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Leukotrienes—Natural Biologically Active Metabolites of Polyunsaturated Acids

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The review deals with the biosynthesis, chemical synthesis, and biological role of leukotrienes—low-molecular-weight bioregulators belonging to the class of eicosanoids—and discusses the prospects for their further investigation and practical application.
The bibliography includes 223 references.

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I. INTRODUCTION

Polyunsaturated aliphatic acids occupy an important place among natural biologically active compounds. The C_{20} polyenoic acids, namely 5Z, 8Z, 11Z-eicosatrienoic, 8Z, 11Z, 14Z-eicosatrienoic (dihomo-γ-linolenic), 5Z, 8Z, 11Z, 14Z-eicosatetraenoic (arachidonic), and 5Z, 8Z, 11Z, 14Z, 17Z-eicosapentaenoic (timnodonic), synthesised in the living organism from polyenoic acids with a smaller number of carbon atoms such as linoleic, linolenic, etc., are especially important. It has been shown during the last twenty years that polyunsaturated acids are not only structural components of cell membrane lipids, lipoprotein complexes in the brain and spinal cord, the heart, liver, and other organs, but are also precursors of a whole series of their biologically active metabolites—prostaglandins (PG), thromboxanes (TX), leukotrienes (LT), and others, combined under the common name eicosanoids.

The formation of these metabolites in the living cell is based on the enzymic oxidation of polyenoic acids with subsequent conversion into the final compounds. Two pathways leading to the enzymic oxidative transformation of polyenoic acids have now been extensively investigated, especially in relation to arachidonic acid: the cyclo-oxygenase pathway, in which cyclic metabolites of polyenoic acids (prostaglandins and thromboxanes) are formed under the influence of polyenzyme complexes, and the lipoxygenase pathway involving the operation of lipoxygenases and leading to the formation of non-cyclic hydroxyeicosapolyenoic acids and leukotrienes (Scheme 1).[1-9]

Prostaglandins have already been fairly thoroughly investigated and are known as intracellular bioregulators of many physiologically important processes, possessing a wide spectrum of activity on the cardiovascular, respiratory, reproductive, and other systems.[1,2]

Considerable advances have been made in the determination of the structure and in the investigation of the functions of thromboxanes, which are closely related to blood generation processes. Prostacyclin, which is a metabolite of arachidonic acid, has a relaxing effect on the smooth musculature of blood vessels and prevents the clotting processes.[1,2]

Among the acyclic eicosapolyenoic metabolites of arachidonic acid, leukotrienes, whose name was taken from the original source where they were discovered (leukocytes), have attracted special attention. In 1979 the structures of a series of compounds of this class, which are lipid-peptide derivatives exhibiting a high biological activity, were first elucidated. A relation was demonstrated between leukotrienes and the immune and inflammatory processes in the organism, namely its hypersensitivity (various allergic reactions). For this reason, the synthesis and study of the structures and biological activities of leukotrienes, their analogues, and the antagonists and inhibitors of their biosynthesis[2] is of great theoreticai and practical interest not only for the recognition of the pathological phenomena in the organism due to the action of leukotrienes, but also for pharmacological purposes, involving the search for effective anti-inflammatory and antiallergic medicinal drugs.[3-9]

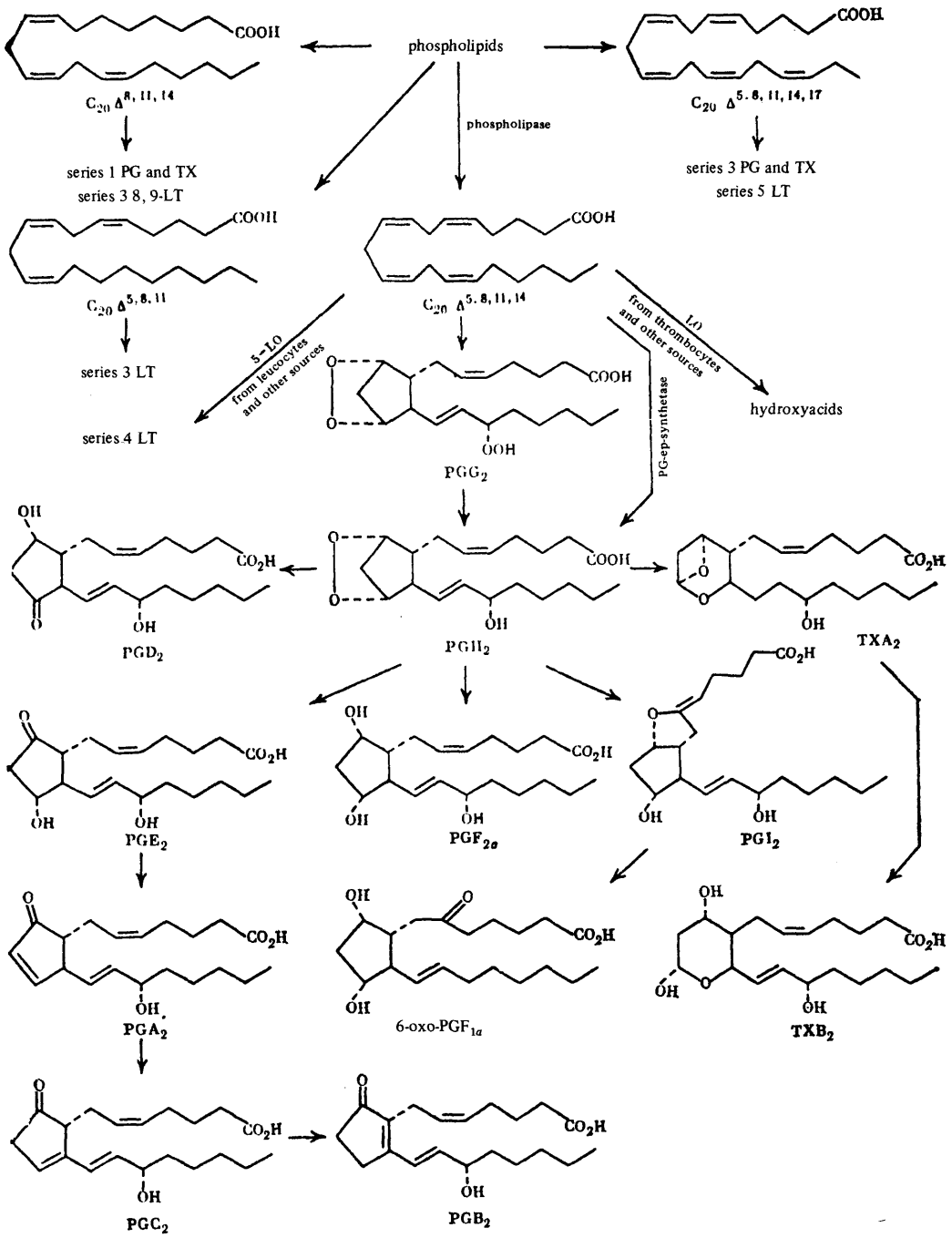
The enormous interest aroused among specialists in various branches of knowledge by the new class of biologically active compounds (leukotrienes) has made it extremely timely to write a review giving a systematic account of data concerning leukotrienes available at the present time.

1. The History of the Discovery of Leukotrienes

The lipoxygenase pathway leading to the oxidation of polyenoic acids in leukocytes leads to the formation of leukotrienes (LT)—a new class of biologically active natural metabolites[1-9] (Scheme 2). However, the elucidation of the metabolic pathway leading to the transformation of arachidonic acid into leukotrienes† was preceded by a long history of the discovery and determination of their structure covering a period of 40–80 years.[7,8]

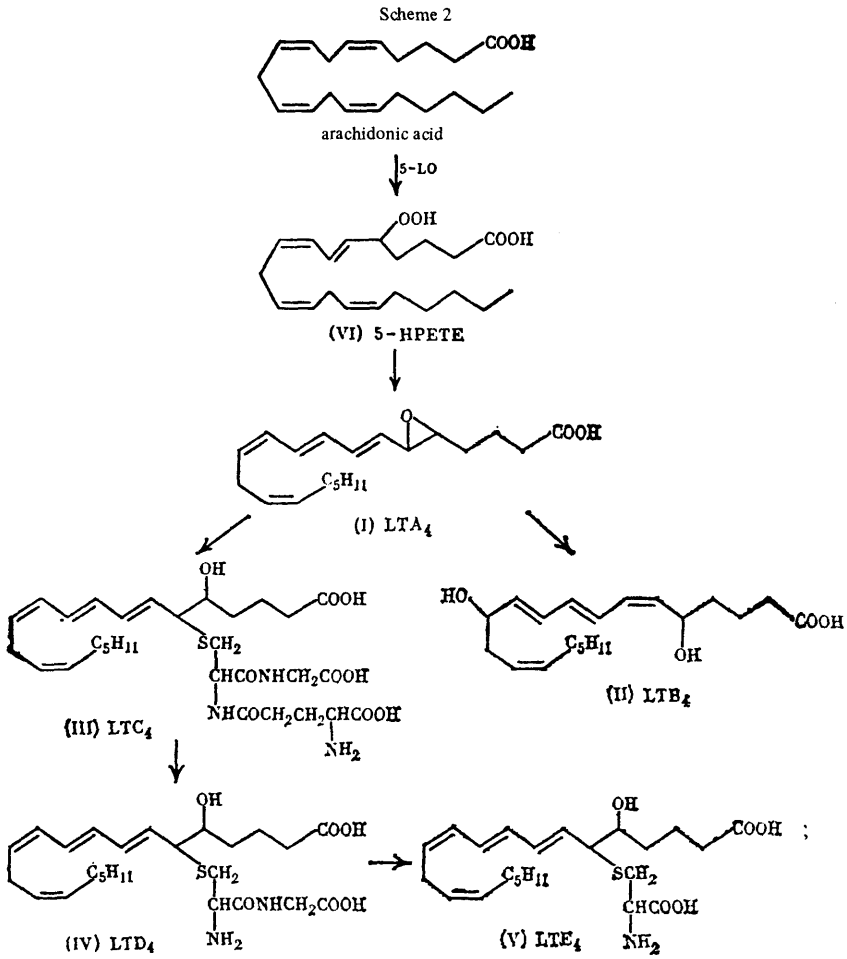
†Leukocytes, the white blood corpuscles, are colourless cells having a nucleus and capable of passing through the walls of blood vessels. They contain proteolytic enzymes and can capture and digest foreign bodies (phagocytosis), performing protective functions in the organism. In terms of their structure, we distinghish granular leukocytes or granulocytes (neutrophils, eosinophils, and basophils) and non-granular leukocytes or agranulocytes (lymphocytes and monocytes).

Scheme 1



Notation: LO = lipoxygenase; PG = ep-synthetase = prostaglandin endoperoxide synthetase.

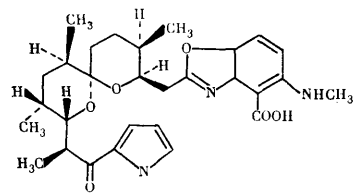
Scheme 2



5-HPETE=Hydroperoxyeicosatetraenoic acid.

A substance isolated from guinea-pig lung tissue on treatment of the latter with cobra venom was described in 1938.[10] A related substance, isolated from the lungs in anaphylactic shock was obtained later.[11]# As a result of its ability to cause a slow contraction of the smooth muscles, this substance has been called the "slow reacting substance of anaphylaxis" (SRS-A)§ to distinguish it from the "slow reacting substance" (SRS) obtained on non-immunological stimulation.

During the ten years following 1950 other sources from which SRS could be isolated were found—various tissues and cell preparations such as the lungs of several species of animals,[13] including human lungs affected by bronchial asthma, cats' paws,[14] the isolated mastocytoma cells¶ from the rat,[15] human leukocytes,[16] and the peritoneal fluid from rats.[17] The possibility of stimulating the isolation of SRS by means of the A23187 calcium ionophore[18] and L-cysteine at a high concentration[19] was demonstrated subsequently.



A23187

#Anaphylaxis (from the Greek ana = against and phylaxis = protection) is a special state with enhanced sensitivity—the hypersensitivity of the organism to the parenteral reintroduction of a foreign non-poisonous protein (for example the blood serum of another animal). The first introduction of a foreign protein (antigen) does not have a pathological effect on the organism but antibodies specific to the given protein introduced into the organism are generated in the latter. If the same protein is reintroduced parenterally after 3 to 4 weeks (when the state of enhanced sensitivity to the given protein has been established, it can persist throughout the life of the organism), severe pathological disorders take place in the organism—anaphylytic shock, which is manifested by a drop of blood pressure, a disorder in cardiac activity, etc. Antigens are substances with characteristic chemical groups which are recognised by the organism as foreign. In response to their introduction into the organism, glycoprotein substances, called antibodies, are generated. They are capable of a specific reaction with antigens.

§SRS-A = slow reacting substance-A (A = anaphylaxis).

¶The mastocytoma cells are tumour mast cells in the connective tissue of vessels characterised by an abundance of basophilic granules.

