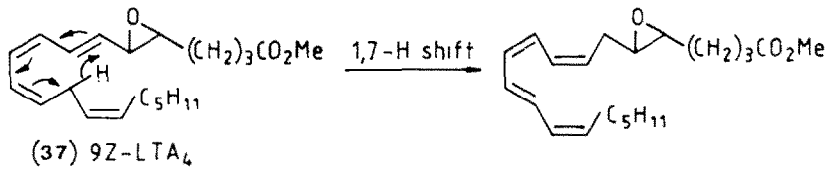
Scheme 11.



Product	Solvent and Isomer Ratio %	
	THF	THF-HMPA
LTA_4	48	17
9Z-LTA_4	40	42
9Z,11E-LTA_4	12	41

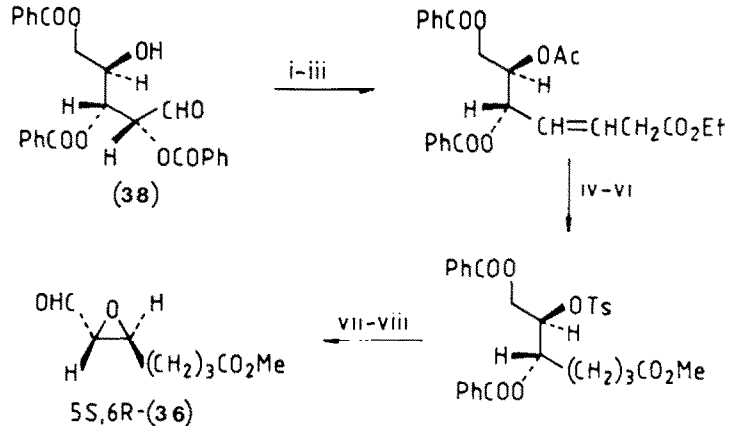
Fig. 3. Preparation of LTA_4 and geometrical isomers.

4-formylbutyrate; the appropriate undecadienyl phosphonium salt was prepared from oct-2-yn-1-ol.[76] The product obtained from the Wittig reaction was initially thought to be a 2:1 mixture of the required 9E-compound and its 9Z-isomer but later work showed that the 9Z,11E-isomer was also present;[77] the ratios of the geometric isomers varied with the reaction conditions (see Fig. 3). Direct comparison of these results is made difficult because of the paucity of experimental detail in these and most other leukotriene papers. The facile 1,7-hydrogen shift noted by Rokach *et al.* (see Scheme 9) also occurred during the formation of 9Z-LTA$_4$ (**37**) (Scheme 12).[77]



Scheme 12.

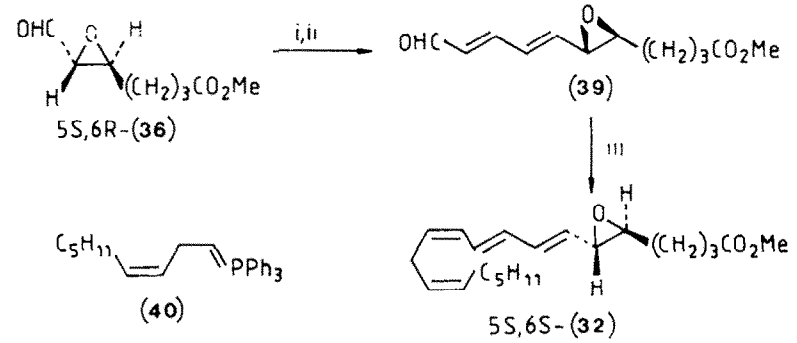
The use of methyl 5(S),6(R)-epoxy-6-formylhexanoate (**36**) as a key synthon in the preparation of natural LTA$_4$ has been described by several groups. Scheme 13 outlines a route to (**36**) from 2,3,



Reagents: i, $Ph_3P{=}CH{\cdot}CO_2Et$, DME, Δ; ii, Ac_2O, H_2SO_4; iii, Zn amalgam, HCl, Et_2O; iv, H_2, Pd/C, MeOH; v, HCl, MeOH; vi, TsCl, Py, 23→50°; vii, K_2CO_3, MeOH; viii, CrO_3, Py.

Scheme 13.

5-tribenzoyl-D(-)-ribose (**38**) which is remarkable because of the high overall yield (83%)[31]. Homologation of 5(S),6(R)-(**36**) with 1-lithio-4-ethoxybutadiene gave the 7E,9E-C_1-C_{11} fragment (**39**) (Scheme 14) and



Reagents: i, $Li^+{\cdot}\bar{C}H{=}CH{\cdot}CH{=}CH{\cdot}OEt{=}OEt$, THF, −78°; ii, CH_3SO_2Cl, Et_3N, CH_2Cl_2, −45°→0°; iii, (40), THF, HMPA, −78°.

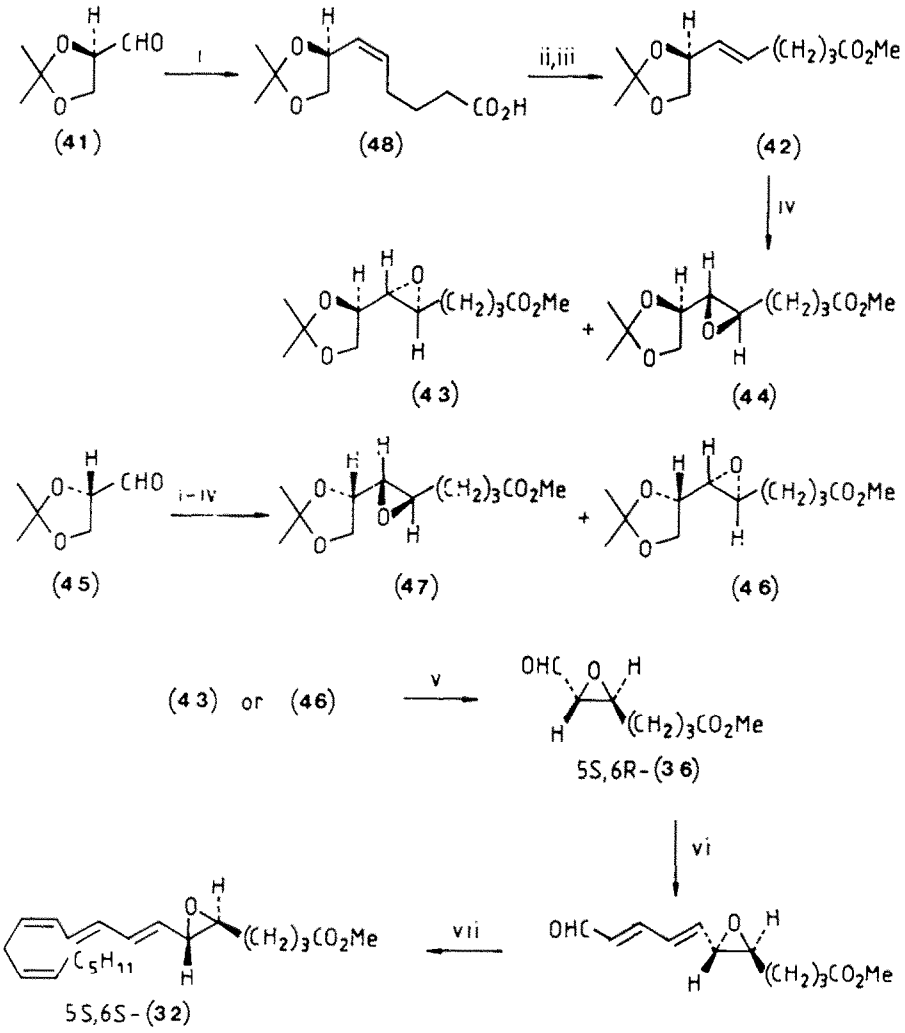
Scheme 14.

the remaining Z-double bonds were introduced by reaction with the phosphorane (**40**) to give enantiomerically pure 5(S),6(S)-LTA_4 methyl ester (**32**). This material was later transformed biologically into natural LTB_4 providing further evidence for the stereochemical assignments.[32]

The 5(S),6(R)-epoxy-ester (**36**) was also converted into a mixture of 9Z-LTA_4 and LTA_4 methyl esters by the process outlined in Scheme 11.[31] The work of Baker *et al.*[77] (*vide supra*) suggested that the 9Z,11E-isomer was present and indeed later work on the analysis of LTC_4 derived from LTA_4 prepared in this manner suggested that the 9Z,11E-isomer was predominant (*vide infra*).

11E-LTA_4 was prepared from 5(S),6(R)-(**36**) by promoting *trans*-olefination in the Wittig reaction featured in Scheme 14.[78]

In a second synthesis of LTA_4 Rokach *et al.* prepared the 5(S),6(R)-epoxy-ester (**36**) from both enantiomers of glyceraldehyde.[79] In the first instance a derivative of D-glyceraldehyde (**41**) was chosen as the starting material. The presence of the acetonide moiety in (**41**) allowed a better separation of diastereomeric intermediates later in the synthetic sequence. Conversion of the acetonide (**41**) into the ester (**42**) followed by epoxidation of the alkene unit gave a mixture of the epoxyesters (**43**) and (**44**) but unfortunately asymmetric induction favoured the undesired isomer (**44**) (the ratio (**43**):(**44**) was 1:2) (Scheme 15). The use of the acetonide of L-glyceraldehyde (**45**) as a starting material rectified the

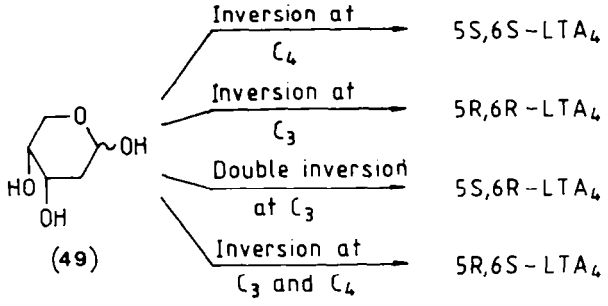


Reagents: i, $Ph_3P{=}CH{\cdot}(CH_2)_3CO_2Na^+$; ii, $h\nu$, PhSSPh; iii, CH_2N_2; iv, m-CPBA; v, AcOH, $NaIO_4$, H_2O; vi, $2\times Ph_3P{=}CH{\cdot}CHO$; vii, 3Z-$Ph_3P{=}CH{\cdot}CH_2{\cdot}CH{=}CH{\cdot}C_5H_{11}$.

Scheme 15.

