The Synthesis of Leukotrienes: A New Class of Biologically Active Compounds Including SRS-A

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1 Introduction

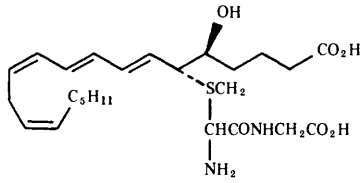
This review deals largely with the synthesis of the leukotrienes and related compounds and covers the literature up to the end of 1981. To provide an adequate background to this topic the work associated with the discovery of SRS and SRS-A and subsequent structure elucidation is briefly reviewed. The biogenesis, nomenclature, and aspects of the pharmacology of the leukotrienes have also been included since it was the potent action of the metabolites on smooth muscle and as mediators of inflammation that motivated the synthetic work.

2 Historical Background

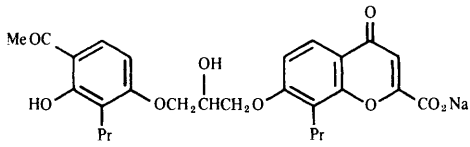
In 1938, Feldberg and Kellaway[1] injected cobra venom into guinea-pig perfused lungs and observed the release of a substance into the perfusate that differed from histamine and caused a slow contraction, long in duration, of guinea-pig jejunum. The agent responsible was referred to as 'slow reacting substance' (SRS). Two years later Kellaway and Trethewie[2] demonstrated that a similar substance was produced in the effluent of guinea-pig perfused lung following challenge with an appropriate antigen. This immunologically produced mediator was later termed 'SRS-A' — 'slow reacting substance of anaphylaxis' by Brocklehurst.[3] Much of the work in the 1950s and 1960s was motivated by the failure of anti-histamine drugs to control asthma. SRS-A became regarded as an important mediator in asthma since it was produced by lung tissue of asthmatics *in vitro* as well as in the guinea-pig model of asthma and it was shown to be a potent bronchoconstrictor of human airways. Since SRS-A was also involved in other 'immediate hypersensitivity' reactions it became regarded as a pathophysiological product with undesirable effects and no beneficial role and therefore an ideal candidate for chemotherapy. Progress was frustated by lack of structural knowledge of the SRS group of compounds, which were difficult to purify and relatively unstable. The break-through came in May 1979 when Samuelsson[4] announced in Washington,

[1] W. Feldberg and C. H. Kellaway, *J. Physiol.*, 1938, **94**, 187.
[2] C. H. Kellaway and E. R. Trethewie, *Quart. J. Exp. Physiol.*, 1940, **30**, 121.
[3] W. E. Brocklehurst, Ciba Symposium on Histamine, Churchill, London, 1956, p. 175; *J. Physiol.*, 1960, **151**, 416; *Progr. Allergy*, 1962, **6**, 540.
[4] (*a*) B. Samuelsson, P. Borgeat, S. Hammarström, and R. C. Murphy, in *Advances in Prostaglandin and Thromboxane Research*, ed. B. Samuelsson, R. Ramwell, and R. Paoletti, Raven Press, New York, Vol. 6, 1980, p. 1. (*b*) B. Samuelsson in ref. 5*b*. p. 45.

at the Prostaglandin Symposium, the lipoxygenase pathway for metabolizing arachidonic acid to give peptidolipids, some of which have the biological properties of SRS. Since compounds of this new class were obtained by metabolism using polymorphonuclear leukocytes (from the peritoneal cavity of rabbits) and each possessed a conjugated triene, Samuelsson proposed the name leukotriene, and showed that SRS from different sources contain varying amounts of different leukotrienes with SRS activity. Morris *et al.*,[5] however, identified SRS-A from perfused guinea-pig lung as (5*S*)-hydroxy-(6*R*)-cysteinylglycinyl-*trans*-7,9, *cis*-11,14-eicosatetraenoic acid to provide a structure forty years after Kellaway and Trethewie reported the biological activity of the immunologically generated material. The original structural work of Samuelsson[4] and Morris[5] and their co-workers did not define the stereochemistry of the leukotrienes, and this follows largely from the synthetic work of Corey *et al.*[6]



(1)



(2)

3 Structure and Biogenesis of the Leukotrienes

Although SRS activity was first reported in 1938, purification procedures prior to 1976 had not led to homogeneous material. The minute amounts of labile SRSs obtained were monitored by contraction of guinea-pig ileum, which contraction could be reversed by action of the SRS antagonist FPL 55712, discovered by Fisons Pharmaceutical Laboratories.[7] Little progress had been

[5] (*a*) H. R. Morris, G. W. Taylor, P. J. Piper, and J. R. Tippins, *Nature*, 1980, **285**, 104. (*b*) H. R. Morris, G. W. Taylor, C. M. Jones, P. J. Piper, J. R. Tippins, and M. N. Samhoun, in 'SRS-A and Leukotrienes', ed. P. J. Piper, J. Wiley and Sons, Chichester, 1981, p. 19.

[6] (*a*) S. Hammarström, B. Samuelsson, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, and E. J. Corey, *Biochem. Biophys. Res. Commun.*, 1980, **92**, 946. (*b*) E. J. Corey, in ref. 4*a*, p. 19.

[7] C. W. Parker in ref. 5*b*, p. 131.

made concerning chemical structure apart from the suggestion that SRS was a polar lipid or an hydroxy-acid derived from arachidonic acid.

The following recent developments led to a rapid advance in the structure elucidation of the SRSs and biogenesis of the leukotrienes.

(i) The *in vitro* generation of SRS from rat peritoneal cavity cells and rat basophilic leukaemia cells after stimulation with ionophore A-23187.[4]

(ii) The purification of SRS by reverse phase h.p.l.c.[4,5]

(iii) The establishment of SRSs as products from metabolism of arachidonic acid by the 5-lipoxygenase pathway.[4,7]

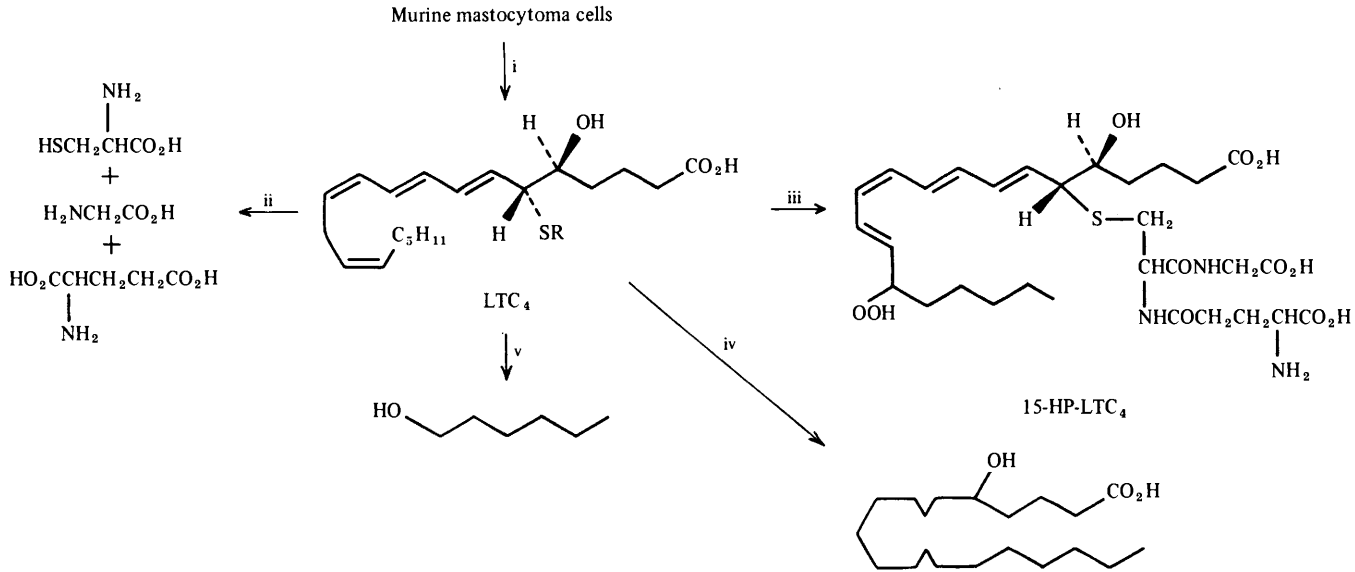
(iv) The incorporation of sulphur-containing amino-acids in the structure was suggested by increased yields of SRS in the presence of L-cysteine.[4]

(v) Purified SRSs gave diagnostic spectral data. Thus, the ultraviolet spectrum shows a characteristic triene triplet at 280 nm and mass spectral analysis of the trimethylsilyl ether *N*-acetyl-methyl ester of SRS from basophilic leukaemia cells and SRS-A from guinea-pig lung gave fragment ions from which the complete covalent structure could be deduced.

(vi) Elegant synthetic work by Corey and his co-workers gave the detailed stereochemistry and made the leukotrienes available by total synthesis.[6]

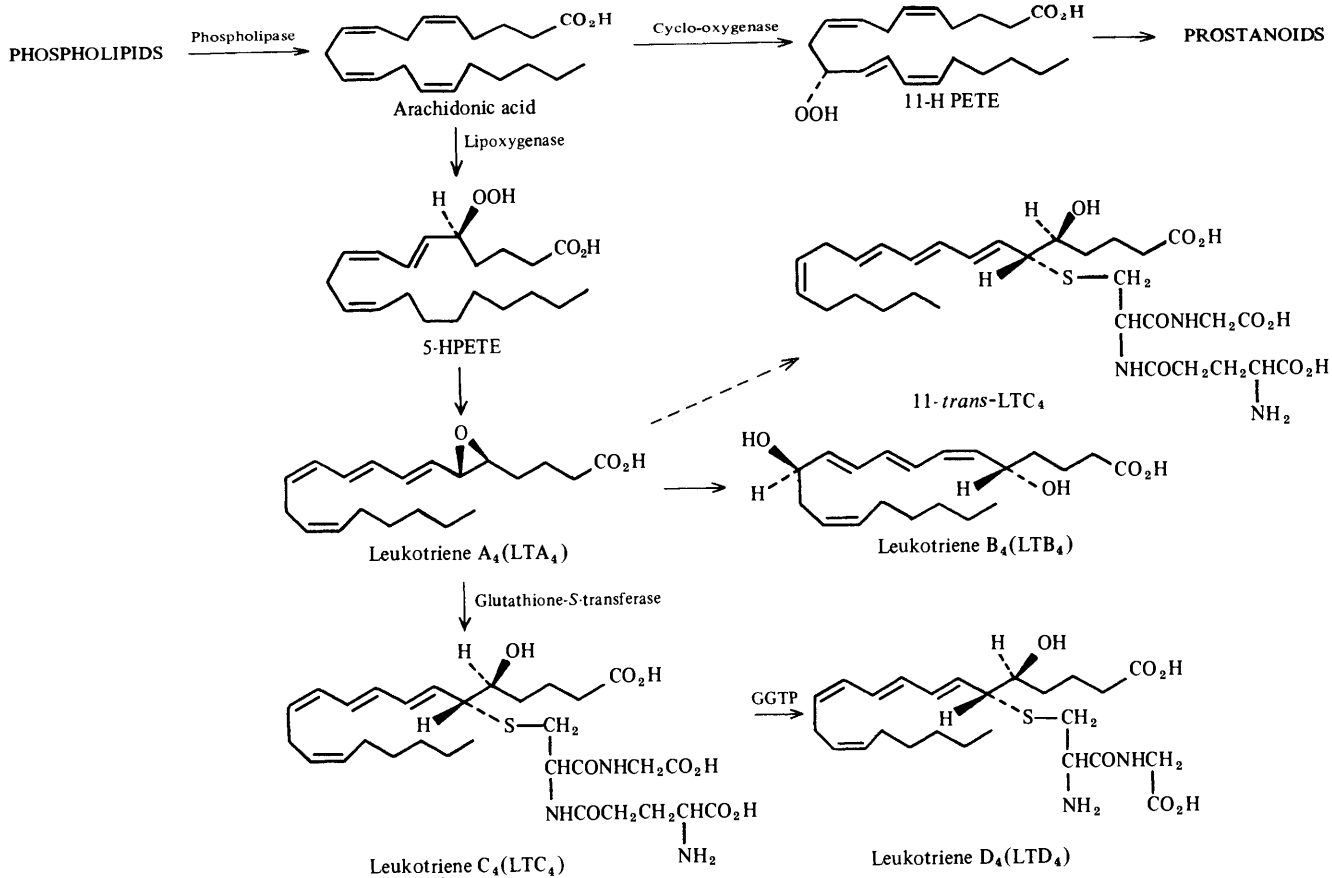
The structure of SRS generated by treating murine mastocytoma cells with ionophore A23187 and L-cysteine, which was elucidated by Samuelsson, is summarized in Scheme 1. The pure spasmogenic material has an absorbance at 280 nm, consistent with a conjugated triene having a non-conjugated sulphur auxochrome. By using labelled precursors it was shown that arachidonic acid, and all three carbon atoms and sulphur from cysteine were incorporated in SRS. Reductive desulphurization with Raney nickel gave 5-hydroxyarachidic acid, which indicated that the sulphur residue was linked to the arachidonic acid derivative by a thioether linkage and that a hydroxy-group was present at C-5. Reductive ozonolysis led to hexan-1-ol, suggesting that the Δ^{14} (ω-6) double bond of arachidonic acid had been retained in SRS. The position of the triene system was located by the unique hydroperoxidation with soybean lipoxygenase that converts the *cis*-1,4-diene system at ω-6 and ω-9 to a conjugated system with introduction of oxygen at ω-6. Thus, treatment of SRS with the lipoxygenase gave a tetraene having an absorption maximum at 310 nm, indicating that SRS has a *cis* double bond at C-14 and C-11 and two additional double bonds at C-9 and C-7. The structural information led to the conclusion that SRS was a derivative of 5-hydroxy-7,9,11,14-eicosatetraenoic acid with the sulphur auxochromic group at C-6. Acid hydrolysis and amino-acid analysis showed the presence of cysteine, glycine, and glutamic acid. Sequence analysis showed that the tripeptide is γ-glutamylcysteinylglycine (glutathione). The synthetic work carried out by Corey *et al.*[6] confirmed these deductions and in addition gave the stereochemistry of SRS from murine mastocytoma cells as (5*S*)-hydroxy-(6*R*)-*S*-glutathionyl-*trans*-7,9,*cis*-11,14-eicosatetraenoic acid, which has been named leukotriene C_4 (LTC_4).

Scheme 2 shows the biosynthetic formation and transformation of the leukotrienes derived from arachidonic acid. Thus, while cyclo-oxygenase first converts



Reagents: i, Ionophore A23187; ii, H^+; iii, soybean lipoxygenase; iv, Raney nickel, H_2; v, O_3, $NaBH_4$

Scheme 1 *Key experiments in the structure elucidation of SRS generated from murine mastocytoma cells*



Scheme 2 *Biosynthetic formation of the leukotrienes*

arachidonic acid into the 11-hydroperoxy-derivative (Scheme 2; 11-HPETE) lipoxygenase forms (5*S*)-hydroperoxy-6,8,11,14-eicosatetraenoic acid (Scheme 2; 5-HPETE), which leads to the major product (5*S*)-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE). However, more polar metabolites were also present and (5*S*,12*R*)-dihydroxy-*cis*-6,*trans*-8,10,*cis*-14-eicosatetraenoic acid [leukotriene B_4 (LTB_4)] was identified and isotopic oxygen experiments demonstrated that the oxygen of the alcohol group at C-5 originated from molecular oxygen, whereas the oxygen at C-12 was derived from water. As a result of trapping experiments, an unstable epoxide intermediate (half-life about 3 minutes) was proposed and its structure and stereochemistry was confirmed as the 5,6-epoxy-7,9,11,14-eicosatetraenoic acid [leukotriene A_4 (LTA_4)] by synthesis. The epoxide undergoes ring-opening enzymatically, by nucleophilic attack of the sulphydryl group of the peptide glutathione (γ-glutamylcysteinylglycine) to give leukotriene C_4 (LTC_4) and 11-*trans*-LTD_4. The former is converted by γ-glutamyltranspeptidase (GGTP) into the biologically more active (5*S*)-hydroxy-(6*R*)-*S*-cysteinylglycine-*trans*-7,9-*cis*-11,14-eicosatetraenoic acid, known as leukotriene D_4 (LTD_4). The thioethers have SRS properties. Samuelsson believes that LTD_4 is the main component of SRS-A from human lung and suggests that the composition of SRS-A will depend on its mode of generation and consists of a mixture of LTC_4 and LTD_4.[4b]

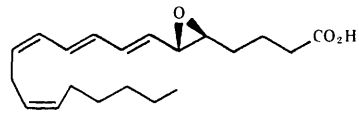
4 Nomenclature of the Leukotrienes

The leukotrienes (LT) represent a new family of acyclic eicosanoids and both systematic and new abbreviated names will replace the terms SRS and SRS-A. The system of nomenclature devised by Samuelsson and Hammarström bears some resemblance to that used for the prostaglandins in that numerical subscripts after the generic name are used to denote the total number of double bonds, and an alphabetical sequence refers to the substituents.

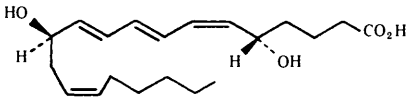
The leukotrienes from arachidonic acid were originally named LTA [*trans*-(5*S*,6*S*)-epoxy-*trans*-7,9-*cis*-11,14-eicosatetraenoic acid], LTB [5*S*,12*R*)-dihydroxy-6,8,10,14-eicosatetraenoic acid], and LTC [(5*S*)-hydroxy-(6*R*)-*S*-glutathionyl-*trans*-7,9-*cis*-11,14-eicosatetraenoic acid] following the discovery of conjugated trienes in leukocytes.[4] Subsequently it was shown that the glutathione (γ-glutamylcysteinylglycine) thioether group at C-6 in LTC is metabolized into the corresponding biologically more potent cysteinylglycine derivative named LTD. Further metabolism gives rise to the cysteinyl derivative LTE. To denote the total number of double bonds present, these metabolites previously referred to as LTA, LTB, LTC, LTD, and LTE, become LTA_4, LTB_4, LTC_4, LTD_4, and LTE_4.[8]

The 5,8,11- and 5,8,11,14,17-eicosaenoic acids are transformed into analogous structures *e.g.* LTC_3 and LTC_5, respectively, and these are illustrated in Scheme 3.

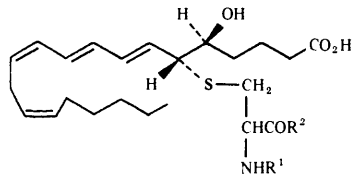
[8] B. Samuelsson and S. Hammarström, *Prostaglandins*, 1980, **19**, 645.



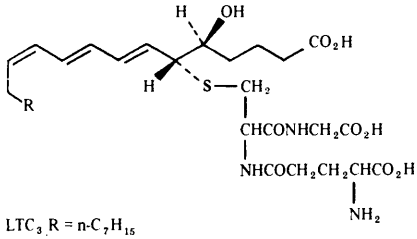
LTA_4 (formerly LTA)



LTB_4 (formerly LTB)



LTC_4 (formerly LTC) R^1 = glutamyl, R^2 = glycine
LTD_4 (formerly LTD) R^1 = H, R^2 = glycine
LTE_4 (formerly LTE) R^1 = H, R^2 = OH



LTC_3 R = n-C_7H_{15}

LTC_5 R = 

Scheme 3 *Nomenclature of the leukotrienes*

5 Pharmacological Properties

Some pharmacological properties of the SRSs have been briefly mentioned. Isolation and synthesis of pure compounds provide further impetus for more precise studies. Thus, both LTD_4 and LTC_4 cause pulmonary changes in anaesthetized monkeys.[9] These effects were a profound increase in lung resistance and more modest decrease in lung compliance. Simultaneous treatment with FPL-55712 (2) prevented these changes. Although both LTD_4 and LTC_4 are potent in producing bronchconstrictions and increasing vascular permeability in skin,[10] LTD_4 is the more active by five- to ten-fold. LTD_4 also causes impaired sputum clearance, thus giving rise to mucous plugging, which is one of the pathological features of asthma. The contractile effects of LTC_3, LTD_3, LTC_5, and LTD_5 on guinea-pig ileum are similar to those for LTC_4 and LTD_4.[11]

[9] M. K. Bach, J. Brashler, H. G. Johnson, and M. L. McNee, in ref. 5*b*, p. 161.
[10] G. P. Lewis in ref. 5*b*, p. 227.
[11] R. A. Lewis, J. M. Drazen, E. J. Corey, and K. F. Austen, in ref. 5*b*, p. 101.

LTB_4 stimulates leukocyte formation (chemotaxis and chemokinesis), induces an increase in capillary permeability, and causes smooth muscle contraction.[12] Its chemotactic potency for macrophage and neutrophils at concentrations of $\sim 1\,ng\,ml^{-1}$ (more potent than any other known lipid chemotactic factor) and its detection in the synovia of patients with rheumatoid arthritis,[13] implies that it is a primary mediator of inflammatory and allergic states. The synthesis of LTB_4 and its analogues has provided the necessary material for detailed structural studies and also for further biological work.