All the SRS described exhibit an analogous type of biological activity, namely a capacity to cause a strong and prolonged contraction of various types of smooth muscle (the guinea-pig trachaea and human bronchi).[7,8]

During the same years, a growing amount of information confirmed the important functions of the SRS in the enhanced sensitivity reactions of the organism. During the next 20 years many research groups attempted to determine the chemical structure of SRS-A, but major successes were not achieved.

Very promising publications about SRS-A appeared in 1960–1970. On the basis of the results of hydrogenation and oxygenation experiments and also physicochemical properties, it was shown that the SRS is an unsaturated aliphatic acid.[20] A number of investigations[18,21–26] confirmed that arachidonic acid is the initial compound in the synthesis of SRS-A. It has been shown[27] that arachidonic acid stimulates the secretion of SRS from basophilic† leukaemic# rat cells and that 5,8,11,14-eicosatetraynoic acid (an inhibitor of the cyclo-oxygenase component of prostaglandin synthesase as well as lipoxygenase) inhibits the secretion of mediators. It is also extremely important that arachidonic acid, labelled with ^{14}C and ^{3}H, has been incorporated in SRS-A. Consequently it has been shown that SRS-A is a hitherto undescribed product of the metabolism of arachidonic acid.[24]

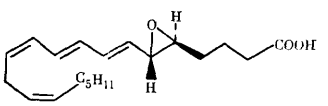
The UV spectrum of the SRS had the characteristic λ_{max} = 280 nm, which corresponds to the presence of a ternary conjugated bond system of a non-aromatic chromopore.[28,29] The positions of the double bonds were determined in two ways. Firstly, by the reductive ozonolysis of the SRS biosynthesised from tritium-labelled arachidonic acid with formation of [^{3}H]-1-hexanol, which confirms the presence of the Δ^{14}-double bond of the precursor.[30] Secondly, a simple enzymic method involving the use of soya bean lipoxygenase was applied.[31] This enzyme is known to be specific to oxidation at the C(6) atom in aliphatic acids containing the 1Z, 4Z-diene system, characteristic of linoleic and arachidonic acids, and the accompanying isomerisation of the alkene bond.[32]

The presence of sulphur in the SRS molecules was first mentioned in connection with the study of the mass spectra[33] and was later confirmed by the incoporation of radioactive sulphur on treatment of sensitive guinea-pig lungs with methionine or radioactive sodium sulphate.[34] The fact[35] that cysteine stimulates the formation of the SRS shows that SRS and SRS-A are derivatives of this sulphur-containing aminoacid.[36] The deactivation of SRS-A as a result of treatment with cyanogen bromide confirms the presence of the sulphide bond.[37] The loss of biological activity as a result of brief treatment of SRS-A with acylating and esterifying agents demonstrated the presence of the functional amino- and carboxy-groups.[37]

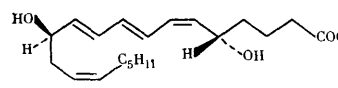
Simultaneously with the study of the structure and role of various slow reacting substances, other groups of investigators discovered that arachidonic acid is metabolised in peritoneal (abdominal) rabbit polymorphonuclear leukocytes.[30–40] Thus, during the last decade there has been a considerable increase in the amount of information available about the biochemical functions of arachidonic acid, which was also assisted by the discovery of prostaglandin endoperoxides, prostaglandins, thromboxanes, prostacyclin,[1–3] and later leukotrienes.[4,8] It was found that the formation of leukotrienes in the living organism is closely related to the appearance of hypersensitive reactions accompanied, as shown previously,[4] by the formation of SRS. This finding as well as structural similarity justified the assignment of SRS to the family of leukotrienes. This was greatly assisted by the major advances in the purification of the SRS, mainly as a result of the application of high-pressure liquid chromatography (HPLC). Morris et al.[28] purified very thoroughly a SRS-A specimen from the guinea-pig lung in a state of anaphylaxis and obtained its UV spectrum, demonstrating the presence of the characteristic absorption bands of leukotrienes. Thus much time and effort by the investigators in many scientific laboratories were needed before Samuelsson, Borgeat, Hammarström, and Murphy[4] reported at the International Congress on Prostaglandins in Washington the completion of studies on the characterisation of the leukotrienes isolated from mouse mastocytoma (tumour) cells and rabbit polymorphonuclear leukocytes (granular). It was also shown that SRS is a set of several leukotrienes, each of which is a C_{20} polyenoic acid with a characteristic system of conjugated double bonds and substituents in various positions in the molecule, among which aminoacids and di- and tri-peptides were found in addition to the epoxy- and hydroxy-groups.[4–10]

2. The Nomenclature and Terminology of Leukotrienes

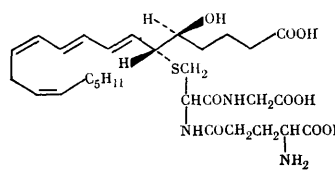
This new class of biologically active natural products was first described in a series of communications[4–8] and represents a set of oxygen-containing aliphatic polyenoic C_{20} acids with various substituents. The compounds were called leukotrienes (LT), since they were first discovered in leukocytes and their structure is characterised by a system of three conjugated double bonds—a conjugated "triene". Owing to the structural differences between the substituents at the 5- and 12-carbon atoms, leukotrienes are divided into groups A, B, C, D, and E. Since leukotrienes are metabolites of 5Z, 8Z, 11Z-eicosatrienoic, 5Z, 8Z, 11Z, 14Z-eicosatetraenoic (arachidonic), and 5Z, 8Z, 11Z, 14Z, 17Z-eicosapentaenoic acids, a digital index (indication of the series) was introduced into the designation of the LT: 3, 4, and 5 respectively, defining the number of double bonds in the leukotriene molecule. The nomenclature and terminology are illustrated in relation to leukotrienes derived from arachidonic acid, since these have been most thoroughly investigated:



5(*S*), 6(*R*)-epoxy-7*E*, 9*E*, 11*Z*, 14*Z*-eicosatetraenoic acid (I)



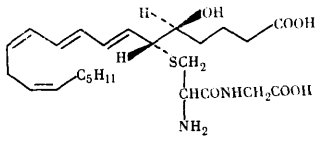
5(*S*), 12(*R*)-dihydroxy-6*Z*, 14*Z*, 8*E*, 10*E*-eicosatetraenoic acid (II)



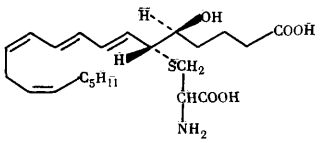
6(*R*)-*S*-glutathionyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*-eicosatetraenoic acid (III)

†Basophilic cells are a variety of granulocytes (granular leukocytes).

#Leukaemic cells are growing immature forms of leukocytes characteristic of malignant diseases of the blood generation system combined under the common name leukaemia.

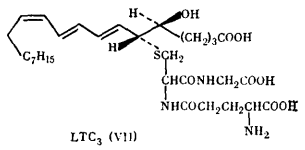


6(*R*)-*S*-cysteinylglycyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*-eicosatetraenoic acid (IV)

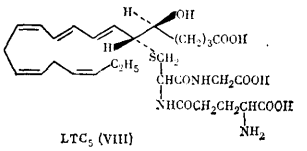


6(*R*)-*S*-cysteinyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*-eicosatetraenoic acid (V)

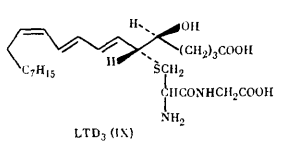
The following metabolites of 5,8,11- and 5,8,11,14,17-eicosapolyenoic acids are known at the present time:[41-44] LTC_3—6(*R*)-*S*-glutathionyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*-eicosatrienoic acid (VII); LTC_5—6(*R*)-*S*-glutathionyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*, 17*Z*-eicosapentaenoic acid (VIII); LTD_3—6(*R*)-*S*-cysteinylglycyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*-eicosatrienoic acid (IX); LTD_5—6(*R*)-*S*-cysteinylglycyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*, 17*Z*-eicosapentaenoic acid (X); LTE_3—6(*R*)-*S*-cysteinyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*-eicosatrienoic acid (XI); LTE_5—6(*R*)-*S*-cysteinyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*, 17*Z*-eicosapentaenoic acid (XII):



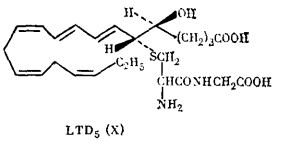
LTC_3 (VII)



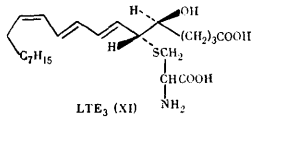
LTC_5 (VIII)



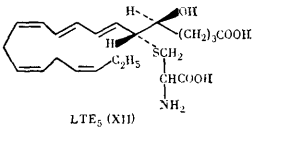
LTD_3 (IX)



LTD_5 (X)



LTE_3 (XI)



LTE_5 (XII)

In order to understand the above literature information, it is necessary to note the following points:[8,45] (1) The first component of SRS, characterised as a leukotriene has been the cysteinyl derivative of 5-hydroxy-7,9,11,14-eicosatetraenoic acid designated as LTC. At the present time this compound is referred to as LTE_4. (2) The initial studies on the purification of leukotrienes led to the preparation of two isomers relative to the C(11) atom involved in the double bond in the glutathione derivative of 5-hydroxy-7,9,11,14-eicosatetraenoic acid. The principal component was designated by LTC-1 [46] and the minor component by LTC-2. These compounds are referred to nowadays as LTC_4 and 11*E*-LTC_4 respectively.[45]

In 1983 studies were published demonstrating the conversion of 8*Z*, 11*Z*, 14*Z*-eicosatrienoic (dihomo-γ-linolenic) acid on incubation with A23187 ionophore, which stimulated the mastocytoma cells, into series 3 leukotrienes.[47,48] This led to the isolation of 8,9-LTC_3, exhibiting a spasmogenic activity comparable to that of LTC_3.[49] It has been suggested that the stoichiometry of 8,9-LTC_3 is analogous to that of the metabolites of polyenoic acids when the latter undergo the lipoxygenase oxidation at C(5).

II. BIOSYNTHESIS AND DETERMINATION OF THE STRUCTURE OF LEUKOTRIENES

The metabolism of arachidonic acid under the influence of lipoxygenase was observed in peritoneal rabbit polymorphonuclear leukocytes. Borgeat et al.[38] incubated arachidonic acid with rabbit leukocytes of the above type and isolated 5(*S*)-hydroxy-6,8,11,14-eicosatetraenoic acid (5-HETE) (XIII) (Scheme 3). Similarly, 8*Z*, 11*Z*, 14*Z*-eicosatetraenoic (dihomo-γ-linolenic) acid is converted into 8(*S*)-hydroxy-9,11,14-eicosatrienoic acid.[48] Another arachidonic acid metabolite, whose structure was determined as 5(*S*),12(*R*)-dihydroxy-6,8,10,14-eicosatetraenoic acid, referred to subsequently as leukotriene B_4, was later isolated from rabbit polymorphonuclear leukocytes.[8,50] This was the first arachidonic acid metabilite isolated which contained three conjugated double bonds.[39]

The presence and positions of the two hydroxy-groups at C(5) and C(12) in compound (II) as well as the four double bonds at the 6-, 8-, 10-, and 14-carbon atoms were demonstrated by gas chromatography and mass-spectrometric analysis for a series of derivatives of compound (II).[39,51]

In the study of the metabolism of arachidonic acid in mammalian polymorphonuclear leukocytes,[39,52] the structures of four minor arachidonic acid metabolites were described in addition to LTB_4 (Scheme 3). These compounds were 5,6-dihydroxy-7,9,11,14-eicosatetraenoic acids, epimeric at C(6) (XIV, a and b), and two geometrical isomers of leukotriene B_4—epimeric at C(12) (XIV, C and D).[52] Although these four compounds probably do not themselves exhibit biological activity, their importance in subsequent studies of the mechanism of the formation of leukotrienes was nevertheless demonstrated.

Experiments showed[40] that, when mammalian polymorphonuclear leukocytes with polymorphic nuclei are incubated with arachidonic acid, the unstable compound (I) is formed, reacting readily with weak nucleophiles—water, ethanol, methanol, etc. Further studies demonstrated that this compound is very labile at low pH but is much more stable in an alkaline medium; its half-life is short (3 min, pH 7.4, T = 37 °C). Other experiments permitted the conclusion that LTB_4 is formed in the enzymic hydrolysis of compound (I), while four other dihydroxy acids, namely (XIV, a and b) and (XIV, c and d), are formed from the same compound but as a result of non-enzymic hydrolysis[8,53] via the corresponding intermediates (Scheme 3).

These data suggested that the unstable intermediate 5,6-epoxy-7,9,11,14-eicosatetraenoic acid, subsequently called leukotriene A_4(LTA_4), is formed from 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid (5-HPETE), which is produced by the lipoxygenase oxidation of arachidonic acid.[40]

Corey et al.[54] published a method of chemical synthesis of 5(*S*)-hydroperoxy-6,11,11,14-eicosatetraenoic acid and of its enzymic synthesis by the incubation of arachidonic acid with lipoxygenase isolated from the potato.