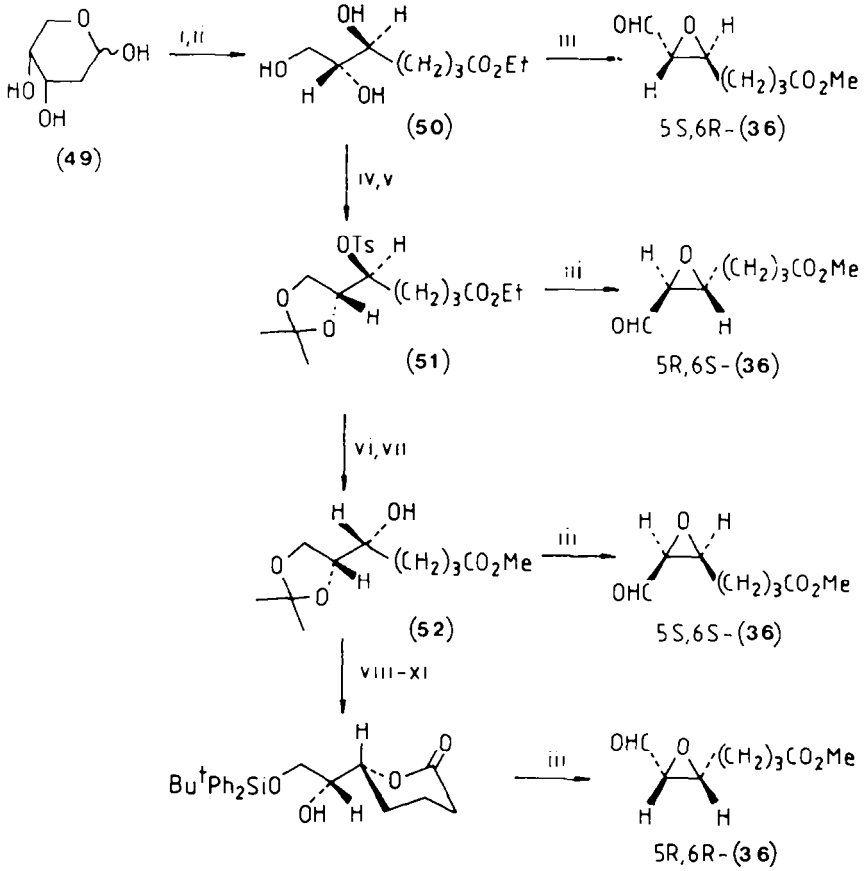
situation, furnishing the epoxide (**46**) as the major product. Hydrolytic cleavage of both the diastereomers (**43**) and (**46**) furnished 5(S),6(R)-formylester (**36**) which was converted into LTA_4 methyl ester 5(S),6(S)-(**32**) by three successive Wittig olefinations. The 5(S),6(S)-stereoisomer of (**36**) was obtained from both the acetonides (**44**) and (**47**); the 5(R),6(R)- and the 5(S),6(S)-diastereomers of the acetonides (**43**) and (**44**) were obtained from the Z-acid (**48**).

The same research group has prepared the four stereoisomers of the epoxy-ester (**36**) (and hence LTA_4) from 2-deoxy-D-ribose (**49**) in two ways. The first approach[80] is outlined in Scheme 16 and



Scheme 16.

described in detail in Scheme 17. 2-Deoxy-D-ribose was converted into the triol-ester (**50**) which served as a convenient intermediate for the 5(S),6(R)-epoxy-ester (**36**). Further transformation of the triol gave

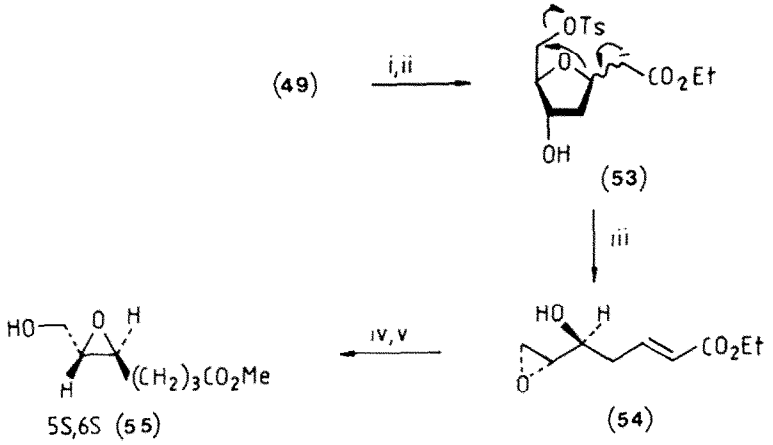


Reagents: i, $Ph_3P{=}CH{\cdot}CO_2Et$; ii, H_2, Pd/C; iii, several steps; iv, Me_2CO, pTsOH; v, TsCl, Py; vi, $PhCO_2^-Na^+$, DMF; vii, NaOMe, MeOH; viii, HCl, THF, H_2O; ix, $^tBuPh_2SiCl$; x, NaOH, H_2O, THF; xi, DCC.

Scheme 17.

the acetal (**51**) [a precursor of 5(R),6(S)-(**36**)] and the acetal (**52**) [a precursor of both 5(S),6(S)-(**36**) and 5(R),6(R)-(**36**)]. The epoxy-esters (**36**) were converted into the corresponding LTA_4 methyl ester diastereoisomers by the three successive Wittig olefination reactions described in Scheme 15.

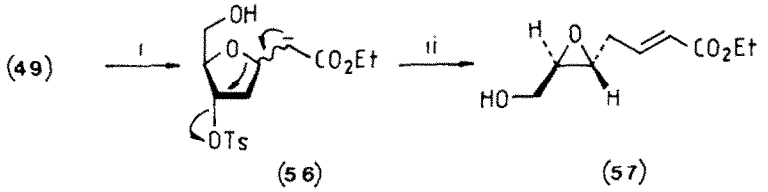
The second preparation of chiral precursors to LTA_4 from 2-deoxy-D-ribose (**49**) was founded on the base-induced intramolecular reaction of the tosylate (**53**) to give the epoxy-ester (**54**)[81] (Scheme 18). This



Reagents: i, $Ph_3P{=}CH{\cdot}CO_2Et$ (2 eqs), THF, Δ, 5 days; ii, TsCl, Py; iii, LDA, THF, −78° → 10°; iv, H_2, Pd/C; v, NaOMe, MeOH.

Scheme 18.

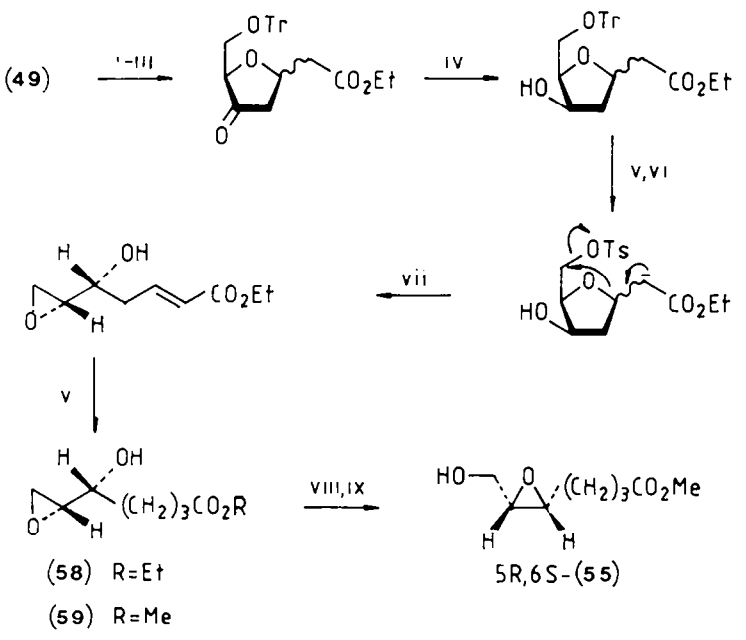
was readily converted into the primary alcohol (**55**), a known intermediate[80] to LTA_4. (In a later paper (**55**) was converted into 14,15-dehydro LTA_4).[43] Alternatively, the use of the C_5 tosylate (**56**) (Scheme 19) gave the hydroxyester (**57**), a precursor of 5(R),6(R)-LTA_4.



Reagents: i, several steps; ii, LDA, THF, −78°.

Scheme 19.

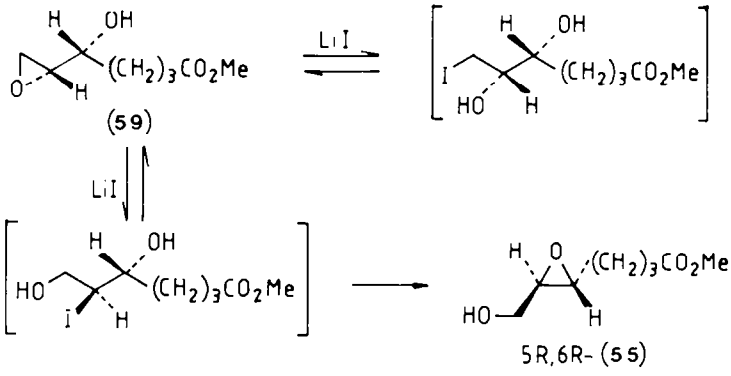
The preparation of the 5(R),6(S) isomer of the hydroxy-ester (**55**) involved inversion of configuration of the secondary hydroxyl group of 2-deoxy-D-ribose (**49**) and tosylation of the primary alcohol (Scheme 20). Base treatment gave the terminal epoxide (**58**). Whereas methoxide treatment of the diastereomer (**54**) effected rearrangement to the desired epoxide, treatment of the compound (**58**) under similar conditions resulted in trans-esterification. However, lithium iodide in methanol promoted the desired rearrangement to furnish the epoxide (**55**); the latter compound is a useful intermediate for the preparation of 5(R), 6(S)-LTA_4. Surprisingly, treatment of the epoxide (**59**) with lithium iodide in hot methanol did not give the



Reagents: i, $Ph_3P{=}CH{\cdot}CO_2Et$ (2 eqs), THF, Δ, 5 days; ii, TrCl, DMAP, Py; iii, CrO_3, Py; iv, Lithium perhydro-9B-boraphenalylhydride; v, H_2, Pd/C; vi, TsCl, Py; vii, LDA, THF; viii, NaOMe, MeOH; ix, DBN, MeOH, 90°.

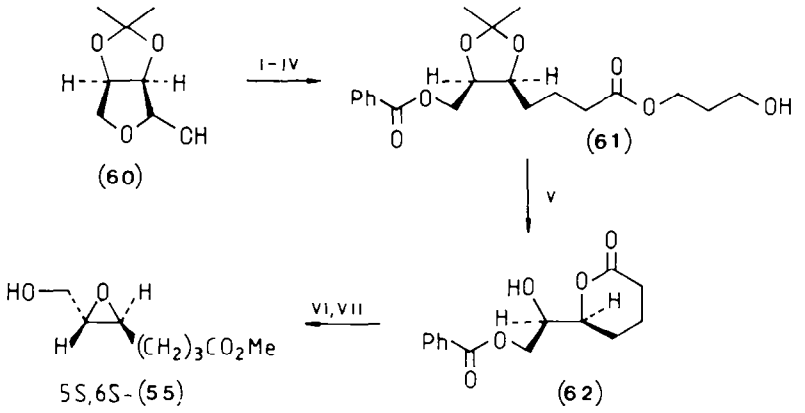
Scheme 20.