6 Approaches to Leukotriene Syntheses

The three approaches that have been largely used for the synthesis of leukotrienes involve (*a*) biomimetic syntheses from arachidonic acid, (*b*) the use of simple unsaturated precursors, and (*c*) the elaboration of carbohydrates for asymmetric syntheses. The successful use of arachidonic acid necessitated chemical methods to mimic lipoxygenase-controlled regioselective oxygenation to prepare hydroxy-, hydroperoxy-, and epoxy-derivatives at each of the double bonds, and the racemic products so obtained serve as standards for enzymatic studies. Corey has reviewed this problem and has shown that the carboxy-group in arachidonic acid can control the introduction of an oxygen function, nearest and farthest from it.[6b] Many of the syntheses were aimed at the preparation LTA_4, since the epoxide ring can be opened by the thiol of the appropriate peptide to give LTC_4, LTD_4, and LTE_4. Synthesis from simple olefin and alcohol precursors remains most attractive, and requires preparation of chiral epoxides. This was achieved by stereoselective epoxidation of an allylic alcohol in the presence of chiral tartrates, or alternatively, by using carbohydrate precursors which already have the correct chirality for asymmetric synthesis.

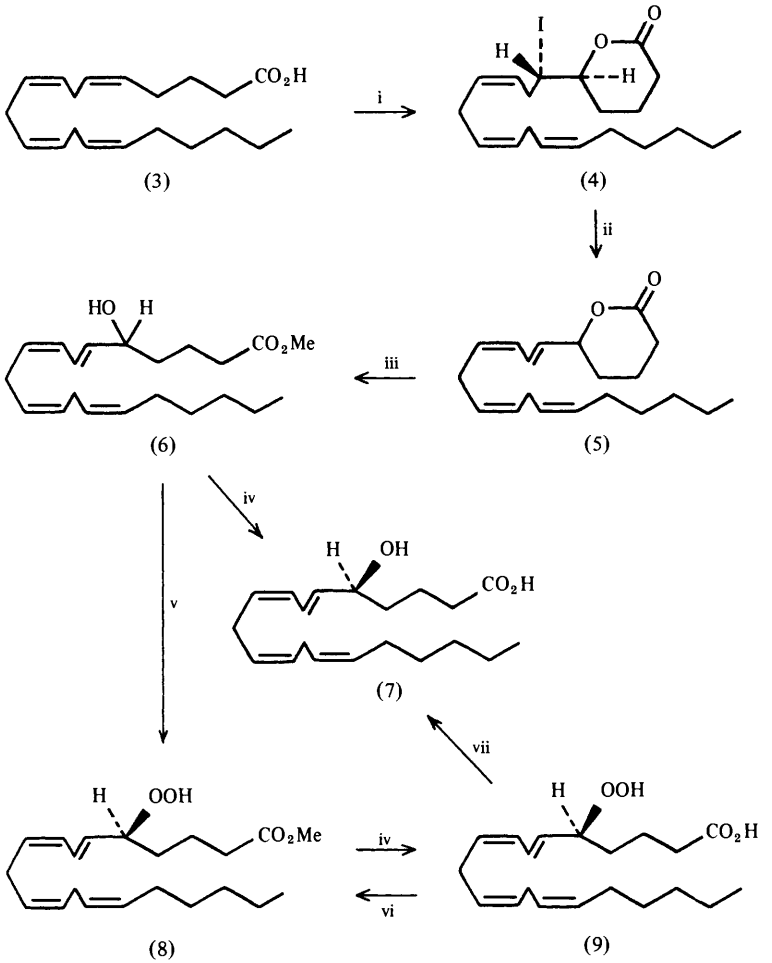
7 Synthesis of Leukotriene A Precursors and Their Analogues

This section reviews the various methods that have been used to prepare precursors of LTA_4 and their analogues. The biogenetic approach involved devising methods for regioselective introduction of oxygen into arachidonic acid by hydroxylation, hydroperoxylation, and epoxidation. The other methods were largely designed to prepare chiral C_7 epoxyaldehydes or alcohols for chain extension by a Wittig reaction. The chiral epoxides have been prepared either from allylic alcohols or from sugar precursors. In one case, a chiral hydroperoxyeicosatetraenoic acid has been prepared from D-glyceraldehyde.

[12] (*a*) A. W. Ford-Hutchinson, M. A. Bray, and M. J. H. Smith, 'Inflammation: Mechanisms and Treatment. Proceedings of Future Trends in Inflammation IV', MTP Press, Lancaster, England, 1980. (*b*) A. W. Ford-Hutchinson, M. A. Bray, M. V. Doing, M. E. Shipley, and M. J. H. Smith, *Nature (London)*, 1980, **286**, 264. (*c*) L. B. Klickstein, T. Shapleigh, and E. J. Goetzl, *J. Clin. Invest.*, 1980, **66**, 1166. (*d*) R. M. J. Palmer, R. J. Stepney, G. A. Higgs, and K. E. Eakins, *Prostaglandins*, 1980, **20**, 411. (*e*) M. A. Bray, A. W. Ford-Hutchinson, and M. J. H. Smith, *Br. J. Pharmacol.* 1981, **73**, 259. (*f*) M. A. Bray, F. M. Cunningham, A. W. Ford-Hutchinson, and M. J. H. Smith, *Br. J. Pharmacol.* 1981, **72**, 483

[13] (*a*) P. Sirois, P. Borgeat, A. Jeanson, S. Roy, and G. Girard, *Prostaglandins and Medicine*, 1980, **5**, 429. (*b*) P. Sirois, J. Roy, and P. Borgeat, *Prostaglandins and Medicine*, 1981, **6**, 153.

A. Chemical and Enzymatic Syntheses of 5-Hydroperoxyeicosa-*trans*-6-*cis*-8,11,14-tetraenoic Acid (5-HPETE) and 5-Hydroxyeicosa-*trans*-6-*cis*-8,11,14-tetraenoic Acid (5-HETE).— This synthesis (Scheme 4) by Corey *et al.*[14] commences from arachidonic acid (3), which is readily converted into the iodolactone (4) in the presence of iodine, potassium iodide, and bicarbonate. This intermediate (4) now has the necessary functionality for introduction of hydroxy- and



Reagents: i, $KI-I_2$; ii, 1,5-diazabicyclo[5.4.0]undec-5-ene; iii, Et_3N in MeOH; iv, LiOH; v, $MeSO_2Cl-Et_3N$, H_2O_2; vi, CH_2N_2; vii, $NaBH_4$

Scheme 4 *Corey's synthesis of 5-HETE and 5-HPETE*

[14] E. J. Corey, J. O. Albright, A. E. Barton, and S.-I. Hashimoto, *J. Am. Chem. Soc.*, 1980, **102**, 1435.

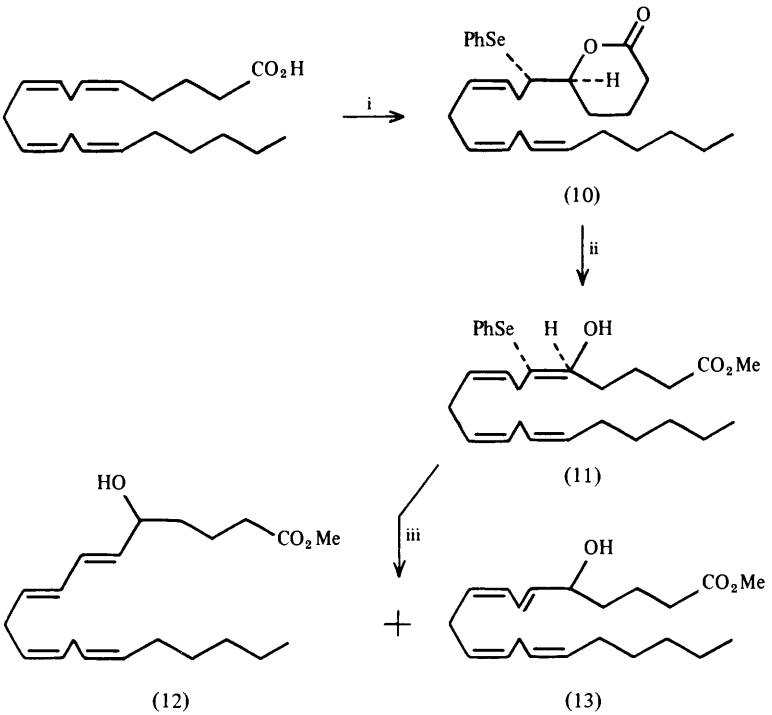
hydroperoxy-groups at C-5 and a *trans* double bond at C-6. Elimination of hydrogen iodide with 1,5-diazabicyclo[5.4.0]undec-5-ene gave the unsaturated lactone (5), which was transformed to the methyl ester of (±)-5-HETE (6) by triethylamine in methanol. Saponification with lithium hydroxide gave (±)-5-HETE (7) quantitatively. The hydroperoxy-group was introduced at C-5 by treating the ester of (±)-5-HETE (6) with methanesulphonyl chloride followed by hydrogen peroxide in ether at −110 °C. Saponification using lithium hydroxide and hydrogen peroxide gave the required (±)-5-HPETE (9), which could be reconverted into its ester (8) with diazomethane, or reduced to (±)-5-HETE (7) with sodium borohydride as illustrated by Scheme 4.

With the availability of (±)-HPETE and (±)-HETE as chromatographic standards, it was now possible to investigate the ability of various plant lipoxygenases to convert arachidonic acid into (5*S*)-HPETE (9), and using the enzyme from potato tubers the conversion was achieved in 15% yield. Reduction with sodium borohydride gave (5*S*)-HETE (9).

B. Phenylselenylation of Arachidonic Acid.—In contrast to Corey's[14] iodolactone route for hydroxylating arachidonic acid at C-5, Baldwin and co-workers[15] used phenylselenolactonization and achieved stereoselective syntheses of (±)-methyl-5-hydroxyeicosa-*trans,trans,cis,cis*-6,8,11,14-tetraenoate (12) and its *cis*-8 isomer (13) (Scheme 5). Treatment of arachidonic acid with phenylselenyl chloride at −78 °C gave the lactone (10), which was converted into the ester (11). Oxidative removal of the phenylselenyl group was studied under several conditions and it was observed that isomerization of the conjugated diene system can occur during selenoxide elimination. Thus, oxidative elimination with either sodium periodate or hydrogen peroxide in buffered aqueous methanol (sodium bicarbonate) favoured isomerization at C-8 and gave a mixture of the hydroxy-*trans,trans*-eicosatetraenoate (12; 85%) and the hydroxy-*trans,cis* isomer (13; 15%) from a 70—75% yield of reaction product. Similar results were also obtained using *m*-chloroperbenzoic acid in tetrahydrofuran, followed by addition to acetic acid and treatment with di-isopropylamine in refluxing benzene. However, when the oxidative elimination with hydrogen peroxide was carried out in strong base (potassium hydroxide) isomerization was reduced and the *trans*-6,*cis*-8-isomer (13) predominated.

C. Selective Epoxidation and Hydroxylation of Eicosa-5,8,11,14-tetraenoic (Arachidonic) Acid and Eicosa-cis-8,11,14-trienoic Acid.—Corey and his co-workers[16,17] have achieved site-selective oxidations of arachidonic acid and related compounds by devising intramolecular reactions that lead to epoxidation of the double bond either farthest or closest from the carboxy-function. Peroxyarachidonic acid (14), prepared from arachidonic acid by reaction with carbonyldi-imidazole and hydrogen peroxide, is transformed on standing at

[15] J. E. Baldwin, N. V. Reed, and E. J. Thomas, *Tetrahedron*, 1981, **37**, 263.
[16] E. J. Corey, H. Niwa, and J. R. Falck, *J. Am. Chem. Soc.*, 1979, **101**, 1586.
[17] E. J. Corey, A. Marfat, J. R. Falck, and J. O. Albright, *J. Am. Chem. Soc.*, 1980, **102**, 1433.



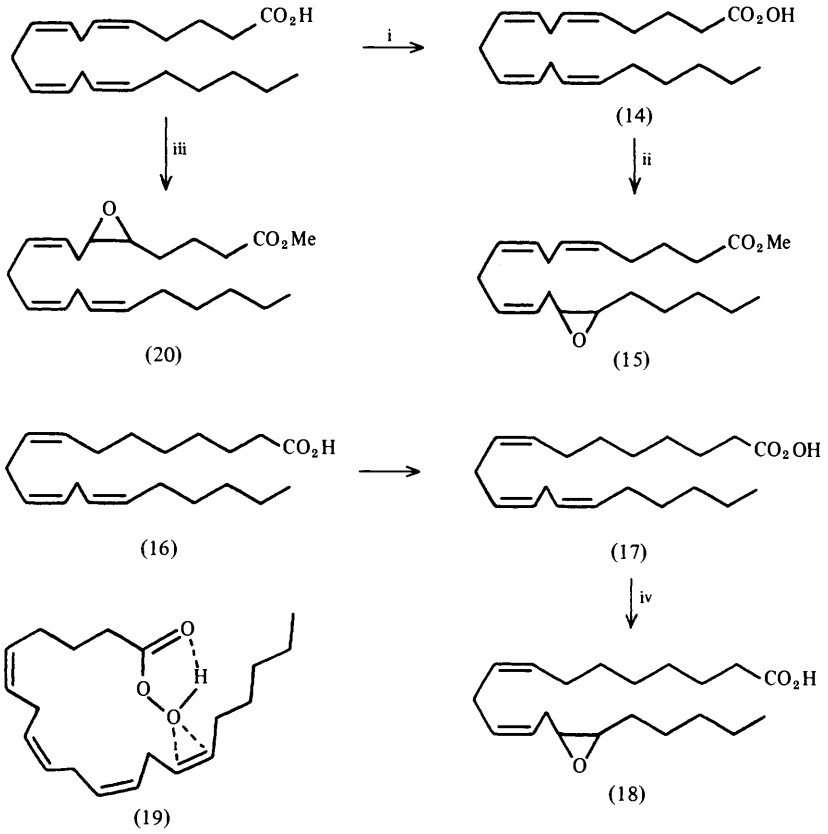
Reagents: i, PhSeCl; ii, LiOH, CH_2N_2; iii, $NaIO_4$

Scheme 5 *Baldwin's phenylselenylation of arachidonic acid*

20 °C to the 14,15-epoxide, which is isolated as the epoxy-ester (15). Space filling models suggest that perarachidonic acid may adopt a J-like shape to achieve intramolecular oxygen transfer by a 15-membered cyclic transition state (19), which is energetically more favourable compared to other geometries involving smaller rings. Eicosa-*cis*-8,11,14-trienoic acid (16) was also converted into the peroxy-acid (17), which rearranged to the $\Delta^{14,15}$ epoxide (18) in high yield (Scheme 6).

The $\Delta^{5,6}$ epoxide of arachidonic acid (20) was obtained from arachidonic acid by first forming an unstable iodo-δ-lactone in the presence of potassium bicarbonate and tri-iodide, followed by immediate treatment with lithium hydroxide.

Attempts to oxidize the *cis,cis*-1,4-dienes of C_{20} polyunsaturated acids with singlet oxygen gave *all* the expected 'ene' oxidation products. In contrast, the magnesium derivative of isopropylcyclohexylamine (MICA), obtained by addition of methylmagnesium bromide in tetrahydrofuran, was found to be remarkably effective for the epoxide → allylic alcohol conversion. Thus, the 14,15-epoxide (15) was transformed to 15-HETE (21) by MICA in 70% yield. Conversion into



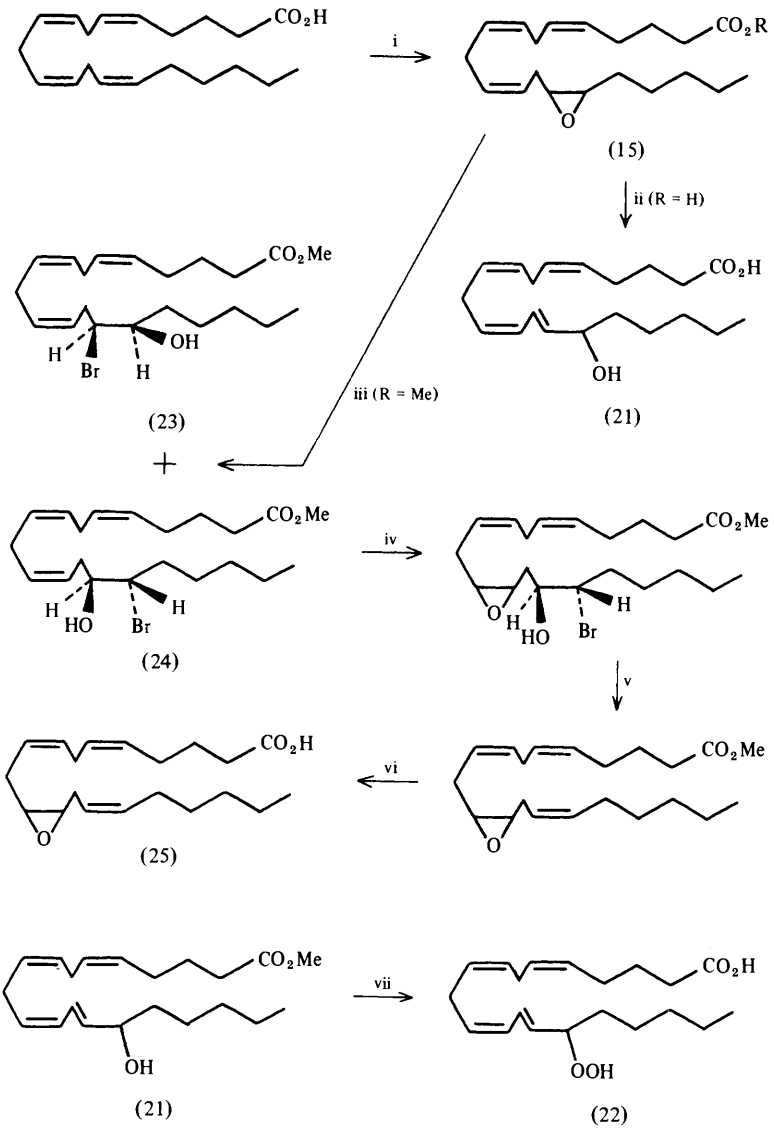
Reagents: i, Carbonyldi-imidazole, H_2O_2, lithium imidazolide; ii, r.t. then CH_2N_2; iii, KI_3, LiOH, CH_2N_2; iv, 0 °C, 70 h

Scheme 6 *Corey's method for epoxidizing arachidonic acid at the double bonds nearest and most remote from the carboxy-group*

the hydroperoxide 15-HPETE (22) occurs on treating the mesylate of 15-HETE with t-butyldimethylsilylhydroperoxide at −42 °C, followed by hydrolysis to remove the silyl group (Scheme 7).

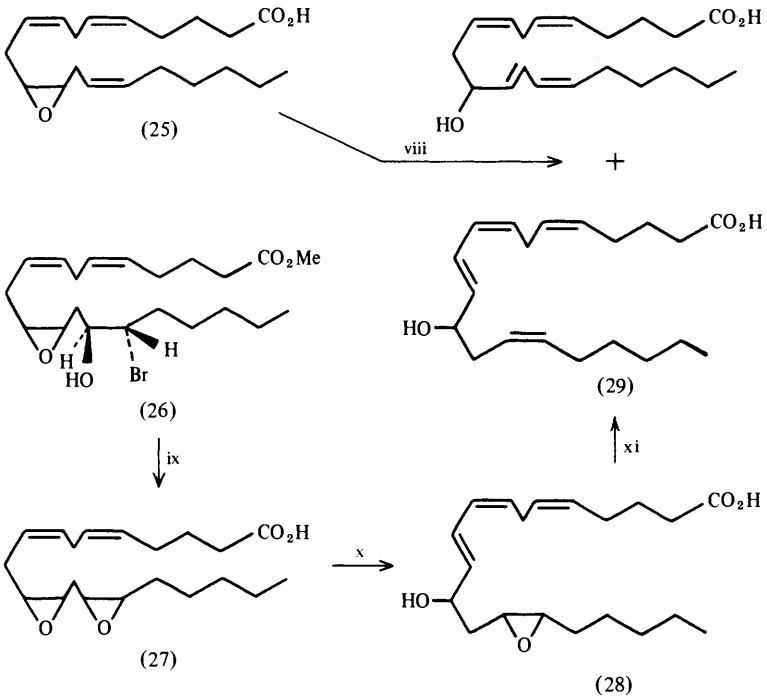
The $\Delta^{11,12}$ epoxide of arachidonic acid was obtained from the corresponding $\Delta^{14,15}$ epoxide (15), which was first converted into a mixture of bromohydrins [(23) and (24)]. The 15-bromo-14-hydroxy-isomer (24) underwent epoxidation at C-12 by the procedure of Sharpless[18] and the *cis* double bond was restored at C-13 by a new method involving reductive elimination of hydroxyl and bromine using trifluoromethanesulphonic anhydride and hexamethylphosphorous triamide (Scheme 7). Reaction of the epoxy-acid (25) with MICA

[18] B. E. Rossiter, T. Katsuki, and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 464.