The epoxide (I) was isolated from human polymorphonuclear leukocytes.[55] It has also been shown that, under the influence of neutrophils,§ compound (I) (LTA_4) is capable of being transformed into LTB_4.[53]

The geometry of the double bonds and the configuration of the epoxy-group in LTA_4 have been confirmed by specific chemical synthesis of this compound and by the study of the products of its degradation.[56,57] The discovery of the leukotrienes D_4 and C_4 was associated with the efforts made

§ Neutrophils are a variety of granulocytes (granular leukocytes) (see above).

to establish the structure of the slow reacting substance of anaphylaxis (SRS-A).[3-8] Simultaneously with these investigations by Borgeat and Samuelsson,[30,38,39] some other investigators joined the research into the slow reacting substance. Thus a highly pure SRS-A specimen was obtained by the HELC method from the lung of the guinea-pig in a state of anaphylaxis whose UV spectrum showed clearly the characteristic features of the leukotrienes.[28] Many experimenters have pointed out the special role of arachidonic acid in the synthesis of SRS-A.[18-24,58-60]

It has been shown that many thiols and especially cysteine stimulate the formation of SRS and SRS-A.[30,36] These studies have confirmed that SRS and SRS-A may be suphonated compounds and thus can behave as conjugate compounds in relation to cysteine and leukotrienes A_4, which readily react with nucleophiles: thiols and alcohols. In their studies on this hypothesis, Murphy et al.[30] obtained SRS from mouse mastocytoma cells by incubating the latter with arachidonic acid, L-cysteine, and the A23187 ionophore.

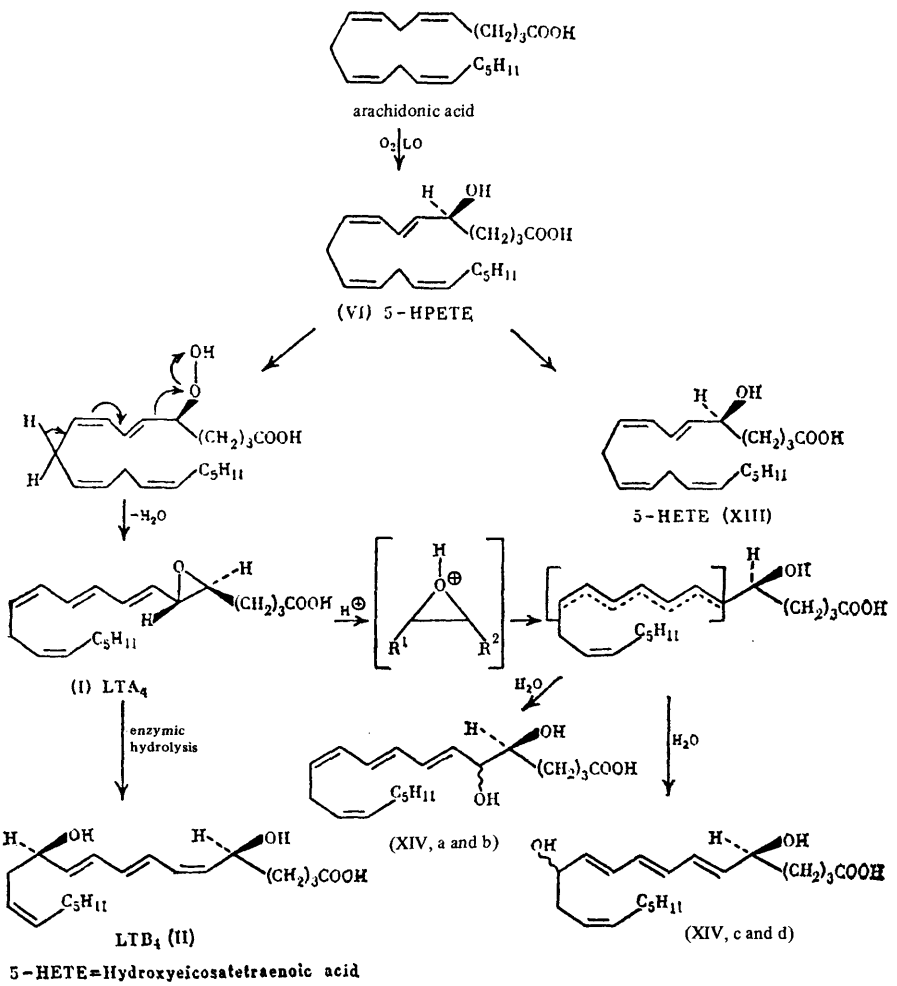
Chemical analyses of the SRS specimen and also of the product of its degradation led to the conclusion that this compound is a derivative of leukotriene A_4.

Subsequently the substituent at C(6) in the SRS isolated from mastocytoma mouse cells was identified[61,62] as glutathione (γ-glutamylcysteinylglycine) and the structure and stereochemistry of the molecule were established by comparing the physicochemical and biological properties of the SRS specimens with a synthetic preparation of known structure.[57] Thus the SRS from the mouse mastocytoma cells was identifed for the first time as 6(*R*)-*S*-glutathionyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*-eicosatetraenoic acid, which was called leukotriene C_4 (Scheme 4).

The role of LTA_4 as an intermediate in the metabolism of arachidonic acid has been confirmed by its conversion into LTC_4 both by mouse mastocytoma cells and by human polymorphonuclear leukocytes with polymorphic nuclei.[63] However, alternative structures of LTC_4 have also been proposed. The possibility of the presence in LTC_4 of the 5-hydroperoxy- or peroxyester group has been indicated.[64] Japanese investigators concluded in 1980 that the aminoacid chain is linked to C(6) in LTC_4 via a sulpho-group and assumed that this linkage is preferable.[65] The uncertainty concerning the structure of LTC_4 was eliminated by the study of the mass spectra and also by chemical synthesis, which confirmed that the natural LTC_4 is not a sulphone[66-68] but contains the sulphide bond at C(6).

In 1980 two groups of investigators[69-71] published data concerning the determination of the structure of the SRS

Scheme 3



from basophilic leukaemic cells in the rate, which was identified as 6(*R*)-cysteinylglycyl-5(*S*)-hydroxy-7,9,11,14-eicosatetraenoic acid, called LTD_4.

The structure of the SRS from basophilic laukaemic cells of the rat has also been determined by Orning et al.[71], who showed that LTD_4 can be obtained by treating LTC_4 with γ-glutamyl transpeptidase. This finding shows that LTC_4 is an intermediate in the biosynthesis of LTD_4 and justifies the assumption that the stereochemistry of the LTD_4 molecule is identical with that of LTC_4.[71]

It has been shown[70,72] that the SRS-A liberated when sensitive guinea-pig lungs were acted upon immunologically was identical with the SRS secreted by basophilic laukaemic cells of the rat (RBL-I) and was identified as LTD_4.[73] The 6-cysteinyl derivative of LTA_4 has been found in the SRS-A isolated from peritoneal rat cells.[74] The chemical structure and stereochemistry of this compound have been confirmed by chemical synthesis,[75] which showed it to be 6(*R*)-cysteinyl-5(*S*)-hydroxy-7*E*, 9*E*, 11*Z*, 14*Z*-eicosatetraenoic acid, which has been referred to as LTE_4.

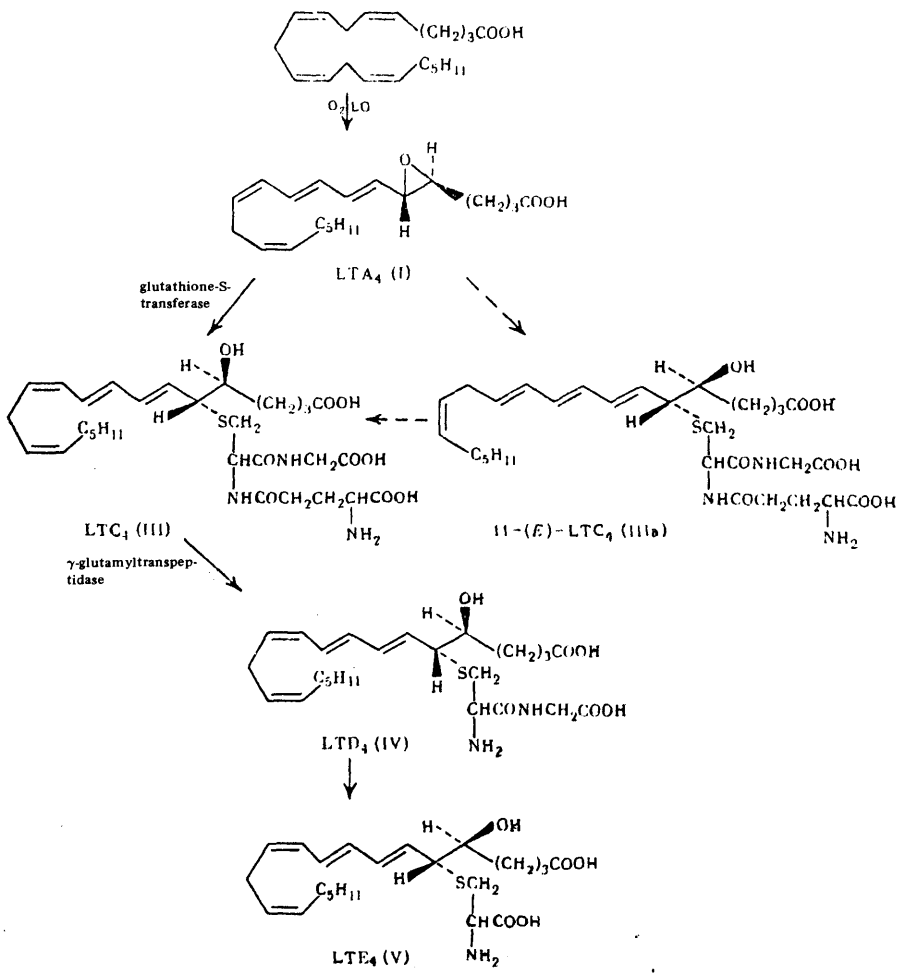
The conversion of LTA_4 into LTC_4, LTD_4, and LTE_4 has been frequently confirmed by experiment.[76-80] The bioconversion of LTC_4 into LTD_4 has also been observed[63] as the enzyme-catalysed removal of the γ-glutamyl residue from LTC_4 in the biosynthesis of LTD_4.[71] LTE_4 has been obtained from LTD_4 using the aminopeptidase component of a specific arylsulphatase.[76]

Since leukotrienes are transformed in the $LTC_4 \rightarrow LTD_4 \rightarrow LTE_4$ metabolic cascade, it is not surprising that the composition of any SRS depends on the source, material, and methods used in its isolation. It has been suggested that the term leukotriene be used for an individual compound and the term SRS be applied to the description of material obtained biologically in which the relative amounts of the leukotrienes present are unknown.

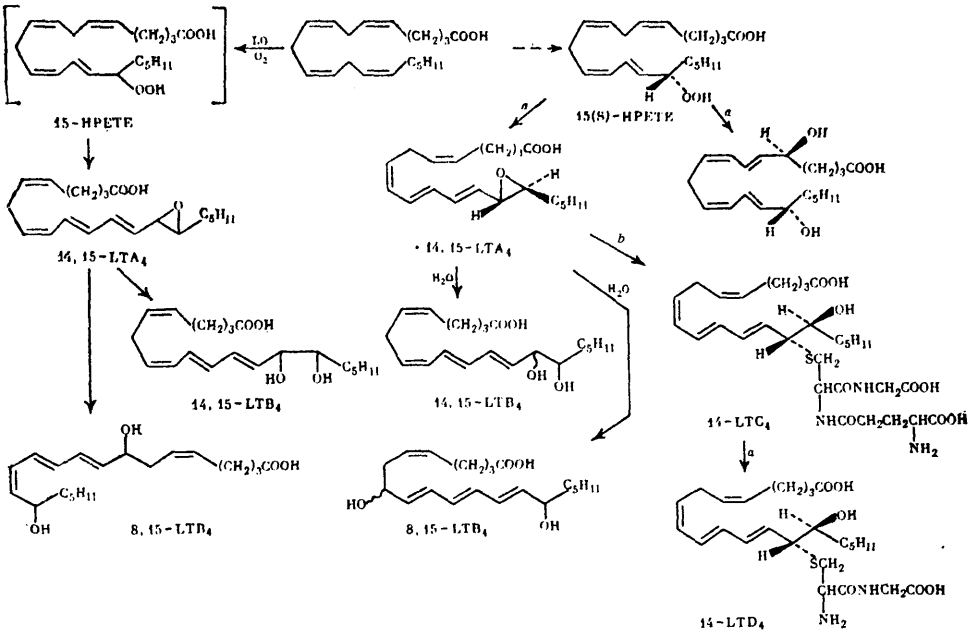
The products obtained from 5-HPETE derived from arachidonic acid are not all confined to leukotrienes (Scheme I). Incubation of arachidonic acid with human leukocytes gives gise to a whole series of metabolites[81-86] which are positional isomers of natural leukotrienes (Scheme 5). Incubation of arachidonic acid with cytochrome P-450 [87] and with the fluid from adrenal cortex[88] leads to product of its oxidation at C(9) and at C(9) and C(15) respectively, which exhibit a high biological activity and are of great interest.[89]

Leukotrienes derives from 4*Z*, 8*Z*, 11*Z*-eicosatrienoic acid and 5*Z*, 8*Z*, 11*Z*, 14*Z*, 17*Z*-eicosapentaenoic acid have also been described in the literature.[41-45] Data have been published concerning the 8,9-LTC_3, whose biosynthesis has been achieved by incubating 8*Z*, 11*Z*, 14*Z*-eicosatrienoic (dihomo-γ-linolenic) acid.[47,48]

Scheme 4



Scheme 5



(a) metabolism in human leukocytes;
(b) metabolism in basophilic leukaemic rat cells.