5(R), 6(S)-epoxide (**55**) but, rather, the isomeric 5(R), 6(R)-epoxide. The authors attribute this finding to the involvement of the mechanism shown in Scheme 21.[81]



Scheme 21

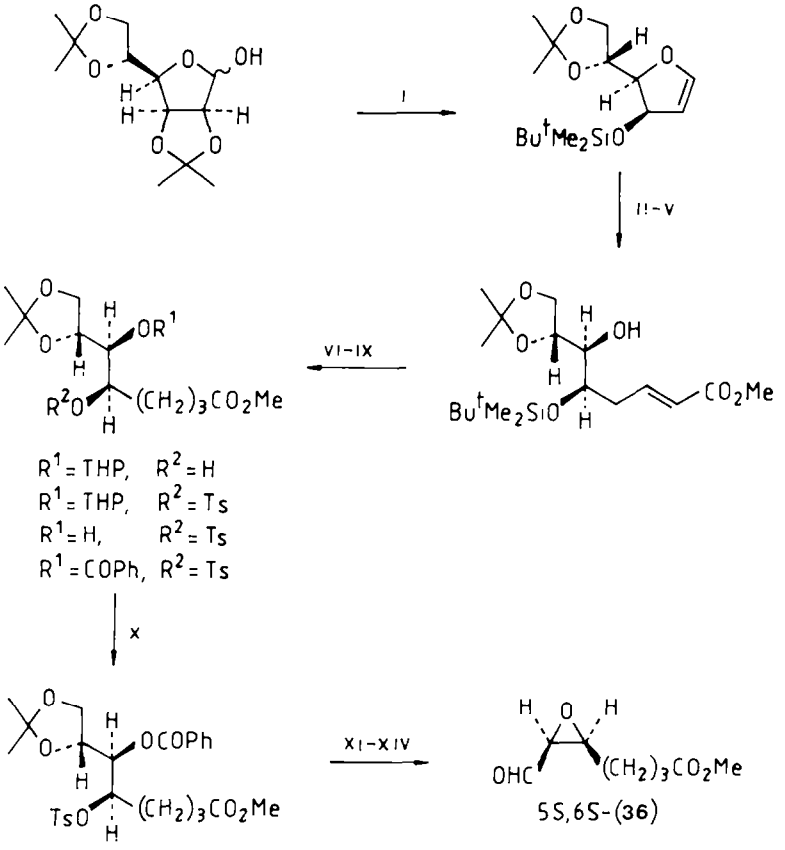
Methyl 7-hydroxy-5(S),6(S)-epoxyheptanoate (**55**) and the 5(S),6(R)-diastereomer (precursors of LTA_4 and 5(S), 6(R)-LTA_4 respectively) have been prepared from 2,3-O-isopropylidene-D-erythrose (**60**) and diethyl L-tartrate.[82] The key step in the synthesis of the 5(S),6(S)-isomer is the conversion of the acetonide (**61**) into the lactone (**62**), a process which differentiated the hydroxyl functions at C_5 and C_6 (Scheme 22). Two more simple transformations provided the required 5(S),6(S)-epoxy-ester (**55**). Diethyl L-tartrate was used to provide the 6-epimer of lactone (**62**) and, hence, the 5(S),6(R)-isomer of (**55**).



Reagents: i, $Ph_3P{=}CH{\cdot}CH_2{\cdot}CH$(O,O) ; ii, PhCOCl, Py; iii, H_2, Pt; iv, O_3; v, TFA, H_2O; vi, CH_3SO_2Cl, Et_3N; vii, K_2CO_3, MeOH.

Scheme 22.

A lengthy route to the 5(S),6(S)-epoxy-ester (**36**), (a precursor of 5(S),6(R)-LTA_4[31]) starting from the bis-acetonide of D-(+)mannose has been described by Corey and Goto (Scheme 23).[83]

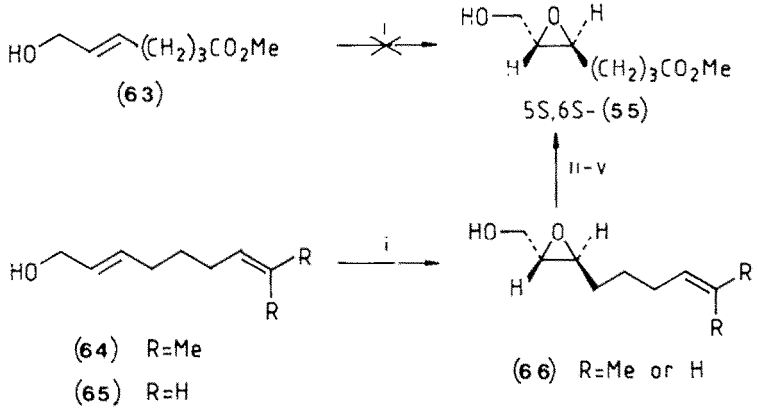


Reagents: i, several steps, ii, $Hg(OAc)_2$, THF, H_2O, 0°; iii, KI, H_2O, 0°; iv, $NaBH_4$, −10°; v, $Ph_3P{=}CH{\cdot}CO_2Me$; vi, H_2, Pt; vii, DHP, $PyH^+{\cdot}Ts^-$; viii, nBu_4NF ; ix, Et_3N, MeOH; x, two steps; xi, K_2CO_3, MeOH; xii, $PyH^+{\cdot}Ts^-$; xiii, K_2CO_3, MeOH; xiv, $Pb(OAc)_4$.

Scheme 23.

Syntheses of leukotrienes using chiral natural products as starting materials frequently need to incorporate lengthy protection-deprotection sequences during the removal or modification of unwanted functional groups. For this reason the development of a method for stereospecific epoxidation of an achiral olefinic alcohol represented a considerable advance in methodology for leukotriene synthesis.

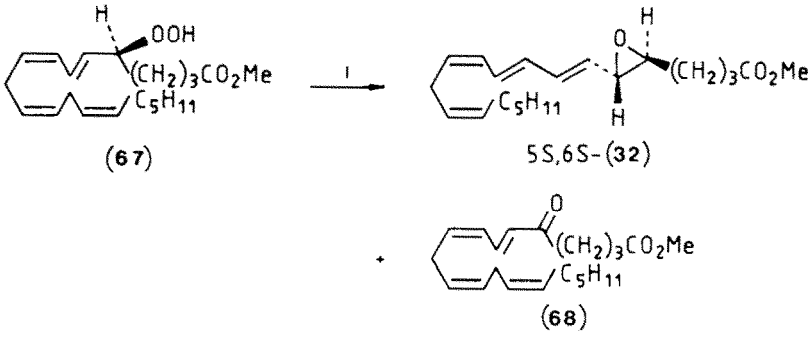
Methyl 7-hydroxyhept-5-enoate (**63**) could not be epoxidised directly using the Sharpless method[84] but two independant reports have described enantioselective epoxidations of the diene alcohols (**64**)[84] and (**65**).[85] Oxidative cleavage of the remaining alkene unit in the epoxides (**66**) followed by esterification gave the ubiquitous leukotriene precursor, 5(S),6(S)-epoxyester (**55**) (Scheme 24).



Reagents: i, ^{t}BuOOH, L(+)diethyl tartrate, $Ti(iPrO)_4$, −23°; ii, Ac_2O, Py; iii, O_3, Jones reagent, −20° or IO_4^-, $RuCl_3$; iv, CH_2N_2; v, K_2CO_3, MeOH.

Scheme 24.

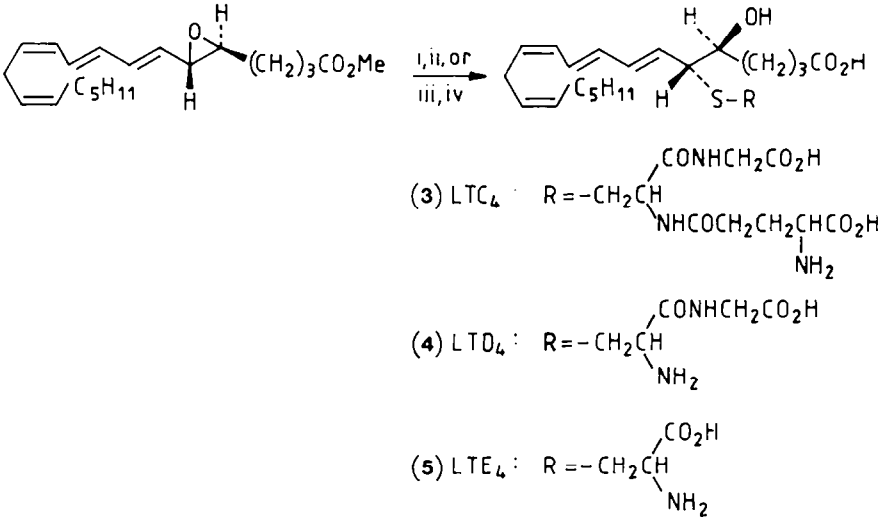
A biomimetic conversion of 5-HPETE methyl ester into LTA_4 methyl ester poses some difficulties.[86] The hydroperoxy group in 5-HPETE has to be activated to nucleophilic attack and yet the reaction conditions must be non-acidic and exceptionally mild to avoid destroying the LTA_4 ester as it is formed. This problem was addressed by Corey *et al.*[86] From 5-HPETE methyl ester (**67**) they obtained a mixture of LTA_4 methyl ester (**32**) and the dienone (**68**) from which the LTA_4 ester was isolated in 25% yield (Scheme 25). Later work showed that 9Z-LTA_4 methyl ester was also produced in this reaction[87] and that the ratio of LTA_4 ester to the dienone (68) was solvent dependant.[88]



Reagents: i, 1,2,2,6,6-pentamethylpiperidine, $(CF_3SO_2)_2O$, CH_2Cl_2, Et_2O, −110°.