Reagents: i, Internal oxygen transfer (98%); ii, magnesium derivative of isopropylcylohexylamine (MICA); iii, acetic acid-saturated aqueous KBr; iv, anhydrous t-butylhydroperoxide, vanadyl acetylacetonate; v, trifluoromethanesulphonic anhydride; vi, LiOH in DME; vii, methanesulphonyl chloride, Et_3N, t-butyldimethylsilylhydroperoxide

Scheme 7 *Corey's route to epoxidizing arachidonic acid at C-11 and preparation of 15-HETE and 15-HPETE*

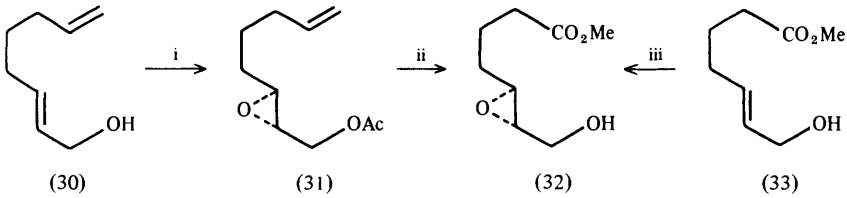


Reagents: viii, MICA in THF; ix, K_2CO_3–MeOH; x, MICA; xi, potassium selenocyanate

Scheme 8 *Corey's method for hydroxylating arachidonic acid at C-11 and C-12*

gave 11-HETE and 12-HETE (ratio 1:1.5), 12-HETE was also prepared from bromohydrin epoxide (26), which formed the 11,12:14,15 bis-epoxide of methylarachidonate. Saponification to the acid (27) and reaction with MICA gave the 14,15-oxide of 12-HETE (28), which underwent deoxygenation with potassium selenocyanate to give 12-HETE (29) (Scheme 8).

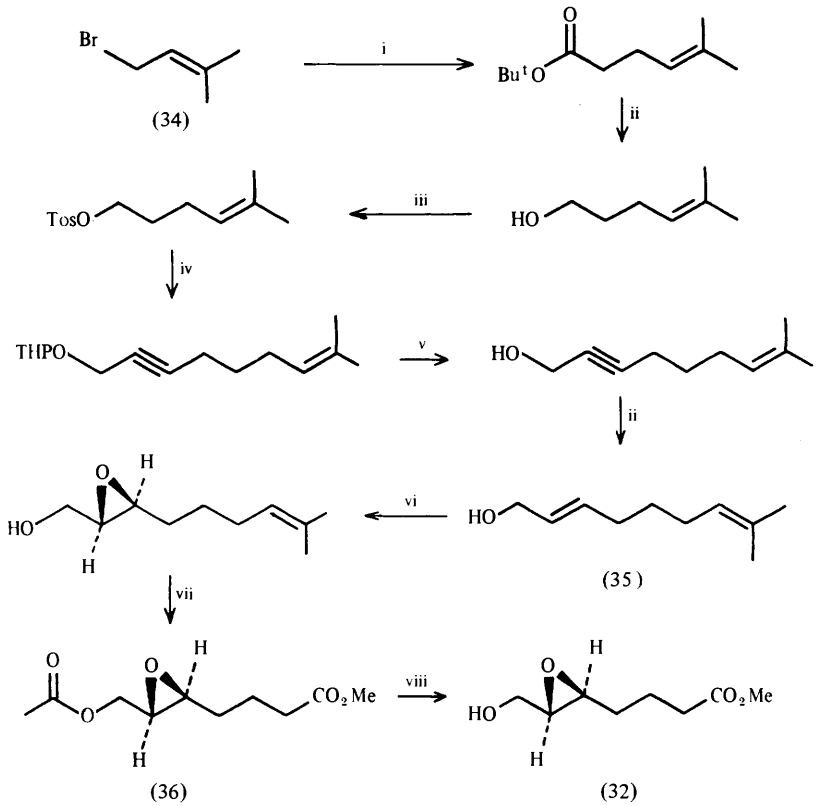
D. Synthesis of an Asymmetric Epoxide Key Intermediate for Leukotriene.— A new procedure[18] has been developed for preparing chiral epoxides from allylic alcohols and this provides the shortest route for obtaining an asymmetric precursor of LTA_4. t-Butylhydroperoxide with titanium(IV) isopropoxide in the presence of optically active diethyl tartrate will epoxidize a wide range of allylic alcohols with high asymmetric induction (>90% e.e.), and enantiomeric tartrates give rise to opposite configurations in the epoxide. Two approaches gave the epoxy-ester (32). The butadiene dimer (30) was epoxidized with t-butylhydroperoxide in the presence of titanium(IV) isopropoxide and (+)-diethyl tartrate, and the product isolated as the acetyl derivative (31). Cleavage of the double bond was achieved with ruthenium tetroxide and



(30) (31) (32) (33)

Reagents: i, Titanium tetraisopropoxide, L-(+)-diethyl tartrate, t-butyl hydroperoxide; ii, IO_4^--RuO_4, CH_2N_2, K_2CO_3; iii, titanium tetraisopropoxide, (+)-di-isopropyl tartrate, t-butylhydroperoxide

Scheme 9 *Chiral epoxidation by Sharpless to provide key synthon for leukotrienes*



(34) (35) (36) (32)

Reagents: i, t-Butyl-lithioacetate; ii, $LiAlH_4$; iii, *p*-toluenesulphonyl chloride, pyridine; iv, lithio derivative of propargyl tetrahydropyranyl ether; v, *p*-toluenesulphonic acid; vi, t-butyl hydroperoxide, L-(+)-diethyl tartrate, titanium isopropoxide; vii, Ac_2O-pyridine, O_3, Jones' reagent, CH_2N_2; viii, 1.5 equiv. K_2CO_3-MeOH

Scheme 10 *Chiral epoxidation by Corey to provide a key intermediate for leukotrienes*

periodate and the resulting acid methylated with diazomethane and hydrolysed with potassium carbonate to give the epoxy-alcohol (32).

In starting from the ester (33) the epoxy-alcohol (32) was prepared by using(+)-di-isopropyl tartrate as the chiral catalyst since it could be separated from the product by chromatography. The work-up procedure also required modification for isolation of the fairly water-soluble product.

In a similar approach by Corey and his co-workers[19] the 8-methylnon-2,7-dien-1-ol (35) was synthesized starting from 1-bromo-3-methylbut-2-ene (34) as shown in Scheme 10. Chiral epoxidation by the Sharpless method[18] and acetylation of the alcohol, followed by oxidative ozonolysis of the double bond and methylation of the resulting acid, gave the epoxy-ester (36) with an optical purity corresponding to 93% e.e. which readily hydrolysed to the chiral epoxy-alcohol (32).

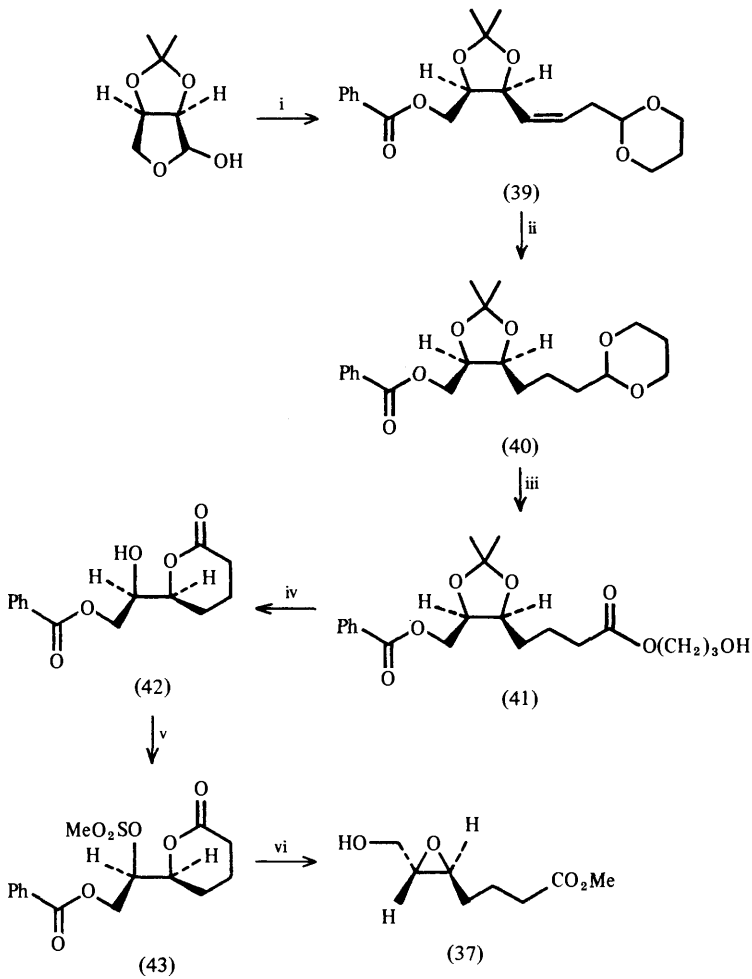
E. Cohen's Synthesis of Optically Active C-7 Leukotriene Intermediates.—In an approach to the leukotrienes and their analogues, Cohen and his collaborators[20] at Hoffmann-La Roche prepared the key C_7 (5*S*,6*S*)-epoxide (37) and its 6-epimer (38) from D-*arabo*ascorbic acid and L-diethyl tartrate respectively.

2,3-*O*-Isopropylidene-D-erythrose, prepared from D-*arabo*ascorbic acid, underwent a Wittig condensation with the phosphorane derived from [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide followed by benzoylation to give the ester acetal (39). Reduction of the double bond by catalytic hydrogenation and exposure of the product (40) to ozone at −78 °C gave the diester (41). The crucial transformation of the synthesis was opening of the acetal with aqueous trifluoroacetic acid to give the 6-hydroxylactone (42) whereby the oxygen functions at C-5 and C-6 have been differentiated. The mesylate (43) formed quantitatively and was converted into the required *trans*-(5*S*,6*S*)-epoxide (37) by opening the lactone ring with methanolic alkali (Scheme 11).

A similar sequence of events was employed for the synthesis from (L)-(+)-diethyl tartrate of the *cis*-(5*S*,6*R*)-epoxide, which was converted into the acetal diol (44). Oxidation of the monobenzoyl derivative (45) gave the aldehyde (46), which was converted into the olefin (47) by the Wittig procedure. Catalytic hydrogenation to (48) and treatment with ozone provided the diester (49), which was transformed with trifluoroacetic acid to the *threo*-hydroxy-ester lactone (50). The mesylate (51) was converted into the required epoxide (38) as before (Scheme 12).

F. Synthesis of a Leukotriene Intermediate from 2-Deoxy-D-ribose.—An improved synthesis of the leukotriene A_4 intermediate (52) was published by Marriott and Bantick[21] starting with 2-deoxy-D-ribose. 2-Deoxy-D-ribose (53) was converted into the methyl 3,5-dibenzoyloxy-2-deoxy-D-*erythro*-pentofuranosides

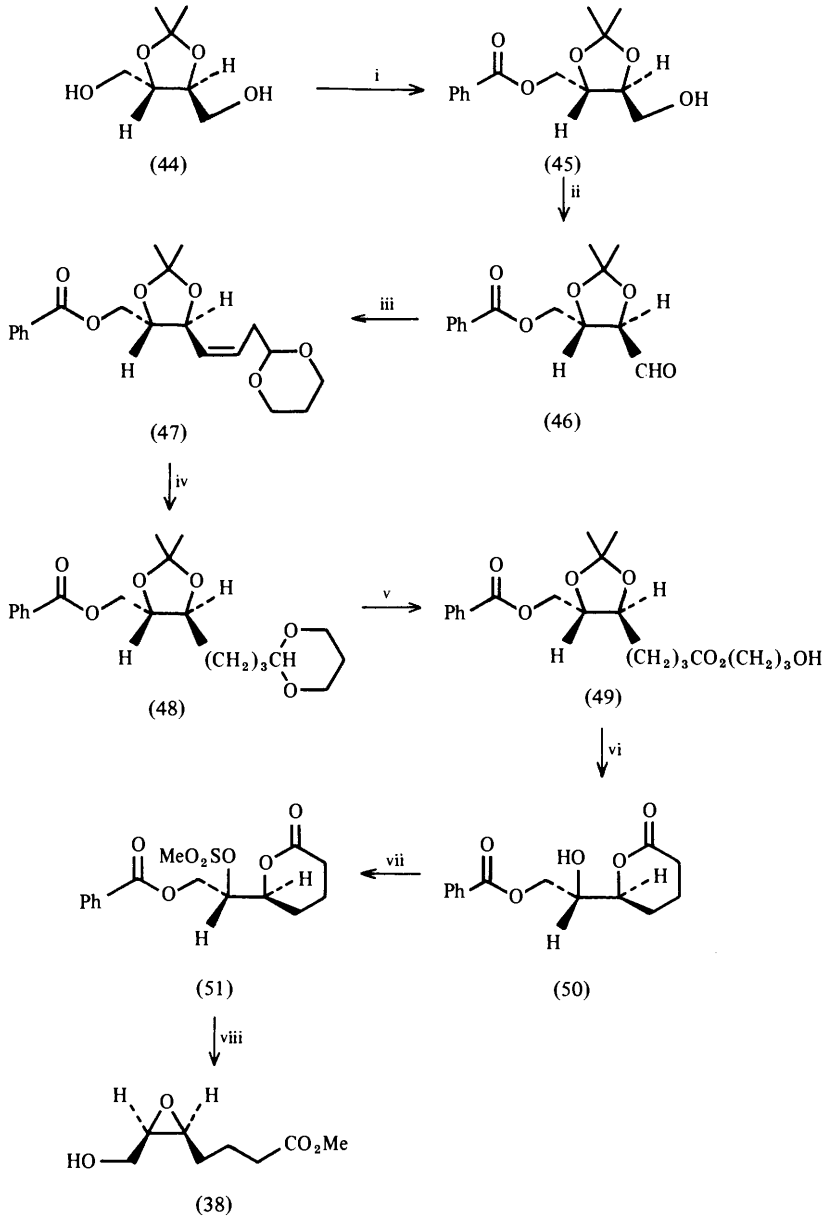
[19] E. J. Corey, S.-I. Hashimoto, and A. E. Barton, *J. Am. Chem. Soc.*, 1981, **103**, 721.
[20] N. Cohen, B. L. Barrier, and R. J. Lopresti, *Tetrahedron Lett.*, 1980, **21**, 4163.
[21] D. P. Marriott and J. R. Bantick, *Tetrahedron Lett.*, 1981, **22**, 3657.



Reagents: i, [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide, n-BuLi; ii, H_2, Pt; iii, O_3; iv, CF_3CO_2H–H_2O; v, mesylation; vi, K_2CO_3–MeOH

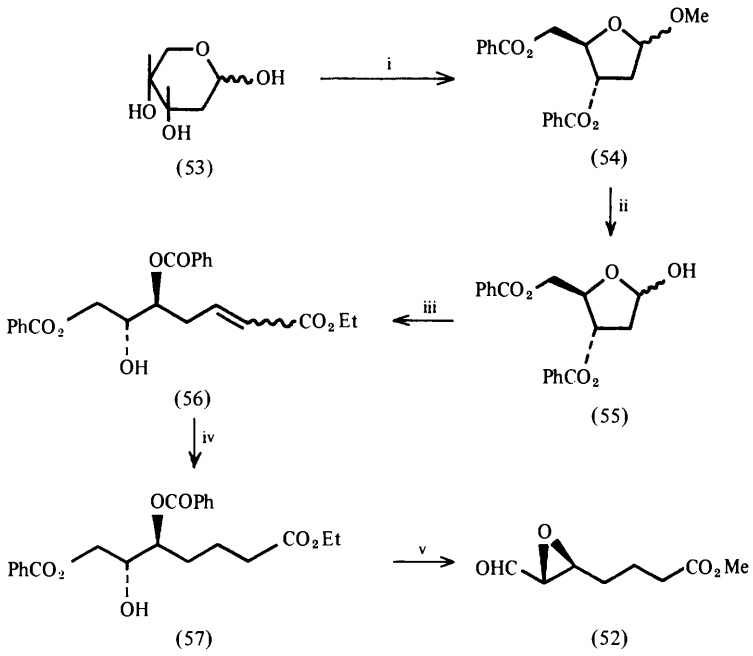
Scheme 11 *Cohen's synthesis of the key* trans-*epoxide, for leukotriene synthesis, from* D-arabo*ascorbic acid*

(54), which on demethylation gave the furanose (55). Without purification the masked aldehyde (55) was converted into a mixture of geometrical isomers (56) (*E*:*Z*; 83:17 by ^{1}H.n.m.r.) by a Wittig reaction. Hydrogenation of (56) afforded the ethyl ester (57) and this was transformed to the methyl ester, which is a known precursor of the epoxy-aldehyde (52)[26] (Scheme 13; see also Scheme 19[26] for alternative).



Reagents: i, PhCOCl, pyridine; ii, oxidation; iii, [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide, n-BuLi; iv, catalytic hydrogenation; v, O_3; vi, aqueous CF_3CO_2H; vii, mesylation; viii, K_2CO_3 in MeOH

Scheme 12 *Synthesis of the chiral* cis*-epoxide (38)*

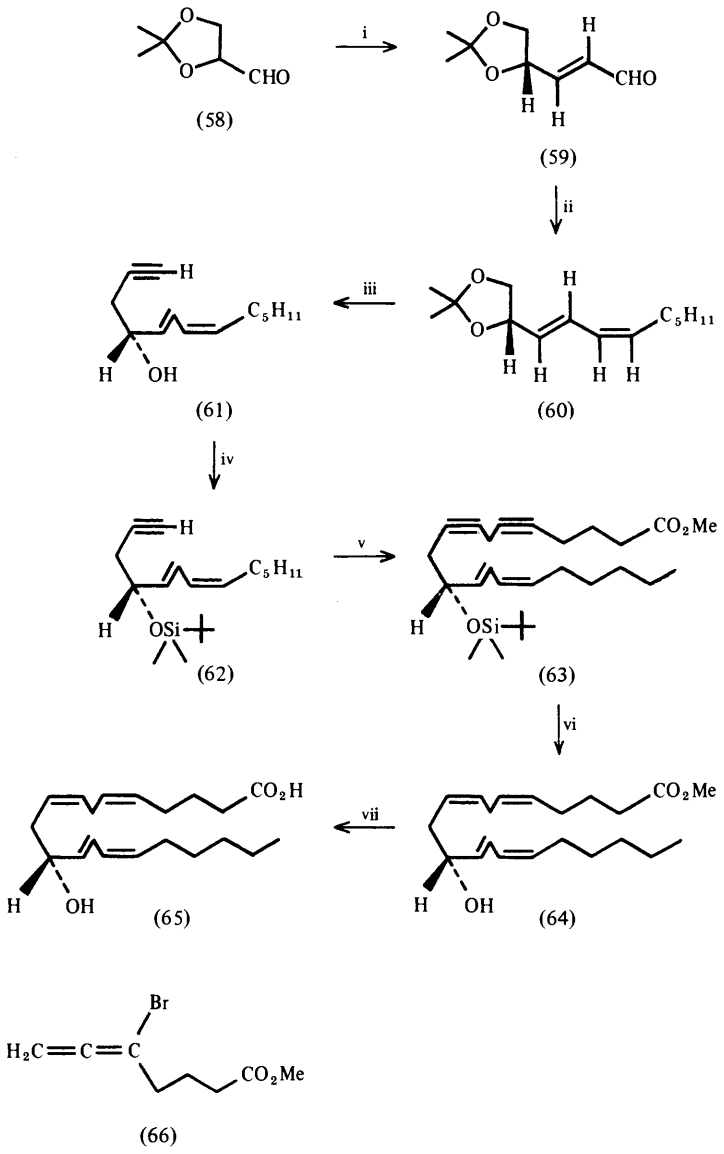


Reagents: i, 0·05% Methanolic HCl, benzoylation; ii, refluxed in dioxan, water, and concentrated HCl; iii, ethoxycarbonylmethylenetriphenylphosphorane; iv, H_2, 10% Pd–C

Scheme 13 *Marriott and Bantick's chiral synthesis of a leukotriene intermediate*

G. Corey's Stereospecific Total Synthesis of (11*R*)-HETE.—Corey and Kang[22] carried out the synthesis of (11*R*)-HETE (Scheme 14) by starting from the acetonide of D-glyceraldehyde to introduce the chiral centre at C-11 and by utilizing a nucleophilic acetylide coupling reaction with an allenic bromide to generate a 1,4-diyne. Thus, the acetonide of D-glyceraldehyde (58) was converted into the *trans*-enal (59) by reaction with lithium ethoxyacetylide, followed by hydrogenation in the presence of Lindlar catalyst and reaction with a trace of methanesulphonic acid in wet methylene chloride. The Wittig reaction of enal (59) with the ylide from n-hexyltriphenylphosphonium iodide provided the *trans-cis* diene (60; 79%). The acetylene carbinol (61) was formed by deketalization of (60), monotosylation of the primary alcohol group, and epoxide formation in the presence of DBU and reaction with lithium acetylide–ethylenediamine complex. Protection of the alcohol as the silylether (62) and conversion into a mixed Gilman reagent with n-butyl-lithium and cuprous cyanide led to formation of the C_{20} diyne (63) by reaction with methyl 5-bromohepta-5,6-dienoate (66). Lindlar reduction of the 1,4-diyne system and

[22] E. J. Corey and J. Kang, *J. Am. Chem. Soc.*, 1981, **103**, 4618.