III. CHEMICAL SYNTHESIS OF LEUKOTRIENES

The first total synthesis of leukotriene A_4 was carried out by Corey and published in 1979.[56,90] The syntheses of virtually all the known leukotrienes, their isomers, and their analogues, including isotopically labelled compounds, have now been achieved.

The synthetic studies have been concerned mainly with series 4 leukotrienes (LTA_4, LTC_4, LTD_4, LTE_4, LTF_4, and LTB_4), i.e. leukotrienes whose precursor is arachidonic acid.

The synthesis of the leukotrienes which have been developed are based on the Wittig reaction, whereby one can condense the key fragments in the synthesis—the "carboxyl-containing" fragment from the C(1) atom in the leukotriene molecule and the "hydrocarbon" fragment ranging up to the C(20) atom. The length of the hydrocarbon chain, the degree of unsaturation, and the functional substituents at the 5- and 6-carbon atoms can be varied in each of these fragments for LTA_4, LTC_4, LTD_4, etc. and at C(12) for LTB_4.

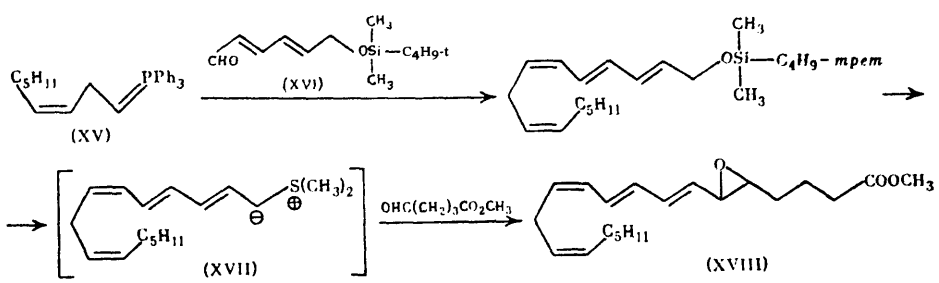
1. The Synthesis of Leukotriene A_4, Its Isomers, and Its Analogues

The earliest of the known syntheses is that of (±)-LTA_4 [56,90,91] involving the Wittig interaction of the monoene fragment (XV) and the diene fragment (XVI) with susequent addition of the hydrocarbon chain in the sulphonium ylide (XVII) and the introduction of the epoxy- and carboxy-groups (Scheme 6).

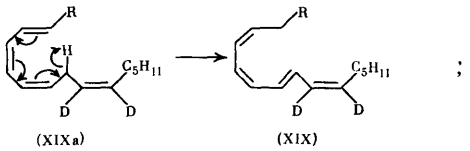
The methyl ester of LTA_4 (XVIII) has been obtained in the form of a 1:1 mixture of the *cis*-epoxide and the natural *trans*-epoxide.

Rokach et al.[92] have also used the sulphonium ylide (XVII) in the synthesis of the methyl ester of (±)-LTA_4 and succeeded in resolving the mixture of the *cis*- and *trans*-epoxides. The same group of investigators[92] attempted to synthesise 9Z-LTA_4 because the geometry of the $\Delta^{9,10}$-double bond in the natural leukotriene was unknown at the time. However, the immediate tetraene (XIXa) underwent the 1,7-hydrogen migration at 18–25 °C, affording the isomer

Scheme 6



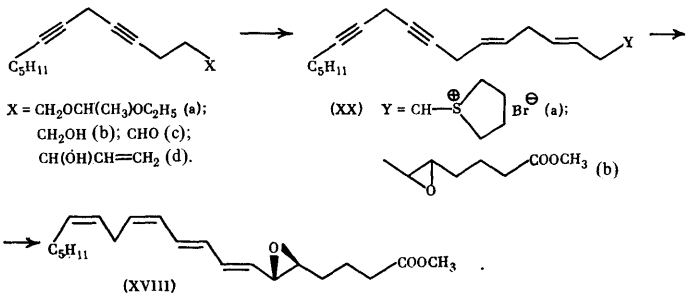
(XIX):



(XIXa) (XIX)

R = $COOCH_3$, CH_2OH .

The methyl ester of (±)-LTA_4 was also synthesised by the selective reduction of the diyne (XXb) obtained from the salt (XXa):[93,94]



X = $CH_2OCH(CH_3)OC_2H_5$ (a); CH_2OH (b); CHO (c); $CH(OH)CH{=}CH_2$ (d).

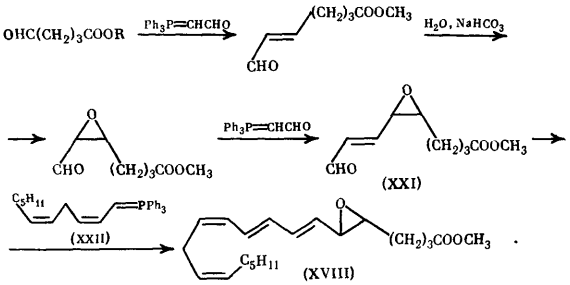
(XX) Y = $CH{-}S^{\oplus}Br^{\ominus}$ (a);

(b)

(XVIII)

Subsequently investigators used in the synthesis of LTA_4 schemes providing for the Wittig condensation of the hydrocarbon and carboxyl-containing fragments in the last stages of the synthesis after the preliminary introduction of the necessary functional groups into each fragment. The epoxyaldehyde (XXI), obtained by a series of stages from 4-formylbutyrate, has been used as the key synthone for the introduction of the carboxyl-containing unit[95,96] (Scheme 7). The undecadiene ylides (XXII),[95,96] prepared from phosphonium salts, are employed as the hydrocarbon fragment. The Z-configuration of the double bonds in compound (XXII) is due to the stereospecific hydrogenation of the corresponding acetylenic precursors. The interaction of compounds (XXI) and (XXII) yields the methyl ester of (±)-LTA_4 [95] (Scheme 7).

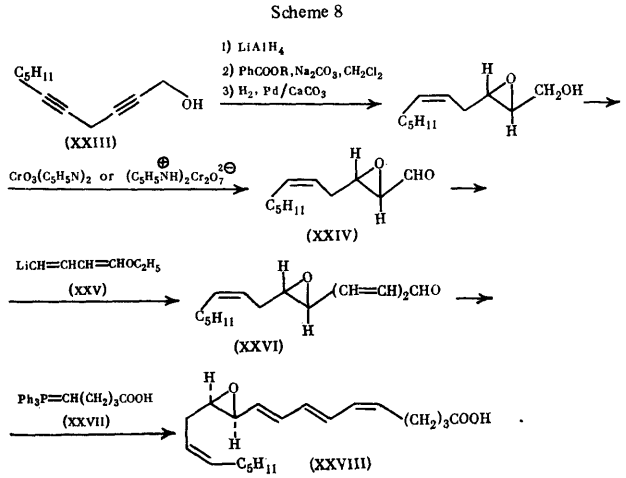
Scheme 7



Gleasson et al.[95] identified the methyl ester of (±)-LTA_4 which they synthesised as a 2:1 mixture of the natural 9*E*-compound and the isomeric 9*Z*-compound. The 1,7-hydrogen shift, noted by Rokach et al.[92] (see above), occurred also in the formation of 9*Z*-LTA_4.[96]

The triene component (XXVI) has been used as the hydrocarbon fragment in the syntheses of the 11,12-epoxides (XXVIII), which are analogues of the LTA_4 (Scheme 8), but, in contrast to the syntheses discussed above, this compound is not an ylide but an aldehyde (Scheme 8).[97] The initial undeca-2,5-diyn-1-ol (XXIII), obtained from acetylene and its derivatives, was converted into the aldehyde (XXIV) via a series of stages.

Scheme 8



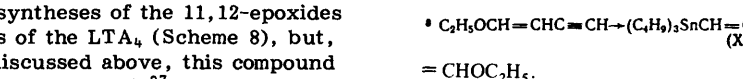
The length of the epoxyaldehyde (XXIV) is increased using 4-ethoxy-1-lithio-butadiene (XXV) as the four-carbon component.¶ The conversion of carbonyl compounds into conjugated dienes with the aid of compound (XXV) has been suggested[98] and has been used by other workers to generate an analogous system of multiple bonds in carboxyl-containing components in the synthesis of the 7-*cis*-isomers of LTA_4 and LTD_4.[99] Subsequently the aldehyde (XXVI) is condensed with the ylide (XXVII) to form the 11,12-epoxy-analogue of LTA_4 (XXVIII).

None of these syntheses described previously allowed the selective formation of the natural enantiomer of LTA_4. In order to solve this problem, the methyl ester of 5(*S*),6(*R*)-epoxy-6-formylhexanoic acid (XXX), which is synthesised from carbohydrates[100–105] or from carbohydrate derivatives[103,104] containing chiral centres in the molecule, has been suggested as the key compound. Corey et al.[100] (Scheme 9) described the synthesis of the aldehyde (XXX) from 2,3,5-tribenzoyl-D-ribose with its subsequent conversion by the Wollenberg method,[98,99] using 4-ethoxy-1-lithiobutadiene, into the 7*E*, 9*E*-C(1)-C(14) fragment (XXXI), whose interaction with the phosphorane (XXXII), obtained from acetylene,[56,90,92,99–106] gives rise to the enantiomerically individual methyl ester of 5(*S*),6(*S*)-LTA_4. The stereochemistry of this compound has been confirmed by its enzymic conversion into the natural LTB_4.[53]

The 5(*S*),6(*R*)-epoxyester (XXX) has also been converted into a mixture of the methyl esters of 9*Z*-LTA_4 and LTA_4.[100] The 11*E*-isomer of LTA_4 has been prepared from the 5(*S*),6(*R*)-epoxyester (XXX) by the *trans*-olefination method via the Wittig reaction[45,101] analogously to Scheme 9.

It has been suggested that D-glyceraldehyde acetonide (XXXIII), obtained from D-mannose and L-glyceraldehyde acetonide (XXIV), which was derived in its turn from L-arabinose, be used as the asymmetric precursor in the synthesis of the 5(*S*),6(*R*)-epoxyester (XXX) [105] (Scheme 10).