Scheme 25

Preparation of leukotrienes C, D and E. Organic chemistry has yet to improve upon nature for a synthesis of these leukotrienes. All the reported syntheses of natural LTC_4, D_4 and E_4 and their diastereomers involve treatment of LTA_4 methyl ester with the appropriate protected amino-acid (Scheme 26). Glutathione will couple in unprotected form.[31,86,38,37] Hydroquinone is a necessary in-



Reagents: i, Glutathione, Et_3N, MeOH (refs. 31, 37, 38, 86) or N-trifluoroacetylglutathione dimethyl ester, Et_3N, MeOH (refs. 31, 50, 79, 88); ii, N-Trifluoroacetyl-L-cysteinylglycine methyl ester, Et_3N, MeOH (refs. 37, 46, 50, 78, 79); iii, N-Trifluoroacetyl-L-cysteine methyl ester, Et_3N, MeOH (refs. 37, 51, 79) or L-cysteine methyl ester, Et_3N, MeOH, H_2O (ref. 75); iv, K_2CO_3, DME, H_2O (refs. 38, 50, 51, 78) or K_2CO_3, MeOH, H_2O (refs. 31, 74, 79) or $KHCO_3$, K_2CO_3, H_2O, MeOH (ref. 31) or LiOH, DME, H_2O (ref. 88) or KOH, MeOH, H_2O (ref. 75).

Scheme 26.

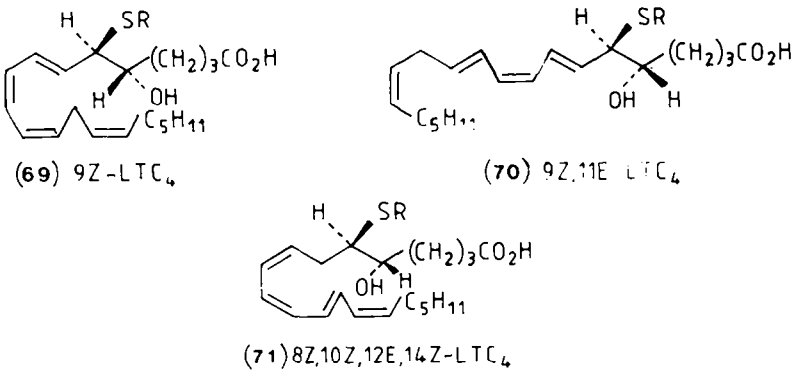
gredient in the hydrolyses of LTE_4 esters to avoid partial isomerisation of the 11Z double bond.[51] The presence of a large excess of lithium perchlorate in attempted preparations of LTC_4 diverts the course of the reaction to produce a diastereomeric mixture of 12-glutathionyl-leukotrienes.[89]

Unnatural diastereomers of LTC_4, D_4 and E_4, have also been prepared from the corresponding diastereomer of LTA_4 by the standard methods of coupling.[83,37]

The use of S-trimethylsilyl derivatives of N-trifluoroacetyl-L-cysteine methyl ester and N-trifluoroacetylglutathione dimethyl ester to prepare LTE_4 and LTC_4 respectively has been reported by Rokach *et al.*[74]

Corey and Samuelsson reported a synthesis of 9Z-LTC_4 (**69**)[31] but a later synthesis of authentic samples of 9Z- and 9Z,11E-LTC_4 by Baker *et al.*[90] suggested that the compound obtained in the earlier work was the 9Z,11E-isomer of LTC_4 (**70**). In Baker's work LTC_4 and isomers were prepared from LTA_4 isomers of known stereochemistry.[77] 9Z-LTC_4 (**69**) was shown to rearrange to the isomer (**71**). Clearly this is an example of the facile 1,7-hydrogen shift noted in earlier work.[74,77]

As previously discussed, uncertainty about the oxidation state of the thio-linkage in natural LTC_4 has been dispelled by mass spectrometric examination of biologically and chemically derived LTC_4[42] and also by preparation of the sulphone of LTC_4 (**72**) through potassium hydrogen persulphate oxidation of LTC_4.[43] However, the latter reaction did not give an unambiguous answer as the C_{14} double bond of LTC_4 is known to be susceptible to oxidation. For this reason a second synthesis was undertaken which was based on 14,15-dehydro-LTA_4 (**73**), a compound whose acetylenic bond is not susceptible to

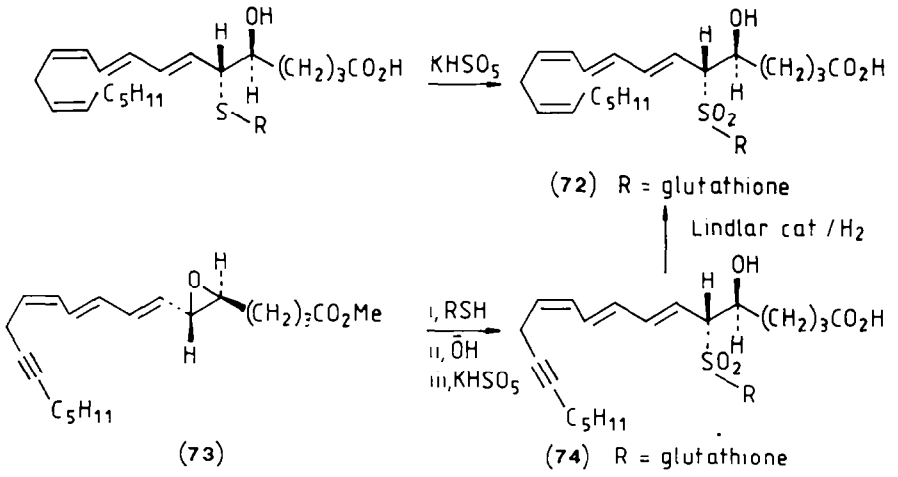


(69) 9Z-LTC_4 (70) 9Z,11E-LTC_4

(71) 8Z,10Z,12E,14Z-LTC_4

R = glutathione

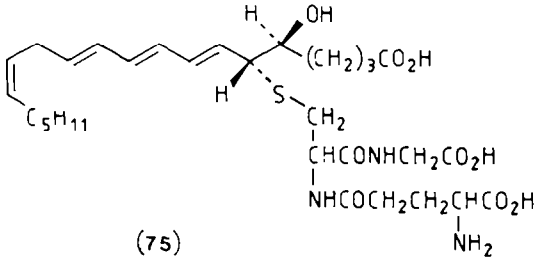
oxidation under the reaction conditions necessary to prepare the sulphone (**74**) (Scheme 27).[43] Reduction of the alkyne (**74**) with Lindlar catalyst gave the sulphone (**72**), identical with the specimen prepared



Scheme 27.

from LTC_4 directly, but distinctly different in its physical properties from natural LTC_4. Both of these synthetic methods were used to prepare sulphones of LTD_4 and LTE_4. Parenthetically, the curious observation was made that during the Lindlar reductions a significant amount of the 11E-isomer was produced, as detected by HPLC.[43] This emphasises the extreme care that is needed in structural assignments of leukotriene isomers.

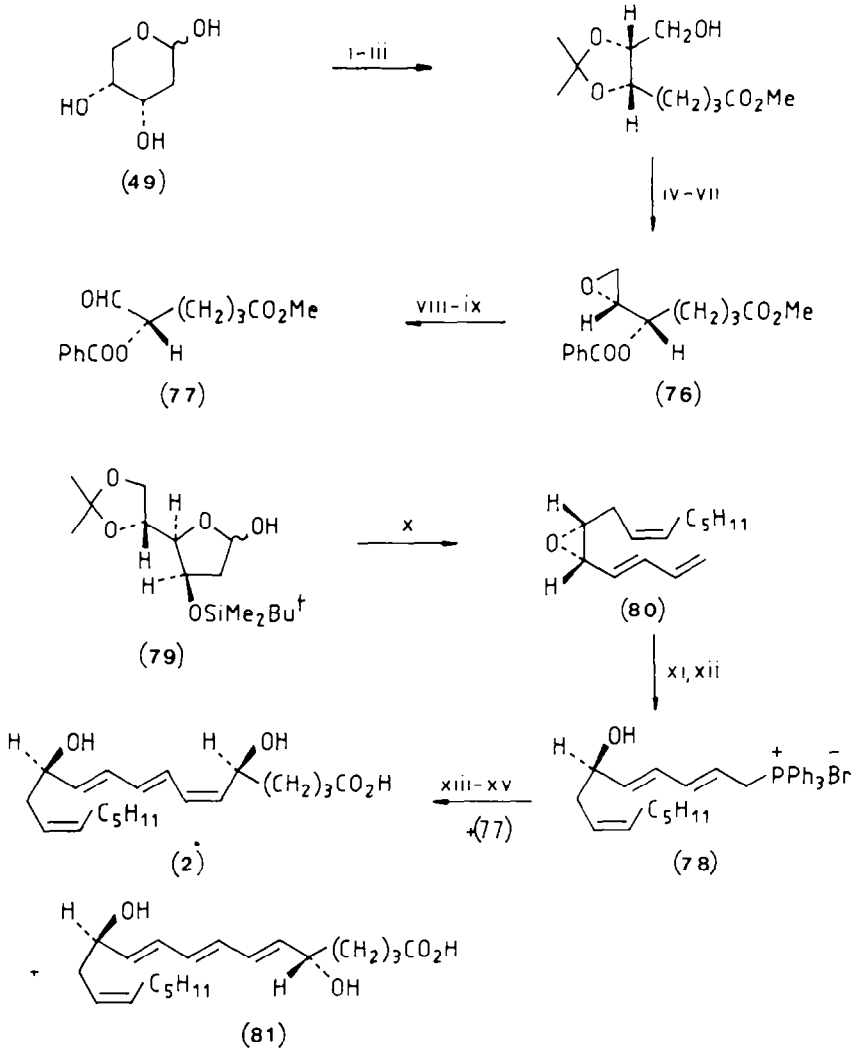
The 11E-isomer of LTC_4 (75) has been isolated from murine mastocytoma cells.[23] It has been prepared by coupling glutathione with 11E-LTA_4, followed by hydrolysis, and also by lithium hydroxide hydrolysis of N-trifluoroacetyl-LTC_4, mono- or tri-methyl ester.[44,78] In the latter route, control experiments showed that the isomerisation occurred during the hydrolysis step and not during the work-up procedure.



(75)

Preparation of leukotriene B_4. The initial studies on LTB_4 did not elucidate the configuration of the double bonds.[27] Because of the paucity of natural LTB_4, synthesis of this material assumed primary importance in structure elucidation.