(58) (59) (60) (61) (62) (63) (64) (65) (66)

Reagents: i, EtOC≡C.Li, H_2–Pd/$CaCO_3$, H^+; ii, n-hexyltriphenylphosphonium iodide; iii, HCl in 4:1 MeCN–H_2O, tosyl chloride, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene, lithium acetylide ethylenediamine complex; iv, t-butyldimethylsilyl chloride–imidazole; v, n-BuLi, Gilman reagent–1.1 equiv. cuprous cyanide, methyl 5-bromohepta-5,6-dienoate; vi, Lindlar catalyst–H_2; vii, 25 °C, absence of air, acidification

Scheme 14 *Corey's stereospecific synthesis of* (*11*R)-*HETE*

removal of the silyl protecting group with tetra-n-butylammonium fluoride gave the chiral methyl ester of (11*R*)-HETE (64), which can be saponified to the relatively unstable acid (65).

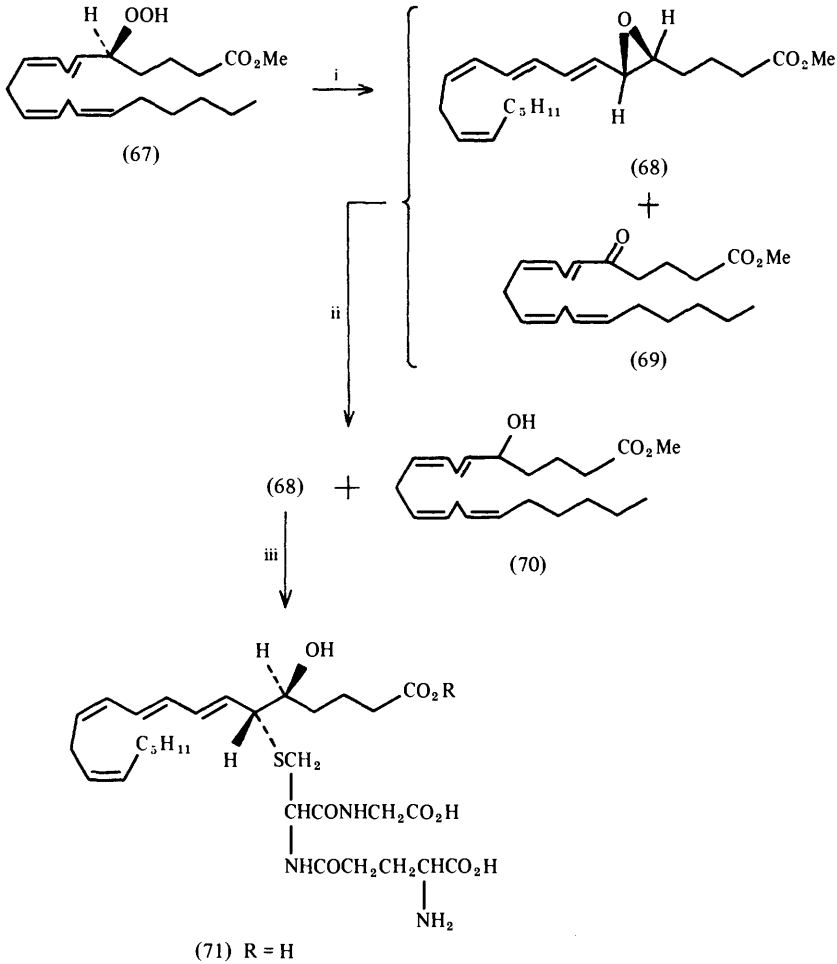
8 Syntheses of LTA_4 and its Diastereomers and Subsequent conversions into LTC_4 and LTD_4, LTE_4 and Related Compounds.—The synthesis of the leukotrienes and their analogues by unambigous methods was particularly important in order (*a*) to confirm the stereochemistry of the natural products, (*b*) to prepare sufficient quantities to make thorough biological studies possible, and (*c*) to compare the biological activity of the natural and unnatural isomers. The synthetic approach included utilizing the intermediates described in the previous sections and, in addition, new syntheses of LTA_4 methyl ester whereby the unstable epoxide unit was introduced at the end of the synthesis.

A. Corey's Biomimetic Synthesis of LTA_4 and LTC_4.—(5*S*)-Hydroperoxy-*trans*-6-*cis*-8,11,14-eicosatetraenoic acid [(5*S*)-HPETE] (67) in the form of its methyl ester was converted into the *trans*-epoxide under mild non-acidic conditions (Scheme 15).[23] Electrophilic oxygen at C-5 was generated by use of the trifluoromethanesulphonate leaving group and 1,2,2,6,6-pentamethylpiperidine as base at $-110\,°C$ to give a mixture of LTA_4 (68) and the conjugated dienone (69). The mixture was separated by chromatography (p.l.c.) only after reducing the ketone (69) to the hydroxy-ester (70), and the LTA_4 ester (68) was converted into LTC_4 (71) by treatment with glutathione followed by hydrolysis.

B. Corey's First Synthesis of Leukotriene A_4 (LTA_4).—The strategy of this synthesis (Scheme 16) involves starting with a C_6 fragment that has *trans* double bonds, which will be at C-7 and C-9 in LTA_4, then joining on a C_9 synthon by a Wittig process to introduce the *cis* double bond, which will be at C-11, and introducing the sensitive epoxide in the last step as a C_5 fragment.[24]

The mono-t-butyldimethylsilyl of *trans*-hexa-2,4-diene-1,6-diol (72) was converted into the aldehyde by oxidation with pyridinium dichromate and condensed with the ylide derived from non-3-en-1-ol (73) to give the tetraene ether (74). Removal of the silyl group with tetra-n-butylammonium fluoride gave the hydroxytetraene (75), which was converted into the mesylate (76). Treatment with dimethylsulphide and coupling of the resulting sulphonium salt (77) in the presence of lithium di-isopropylamide with methyl 4-formylbutyrate gave the required epoxy-ester (78) and an equal amount of the *cis*-5,6-epoxide. The ester (78) was saponified with cold aqueous base under argon and the salt could be reconverted to the epoxy-ester (78) with dimethylsulphate.

[23] E. J. Corey, A. E. Barton, and D. A. Clark, *J. Am. Chem. Soc.*, 1980, **102**, 4278.
[24] E. J. Corey, Y. Arai, and C. Miostowski, *J. Am. Chem. Soc.*, 1979, **101**, 6748.

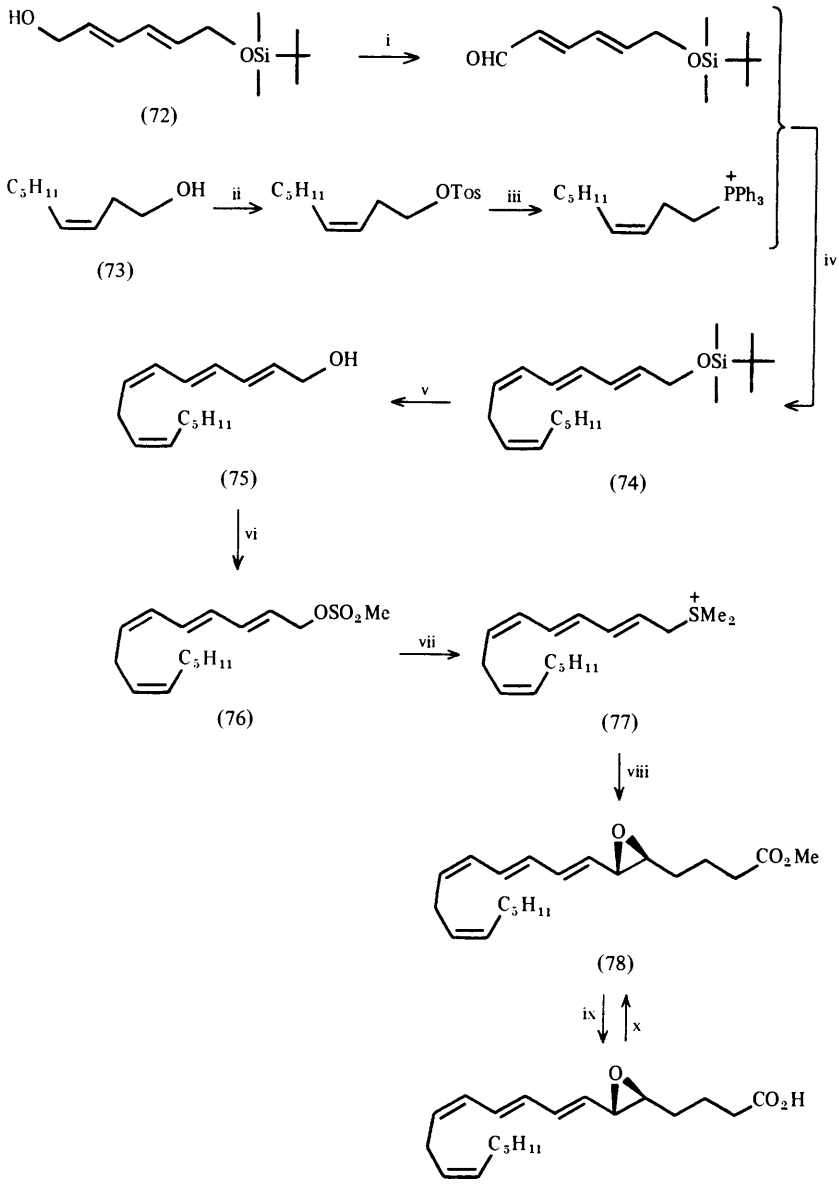


Reagents: i, 1,2,2,6,6-pentamethylpiperidine, trifluoromethanesulphonic anhydride; ii, $NaBH_4$ iii, MeOH, Et_3N, glutathione

Scheme 15 *Corey's synthesis of LTC_4 from arachidonic acid*

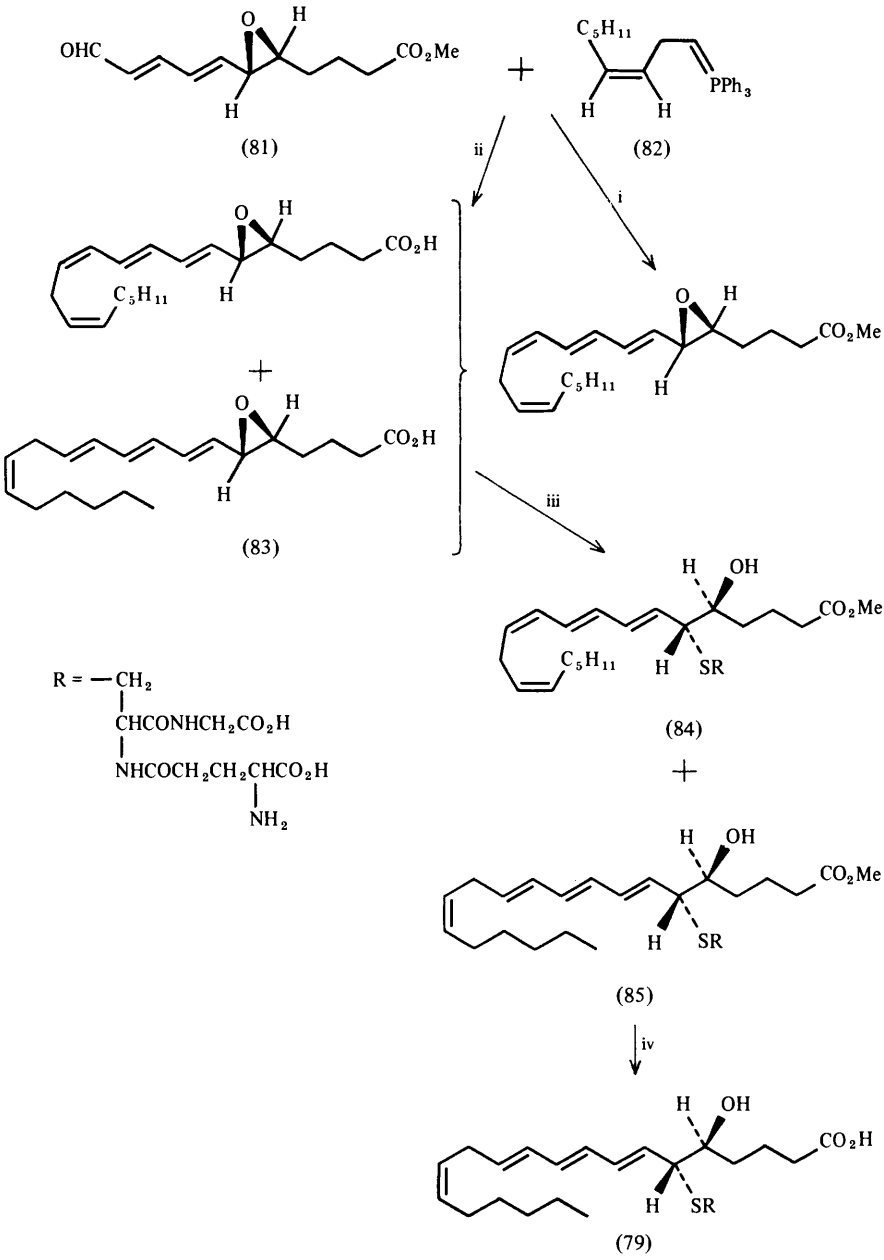
C. Corey's Synthesis of *trans*-11-LTC_4 and LTD_4.—The synthesis of *trans*-11-LTC_4 (79) (Scheme 17) and LTD_4 (80) (Scheme 18) was achieved by studying the factors which controlled the stereochemistry in the Wittig reaction between the C_{11} *trans,trans*-dienal ester (81) and the C_9 ylide (82).[25] Thus, LTA_4 methyl ester was exclusively formed when the reaction was carried out in tetrahydrofuran

[25] E. J. Corey, D. A. Clark, A. Marfat, and G. Goto, *Tetrahedron Lett.*, 1980, **21**, 3143.



Reagents: i, Pyridinium dichromate; ii, *p*-toluenesulphonyl chloride; iii, NaI, triphenylphosphine; iv, n-BuLi; v, tetra-n-butylammonium fluoride; vi, methanesulphonyl chloride; vii, dimethyl sulphide; viii, methyl 4-formylbutyrate; ix, cold aqueous base; x, Me_2SO_4

Scheme 16 *Corey's first synthesis of* LTA_4

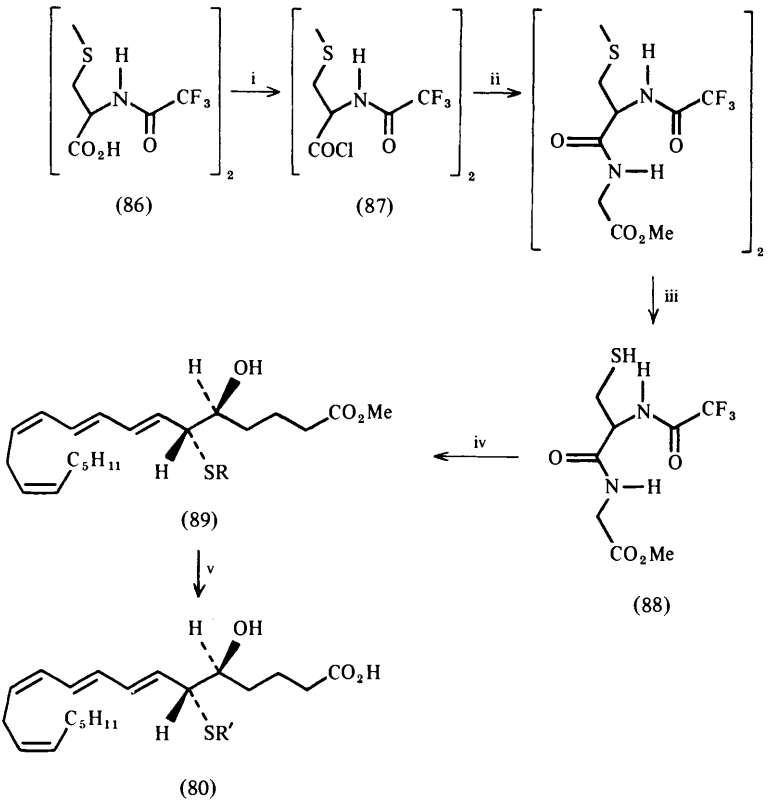


Reagents: i, THF–HMPA, −78 °C; ii, LiI; iii, glutathione, Et_3N, MeOH; iv, K_2CO_3

Scheme 17 *Corey's synthesis of* trans-*11-LTC*$_4$

and hexamethylphosphoric triamide, whereas with an ethereal solution of lithium iodide and tetrahydrofuran a mixture of LTA_4 and its *trans*-11-isomer (83) methyl esters were obtained. The mixture was separated after conversion into LTC_4 and *trans*-11-LTC_4 methyl esters [(84) and (85)]. Hydrolysis with 0.1M potassium carbonate gave *trans*-11-LTC_4 (Scheme 17).

For the synthesis of LTD_4 (80) the methyl ester of LTA_4 was treated with *N*-trifluoroacetylcysteinylglycine methyl ester (88). The peptide portion was synthesized from *N*-trifluoroacetyl-L-cystine (87), which was converted into

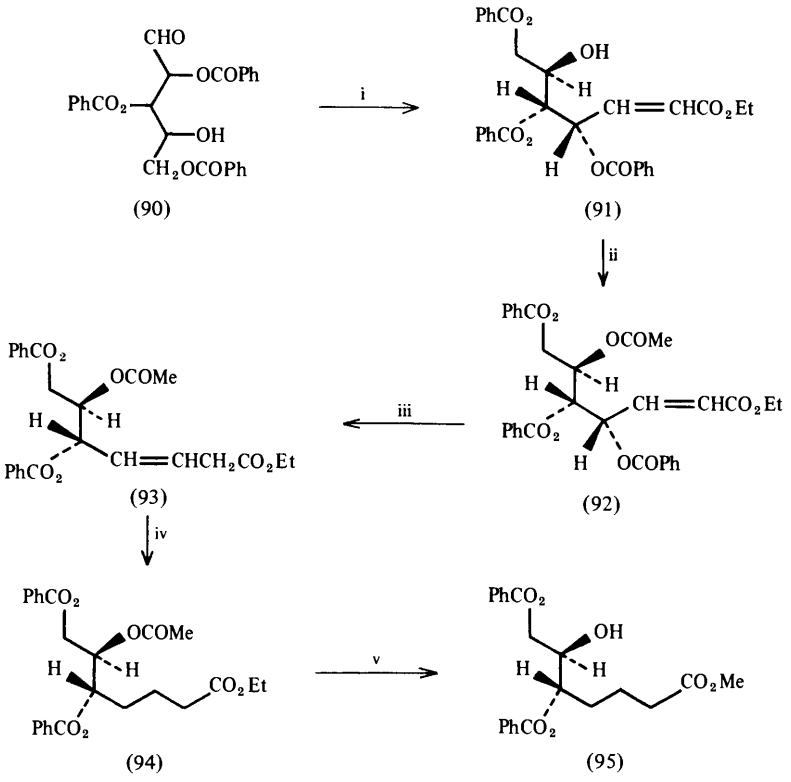


Reagents: i, PCl_5; ii, glycine methyl ester; iii, triphenylphosphine; iv, methyl ester of LTA_4, Et_3N, MeOH; v, K_2CO_3

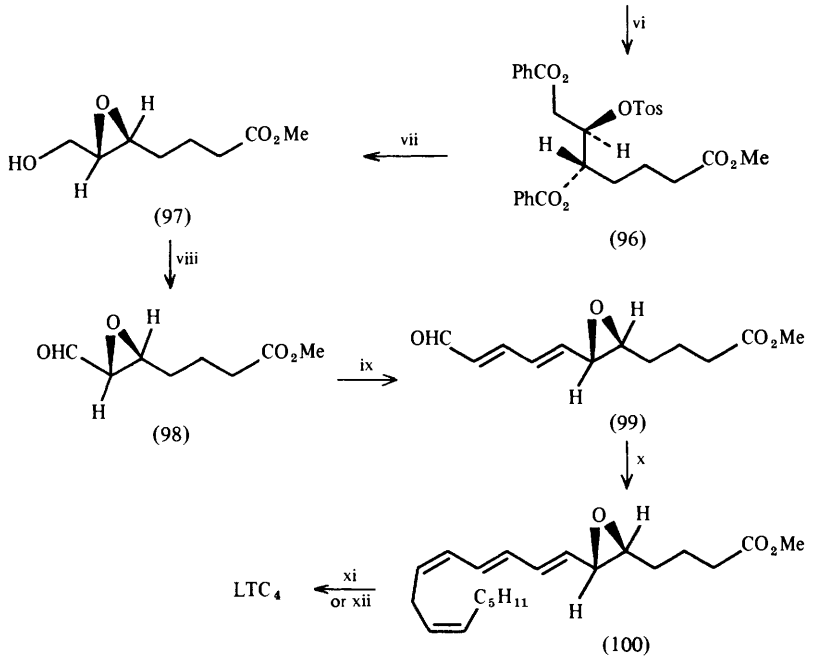
Scheme 18 *Corey's synthesis of* LTD_4

the acid chloride (87) and then treated with glycine methyl ester. Reduction of the crystalline cysteine derivative with triphenylphosphine in aqueous dimethoxy-ethane (2:1) gave the required peptide (88). LTD_4 was obtained from the diester (89) by hydrolysis with aqueous methanolic potassium carbonate (Scheme 18).