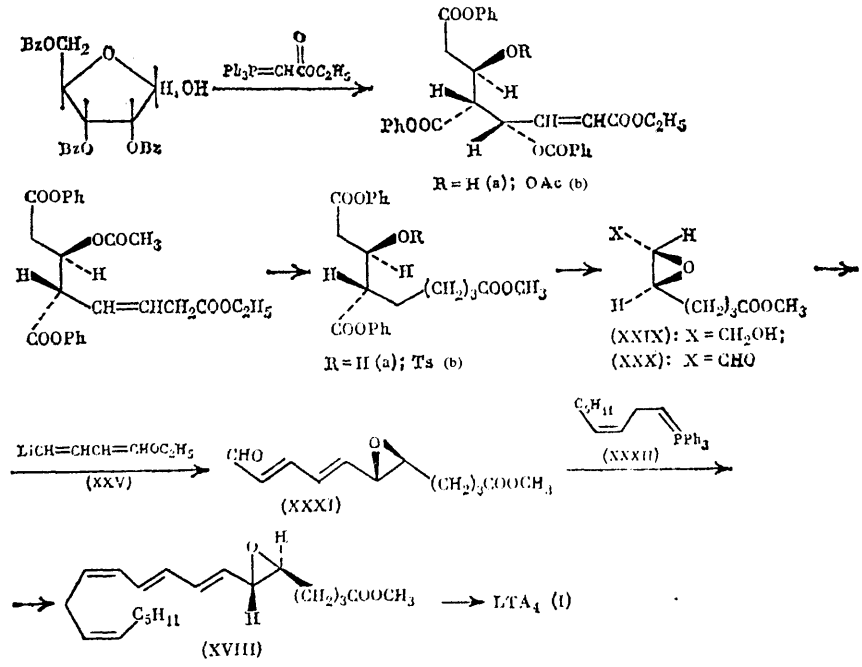
¶



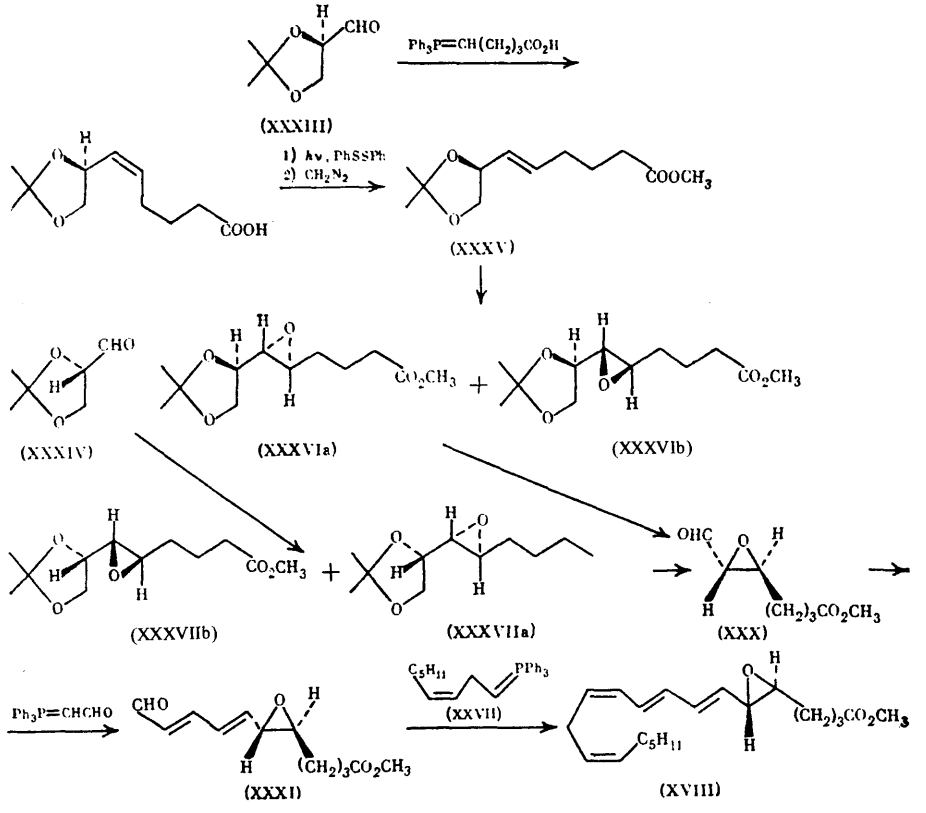
(XXVa) (XXV)

The hydrostannylation of 1-ethoxybut-1-en-3-yne yields vinyl stannate (XXVa), whose *trans*-metallation with n-butyllithium yields 4-ethoxy-1-lithiobutadiene (XXV).[98]

Scheme 9



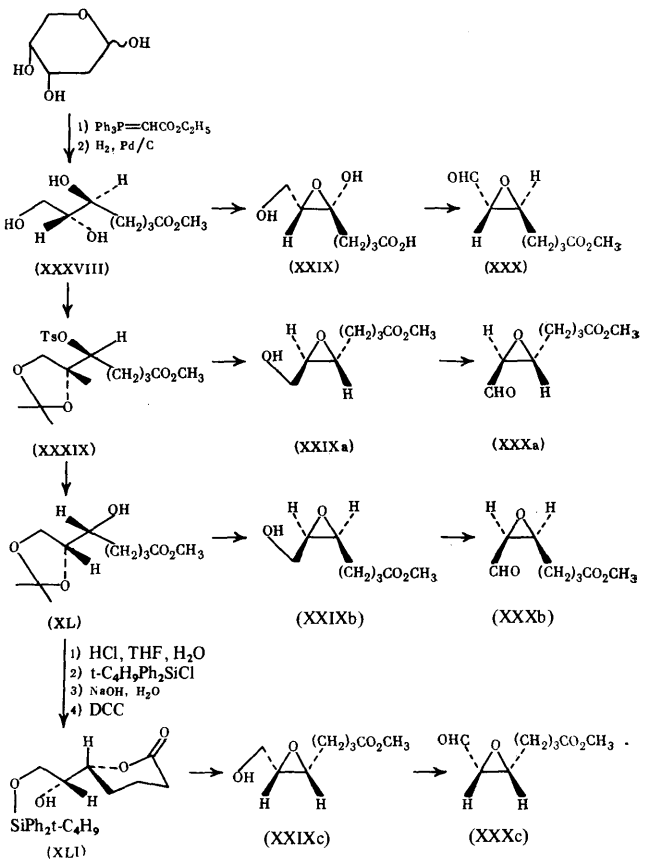
Scheme 10



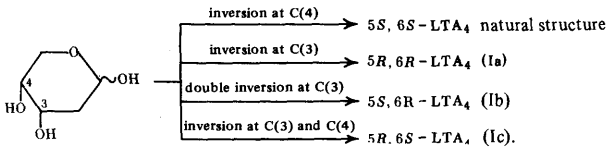
The conversion of the acetonide (XXXIII) into the ester (XXXV) with subsequent epoxidation of the double bond yields a 1:2 mixture of the epoxyesters (XXXVIa) and (XXXVIb) with the preferential formation of the isomer (XXXVIb) having the unnatural stereochemistry of the substituents at the C(5) and C(6) atoms. The epoxide (XXXVIIa) is formed preferentially from L-glyceraldehyde acetonide (XXXIV). The hydrolytic cleavage of both diastereoisomers, (XXXVIa) and (XXXVIIa), leads to the 5(*S*),6(*R*)-formyl ester (XXX), which is converted by three consecutive Wittig reactions into the methyl ester 5(*S*),6(*S*)-LTA_4. The 5(*S*),6(*S*)-stereoisomer (XXXb) is synthesised from the acetonides (XXXVIb) and (XXXVIIb).[105]

Using D-2-deoxyribose, Rokach et al.[106] later developed new stereospecific methods of synthesis of the 5(*S*),6(*R*)-, 5(*R*),6(*S*)-, 5(*S*),6(*S*)-, and 5(*R*),6(*R*)-stereoisomers of the aldehydoepoxyester (XXX) and on this basis obtained the natural LTA_4: the 5(*S*),6(*S*)-epimer and the 5-epi,6-epi-5(*R*),6(*R*)-, 6-epi,5(*S*),6(*R*)-, and 5-epi-5(*R*),6(*S*)-isomers of LTA_4 [compounds (Ia), (Ib), and (Ic) respectively] in the form of their methyl esters (XVIII), (XVIIIa), (XVIIIb), and (XVIIIc) respectively. In these studies, the authors took into account the disadvantage of using D-ribose in such syntheses,[100,102] consisting in the fact that the hydroxy-group at the C(2) atom had to be removed by reductive elimination, which entailed additional complications as regards the protection of the hydroxy-group at the C(4) atom, and developed the syntheses from D-2-deoxyribose.

Scheme 11



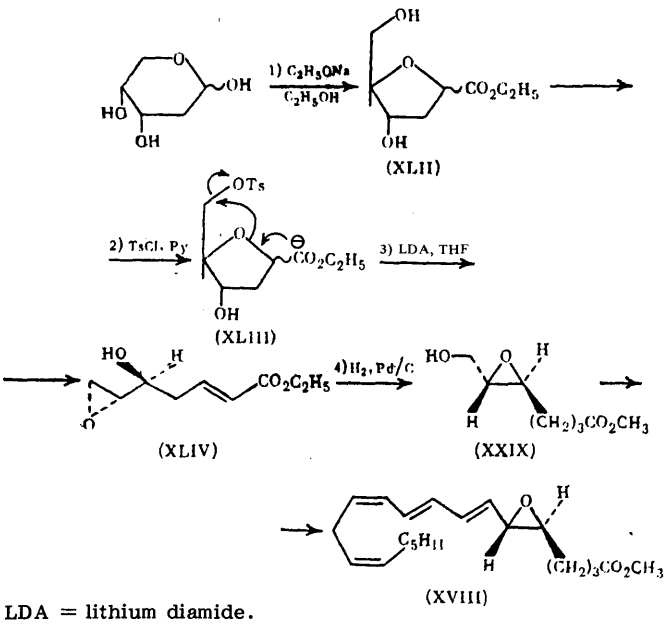
The main strategy used in these syntheses involved the appropriate manipulations of the chiral centres at the C(3) and C(4) atoms in D-2-deoxy-D-ribose in such a way that these two centres become chiral centres at the C(5) and C(6) atoms in the leukotrienes (I), (Ia), (Ib), and (Ic) synthesised, which can be represented schematically in the following way:



2-Deoxy-D-ribose is converted by a series of consecutive chemical reactions[106] into the triol (XXXVIII), the acetals (XXXIX) and (XL), and the lactone (XLI). Each compound obtained is a precursor of the diastereoisomeric epoxy-alcohols (XXIX), (XXIXa), and (XXIXb), (XXIXc), which are then oxidised[97] to the 5(*S*),6(*R*)-, 5(*R*),6(*S*)-, 5(*S*),6(*S*)-, and 5(*R*),6(*R*)-epoxyaldehydes [(XXX), (XXXa), (XXXb), and (XXXc) respectively] (Scheme 11).

The diastereoisomeric aldehydes (XXX), (XXXa), (XXXb), and (XXXc) obtained in this way by means of three consecutive Wittig olefination reactions,[105,106] as described above, are converted into the ethyl esters of LTA_4 (XVIII), 5-epi,6-epi-LTA_4 (XVIIIa), 6-epi-LTA_4 (XVIIIb), and 5-epi-LTA_4 (XVIIIc) respectively.[106]

Another method in which 2-deoxy-D-ribose is used to synthesise the epoxyesters (XXIX), (XXIXa) and (XXIXc) has been proposed.[107] It is based on the conversion of 2-deoxy-D-ribose into the *C*-glycoside (XLII)[108,109] with subsequent initiation of the intramolecular reaction of the tosylate (XLIII), leading to the formation of the epoxy-compound (XLIV), which is readily converted into the primary alcohol (XXIX) from which the methyl ester of LTA_4 is obtained after a series of known stages:

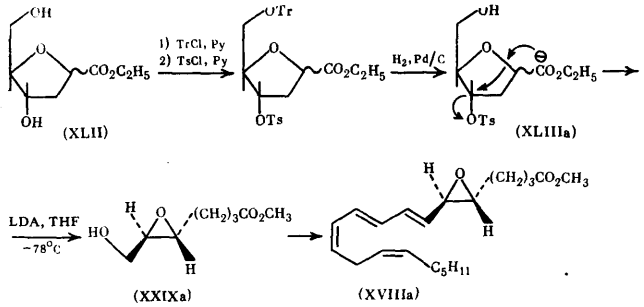


LDA = lithium diamide.

14,15-dehydro-LTA_4 has also been obtained from the hydroxyester (XXIX).[66,110]

The use of the tosylate (XLIIIa) leads to the inversion of the configuration at C(5) in the glycoside and the formation of the hydroxyester (XXIXa), which is converted further

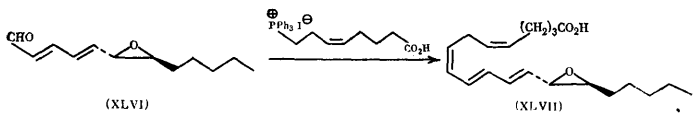
into the ester of 5-epi,6-epi-LTA$_4$:



The synthesis of the hydroxyester (XXIXc), a precursor of the ester of 5-epi-LTA$_4$, involves the inversion of the configuration of the secondary hydroxy-group of the *C*-glycoside (XLII) and the tosylation of the primary hydroxy-group in compound (XLV), as shown in Scheme 12.

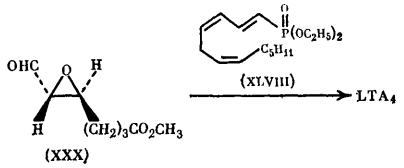
Simultaneously with the studies by Rokach and co-workers,[106,107] Mariotti and Bentick[111] proposed a somewhat modified synthesis of the epoxyalcohol (XXIX) also on the basis of 2-deoxy-D-ribose.