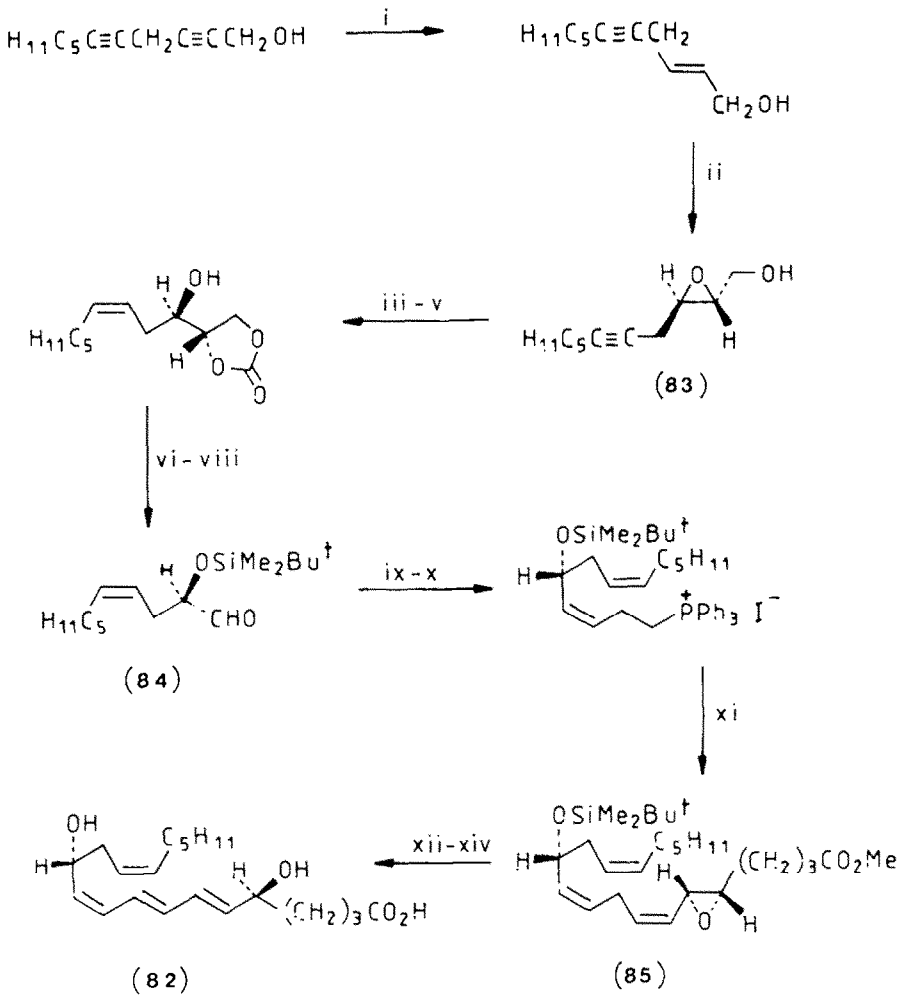
The first synthesis of LTB_4 was reported by Corey *et al.* (Scheme 28).[28] 2-Deoxyribose (**49**) was



Reagents: i, CH_2=C(OMe)CH_3, PyH$^+$ Ts^-; ii, Ph_3P=CH·CO_2Me; iii, H_2, Pd/C; iv, TsCl, Py; v, HCl, MeOH; vi, K_2CO_3, MeOH; vii, PhCOCl, Py; viii, $(MeO)_3CH$, H_2O, $HClO_4$; ix, $Pb(OAc)_4$; x, eight steps; xi, HBr (g); xii, PPh_3; xiii, nBuLi, THF, HMPA; xiv, K_2CO_3, MeOH; xv, LiOH, H_2O, MeOH.

Scheme 28.

converted in seven steps into the epoxy-diester (**76**) and thence into the chiral C_1–C_6 fragment (**77**). The residual C_7–C_{20} moiety was provided by the phosphonium salt (**78**). This salt was synthesised stereospecifically from the protected sugar (**79**), (a compound previously prepared as an LTA_4 intermediate[83]), by means of acid-catalysed opening of the triene epoxide (**80**). Coupling of the two components (**77**) and (**78**), followed by hydrolysis gave LTB_4(**2**) and 6E-LTB_4(**81**). The synthetic LTB_4 was indistinguishable from natural LTB_4 by bioassay and chromatography while 6E-LTB_4 was identical to one of the 5, 12-diols produced by non-enzymic, acid-catalysed hydrolysis of LTA_4. However, the remaining isomers of LTB_4 still needed to be prepared in order to establish the homogeneity of LTB_4 isolated from natural sources. The 6E,10Z-isomer of LTB_4(**82**) was prepared from 2,5-undecadiyn-1-ol by way of a



Reagents: i, $LiAlH_4$; ii, $^tBuO_2H$, $Ti(iPrO)_4$, (S, S), DMTA; iii, H_2, Lindlar catalyst; iv, Ph·NCO; v, $HClO_4$, MeCN; vi, $^tBuMe_2SiCl$, imidazole; vii, $LiAlH_4$; viii, $Pb(OAc)_4$; ix, $Ph_3P{=}CH{\cdot}CH_2CH_2O{\cdot}CH_2{\cdot}CH(OMe){\cdot}CH_3$; x, three steps; xi, nBuLi, methyl 5S, 6S, oxido-7-oxoheptanoate; xii, LiOH, DME, H_2O; xiii, $iPr(C_5H_{11}){\cdot}N{\cdot}MgBr$; xiv, $nBu_4N^+{\cdot}F^-$.

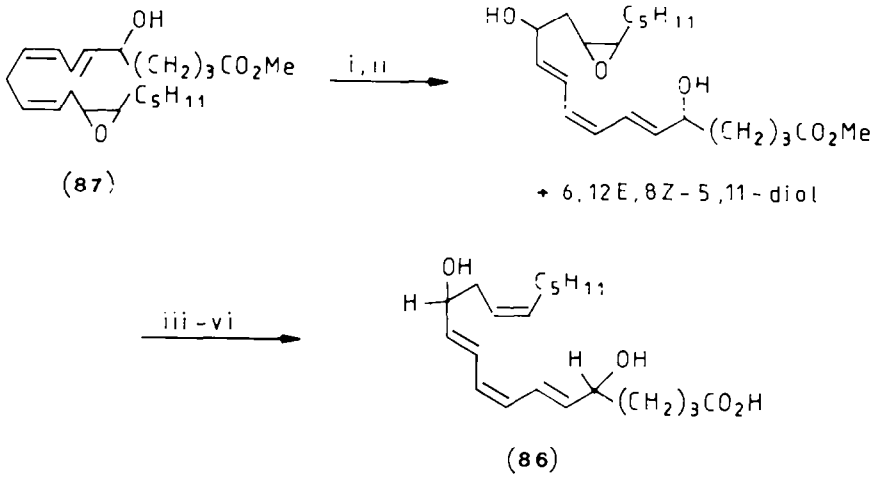
Scheme 29.

enantioselective oxidation (Scheme 29).[91] Manipulation of the resulting epoxide (**83**) gave the aldehyde (**84**) which was chain-extended with concomitant introduction of the 10Z-double bond. The E-double bonds were introduced by rearrangement of the allylic epoxide (**85**) to give, after deprotection, the required 6E,10Z-isomer of LTB_4 (**82**). This was clearly different from LTB_4 by chromatography. Moreover bio assay showed this isomer to be totally inactive as a chemotactic agent.

(±)-6E,8Z-Leukotriene-B_4 (**86**) was prepared from the epoxy-alcohol (**87**) by photo-sensitised oxygenation followed by deoxygenation and hydrolysis (Scheme 30).[91] Both diastereomers of (**86**) were obtained by reverse phase HPLC and one displayed considerable chemotactic activity, albeit two orders of magnitude less than LTB_4. This diastereomer displayed the same mobility on HPLC as LTB_4 but was clearly differentiated from LTB_4 by UV spectroscopy. The 5(S),12(S)-stereochemistry of the active diastereomer was proved by preparation of an authentic sample by a stereochemically unambiguous route (Scheme 31).[92]

Comparative bioassay of the four synthetic leukotriene B isomers (**2**), (**81**), (**82**) and (**86**) conclusively proved that naturally occurring LTB_4 possessed the 6Z,8E,10E,14Z-configuration.[93]

Acid catalysed hydrolysis of LTA_4 gave a mixture of 5,12-diols[28] whose structures were confirmed by stereospecific syntheses (Scheme 32).[94] The 5(S),12(S)-stereoisomer was obtained from the inter-

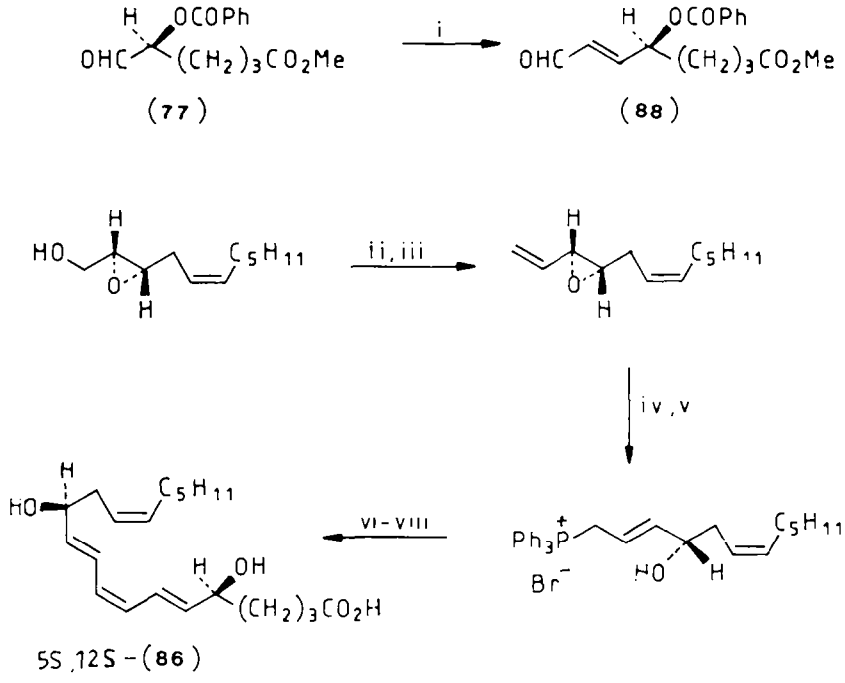


Reagents: i, hν, O_2, methylene blue; ii, Ph_3P; iii, KSeCNO; iv, LiOH, H_2O, MeOH; v, AcOH; vi, RP, HPLC.

Scheme 30.