D. Corey's Enantiospecific Synthesis of LTA_4 from D-(−)-Ribose.—A key intermediate for the synthesis of LTC_4, LTD_4, and LTE_4 with the naturally occurring antipodal form is (−)-methyl *trans*-(5*S*,6*S*)-epoxy-*trans*-7,9-*cis*-11,14-eicosatetraenoate, LTA_4. To introduce the correct asymmetry into the epoxide, Corey used the chirality at C-3 and C-4 in D-(−)ribose, and the functionality at the terminii to introduce the remaining carbon atoms (Scheme 19).[26] The tribenzoyl derivative of D-(−)ribose (90) was treated with ethoxycarbonylmethylenetriphenylphosphorane to give the α,β-unsaturated ester (91). Acetylation of the hydroxy-group to give (92) and removal of the unwanted chiral centre



[26] E. J. Corey, D. A. Clark, G. Goto, A. Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarström, *J. Am. Chem. Soc.*, 1980, **102**, 1436, 3663.



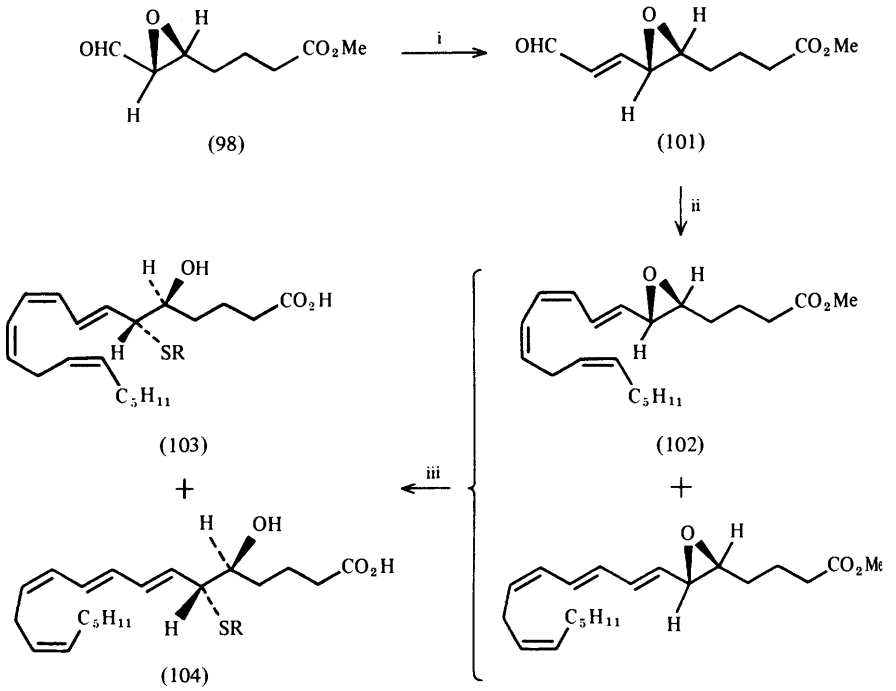
Reagents: i, Ethoxycarbonylmethylenetriphenylphosphorane; ii, Ac_2O; iii, zinc amalgam; iv, 10% Pd–C,H_2; v, HCl, MeOH; vi, tosyl chloride, pyridine; vii, K_2CO_3, MeOH; viii, Collins reagent; ix, 1-lithio-4-ethoxybutadiene, methane sulphonyl chloride, Et_3N, pH 7 phosphate buffer; x, n-BuLi; xi, *N*-trifluoroacetylglutathione dimethyl ester, K_2CO_3–0.03M-$KHCO_3$ in 95:5 H_2O–MeOH; xii, glutathione–Et_3N–MeOH, K_2CO_3 in H_2O–MeOH

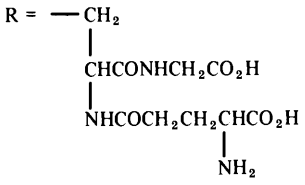
Scheme 19 *Corey's enantiospecific synthesis of LTA_4 and LTC_4 from* D-(−)-*ribose*

gave the β,γ-unsaturated ester (93) which was hydrogenated to the saturated ester (94). The acetyl group in (94) was transformed to a tosylate (96) by hydrolysis to the alcohol (95) followed by reaction with *p*-toluene sulphonyl chloride. The *trans*-epoxide (97) was cleanly formed by hydrolysis to the benzoyl groups in the presence of potassium carbonate in methanol. The *trans* double bonds at C-7 and C-9 were introduced by treating the epoxy-aldehyde (98) with 1-lithio-4-ethoxybutadiene at −78 °C, giving a secondary alcohol that was eliminated on treatment with methane sulphonyl chloride to form the resulting dienal ester (99). The synthesis of LTA_4 methylester (100) was finalized by a Wittig reaction with non-3-enyltriphenylphosphorane. This synthesis was improved by Marriott and Bantick who prepared the key chiral intermediate from 2-deoxy-D-(−)-ribose (see p. 336).[21]

LTA_4 methyl ester was converted by sulphydryl compounds and triethylamine into 5-hydroxy-6-thioether derivatives. LTC_4 was made in this way by reaction with glutathione or *N*-trifluoroacetylglutathionedimethyl ester followed by hydrolysis.

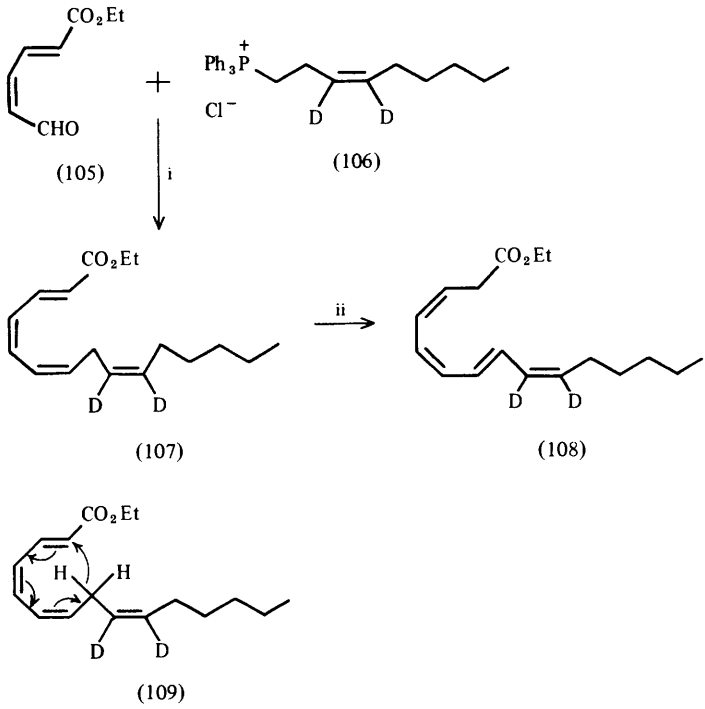
The availability of the epoxy-aldehyde (98) enabled Corey and his co-workers also to synthesize *trans*-(5*S*,6*S*)-epoxy-*trans*-7-*cis*-9,11,14-eicosatetraenoate (102). The α-lithio-derivative of the t-butylimine of trimethylsilylacetaldehyde was treated with the epoxy-aldehyde (98) to give the enal ester (101). A Wittig condensation with the ylide generated from undec-2,5-dienyltriphenylphosphonium mesylate gave a mixture of the required epoxytetraene (102) and LTA_4. The mixture proved difficult to separate but reaction with glutathione gave LTC_4 (104), and its isomer (103), which were separated by h.p.l.c. (Scheme 20).





Reagents: i, t-Butylimine of trimethylsilylacetaldehyde, s-butyl-lithium, pH 7 phosphate buffer; ii, ylide generated from corresponding phosphonium mesylate by reaction with 1 equiv. LDA; iii, glutathione, Et_3N; 0.1M-K_2CO_3, H_2O-MeOH

Scheme 20 *Corey's synthesis of the* cis-9-*isomer of* LTA_4 *and* LTC_4



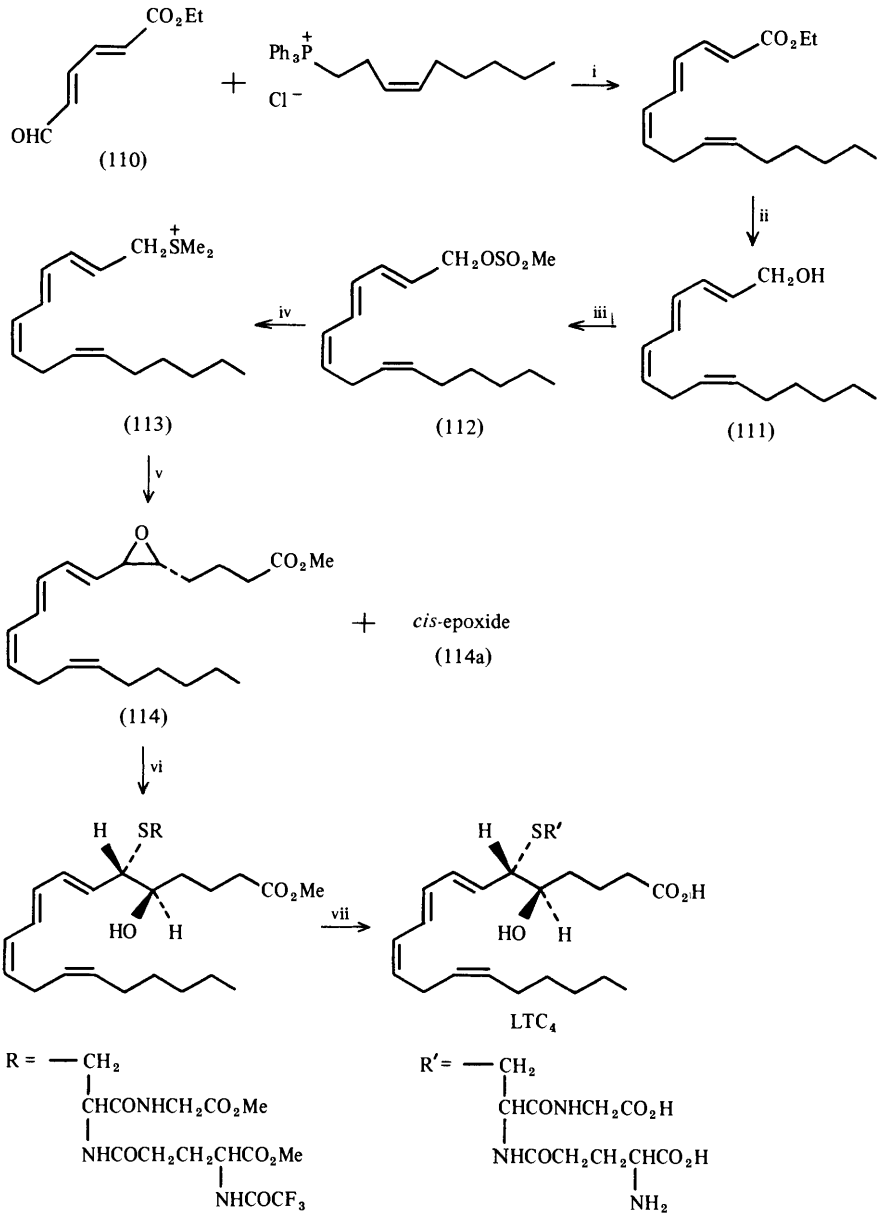
Reagents: i, BuLi; ii, room temperature

Scheme 21 *Synthesis of ethyl pentadeca* trans-2-cis-*4,6,9-tetraenoate and its subsequent [1,7]-hydrogen migration*

E. Rokach's First Synthesis of LTC_4.—In the first synthesis by Rokach and his co-workers[27] of LTA_4 and LTC_4 it was believed that the geometry of the double bonds was *cis* at C-9, C-11, and C-14 and *trans* at C-7. The strategy of the synthesis was therefore to prepare a C-15 fragment having the required geometry at the double bonds which could be condensed as the sulphonium ylide with methyl 5-oxopentanoate. Thus the *trans,cis*-dienal ester (105) was condensed with the ylide from the phosphonium salt (106) to give the tetraene ester (107). However, on standing at room temperature a [1,7]-hydrogen migration took place as in (109) to give (108) (Scheme 21). This spontaneous hydrogen migration cast doubts on the *cis* geometry at the 9,10 double bond in the leukotrienes since a similar migration would be anticipated.

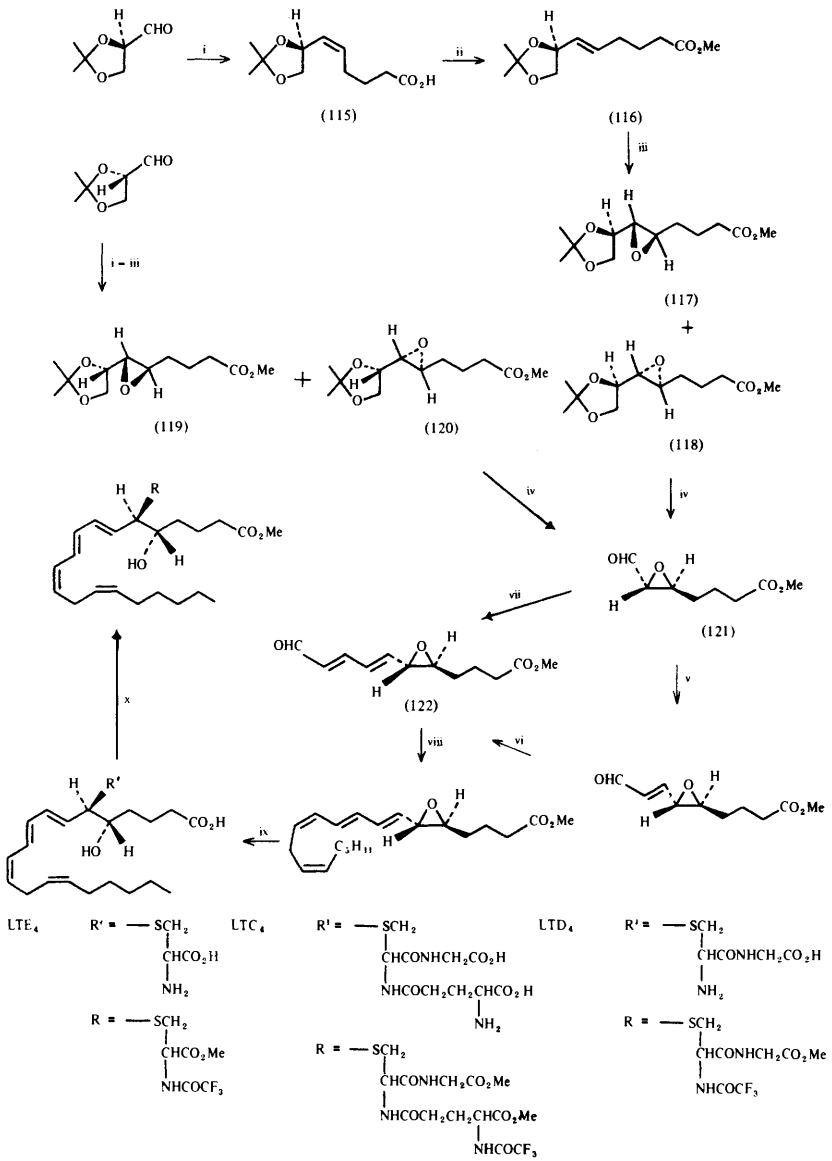
Subsequent work was therefore directed at preparing the *trans,trans,cis,cis*-tetraene alcohol (111) from the dienal ester (110) as shown in Scheme 22. The alcohol (111) was converted into the mesylate (112) and then the

[27] J. Rokach, Y. Girard, Y. Guindon, J. G. Atkinson, M. Larue, R. N. Young, P. Masson, and G. Holme, *Tetrahedron Lett.*, 1980, **21**, 1485.



Reagents: i, BuLi; ii, AlH_3; iii, mesylation; iv, dimethyl sulphide; v, transformed to sulphonium ylide and treated with methyl 5-oxopentanoate; vi, *S*-trimethylsilyl glutathione dimethyl ester *N*-trifluoroacetamide; vii, K_2CO_3

Scheme 22 *Rokach's synthesis of* LTC_4



Reagents: i, (4-Carboxybutyl)triphenylphosphonium bromide, dimsyl sodium; ii, *hv*; CH_2N_2; iii, MCPBA; iv, AcOH, $NaIO_4$; v, formylmethylenetriphenylphosphorane (84%); vi, formylmethylenetriphenylphosphorane (34%); vii, formylmethylenetriphenylphosphorane; viii, triphenyl[(*Z*)-non-3-en-1-yl]phosphonium chloride; ix, RSH,Et_3N, MeOH; x, K_2CO_3, H_2O, MeOH

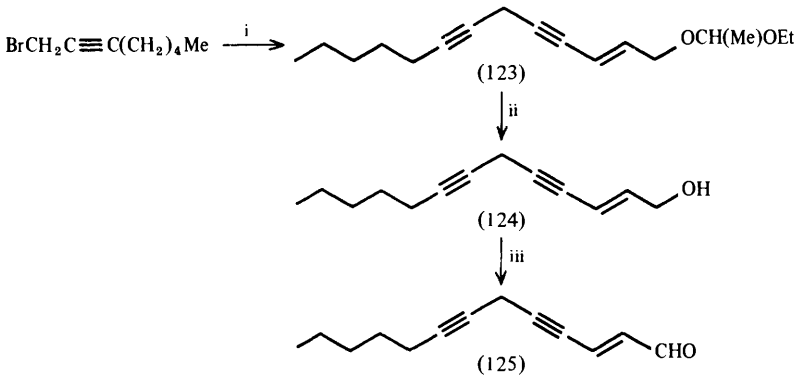
Scheme 23 *Rokach's synthesis of LTA*$_4$, *C*$_4$, *D*$_4$ *and E*$_4$ *from* D- *and* L-*glyceraldehyde*

sulphonium salt (113) prior to condensation with methyl 5-oxopentanoate to give a mixture of *cis* and *trans* epoxides (114a and 114), which were separated by h.p.l.c.