2-Deoxy-D-ribose has been used successfully in the synthesis of the epoxyaldehyde (XLVI),[112] from which 14(*S*),15(*S*)-epoxy-5*Z*, 8*Z*, 10*E*, 12*E*-eicosatetraenoic acid 14,15-LTA$_4$ (XLVII) was obtained by a standard method:[107,112]

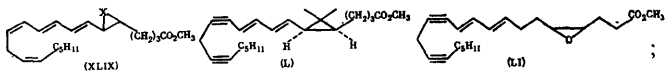


The methyl ester of 5(*S*),6(*S*)-epoxy-7-hydroxyheptanoic acid (XXIX) and its 5(*S*),6(*R*)-diastereoisomer (XXIXb), which are precursors of LTA$_4$ and 6-epi-LTA$_4$, have also been synthesised from 2,3-*O*-isopropylidene-D-erythrose[113] and 5(*S*),6(*S*)-epoxyaldehyde (XXXb) has been obtained from bis-isopropylidene-D-(+)-mannose.[114]

A synthesis of LTA$_4$ in which the phosphonates (XLVIII) were used instead of the phosphonium salts as the C(13) to C(20) fragment was published in 1982:[115]



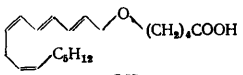
The diacetylene analogue (XLVIII) was used in the synthesis of the methyl ester of (±)-LTA$_4$.[116] A phosphonate, whose structure resembled that of compound (XLVIII), has also been used to synthesise the methyl ester of 5,6-methanoleukotriene A$_4$ (XLIXa) [117,118] (a stable biologically active analogue of LTA$_4$), bisdehydrodimethylmethanoleukotriene A$_4$ (L), [119,120] and a bisdehydro-analogue of LTA$_4$ (LI): [120,121]



X = CH_2 (a); S (b); N (c).

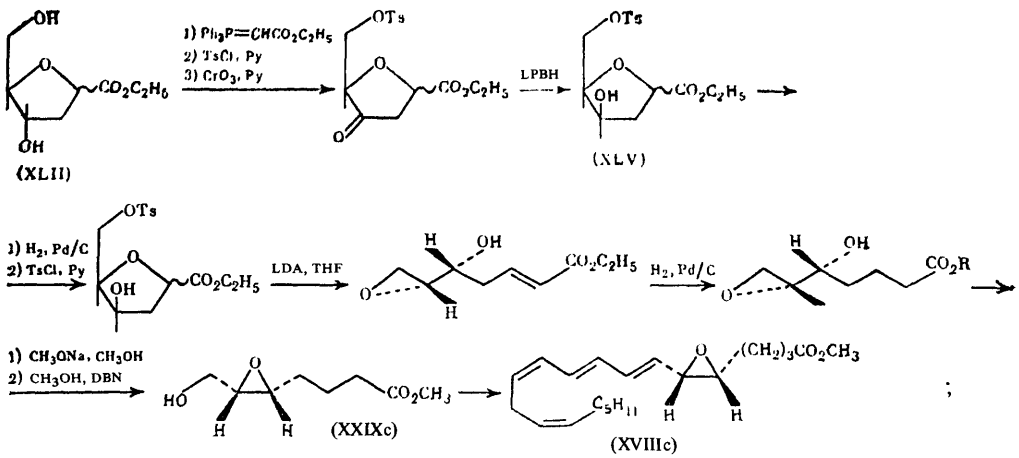
A thio-analogue of LTA$_4$ (XLIXb) has been prepared by the same methods.[120] An aza-analogue of LTA$_4$ (XLIXc) has been synthesised[123] using 5-epi,6-epi-LTA$_4$.[106] The acetylenic analogues of LTA$_4$ serve as the initial compounds for the synthesis of tritium-labelled leukotrienes.[123,124]

6-Oxa-8*E*, 10*E*, 12*Z*, 15*Z*-eicosatetraenoic acid, secoleukotriene A$_4$ (LII), whose synthesis has been published recently,[125,126] is also an analogue of LTA$_4$.



The syntheses of LTA$_4$ using initial chiral compounds (carbohydrates and their derivatives) [100–114] involve many stages and require a large number of protecting operations and the removal of various groups to ensure the inversion of substituents at the initial chiral centres to give the configuration characteristic of the leukotriene structure. The stereospecific oxidation of achiral alcohols by a reagent comprising diethyl L-(+)-tartrate, t-butyl hydroperoxide,

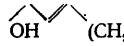
Scheme 12



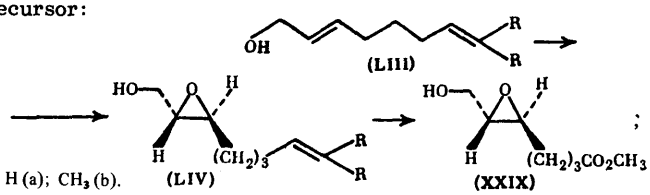
LPBH = lithium perhydro-9B-boraphenylallyl hydride;
DBN = 1,5-diazabyclo[4,3,0]non-5-ene.

and tetraisopropoxytitanium, proposed by Katsuki and co-workers,[127,128] has been a major advance in the methology of the synthesis of leukotrienes.

However, there is evidence that methyl 7-hydroxy-5-heptenoate



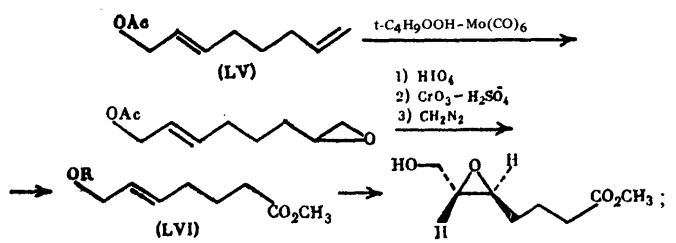
is epoxidised under these conditions with low yields.[103,127,128] At the same time, two research groups developed the selective epoxidation of the diene alcohols (LIIIa) [128] and (LIIIb).[103] The oxidative cleavage of the alkene structure of the epoxide (LIV) with subsequent esterification gives rise to the 5(*S*),6(*S*)-epoxyalcohol (XXIX) as the LTA_4 precursor:



R = H (a); CH_3 (b). (LIV) (XXIX)

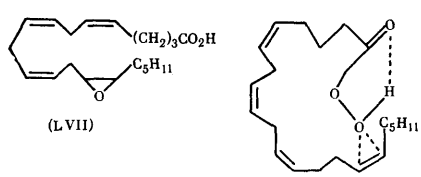
The epoxide (XXIX) has been synthesised[120,129] from 1-acetoxy-2*E*,7-octadiene (LV) by the chiral epoxidation of methyl 7-hydroxy-5*E*-heptenoate (LVIa) or its acetate (LVIb) using the Sharpless–Katsuki method (Scheme 13):

Scheme 13



R = Ac (a); H (b). (XXIX)

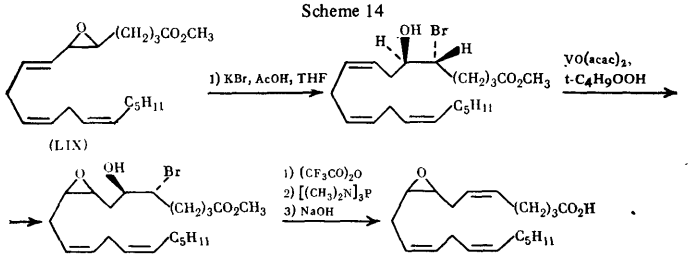
This method[127,128] has been used also in the synthesis of 8,9-LTA_3.[47,130] Corey and co-workers[131–133] achieved the selective epoxidation of the double bond nearest to ($\Delta^{5,6}$) and most remote from ($\Delta^{14,15}$) the carboxy group in arachidonic acid. The 14,15-epoxide (LVII) has been synthesised by the novel intramolecular transfer of oxygen in peroxyarachidonic acid, which isomerises preferentially via the intermediate (LVIII):



(LVII) (LVIII)

8,8-Epoxyarachidonic acid (LIX) has been synthesised from the methyl ester of the 5,6-epoxyacid (LX),[87,134] (Scheme 14):

Scheme 14



(LIX) (LX)

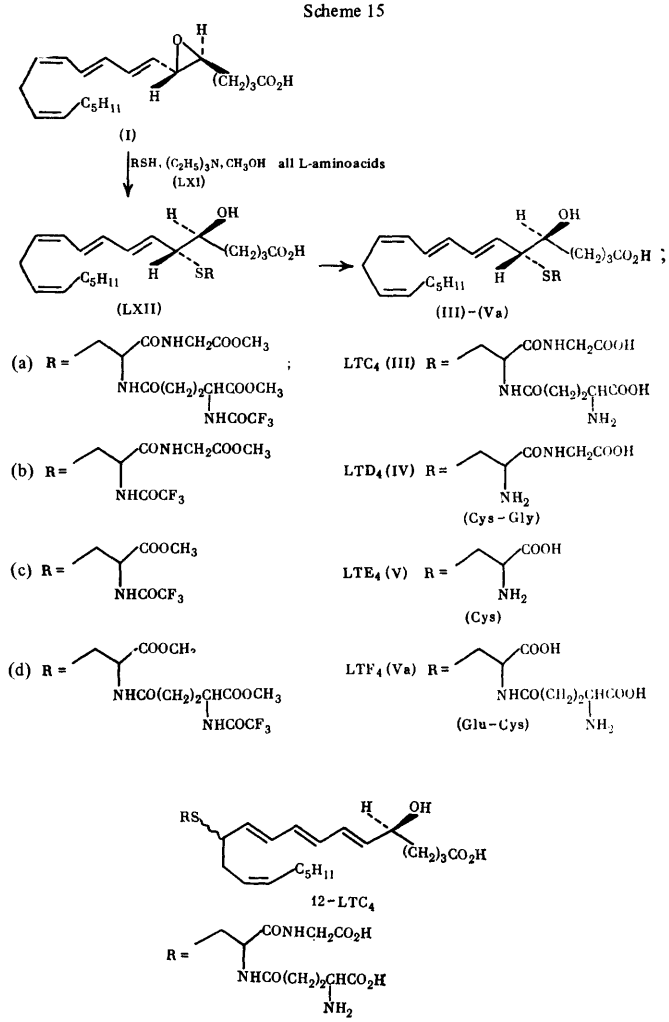
Compound (LX) has also been isolated from natural sources.[87]

A biospecific synthesis of the methyl ester of LTA_4 from 5-HPETE (VI) is known.[46,135–137] Other natural epoxides have also been obtained by biospecific synthesis.[112,136]

2. The Syntheses of the Leukotrienes C_4, D_4, E_4, and F_4, Their Isomers, and Their Analogues

The syntheses of LTC_4,[92–97,100–105,111,124,128–132,136–142] LTD_4,[92–105,114,124,130–142] LTE_4,[93,94,100,103,105,124,140–143] LTF_4,[94,143] their isomers, and their analogues[93,96,102,111,124,139–144] are based on the introduction in the 6-position in the LTA_4 molecule of the thio-derivatives (LXI), whose role is assumed by the corresponding protective aminoacids and peptides in LTA_4 [100,105] (Scheme 15).

Scheme 15



(I) (LXII) (III)–(Va)

(a) R = LTC$_4$ (III) R =

(b) R = LTD$_4$ (IV) R = (Cys-Gly)

(c) R = LTE$_4$ (V) R = (Cys)

(d) R = LTF$_4$ (Va) R = (Glu-Cys)

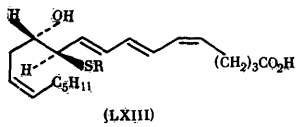
12-LTC_4

The removal of protecting groups from compounds (LXII, a–d), depends on the nature of the peptide substituent. There are data concerning the addition of glutathione in the unprotected form.[57,61,62,119–121,135] Hydroquinone, which is an essential component in the hydrolysis of the LTE_4 esters, leads to the partial isomerisation of the double bond in the 11-position in leukotrienes.[75] The use of an excess of lithium perchlorate when it is necessary to alter the direction of the LTC_4 formation reaction leads to the synthesis of 12-glutathionylleukotrienes (12-LTC_4),[102] which exhibit an extremely low biological activity and apparently do not make a significant contribution to the biological role of the members

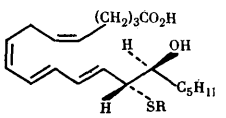
of the family of leukotrienes. This finding is important for the elucidation of the structure of the SRS components.[145]

The recently isolated LTF_4 (Va) has been synthesised by means of Scheme 15 described above from LTA_4 and protected glutamylcysteine.[134] The compound has been obtained in a mixture with its 5(*R*),6(*S*)-diastereoisomer and proved to be 200 times less active in its effect on human bronchi than LTD_4.[143] The 5(*R*),6(*S*)-diastereoisomers of LTC_4, LTD_4, and LTE_4 were synthesised in the same investigation.[143] Their biological activities proved to be lower by two orders of magnitude than that of the natural product. Other LTC_4, LTD_4, and LTE_4 diastereoisomers have also been synthesised.[61,111,114]

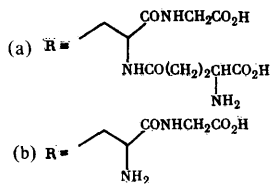
11-Glutathionyl- [11-LTC_4 or (LXIIIa)], 11-cysteinylglycyl- [11-LTD_4 or (LXIIIb)], 14-glutathionyl-LTC_4 [14-LTC_4 or (LXIVa)], and 14-cysteinylglycyl-leukotrienes [14-LTD_4 or (LXIVb)] have been synthesised from 11,12- and 14,15-epoxy-analogues of LTA_4 and protected peptides. These leukotrienes are positional analogues of the natural LTC_4 and LTD_4.[97]



(LXIII)