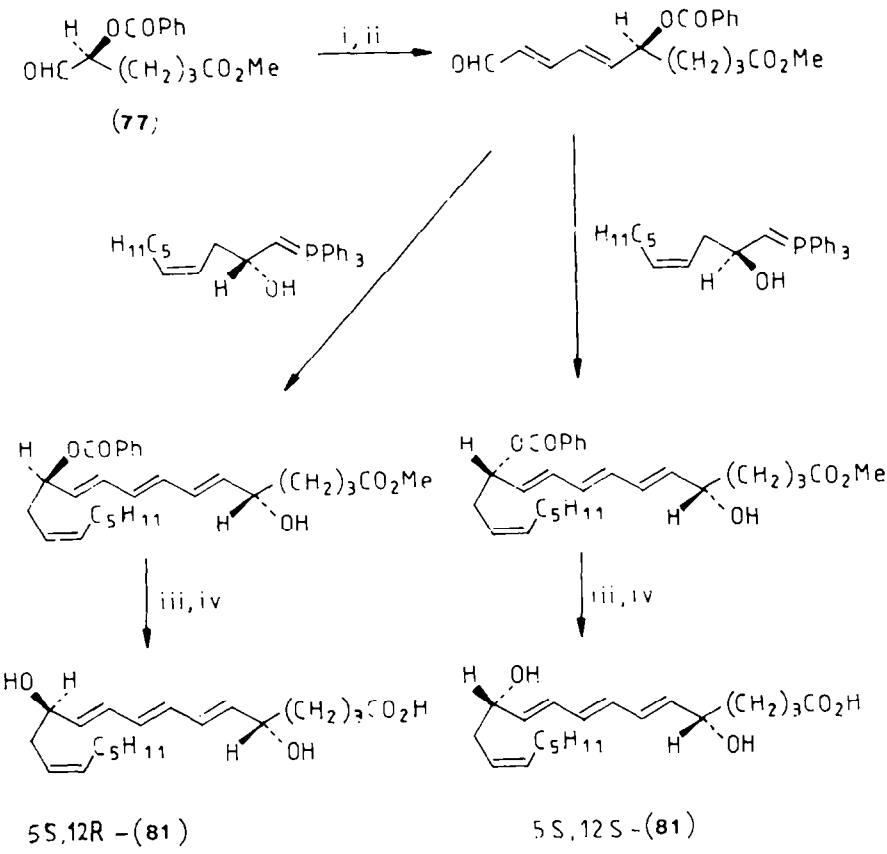
mediates (77)[38] and 2(S)-hydroxy-4Z-nonenyltriphenylphosphorane[95] while the 5(S),12(R)-diastereomer was derived from R-(+)-malic acid.

Efficient preparations of natural LTB_4 are of paramount importance as this powerful chemotactic factor is of great interest in studies of the inflammatory state. An elegant synthesis of LTB_4 has been described by Corey *et al.* in which the all-*cis* triene (89) was converted into LTB_4 in 75% yield by a base



Reagents: i, Ph_3P=CHCHO; ii, CrO_3, Py; iii, Ph_3P=CH_2; iv, HBr(g), CH_2Cl_2; v, Ph_3P; vi, (88), nBuLi, THF, HMPA; vii, K_2CO_3, MeOH; viii, LiOH, MeOH, H_2O.

Scheme 31.

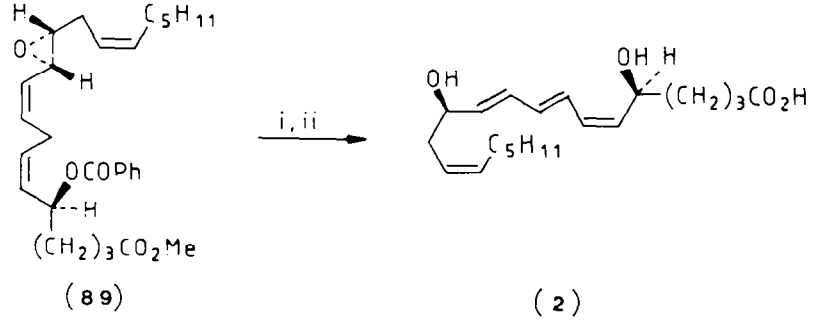


Reagents: i, Li·(CH=CH)$_2$·OEt; ii, CH_3SO_2Cl, Et_3N; iii, K_2CO_3, MeOH; iv, LiOH, H_2O.

Scheme 32.

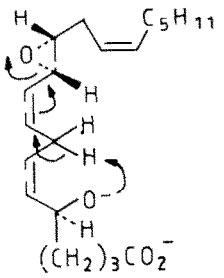
catalysed hydrolysis (Scheme 33).[96] This remarkable stereospecific transformation is believed to occur by an intramolecular rearrangement (see compound **90**).

Rokach *et al.* have described a synthesis of LTB_4 from 2-deoxyribose (Scheme 34).[97] Thus, the tetrahydrofuran (**91**) was prepared in eight steps from 2-deoxyribose and transformed into the E, E-dienoate (**92**) by treatment with sodium ethoxide. The dienoate (**92**) was converted into the phosphonium salt (**93**) and the derived phosphorane was reacted with the aldehyde (**94**), itself derived from 2-deoxyribose, to give a separable mixture of LTB_4 (**2**) and 6E-LTB_4 (**81**).

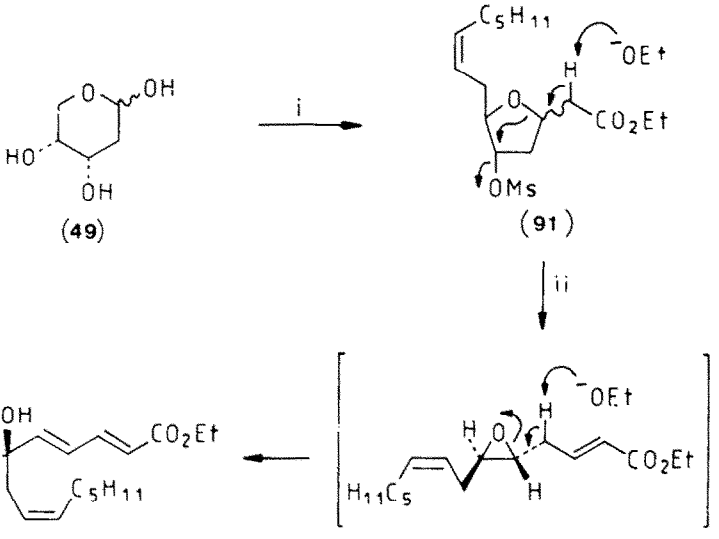


Reagents: i, 1.5 M K_2CO_3, MeOH, H_2O; ii, AcOH.

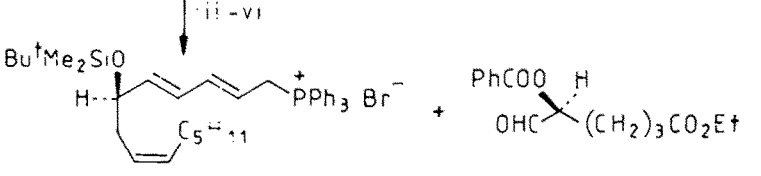
Scheme 33.



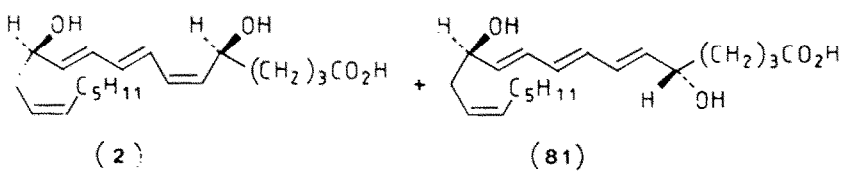
(90)



(49) (91) (92)



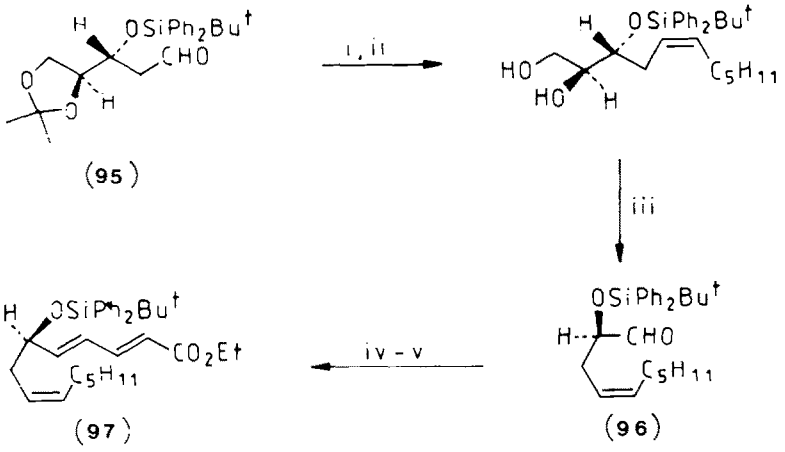
(93) (94)



(2) (81)

Reagents: i, eight steps; ii, NaOEt, EtOH, RT; iii, $^tBuPh_2SiCl$, Et_3N; iv, AlH_3; v, Ph_3P, CBr_4; vi, Ph_3P; vii, nBuLi, THF; viii, $nBu_4N^+F^-$; ix, K_2CO_3, MeOH, H_2O

Scheme 34.



Reagents: i, $Ph_3P{=}CH{\cdot}C_5H_{11}$; ii, TFA, THF, H_2O; iii, $Pb(OAc)_4$, Na_2CO_3; iv, $Ph_3P{=}CH{\cdot}CHO$; v, $(EtO)_2P(O)\bar{C}H{\cdot}CO_2Et$.

Scheme 35.

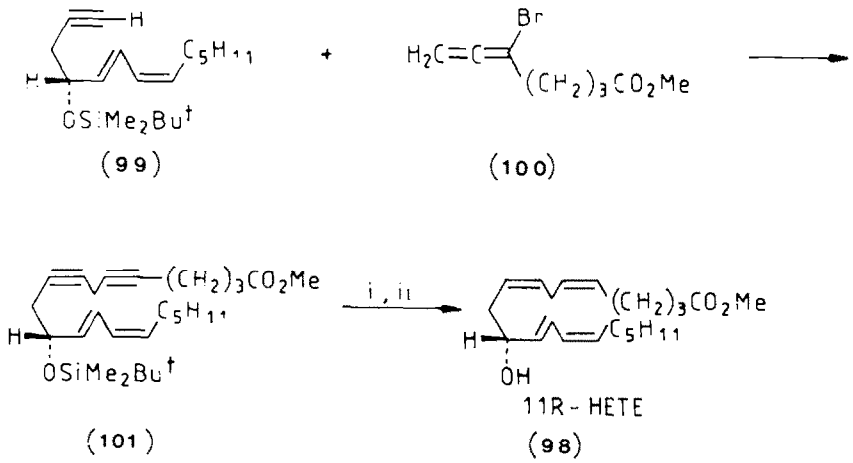
The most flexible approach to LTB_4 is described in Scheme 35.[98] The key intermediate (**95**), prepared in six steps from L-arabinose, can be considered to be a protected form of 2(R)-hydroxybutanedial. Reaction of the aldehyde (**95**) with hexylidenetriphenylphosphorane, hydrolysis of the acetonide group, and cleavage of the unmasked diol unit gave the aldehyde (**96**). Two successive olefinations on the aldehyde (**96**) gave the dienoate (**97**) which was converted into LTB_4 as described in Scheme 34. 12(S)-LTB_4 was prepared from D-arabinose in a similar manner.