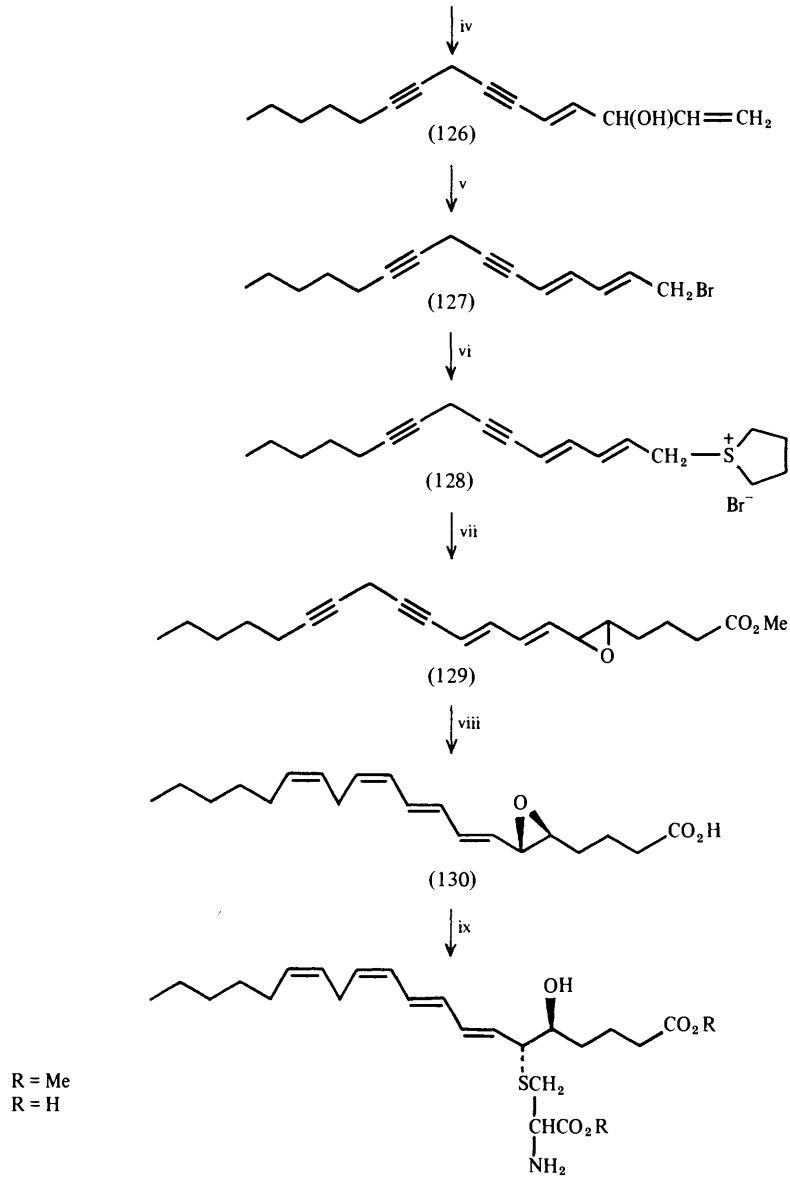
Treatment of the *trans*-epoxide (114) with a *S*-trimethylsilyl derivative of glutatathione gave two diastereomers which were separated by h.p.l.c. After hydrolysis, biological tests showed one of the products to have the biological activity of LTC_4 (SRS) (Scheme 22). Epoxide openings with other thiotrimethylsilyl derivatives were also examined.[27]

F. Rokach's Synthesis of Natural Leukotrienes From the Acetonides of D- and L-Glyceraldehyde.—The synthesis (Scheme 23)[28] involves preparation of the key chiral epoxy-aldehyde (121), whereby a chiral centre is introduced into separate diastereomeric products from epoxidation of a chiral alkene [*e.g.* (116)]. The acetonide of D-glyceraldehyde was converted into the *cis*-olefinic acid (115) by a Wittig reaction and then converted into the *trans*-isomer (116) photochemically, in the presence of diphenyldisulphide. Methylation with diazomethane and epoxidation of the ester (116) with *m*-chloroperbenzoic acid gave a mixture of two epoxides [(117) and (118)] in a 2:1 ratio, and these were readily separated by chromatography. By a similar sequence the acetonide of L-glyceraldehyde gave epoxy-esters [(119) and (120)] in a 1:2 ratio. Cleavage of the ketals [(118) and (120)] and oxidation of the diols gave the epoxy-aldehyde (121) which was converted into the dienalepoxy-ester (122) by two successive Wittig reactions. The product (122) was treated with the ylide from triphenyl [(*Z*)-non-3-en-1-yl]phosphonium chloride to give LTA_4 methyl ester, which was subsequently converted into LTC_4, LTD_4, and LTE_4 as shown in Scheme 23.

G. Rosenberger and Neukom's Synthesis of LTE_4.—This route (Scheme 24)[29] to LTE_4 involves preparation of the racemic *trans*-epoxide (130) from a diyne



[28] J. Rokach, R. N. Young, M. Kakushima, C.-K. Lau, R. Seguin, R. Frenette, and Y. Guindon, *Tetrahedron Lett.*, 1981, **22**, 979.
[29] M. Rosenberger and C. Neukom, *J. Am. Chem. Soc.*, 1980, **102**, 5426.



Reagents: i, CuCl, EtMgBr, ethyl vinyl ether adduct of (*E*)-1-hydroxypent-2-en-4-yne; ii, acetone, 0.2N-H_2SO_4; iii, pyridinium dichromate; iv, vinylmagnesium chloride; v, PBr_3; vi, tetrahydrothiophene; vii, methyl 4-formylbutyrate, benzyltrimethylammonium chloride; viii, H_2, Lindlar catalyst; ix, methyl ester of L-cysteine

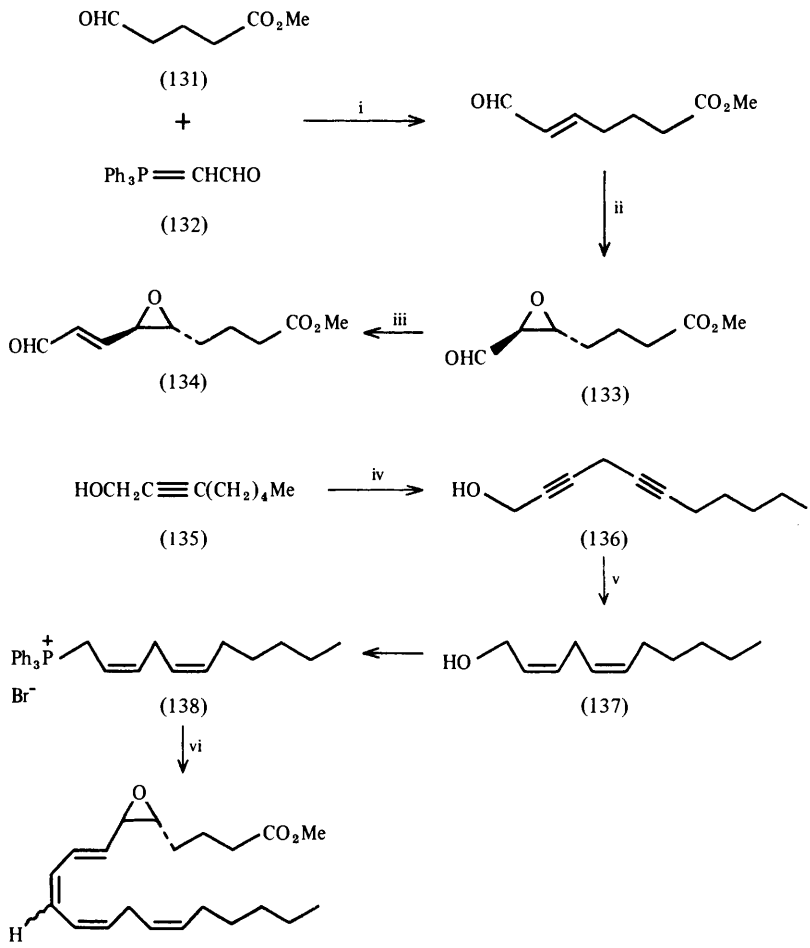
Scheme 24 *The Hoffmann-La Roche synthesis of* LTE_4

(123) whereby the *cis* double bonds at C-11 and C-14 can be introduced by catalytic reduction with a Lindlar catalyst. Copper-catalysed coupling of 1-bromo-oct-2-yne with the ethyl vinyl ether adduct of (*E*)-1-hydroxypent-2-en-4-yne gave the enediyne (123), which was hydrolysed to the alcohol (124) and then oxidized to the C_{13} aldehyde (125). Conversion of (125) into the vinylalcohol (126) with vinylmagnesium bromide followed by treatment with phosphorus tribromide gave the all *trans* bromide (127), which yields the sulphonium salt (128) with tetrahydrothiophene. The reaction of the product (128) with methyl 4-formylbutyrate gave the *trans*-epoxide (129; 38%) and its *cis*-isomer (12%), which were separated by chromatography. Hydrogenation of the *trans*-epoxide (129) gave the racemic tetraene (130). Addition of the methyl ester of L-cysteine generated a pair of diastereomers which were separated on silica gel. Hydrolysis of the esters gave LTE_4 and its (5*R*,6*S*)-isomer, with LTE_4 showing the greater spasmogenic activity in the guinea-pig ileum assay.

H. Gleason's Convergent Synthesis of LTA_4 Methyl Ester.—This synthesis (Scheme 25)[30] involved coupling a C_{11} (*Z*,*Z*)-diene ylide (138), prepared from oct-2-yn-1-ol, with a C_9 γ-epoxy-α,β-unsaturated aldehyde (134) prepared from methyl 4-formylbutyrate. The reaction of the stabilized ylide (132) with methyl 4-formylbutyrate (131), followed by epoxidation, gave the epoxy-aldehyde (133) which was then treated with the same ylide (132) to give methyl 9-oxo-*trans*-5,6-epoxy-(7*E*)-enoate (134). For the second fragment oct-2-yn-1-ol (135) was converted into 1-bromo-oct-2-yne and treated with the Grignard derivative of propargyl alcohol to give the diynol (136). Catalytic hydrogenation gave exclusively the (*Z*,*Z*)-diene (137) which was converted into the ylide (138) for coupling with the epoxy-aldehyde (134). The final product was ~2:1 mixture of *E* and *Z* isomers about the C-9 double bond.

I. Sih's Re-investigation of the Biomimetic Synthesis of LTA_4, LTC_4, and Related Compounds.—The group at the University of Wisconsin examined the stereospecificity of converting (±) 5-HPETE methyl ester (139) into LTA_4 methyl ester (Scheme 26).[31] Treatment of (±) 5-HPETE (139) with methanesulphonyl chloride and dicyclohexylamine gave not only LTA_4 methyl ester (140) and the 5-ketone (141) but also the (7*E*,9,11,14*Z*)-isomer of LTA_4 methyl ester (142), which at room temperature is transformed into the known tetraene (143) by a 1,7-hydrogen shift. The reaction of the epoxides [(140) and (142)] with glutathione led to LTC_4 and the analogues (5*R*,6*S*)-LTC_4 (144) (9*Z*)-LTC_4 (146) and (5*R*,6*S*,9*Z*)-LTC_4 (145). In an attempt to find stereospecific conditions for converting 5-HPETE into LTA_4, in accordance with a previous report,[23] various reaction conditions were studied for the 1,7-elimination

[30] J. G. Gleason, D. B. Bryan, and C. M. Kinzig, *Tetrahedron Lett.*, 1980, **21**, 1129.
[31] V. Atrache, J.-K. Pai, D.-E. Sok, and C. J. Sih, *Tetrahedron Lett.*, 1981, **22**, 3443.

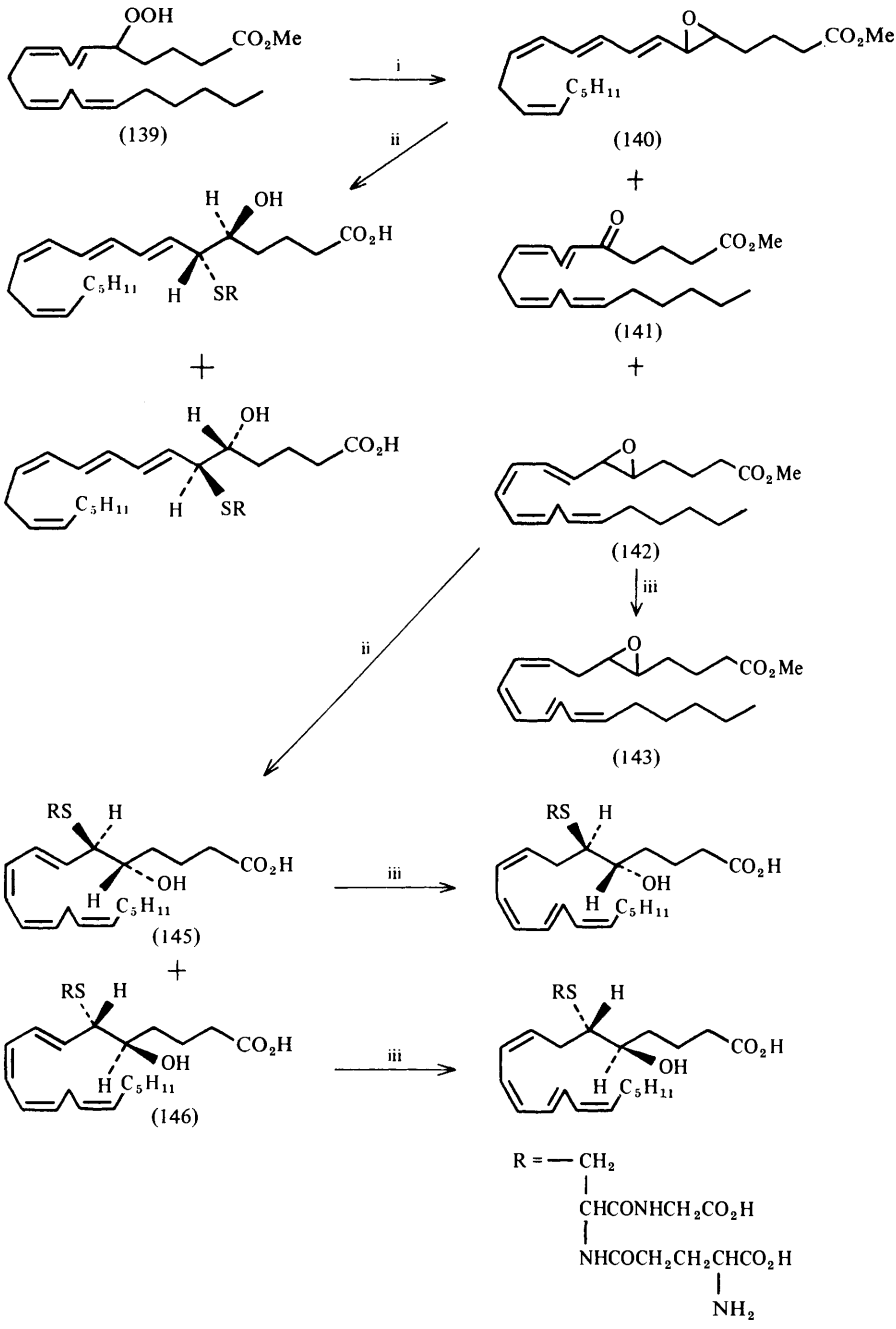


Reagents: i, Refluxing toluene; ii, H_2O_2, $NaHCO_3$, iii, $Ph_3P{=}CHCHO$; iv, PBr_3; $HOCH_2C{\equiv}CH$, EtMgBr; v, Pd, $BaSO_4$, H_2; vi, transformed *via* the allylic bromide to the phosphonium salt [70% from (135)]; vii, BuLi, aldehyde

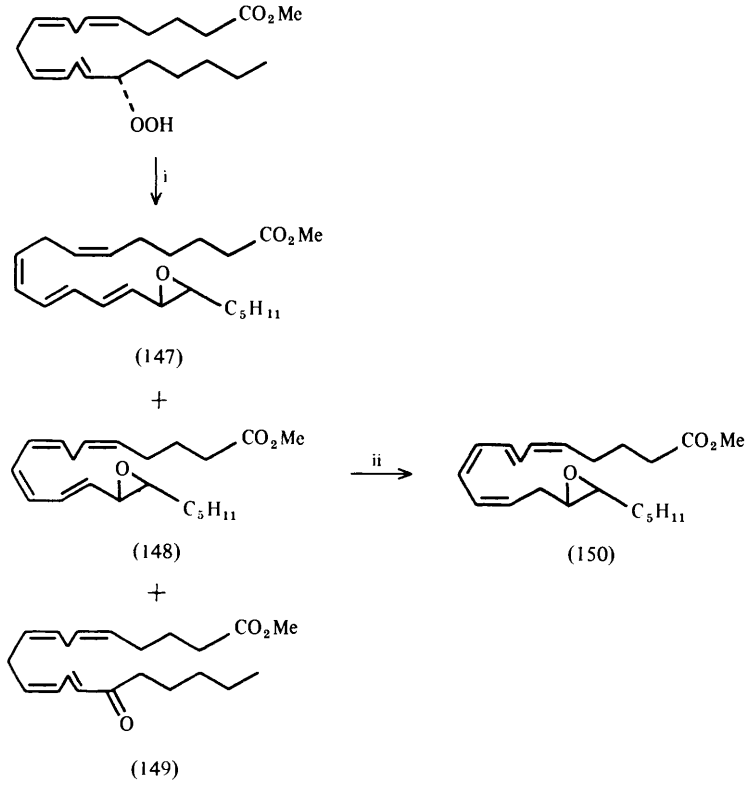
Scheme 25 *Gleason's convergent total synthesis of* LTA_4

process, and in addition the triflate leaving group was used. Although a *trans*-epoxide was always formed to the exclusion of the *cis*-isomer, a mixture of (9*E*)- and (9*Z*)-epoxides [(140) and (142)] and 5-ketone (141) was obtained under various conditions, with a higher dilution of methylene chloride–ether (1:1) solvents giving the epoxides [(140) and (142)] in a 1:1 ratio (13% and 15%) with a decreased proportion of the ketone (141; 7%).

Recently, four new dihydroxyeicosatetraenoic acids were isolated from a human leukocyte preparation which had been incubated with arachidonic


OOH
CO2Me
(139)
i
ii
O
CO2Me
C5H11
(140)
+
H
OH
CO2H
C5H11
H
SR
O
CO2Me
(141)
+
+
H
OH
CO2H
C5H11
H
SR
O
CO2Me
(142)
iii
O
CO2Me
(143)
ii
RS
H
CO2H
OH
H
C5H11
(145)
iii
+
RS
H
CO2H
OH
H
C5H11
(146)
iii
R = — CH2
CHCONHCH2CO2H
NHCOCH2CH2CHCO2H
NH2

acid.[32] These are 14,15-dihydroxy-5,8,10,12-eicosatetraenoic acid (two isomers) and 8,15-dihydroxy-5,9,11,13-eicosatetraenoic acid (two isomers) and all of them probably originate from 14,15-epoxy-5,8,10,12-eicosatetraenoic acid (14,15-LTA_4), which in turn would be derived from 15-HPETE. The Wisconsin group therefore re-investigated the conversion of 15-HPETE into 14,15-epoxides[33] and found that two isomeric epoxides [(147) and (148)] and the ketone (149) were obtained.[31] The *cis*-10 isomer (148) undergoes rearrangement by a 1,7-hydrogen shift to the tetraene (150) (Scheme 27).



Reagents: i, $(CF_3SO_2)_2O$, 1,2,2,6,6-pentamethylpiperidine; ii, 1,7-hydrogen shift

Scheme 27 *Sih's re-investigation of the synthesis of 14,15-LTA_4 and its isomers*

[32] W. Jubiz, O. Radmark, J. A. Lingren, C. Malmsten, and B. Samuelsson *Biochem. Biophys. Res. Commun.*, 1981, **99**, 976.
[33] E. J. Corey, A. Marfat, and G. Goto, *J. Am. Chem. Soc.*, 1980, **102**, 6607.