(LXIV)

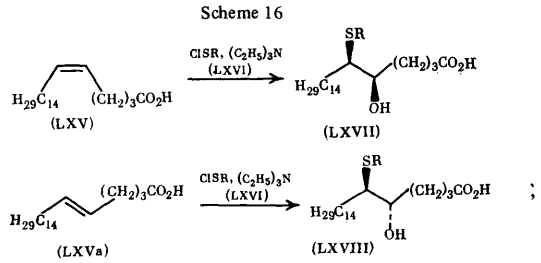


The 7-*cis*-isomer of LTD_4, whose activity amounted to one-tenth of that of the natural LTD_4, has been obtained by the same method.[99]

It has been suggested that the *S*-trimethylsilyl derivatives [R-S-Si$(CH_3)_3$] of the *N*-trifluoroacetylglutathione and *N*-trifluoroacetyl-L-cysteine esters be used in the synthesis of LTC_4 and LTE_4.[92]

The stereoisomers of fully saturated octahydro-analogues of the leukotrienes C_4 [(LXViia) and (LXVIIIa)], D_4 [(LXVIIb) and (LXVIIIb)], and E_4 [(LXVIIc) and (LXVIIIc)] have been synthesised[139,140] by the stereoselective interaction of sulphenyl halides (LXVI) with the 5*E*- and 5*Z*-eicosenoic acids (LXVa) and (LXVb) (Scheme 16):

Scheme 16

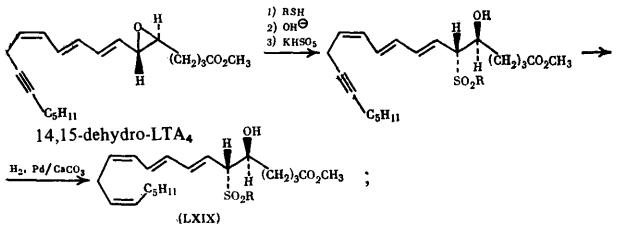


(a) R = glutathione; (b) R = Cys–Gly; (c) R = Cys.

9*Z*- and 9*Z*, 11*E*-LTC_4 have been synthesised from LTA_4 isomers with known stereochemistry.[138]

The 11*E*-isomer of LTC_4, isolated previously from mastocytoma cells,[30] has been synthesised from 11*E*-LTA_4 and glutathione.[68,101]

The uncertainty of the state of oxidation of the thio-bond in the natural LTC_4 in the determination of its structure (LXVII) made it essential to synthesise the LTC_4 sulphone (LXIX):



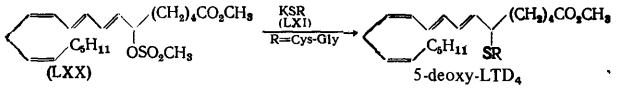
14,15-dehydro-LTA_4

(LXIX)

R = glutathione.

Comparison of the physicochemical and biological properties of the sulphone (LXIX) with those of the natural LTC_4 confirmed the presence of the sulphide linkage in the latter.[66,67]

The study of the molecular binding of leukotrienes and the determination of the structure of the possible receptor led to the problem of the synthesis of 5-deoxy-LTD_4,[142–147] which was achieved by the interaction of the methane-sulphonate (LXX)[102] with the potassium thiolate derived from the methyl ester of *N*-trifluoroacetyl-L-cysteinylglycine (LXI):[142]

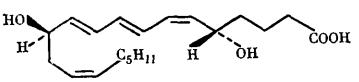


(LXX) 5-deoxy-LTD_4

All the diastereoisomers of 5-deoxy-LTD_4 synthesised exhibited only 1% of the activity of the natural LTD_4, which indicates the importance of the hydroxy-group at C(5) for the manifestation of the biological activity of LTD_4.

3. The Synthesis of Leukotriene B_4 and its Isomers and Analogues

Leukotriene B_4, namely 5(*S*),12(*R*)-dihydroxy-6*Z*, 8*E*, 10*E*, 14*Z*-eicosatetraenoic acid, is a chemotactic and chemokinetic† factor, which plays an important role in inflammatory processes and is a metabolite of arachidonic acid in its lipoxygenase oxidation, namely in the stage involving the enzymic hydrolysis of LTA_4 (Scheme 3).



LTB_4 (II)

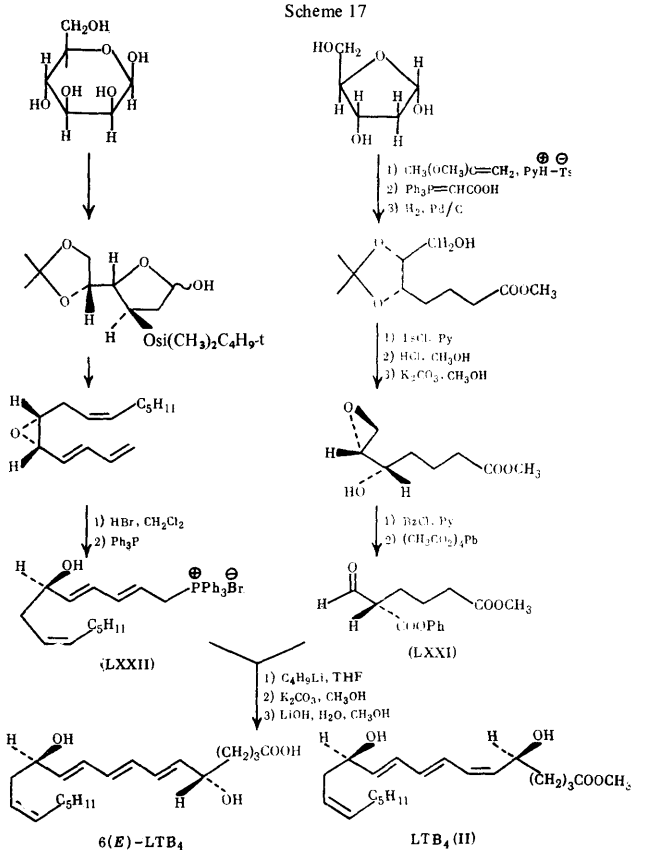
The synthesis of LTB_4 is based on the same principles as the synthesis of LTA_4, but the characteristic features of the structure, namely the presence of hydroxy-groups at C(5) and C(12) in the hydrocarbon chain, introduced definite differences into the construction of the LTB_4 molecule. The synthesis is carried out by the Wittig condensation of two fragments—the hydrocarbon fragment [up to C(20)] and the carboxyl-containing fragment [from C(1)].[51,148–169] The aldehyde functional group, which is essential for the Wittig reaction, is located in the carboxy-fragment, while the hydrocarbon component is constructed in such a way that, before the Wittig condensation, it contains either the hydroxy-group at the C(12) carbon atom or groups which are readily converted to such a hydroxy-group, as well as three double bonds.

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†Chemotaxis is the motor response of freely migrating cells of multicellular organisms under the influence of a unilateral chemical irritant.

The synthesis of natural LTB_4 was first proposed by Corey and was important in the determination of the structure of this compound[51,114,148] (Scheme 17). The chiral aldehyde (LXXI), the C(1)–C(6) fragment of the LTB_4 molecule, was obtained from 2-deoxyribose in several stages. The phosphonium salt (LXXII) [the C(7)–C(20) fragment] was synthesised from D(+)-mannose, as described previously.[114] The Wittig reaction of compound (LXXI) and (LXXII) followed by hydrolysis afforded LTB_4 with an admixture of 6*E*-LTB_4. The synthetic LTB_4 specimen is identical with the natural product and has the 6*Z*, 8*E*, 10*E*, 14*Z*-configuration of the double bonds.

Scheme 17



In order to confirm the structure of the natural LTB_4,[148–153] its 6*E*, 8*Z*- and 6*E*, 10*Z*-isomers, which possess no biological activity, were synthesised.[149] For this purpose, the stereospecific syntheses of the biologically active 5(*S*),12(*S*)-stereoisomer of 6*E*, 8*Z*-LTB_4,[143,149–152] and the 5(*S*),12(*R*)- and 5(*S*),12(*S*)-stereoisomers of 6*E*-LTB_4 [152–158] were carried out.

After the determination of the structure, more convenient methods of synthesising the natural LTB_4 were sought. A synthesis of LTB_4 from the epoxyphosphonium salt (LXIII) [97,106,149] and the aldehydoester (LXXI) [122] in accordance with Scheme 18 has been proposed.[150]

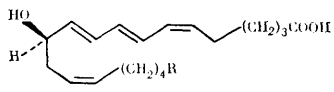
A stereospecific synthesis of LTB_4 from 2-deoxy-D-ribose, used previously by the same workers in the synthesis of series 4 leukotrienes ranging from LTA_4 to LTF_4 and their isomers,[155] was proposed in 1982.[154]

In another synthesis of LTB_4 and its 12(*S*)-epimer (IIa) (Scheme 20), the authors[156] used L- and D-arabinose respectively as the initial compounds to generate the chiral centre at C(12). L-Arabinose is converted by a standard method[157,158] in six stages to the aldehyde (LXXIV), which is then transformed by means of a series of reactions into LTB_4. The 12(*S*)-isomer of LTB_4 was obtained analogously from D-arabinose.

Enantiomeric epoxidation[127,128] greatly simplified the synthesis of the natural LTB_4.[159]

In 1983 it was suggested[160] that the optically active aldehydes (LXXI) [148,151,152,154] and (LXXV) [156] be synthesised from cinnamaldehyde rather than from carbohydrates.

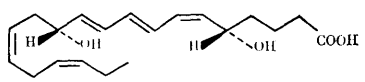
Two LTB_4 metabolites have been isolated and identified comparatively recently: ω-carboxy-LTB_4 (LXXVIa) [161–167] and ω-hydroxy-LTB_4 (LXXVIb),[161–167] which were synthesised[163] via a scheme developed previously:[154–156]



(LXXVI)

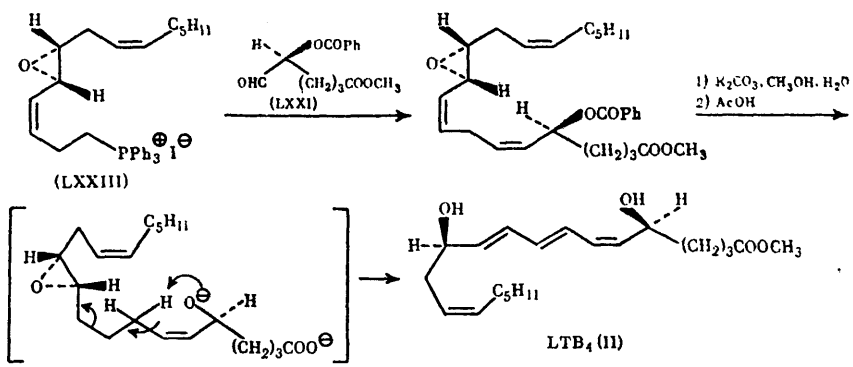
R = COOH; CH_2OH

LTB_5 (LXXVII), previously obtained by biosynthesis,[169] was synthesised in 1983:[168]

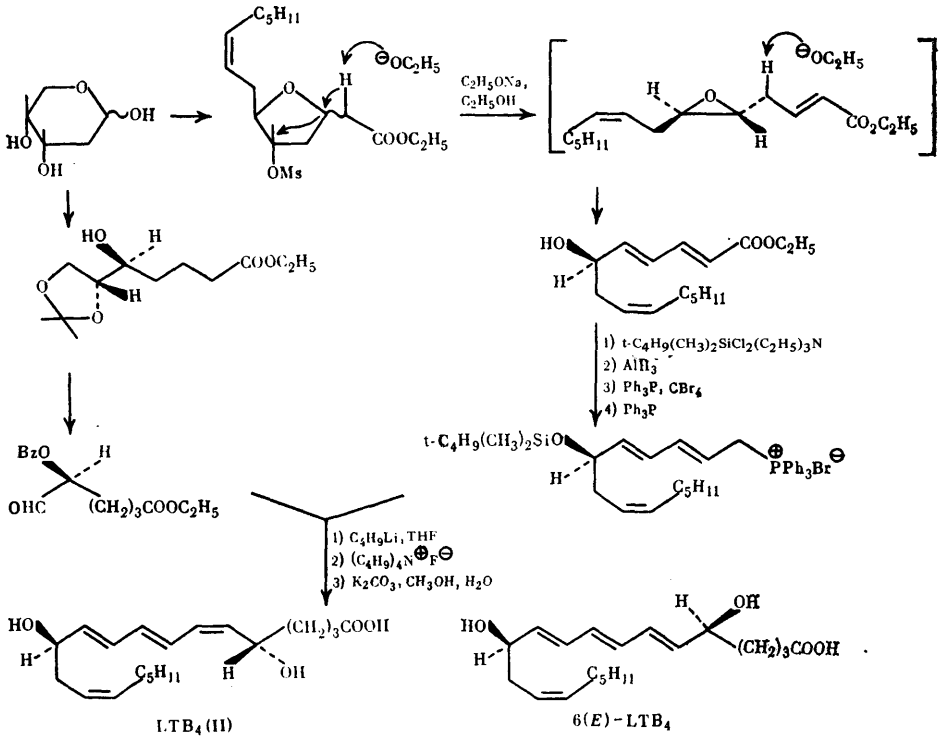


LTB_5 (LXXVII)