LEUKOTRIENE ANALOGUES

The preparation of geometric and stereoisomers of leukotrienes has been discussed in the preceding section. In many cases the configuration of a naturally occurring leukotriene was proved by comparison of its physicochemical and biological properties with those of isomers prepared by unambiguous chemical syntheses.

A number of positional isomers of leukotrienes and the corresponding intermediates have been prepared, generally using chemical procedures similar to those employed for the synthesis of the naturally occurring compounds.

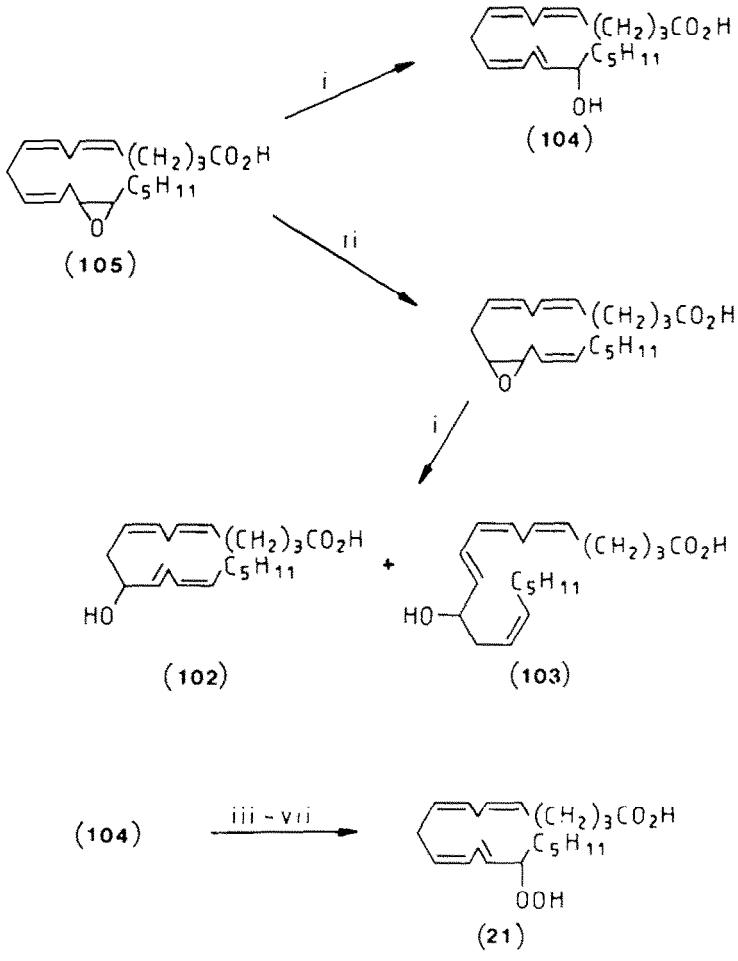
Corey and Kang[99] prepared 11(R)-HETE methyl ester (**98**) by the unusual coupling of the acetylene (**99**) with allenic bromide (**100**) to give the 1, 4-diyne (**101**). This avoided the formation of an allene which usually occurs to some extent during the coupling of a nucleophilic acetylide with a propargylic halide. Reduction and desilylation furnished the methyl ester of 11(R)-HETE (**98**) (Scheme 36). The same



Reagents: i, H_2, Lindlar catalyst, hexane, Et_3N; ii, n-Bu_4NF, THF, 25°.

Scheme 36.

research group[100] also prepared the 11-(**102**), 12-(**103**), and 15-(**104**) substituted isomers of HETE from 14, 15-epoxyarachidonic acid (**105**) (*vide infra*). The 15-hydroxy acid (**104**) was converted into the hydroperoxide (**21**) which was identical with material produced by the action of soya bean lipoxygenase on arachidonic acid (Scheme 37).

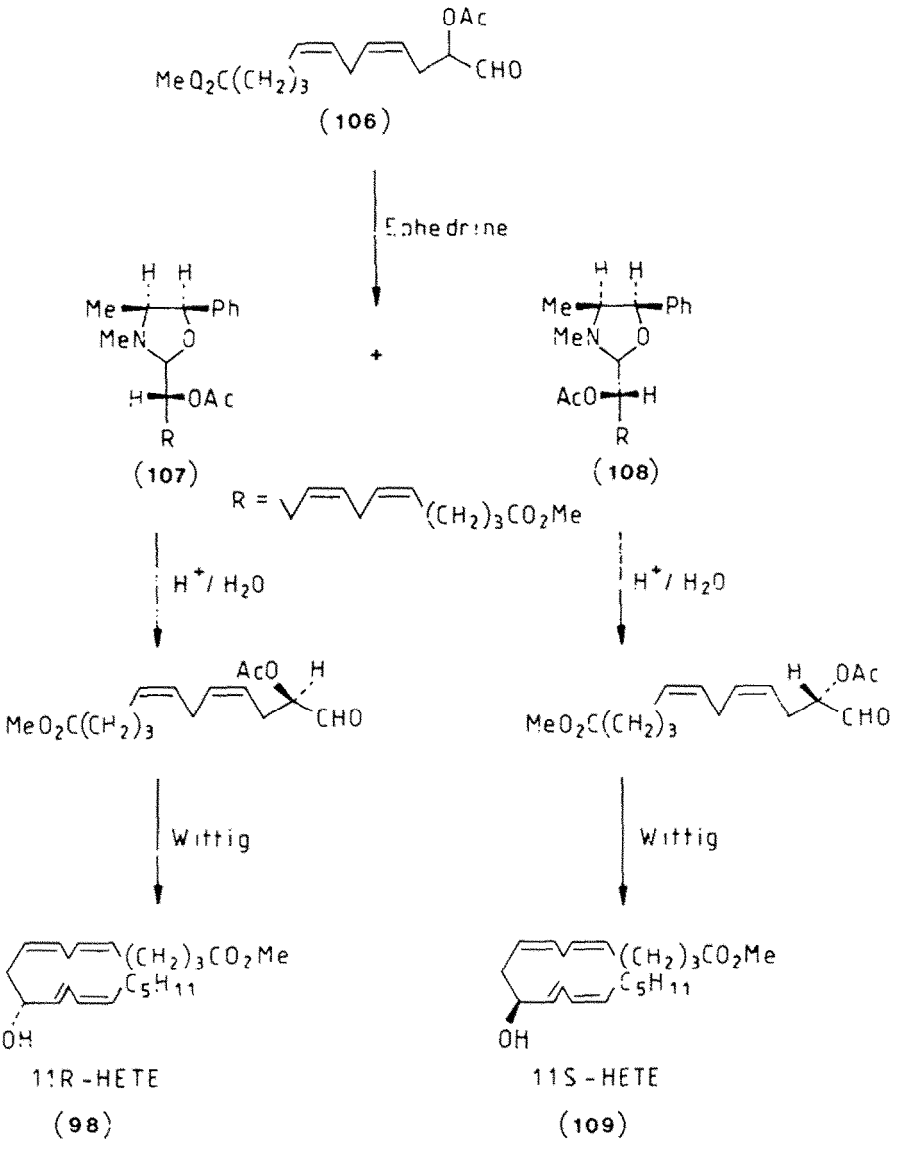


Reagents: i, i-Propylcyclohexylamine, MeMgBr; ii, several steps; iii, $MeSO_2Cl$, Et_3N; iv, peroxide; v, t-$BuMe_2SiCl$; vi, 1:1:1 HAc:H_2O:THF, 20°C; vii, LiOH, DME, H_2O.

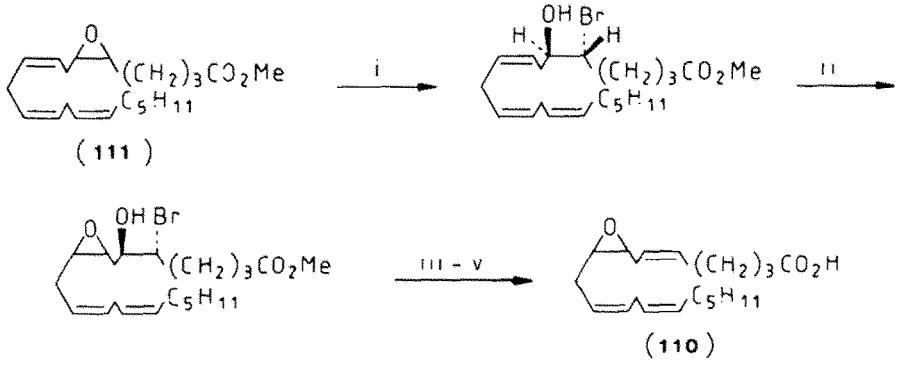
Scheme 37.

Just *et al.*[101] have prepared (±)-11-HETE: in addition they have described a novel method for the resolution of a key intermediate (Scheme 38).[102] Reaction of the acetoxyaldehyde (**106**) with ephedrine gave two diastereomeric oxazolidines (**107**) and (**108**) which were readily separated by chromatography. Hydrolysis and subsequent Wittig homologation furnished the methyl esters of 11(R)-(**98**) and 11(S)-HETE(**109**).

Various isomers of LTA have been prepared and some have been converted into the corresponding LTCs and LTDs. Falck[66] prepared 8,9-epoxyarachidonic acid (**110**) from the methyl ester of the 5, 6-analogue (**111**) (Scheme 39) and compared it with an LTA_3 isomer isolated from natural sources. Corey has demonstrated that selective epoxidation of the double bond either nearest or furthest away from the carboxyl function of arachidonic acid can be achieved.[103] The 5,6-epoxide (**112**) was produced *via* an unstable iodo δ-lactone (presumably **113**) while the 14,15-epoxide (**114**) was formed by a remarkable intramolecular oxygen transfer. Peroxyarachidonic acid isomerizes with selective epoxidation of the 14, 15-double bond presumably *via* the cyclic intermediate (**115**).

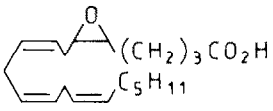


Scheme 38.



Reagents: i, KBr, AcOH, THF; ii, $VO(acac)_2$, t-BuOOH; iii, $(CF_3CO)_2O$; iv, $(Me_2N)_3P$; v, NaOH.

Scheme 39.