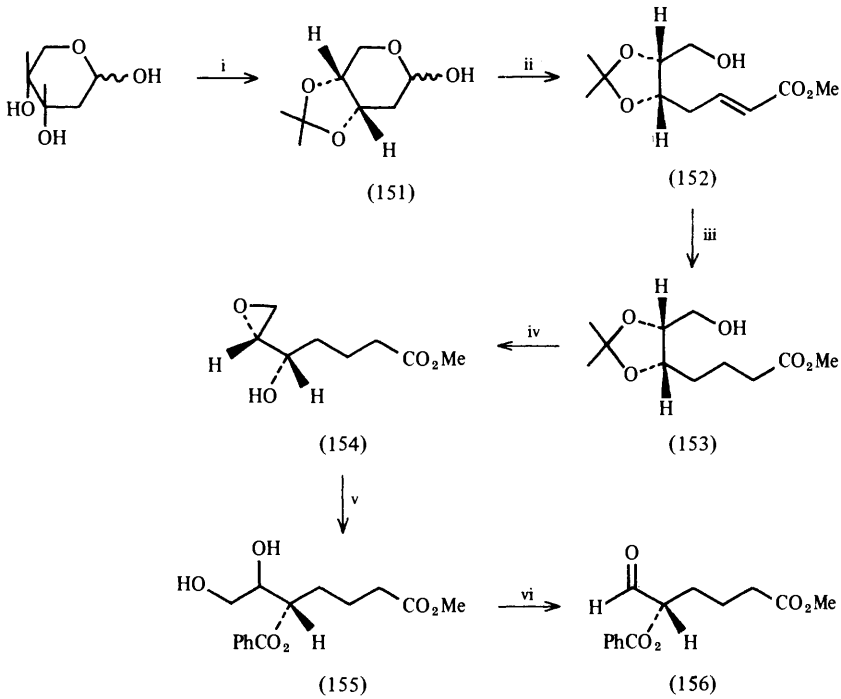
Reagents: i, CH_2Cl_2, CH_3SO_2Cl, DCMA; ii, glutathione, Et_3N; ester cleavage; iii, room temperature, 1,7-hydrogen shift

Scheme 26 *Sih's biomimetic synthesis of LTA_4*

9 Synthesis of Leukotriene B_4 (LTB_4)

The three syntheses of LTB_4 described in this review involve the preparation of two chiral synthons, which are then joined by a *cis*-Wittig reaction. One synthon comprises C-1 to C-6 of LTB_4 with the (5*S*) stereochemistry while the other segment consists of C-7 to C-20 with the (12*R*) configuration of the hydroxy-group incorporated.[34-36]

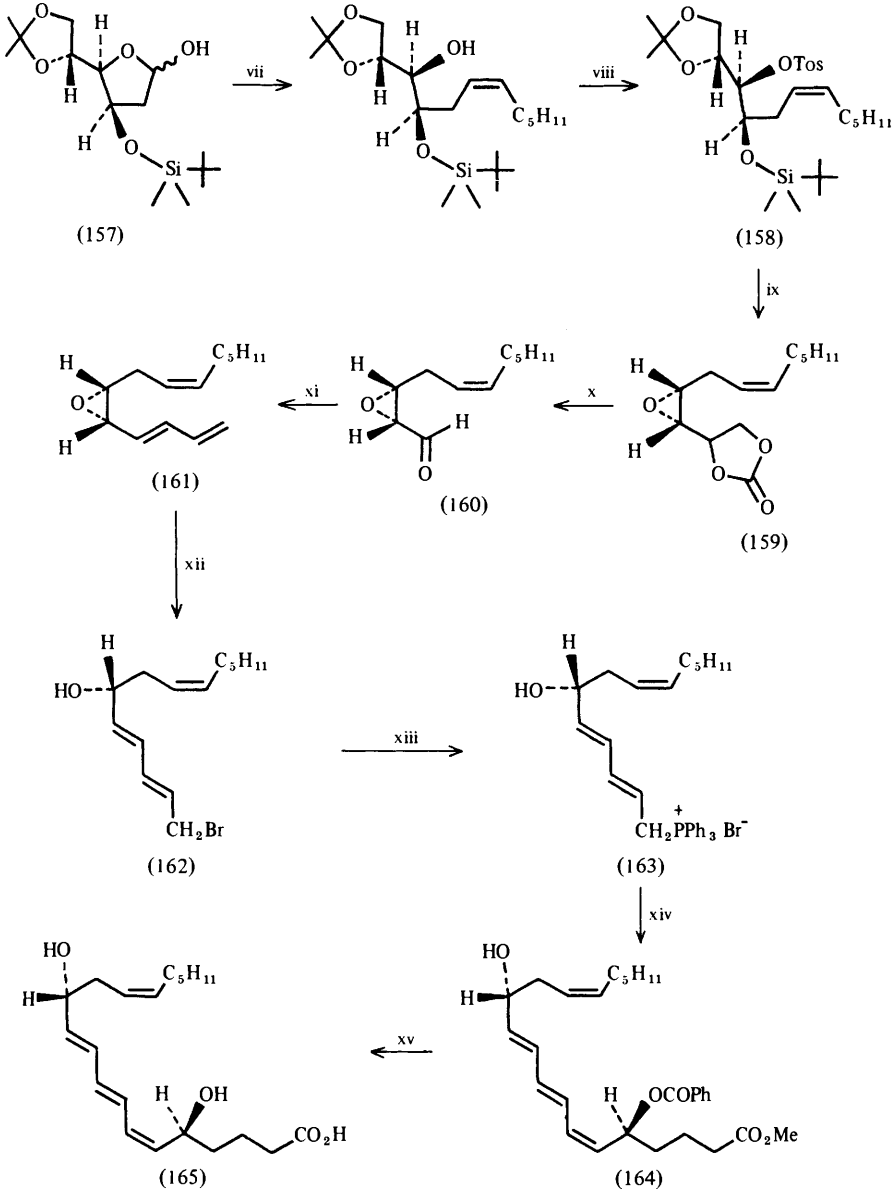
A. Corey's First Synthesis of LTB_4.—At the outset of this synthesis the geometry of the conjugated triene system was uncertain but Corey[34] considered that, by analysis of the transition state of cation formation from LTA_4, LTB_4 should have a *cis*-6,*trans*-10-triene system (165) and this was confirmed by total synthesis and bioassay of the product.



Reagents: i, 2-Methoxypropene, pyridinium tosylate; pH 5.5 phosphate buffer; ii, methoxycarbonylmethylenetriphenylphosphorane; iii, H_2, Pd–C; iv, tosyl chloride, pyridine; 2% HCl, MeOH, and ketal; 2 equiv. K_2CO_3, MeOH; v, benzoyl chloride, pyridine; dimethyl carbonate–H_2O–70% perchloric acid; vi, $Pb(OAc)_4$

Scheme 28 *Corey's first synthesis of LTB_4*

[34] E. J. Corey, A. Marfat, G. Goto, and F. Brion, *J. Am. Chem. Soc.*, 1980, **102**, 7986.
[35] E. J. Corey, A. Marfat, J. Munroe, K. S. Kin, P. B. Hopkins, and F. Brion, *Tetrahedron Lett.*, 1981, **22**, 1077.
[36] Y. Guindon, R. Zamboni, C.-K. Lau, and J. Rokach, *Tetrahedron Lett.*, 1982, **23**, 739.



(157) (158) (159) (160) (161) (162) (163) (164) (165)

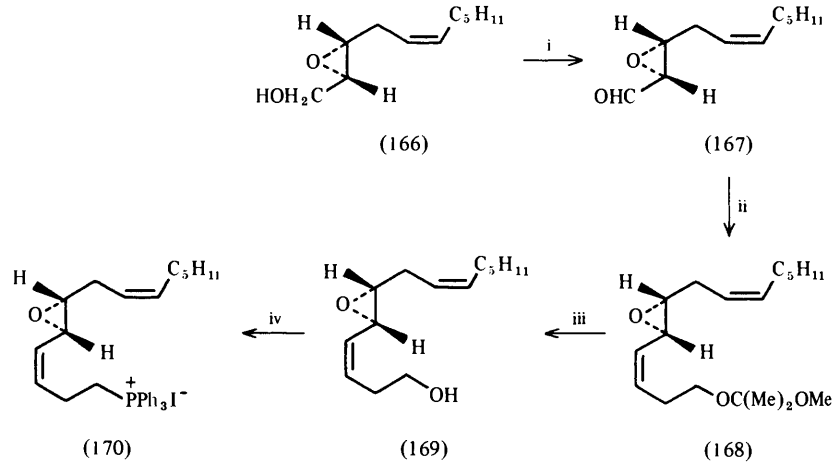
Reagents: n-Hexylidenetriphenylphosphorane; viii, tosyl chloride, pyridine; ix, 10% HCl, MeOH; 1.1 equiv. phenyl chloroformate; diazabicyclo[4.3.0]nonene; x, LiOH; $Pb(OAc)_4$; xi, allylidenetriphenylphosphorane; xii, HBr, CH_2Cl_2; xiii, triphenylphosphine; xiv, n-BuLi; aldehyde (156); xv, K_2CO_3, MeOH

Scheme 29 *Corey's first synthesis of* LTB_4

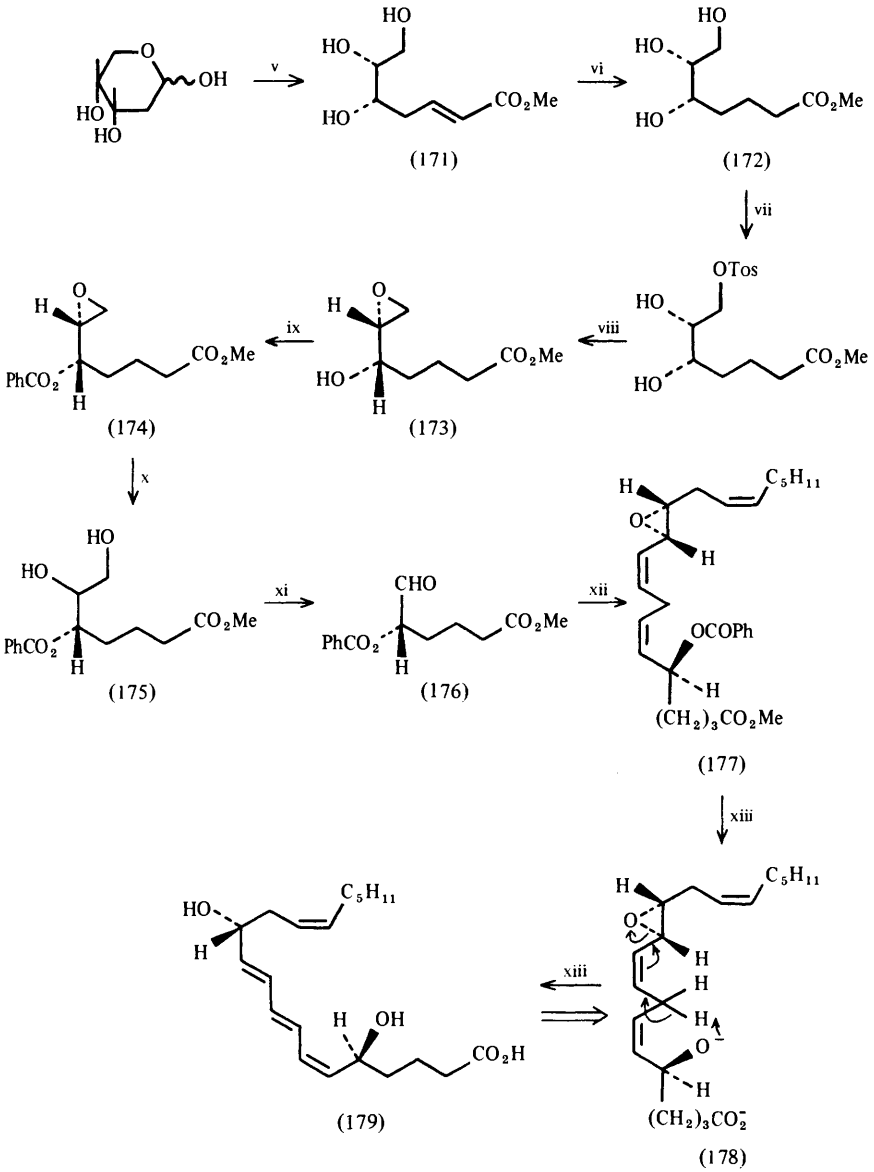
The C-1—C-6 segment was constructed from 2-deoxyribose, whereas the C-7—C-20 portion was constructed from D-(+)-mannose and the correct stereochemistry at C-5 and C-12 was incorporated from the sugars. 2-Deoxyribose was converted into the acetonide (151) with 2-methoxypropene and coupled with methoxycarbonylmethylenetriphenylphosphorane to give the α,β-unsaturated ester (152) which was hydrogenated to the hydroxy-ester (153). Tosylation of the primary alcohol group and deketalization led to the formation of the epoxy-ester (154). The (5*S*)-hydroxyl was protected as the benzoyl derivative and the epoxide ring converted into the glycol (155) and cleaved to the aldehyde-ester (156) with lead tetra-acetate (Scheme 28).

The second segment came from the cyclic hemiacetal (157) synthesized from D-(+)-mannose. Chain extension with n-hexylidenetriphenylphosphorane and tosylation produced the *cis*-olefin (158) which was converted into the *cis*-epoxide (159) by removal of the protecting groups and treatment with phenyl chloroformate. Hydrolysis of the carbonate group and glycol cleavage gave the aldehyde (160) which was converted into the triene-epoxide (161) on reaction with allylidene triphenylphosphorane. Addition of hydrogen bromide gave the bromo-alcohol (162) which formed the phosphonium salt (163). Conversion of (163) into its ylide followed by coupling with the aldehyde (156) afforded the 5-benzoyl derivative of LTB_4 methyl ester (164). Hydrolysis of ester groups gave the desired LTB_4 (165) and ~15% of the 6-*trans*-isomer, which were separated by reverse-phase h.p.l.c.

B. Corey's Second Synthesis of LTB_4.—The second synthesis by Corey (Scheme 30)[35] again involves joining C_6 and C_{14} synthons with the final stage and utilizes a novel internal elimination reaction to form a new double bond and open an epoxide ring by taking advantage of the hydroxy-group at C-5 and the *cis*-alkene at C-6 to provide the low energy pathway [(178)→(179)].

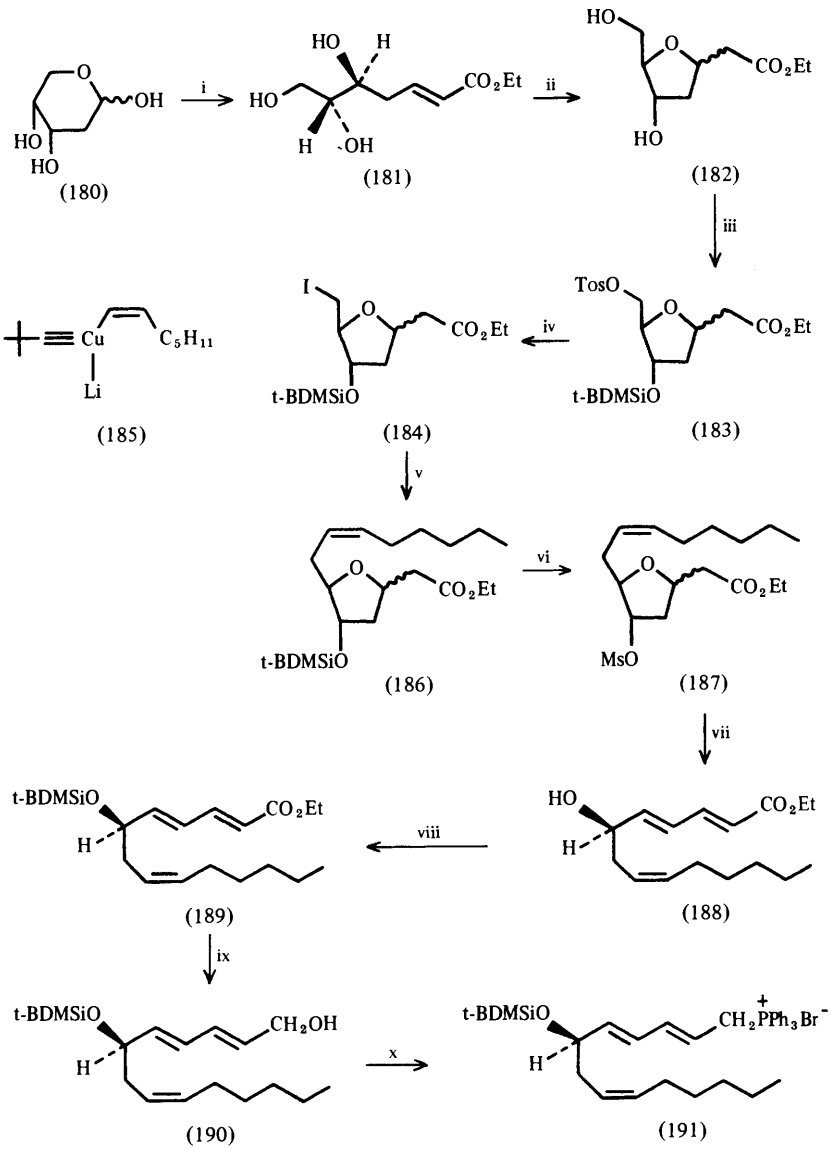


(166) (167) (168) (169) (170)



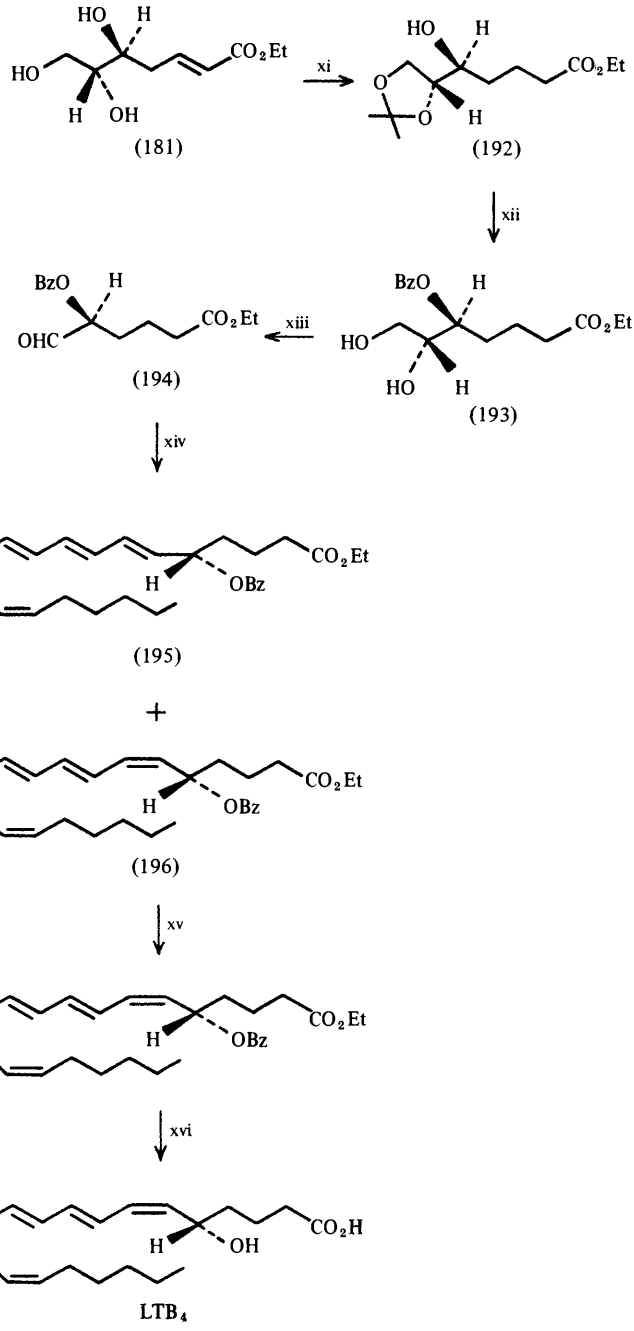
Reagents: i, CrO_3–2Pyr; ii, 2-methoxy-2-propyl ether of 3-hydroxypropyltriphenylphosphonium bromide, n-BuLi; iii, $MeCO_2H$; iv, tosylation; halogenation; triphenylphosphine; v, methoxycarbonylmethylenetriphenylphosphorane; vi, H_2, Pd–C; vii, tosyl chloride–pyridine; viii, K_2CO_3, MeOH; ix, benzoyl chloride, pyridine; x, dimethyl carbonate–H_2O, perchloric acid; xi, $Pb(OAc)_4$; xii, (170), n-BuLi; xiii, K_2CO_3

Scheme 30 *Corey's second synthesis of* LTB_4



Reagents: i, Ethoxycarbonyltriphenylphosphorane; ii, NaOEt; iii, TosCl, pyr; 2 equiv. t-butyldimethylsilyl chloride; iv, NaI, refluxing acetone; v, heterocuprate reagent (185); vi, n-Bu_4NF; MsCl, Et_3N; vii, NaOEt, EtOH; viii, t-butyldiphenylsilylchloride; ix, AlH_3; x, CBr_4, Ph_3P; xi, hydrogenation, formation of acetonide: xii, BzCl, Et_3N; 1N-HCl in MeOH; xiii, $Pb(OAc)_4$; xiv, phosphonium salt (191), BuLi; (194): xv, n-Bu_4NF; xvi, K_2CO_3, MeOH–H_2O

Scheme 31 *Rokach's stereospecific synthesis of* LTB_4


HO
H
CO2Et
HO
H
OH
(181)
xi
HO
H
CO2Et
O
O
H
(192)
xii
BzO
H
CO2Et
HO
HO
H
(193)
xiii
BzO
H
CO2Et
OHC
(194)
xiv
t-BDPSiO
H
CO2Et
H
OBz
(195)
+
t-BDPSiO
H
CO2Et
H
OBz
(196)
xv
HO
H
CO2Et
H
OBz
xvi
HO
H
CO2H
H
OH
LTB4

The C_{14} fragment was synthesized from *trans*-2,3-epoxy-undeca-*cis*-5-en-1-ol (166) by oxidation to the aldehyde (167) followed by chain extension with the ylide prepared from the 2-methoxy-2-propyl ether of 3-hydroxypropyltriphenylphosphonium bromide to give the *cis*-alkene (168) in 92% yield. Deprotection of (168) gave the alcohol (169) which was converted *via* the corresponding tosylate and iodide into the phosphonium salt (170). The C_6 synthon was prepared from 2-deoxyribose which gave, by a Wittig condensation with methoxycarbonylmethylenetriphenylphosphorane, the triol ester (171). Conversion of (171) into the epoxy-diester (174) was achieved by (a) hydrogenation to the saturated triol ester (172), (b) monotosylation of the primary hydroxy-group, and (c) oxirane ring closure to (173) with potassium carbonate followed by benzoylation. The key C_6 aldehyde (176) was produced by opening the epoxide ring followed by glycol (175) cleavage with lead tetra-acetate. A Wittig reaction of the aldehyde (176) and the ylide from phosphonium salt (170) produced the all *cis*-triene diester (177). Hydrolysis of the ester (177) with aqueous methanolic potassium carbonate also led to the facile epoxide-allylic alcohol conversion [(178)→(179)] to give LTB_4.

C. Rokach's Stereospecific Synthesis of LTB_4.—This synthesis (Scheme 31)[36] utilises 2-deoxy-D-ribose for the preparation of the C-1 to C-6 and also the C_7 to C_{20} fragments of LTB_4. For the synthesis of the larger fragment, 2-deoxyribose (180) is coupled with ethoxycarbonylmethylenetriphenylphosphorane to give the triol-ester (181), which cyclises to the *C*-glycoside (182). Tosylation of the primary-alcohol group followed by silylation gave the ether (183). Displacement of the tosyl group to give the iodo-*C*-glycoside (184) followed by chain extension with the cuprate (185) gave the C_{14} unit (186). Removal of the silyl protecting group and mesylation gave the key intermediate (187). Ring opening of the glycoside ring with sodium ethoxide gave the hydroxy-triene (188). Some *C*-glycosides with a tetrahydrofuran ring are masked diene precursors and treatment with base causes β-elimination to give an epoxide which undergoes further ring opening.[36]

The product (188) was converted into the phosphonium salt (191) by (*a*) protecting the alcohol group as the ether (189), and (*b*) converting the ester group into the alcohol (190) and then into the bromide, which was displaced with triphenylphosphine.

For the C-1 to C-6 fragment the chirality at C-3 of 2-deoxyribose was incorporated into the hydroxy-group at C-5. The intermediate (181), used previously for preparation of the C_{14} synthon, was hydrogenated and converted into the acetonide (192). Benzoylation and removal of the ketal group gave the diol (193) which was cleaved to the aldehyde (194) in the presence of lead tetra-acetate. Coupling of the C_6 fragment (194) with the C_{14} fragment (191) by a Wittig reaction gave a mixture of the $\Delta^{6,7}$ *cis*-ester (196) and its *trans*-isomer (195) which were separated by h.p.l.c. The *cis*-isomer (196) was converted into LTB_4 by ether cleavage and ester hydrolysis.

10 Inhibitors of SRS-A Activity

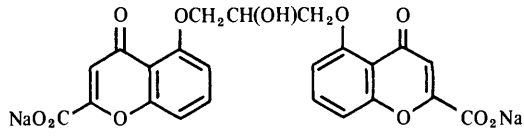
From some years prior to the elucidation of the structures of the leukotrienes, sodium chromoglycate (197), also known as Intal, has been used as an anti-allergy agent in the treatment of asthma. Chromone-2-carboxylic acids of this class are not direct end-organ antagonists of putative mediators, including SRS-A, but are believed to act primarily by inhibiting mediator-release in immediate hypersensitivity reactions.[37]

A selective antagonist of SRS-A is FPL 55712 (2), mentioned previously, and its properties have been reviewed.[37] A series of anti-allergic 4-hydroxycoumarins has been prepared by Buckle *et al.*[38] and one of the most potent is BRL 19880 (198), which not only antagonises the action of SRS-A but also acts as an inhibitor of histamine release.[37,38]

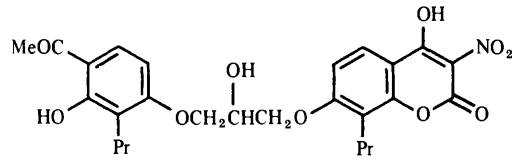
Another compound of interest is FPL 59257, the chromonepropionic acid (199), which lacks the alcoholic hydroxy-group often present in potent chromones. This compound, while not as potent as FPL 55712, is a selective antagonist of SRS-A with a longer duration of activity.[37]

Rotenone (200) the natural chromanochromanone and some related compounds have also been found to be SRS-A antagonists.[39]

With knowledge of the structure of the SRS group of compounds, it is now possible to design and prepare fatty-acid derivatives which may inhibit leukotriene biosynthesis and examples of this approach are now described.



(197)

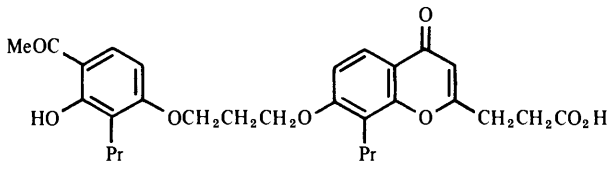


(198)

[37] P. Sheard in ref. 5*b*, p. 209.

[38] D. R. Buckle, D. J. Outred, J. W. Ross, H. Smith, R. J. Smith, B. A. Spicer, and B. C. Gasson, *J. Med. Chem.*, 1979, **22**, 158.

[39] R. J. Ashack, L. P. McCarty, R. S. Malek, F. R. Goodman, and N. P. Peet, *J. Med. Chem.*, 1980, **23**, 1022.



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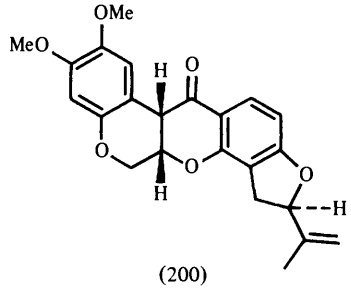


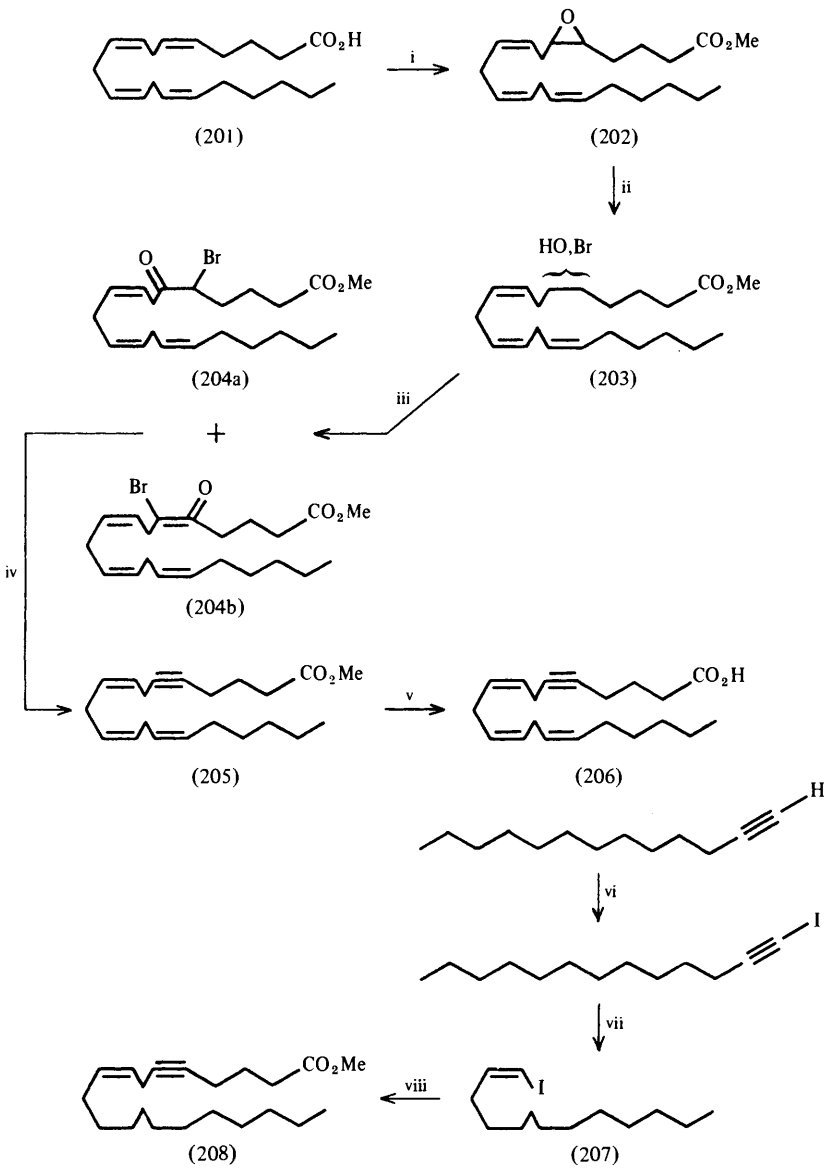
(200)

A. Synthesis of Three C_{20} Potential Inhibitors of Leukotriene Biosynthesis.— Corey *et al.* synthesized three unsaturated eicosanoic acids as possible candidates to antagonise the action of leukotriene antagonists by inhibiting their biosynthesis.[40] 5,6-Dehydroarachidonic acid (206) was synthesized from arachidonic acid (201) starting from the 5,6-epoxide of methyl arachidonate (202) which was converted into a mixture of position isomeric bromohydrins (203). Treatment of the mixture (203) with Jones' reagent gave a mixture of the position isomers of bromo-ketones (204a, b). Treatment of this mixture with 2,4-dinitrobenzenesulphonyl hydrazine afforded the methyl ester (205). Hydrolysis of the methyl ester yielded the desired 5,6-dehydroarachidonic acid (206) (Scheme 32).

To obtain the methyl ester of *cis*-8-eicosen-5-ynoic acid the following reaction procedure was used. 1-Tridecyne on reaction with iodine and morpholine gave 1-iodo-1-tridecyne which was reduced to *cis*-1-iodo-1-tridecene (207). Lithiation and treatment with cuprous iodide–dimethylsulphide complex generated the corresponding Gilman reagent which coupled to methyl 7-iodo-5-heptynoate producing the desired methyl ester (208) (Scheme 32).

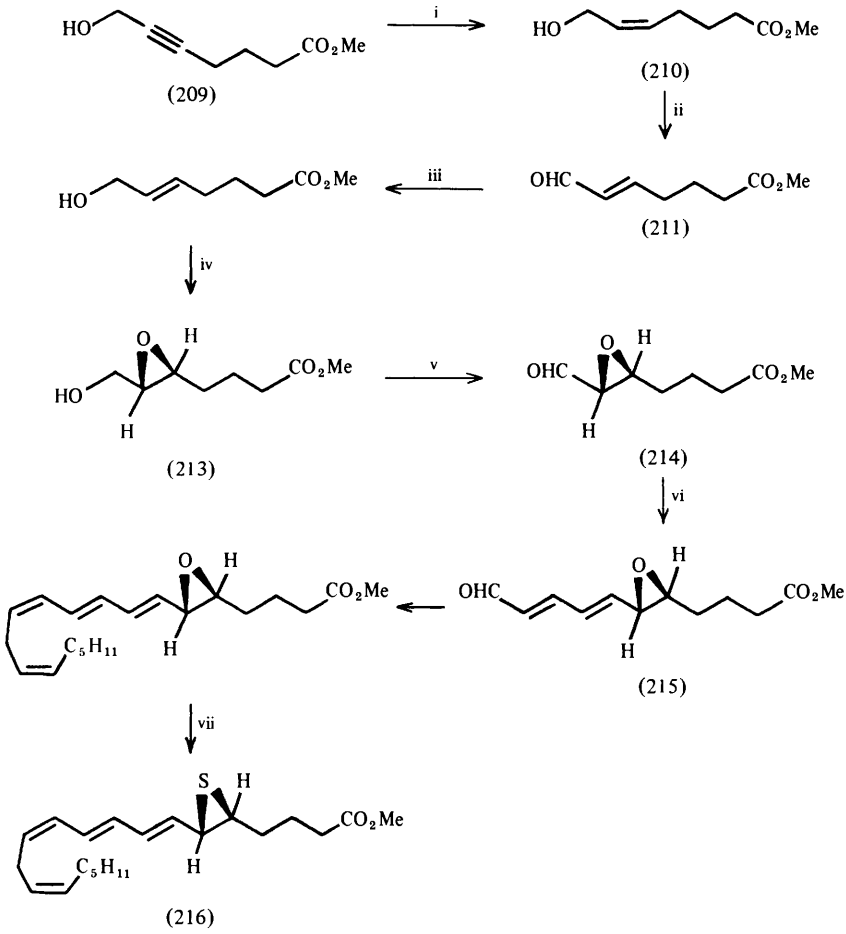
Synthesis of the racemic methyl ester of the thio-analogue of LTA_4 (216) started from reduction of methyl 7-hydroxy-5-heptynoate (209) to the *cis*-olefin (210) followed by oxidation and concurrent isomerization to the *trans*-α,β-unsaturated aldehyde (211). Reduction of the aldehyde gave the 7-hydroxy-*trans*-5-heptenoate (212), which on epoxidation afforded the epoxy-alcohol (213). Oxidation of the alcohol yielded the epoxy-aldehyde (214) which by

[40] E. J. Corey, H. Park, A. Barton, and Y. Nii, *Tetrahedron Lett.*, 1980, **21**, 4243.



Reagents: i, $KHCO_3$, potassium tri-iodide; LiOH, THF–H_2O; CH_2N_2; ii, solid solution KBr in HOAc–H_2O–THF; iii, Jones' reagent; iv, 2,4-dinitrobenzenesulphonylhydrazine; v, LiOH, THF–H_2O; vi, I_2, morpholine in benzene; vii, potassium azodicarboxylate, HOAc, MeOH–pyridine; viii, 2 equiv. t-butyl-lithium; cuprous iodide–dimethyl sulphide; methyl 7-iodo-5-heptynoate

Scheme 32 *Synthesis of* cis-*8-eicosen-5-ynoic acid*



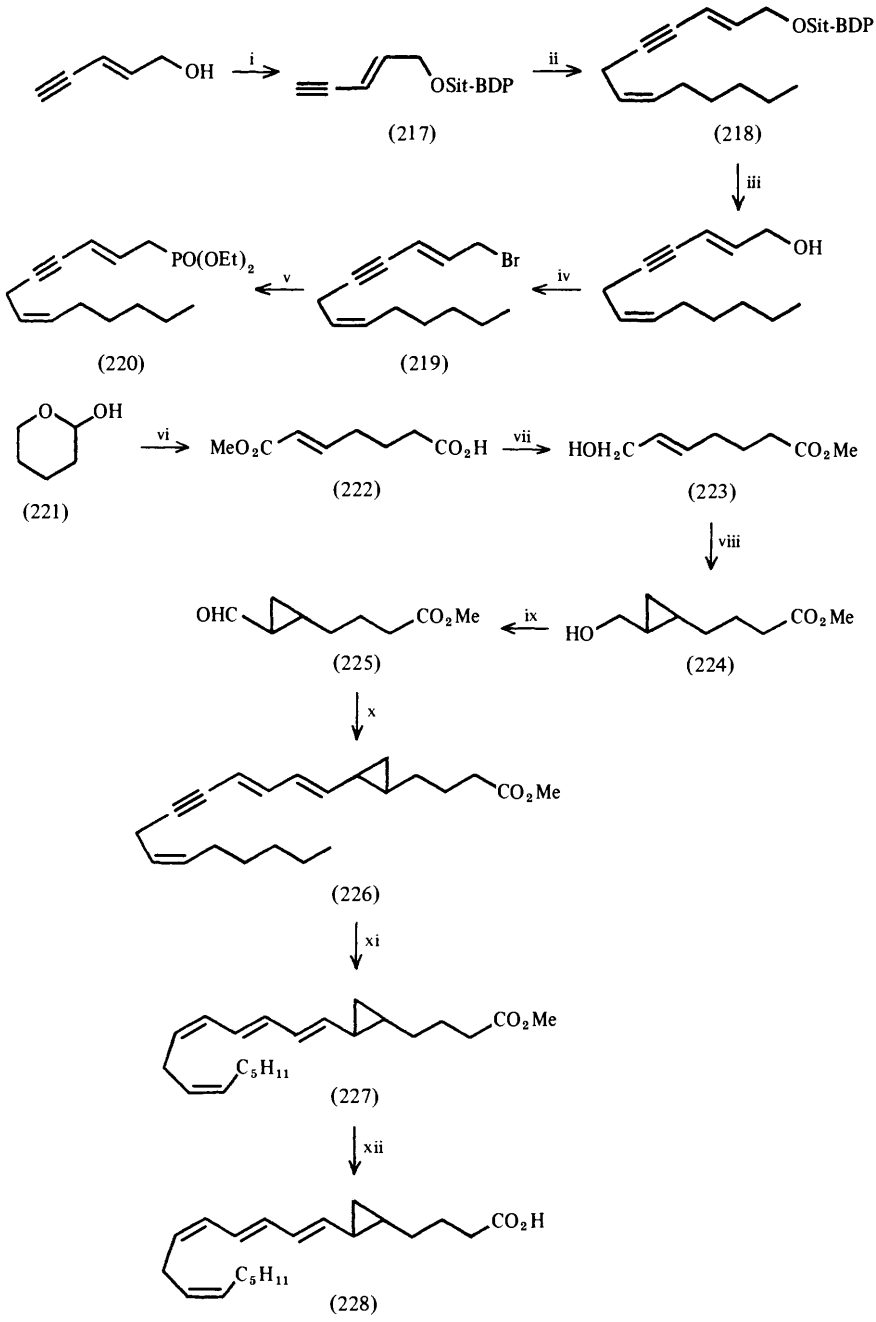
Reagents: i, H_2 Lindlar catalyst; ii, pyridinium chlorochromate; iii, $NaBH_4$; iv, MCPBA; v, Py_2–CrO_3; vi, triphenyl[(*Z*)-non-3-en-1-yl]phosphonium iodide, *n*-BuLi; vii, 0.05M sodium thiocyanate.

Scheme 33 *Synthesis of the thio-analogue of* (±) *LTA*$_4$

Wittig reactions was chain-extended to the dienal (215) and then to the methyl ester of (±)-LTA_4. Treatment of (±)-LTA_4 with sodium thiocyanate gave the methyl ester of the racemic thiirane (216) (Scheme 33).

Reagents: i, Bu^tPh_2SiCl, imidazole, DMF; ii, coupled to (*E*)-1-bromo-oct-2-ene, n-BuLi; iii, HF-pyridine; iv, CBr_4–PPh_3; v, $(EtO)_3PO$; vi, excess methyl(triphenylphosphoranylidene)acetate; Jones' oxidation; vii, di-isobutyl aluminium hydride; CH_2N_2; viii, CH_2I_2–Zn–CuCl; ix, CrO_3–pyridine; x, (220), LDA; xi, H_2, Lindlar catalyst; xii, LiOH

Scheme 34 *Nicolaou's synthesis of 5,6-methanoleukotriene* A_4


OH
i
OSit-BDP
ii
OSit-BDP
(217)
(218)
iii
OH
PO(OEt)2
v
Br
iv
(220)
(219)
O
OH
vi
MeO2C
CO2H
vii
HOH2C
CO2Me
(221)
(222)
(223)
viii
OHC
CO2Me
ix
HO
CO2Me
(225)
(224)
x
CO2Me
(226)
xi
CO2Me
C5H11
(227)
xii
CO2H
C5H11
(228)

B. Synthesis of 5,6-Methanoleukotriene A_4, A Selective Inhibitor of Biosynthesis.— Nicolaou *et al.*[41] synthesized a stable analogue of LTA_4, 5,6-methano-leukotriene A_4 (Scheme 34), which after preliminary studies appears to be potent and selective inhibitor of leukotriene biosynthesis.[41]

For the preparation of a C_{13} synthon, pent-2-en-4-yn-1-ol was protected as its t-butyldiphenylsilyl ether (217) and coupled to (*E*)-1-bromo-oct-2-ene to afford product (218). Removal of the silyl ether followed by treatment with CBr_4–PPh_3 led to the bromide (219) which was converted into the required phosphonate (220) by exposure to an excess of triethylphosphite in acetonitrile. The second component required to assemble the leukotriene skeleton was constructed from δ-valerolactone. δ-Valerolactol (221) was treated with an excess of methyl(triphenylphosphoranylidene) acetate to afford, after Jones' oxidation, the α,β-unsaturated methylcarbonyloxy-carboxylic acid (222). Treatment of this mono-ester (222) with di-isobutylaluminium hydride followed by esterification with diazomethane gave the allylic alcohol (223), which on cyclopropanation in the presence of methylene iodide, zinc, and cuprous chloride afforded (224). Oxidation of (224) gave aldehyde (225) which was required as the second component. Generation and stereocontrolled coupling of the lithium salt of the phosphonate (220) with the aldehyde (225) produced the compound (226). Selective hydrogenation in the presence of Lindlar catalyst led to the methyl ester (227). Finally, hydrolysis gave the required 5,6-methanoleukotriene A_4 (228).

11 Concluding Comments

The number of papers that have been published, mostly in preliminary form, on the synthesis of leukotrienes since their structures were announced in 1979, emphasises the importance of this field of research. The contributions from the laboratory of Professor E. J. Corey at Harvard University are outstanding, not only for the asymmetric syntheses of molecules that are often unstable, but also for the new methods that have been devised for the purpose. We may confidently expect further progress in the syntheses of leukotrienes in order to make the compounds more readily available for bio-assay, as well as progress in the design and preparation of analogues which may be of value as anti-allergy drugs.

One of us (J.A.) thanks the SERC for the award of a studentship.

[41] K. C. Nicolaou, N. A. Petasis, and S. P. Seitz, *J. Chem. Soc., Chem. Commun.*, 1981, 1195.