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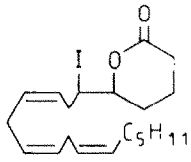

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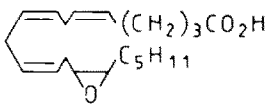

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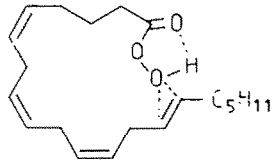
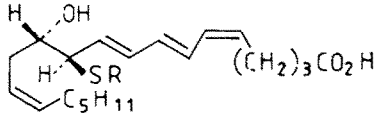
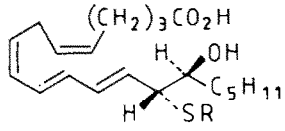


(115)

Analogues of LTC_4 and LTD_4 with the peptide moiety at C_{11} (**116** and **117**) and at C_{14} (**24** and **25**) have been prepared from the relevant LTA_4 analogue.[104] The synthesis of the 12-glutathionyl diastereomers **118** from LTA_4 methyl ester (Scheme 40) has been described.[89]



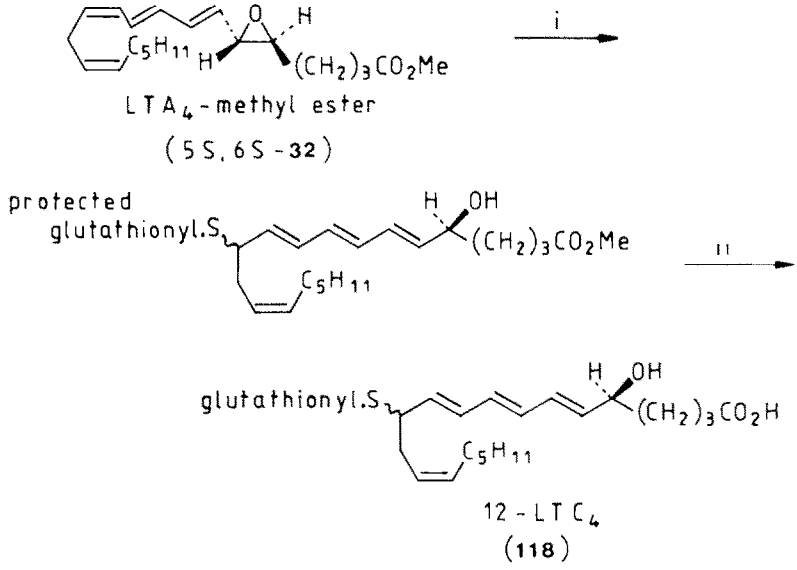


(116) R = $CH_2CHCONHCH_2CO_2H$ with $NHCOCH_2CH(NH_2)CO_2H$ (24)

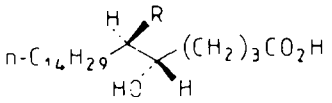
(117) R = $CH_2CHCONHCH_2CO_2H$ with NH_2 (25)

Octahydro-leukotriene-C, -D and -E analogues have recently been prepared by reaction of a sulphenyl halide with 5(E)- and 5(Z)-eicosenoic acids.[105]

Leukotriene antagonists and inhibitors of leukotriene biosynthesis are of interest as potential



Reagents: i, N-Trifluoroacetylglutathione dimethylester, $LiClO_4$, THF, H_2O; ii, K_2CO_3, MeOH.
Scheme 40.

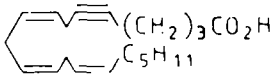


R = $SCH_2CHCONHCH_2CO_2H$ with $NHCOCH_2CH_2CHCO_2H$ (NH_2) — octahydro-LTC

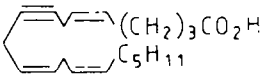
$SCH_2CHCONHCH_2CO_2H$ (NH_2) — octahydro-LTD

SCH_2CHCO_2H (NH_2) — octahydro-LTE

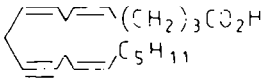
pharmaceutical agents and as tools for unravelling the detailed biological role of the naturally occurring intermediates. Corey reasoned that a dehydroarachidonic acid in which one double bond was replaced by an acetylene unit might be more strongly bound to the lipoxygenase enzyme and be more susceptible to lipoxygenation.[106] To test this theory, 5,6-(**119**), 8,9-(**120**), 11,12-(**121**) and 14,15-dehydroarachidonic acid (**122**) were prepared and their inhibitory properties studied.[106,107] It was found that the 5,6-dehydro



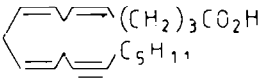
(**119**)



(**120**)

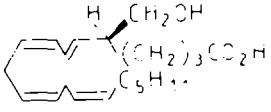


(**121**)

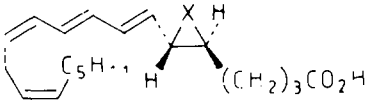


(**122**)

compound (**119**) irreversibly inhibited C_5-lipoxygenation of arachidonic acid thus preventing leukotriene biosynthesis.[108] Similarly lipoxygenation at C_{11}[108] and C_{15}[107] was inhibited by the corresponding acetylenic analogues (**121**) and (**122**). 5-Hydroxymethyleicosatetrenoic acid (**123**)[109], 5,6-methanoleukotriene A_4 (**124**)[109,110] and the thio-analogue of LTA_4 (**125**)[111] have all been prepared and shown to be selective inhibitors of leukotriene biosynthesis.



(**123**)



(**124**) X = CH_2

(**125**) X = S

BIOLOGICAL ACTIVITY

Purified SRS-A and synthetic LTC_4, LTD_4 and LTE_4 are routinely assayed by their ability to contract strips of guinea pig ileum in the presence of histamine antagonists. Studies in guinea pigs showed that LTC_4 and LTD_4 increased microvasculature permeability and were selective agonists acting on peripheral airway smooth muscle: LTD_4 is about 1000 times more active than LTC_4.[112] The effects of LTD_4 as a function of concentration in the presence and absence of FPL 55712 (a selective inhibitor of

SRS-A and leukotrienes)[113] suggested the existence of two discrete peripheral airway receptors. Studies of the effects of LTC_4 and LTD_4 on pulmonary mechanics and systemic arterial blood pressure,[112] coupled with the finding that both leukotrienes are potent constrictors of human bronchi[114] (about 1000 times more active than histamine), has led to the suggestion that LTC_4 and LTD_4 act as mediators of the bronchospasm of bronchial asthma and other immediate hypersensitivity reactions. The discovery of the leukotrienes and the potent biological activity of LTC_4 and LTD_4 compared to histamine could in part explain why early attempts to alleviate the symptoms of asthma with antihistamine preparations were unsuccessful. That the same endogenous precursor can be converted into both prostaglandins and leukotrienes could explain the adverse effects of non-steroidal anti-inflammatory agents on the asthmatic condition in certain aspirin sensitive patients. Thus the balance of arachidonic acid metabolism is disturbed by cyclo-oxygenase inhibition and this could lead to elevated concentrations of leukotrienes with a concomitant increase in the intensity of bronchoconstriction.

Measurements of the contractile response of smooth muscle to a number of analogues of LTC_4 and LTD_4 have allowed some structural requirements for biological activity to be defined. Positional isomers having the peptide attached at positions other than C_6 elicit a very weak contractile response.[89,115] The strict requirement for the 5(S),6(R)-configuration has been demonstrated.[89,116] Fully saturated analogues of LTC_4, LTD_4 and LTE_4 are essentially inactive[105] whilst a change in double bond geometry from 11Z to 11E resulted in a modest loss of activity.[51,116] On the basis of results obtained from thirty-nine analogues of leukotrienes, Corey[115] and Austen[117] observed that a hydrophobic region was necessary for contractile activity. The length of the hydrophobic moiety was critical but the stereochemical features within this region were much less important. A terminal amino group in the peptide side chain, the glycine carboxylic acid group, and the C_5 hydroxyl function were all essential for maximum biological activity. On the other hand the carboxylic acid group at C_1 was *not* an essential component. Changes in the amino-acid residues present in LTD_4 resulted in some loss of biological activity. From these results it was concluded that the receptor for LTD_4 might contain a loose hydrophobic bonding site adjacent to a multi-component active site. The latter site must accommodate the non-ionised C_1-carboxylic acid group, the C_5-hydroxyl group, and the peptide function containing an unprotonated amino group.[117]

LTB_4 induces contractions in a number of guinea pig smooth muscle preparations.[118] The duodenum is the most sensitive organ but the greater stability of the lung parenchymal strip makes this the tissue of choice for routine assay. Certain biological properties of LTB_4 point to its involvement in the inflammatory process. It is chemotactic and chemokinetic for neutrophils and eosinophils (both present in high numbers at inflammatory sites) at concentrations as low as 3×10^{-9}M.[119] This activity is comparable to the complement peptide C5a and is 2–3 orders of magnitude greater than that of the mono-HETEs. Elevated levels of LTB_4 have been detected in the synovial fluid of patients with inflammatory diseases.[120] LTB_4 in combination with vasodilators (e.g. prostaglandin E_2) increased vascular permeability in the skin of various species.[121] The prostaglandin synergises this effect by increasing blood flow.[122] The release of lysosomal enzymes by a product of the lipoxygenase metabolism of arachidonic acid has been described.[123] This effect was not produced by prostaglandin precursors and although the agent was not identified, it is likely that LTB_4 was involved. Low concentrations of hydroxyeicosatetrenoic acids increase C-GMP levels[124] which, in turn, are thought to favour the release of lysosomal enzymes.[125]

The biological activity of LTB_4 is peculiar to the molecule bearing the naturally occurring stereochemical features. Alterations to the double bond geometry of the conjugated triene[28,91,93] and the configuration of the C_{12} hydroxyl[98] group results in much reduced biological activity.

CONCLUDING REMARKS

Over forty years elapsed between the isolation of a slow reacting substance and the publication of the structure of SRS released from mouse mastocytoma cells. Initial progress towards structure elucidation was slow for a number of reasons. The amount of material released into biological fluids is very low, possibly in the picogram range, and the natural product is relatively unstable. This made the isolation and purification of the material very difficult to achieve. The molecular weight and high polarity of the molecules limited the use of conventional gas chromatography and mass spectrometry techniques for analysis and identification. Eventually two seemingly different lines of research led to the structural elucidation of different members of the same family of compounds. The metabolic fate of arachidonic acid in leukocytes provided the structure of the immediate precursor of SRS and led to an understanding of its formation. Once the relationship between SRS and the leukotrienes had been established the

synthetic organic chemist became involved. Invariably, total synthesis confirmed the proposed structures; in particular, key stereochemical features were elucidated by the comparison of natural and synthetic compounds.

The availability of synthetic leukotrienes will facilitate the continuing studies on the biological activities of these compounds. Obviously, the role of LTC_4 and LTD_4 in asthma and other immediate hypersensitivity reactions is an area which will receive much attention. Similarly, investigations into the involvement of LTB_4 in the inflammatory process may lead to a better understanding of rheumatoid arthritis and other inflammatory states. Finally, a knowledge of the structures and the mechanism of biosynthesis of the leukotrienes can be used to develop leukotriene antagonists and inhibitors of leukotriene biosynthesis for therapeutic purposes.

Acknowledgements—The authors thank Mr. D. Culshaw and Mr. K. Reeve for constructing the diagrams, Miss J. Bradshaw for conducting literature searches, and Dr. S. Roberts, Mrs. S. Davies and Mrs. L. Barber for assistance in the preparation of the manuscript.

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