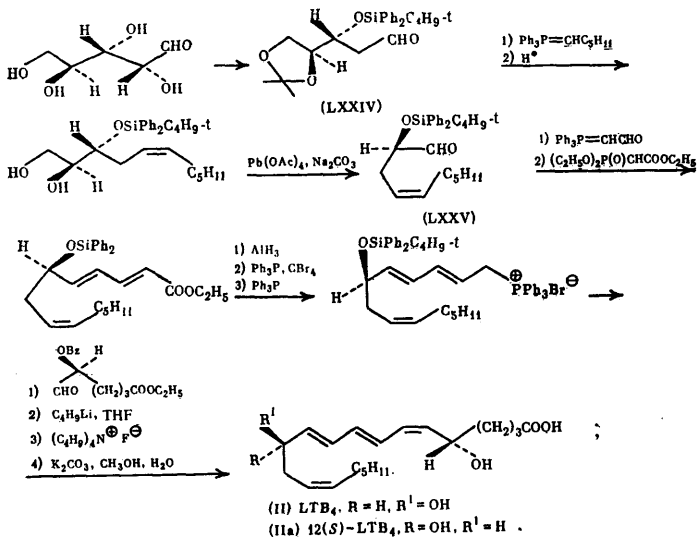
Scheme 18



Scheme 19



Scheme 20



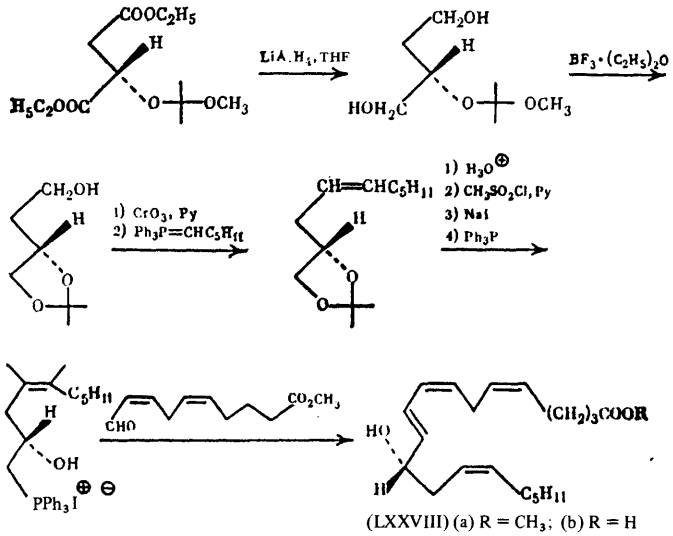
IV. THE SYNTHESES OF OTHER OXYGEN-CONTAINING ACYCLIC ARACHIDONIC ACID METABOLITES

The initial compounds arising in the enzymic oxidation of arachidonic acids are the hydroperoxyeicosatetraenoic acids (VI) and the hydroxyeicosatetraenoic acids (XIII), which were designated in the literature by the abbreviations 5-TPETE and 5-HETE# [8,137,170–180] (Scheme 3) respectively. These biologically active compounds have been discovered in the human and animal organisms. Extremely little is known about the biological role of HETE in cell functions or about their biological precursors (HPETE). However, the fact that their formation from arachidonic acid is not inhibited by aspirin and indomethacin, in contrast to the prostaglandin endoperoxides (PGG_2 and PGH_2), and their high content in certain tissues (for example, human epidermic tissues in persons suffering from the skin disease psoriasis) makes them extremely interesting for comprehensive study.[8,176]

#Apart from 5-HETE, 11-, 12-, and 15-HETE are known for arachidonic acid,[8,171–175] and their corresponding HPETE precursors.[8,171]

The total synthesis of 12(*S*)-hydroxy-5*Z*, 8*Z*, 14*Z*, 10*E*-eocosatetraenoic acid (LXXVIIIb), which has been called "Samuelsson's HETE" was first achieved in 1978 [104] in accordance with Scheme 21:

Scheme 21



(LXXVIII) (a) R = CH_3; (b) R = H

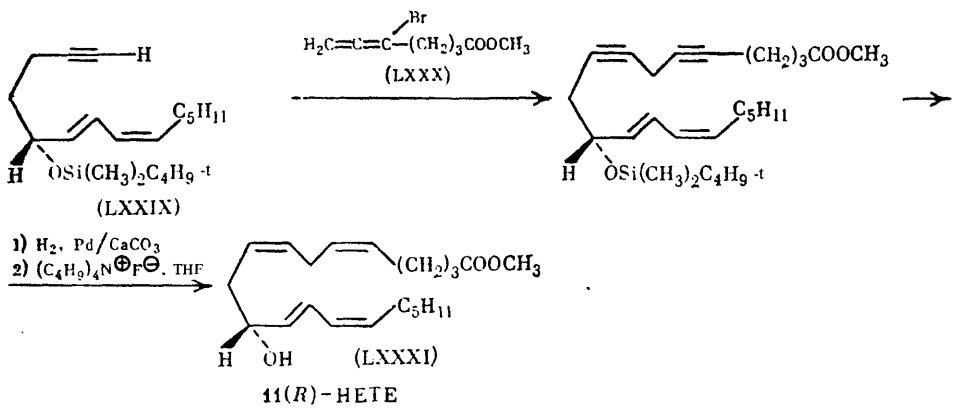
The oxidation of arachidonic acid by oxygen[177,178] leads as a rule to a random mixture of HPETE and HETE which is extremely difficult to use for comparative purposes.[179] However, it has been suggested[54] that (±)-5-HETE and (±)-5-HPETE be synthesised by selective substitution at the C(5) atom in the arachidonic acid molecule. (±)-5-HETE has been prepared by other investigators[181] in accordance with an analogous idea involving the introduction of the phenylseleno-group into arachidonic acid.

The (*S*)-enantiomer of 5-HETE discovered in natural sources, which is an important biological mediator functioning as a chemotactic agent for human leukocytes (eosinophils and neutrophils), and its (*R*)-enantiomer have been obtained by the chromatographic separation of the diastereoisomeric urethanes.[54,182] 5-(*S*)-HETE (VI) is a stronger chemotactic factor than 8-, 9-, 11-, 12-, and 15-HETE and its importance is comparable to that of the peptide derivatives involving the C(5) carbon atom.[182]

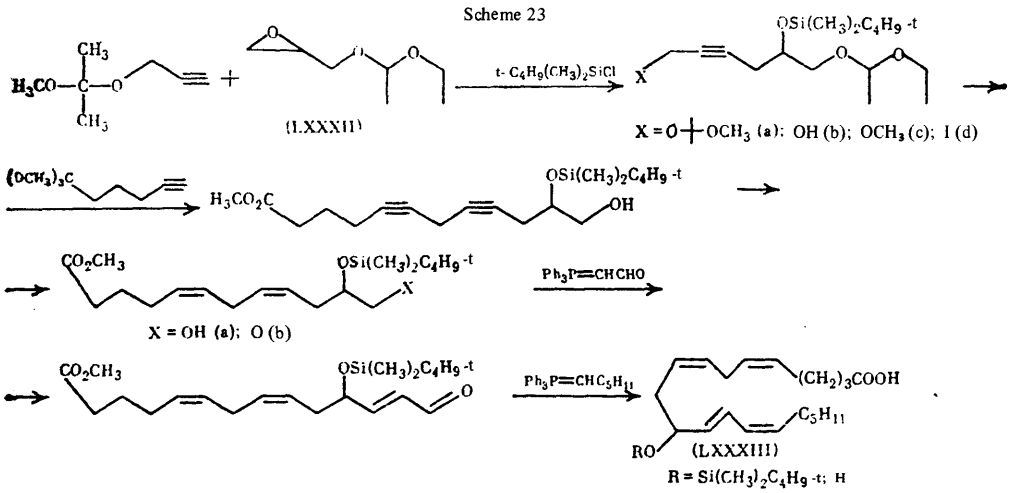
The synthesis of 5(*S*)-HETE (VIa) and 5(*R*)-HETE (VIb) via a scheme developed using the Wittig reaction[106,154,184] has been published.[183]

The methyl ester of 11(*R*)-HETE (LXXXI) has been synthesised[185] by a novel reaction of allene bromide (LXXX) with silyl derivatives of a terminal acetylenic diene (LXXIX) (Scheme 22). The same workers[171] achieved the synthesis of 11-, 12-, and 15-HETE from 11,12- and 14,15-epoxyarachidonic acids.

Scheme 22



Scheme 23



An alternative synthesis of 11(*R*,*S*)-HETE (LXXXIII) has been achieved[186] using the glycidol derivatives (LXXXII) (Scheme 23).

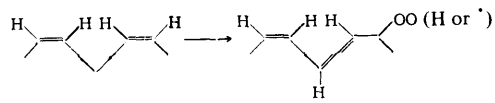
The 11(*R*)- and 11(*S*)-isomers of HETE have been synthesised by a new method involving the resolution of the initial mixture of diastereoisomeric acetoxyaldehydes with the aid of ephedrine.[187]

The syntheses of HPETE, which are precursors of HETE, have been described in a number of studies.[97,102,182]

V. THE SYNTHESES OF INHIBITORS OF THE ENZYMIC OXIDATION OF ARACHIDONIC ACID

Four oxidative pathways leading to the biosynthesis of biologically active eicosanoids from arachidonic acid under the influence of lipoxygenase are known.[188] Among them the pathway leading to the formation of leukotrienes [the 5-lipoxygenase (5-LO) pathway] is of special interest.[188,189] The biosynthesis of prostaglandins (PG) and thromboxanes (TX) via the lipoxygenase reaction of arachidonic acid involving C(11), catalysed by the enzyme cyclo-oxygenase (CO), has been studied to a considerable extent.[190]

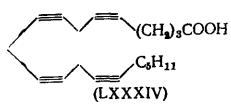
Both pathways involve the initial oxidation of the lipoxygenase type in which the 1*Z*, 4*Z*-pentadiene unit (A) is converted into the 1-oxygenated 2*E*, 4*Z*-pentadiene fragment (B):[171,188,191,192]



(A) (B)

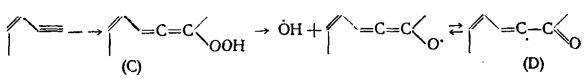
Studies using various lipoxygenase, namely 5-LO from mammalian leukocytes,[8,180,192] potato tubers,[8,180,192] and other sources,[8] 12-LO from thrombocytes,[192] 15-LO from soya beans,[8,171,189,193] and others,[8] justify the hypothesis that the transformation A → B may be specific to the lipoxygenase catalysis.[192,194,195]

It has been found that aspirin, indomethacin, and a number of other non-steroid anti-inflammatory agents inhibit the biosynthesis of prostaglandins by blocking the initial stage of the lipoxygenase reaction of arachidonic acid at C(11), catalysed by cyclo-oxygenase.[8,189–191,196] The mechanism of the action of these empirically discovered and therapeutically important inhibitors of the prostaglandin biosynthesis is obscure but it has been demonstrated convincingly that they block the action of 11-LO but are ineffective as inhibitors of other biological oxidation pathways, including the 5-LO pathway.[189–191] 5,8,11,14-Eicosatetraynoic acid (LXXXIV), which has been synthesised by the author of this review,[197,198] inhibits the 11-, 12-, and 5-lipoxygenase reactions of arachidonic acid.[190]



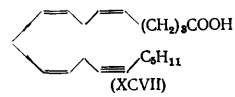
(LXXXIV)

It has been suggested[189,199] that monodehydroarachidonic acid should bind more strongly and more selectively to lipoxygenase, preventing the oxidation of natural arachidonic acid. The lipoxygenation of the acetylenic linkage gives rise to the olefinic hydroperoxide (C) and the dissociation of the O–O bond leads to the formation of the radicals OH• and (D),[189] which evidently results in the deactivation of lipoxygenase:



(C) (D)

To confirm this hypothesis, Corey and Kang[199] synthesised 5,6-, 8,9-, and 11,12-dehydroarachidonic acids (DHA) [compounds (LXXXV), (LXXXVI), and (LXXXVII) respectively] and investigated them in lipoxygenase oxidation processes.[188,189] A fundamentally new method for the formation of the C–C bond in the construction of the *Z*-RCH=CHCH$_2$C≡R structure by the reaction of the iodo-olefins (LXXXIXb), (XCI), (XCII), and (XCb), obtained from the butylstannanes (LXXXVIII),[199,200] (LXXXIXa),[201] and (XCa),[201] with the iodoallenes (XCIII) and (XCIV),[185] (XCV),[202] and (XCVI) respectively, has been proposed in the syntheses of DHA (Scheme 24).[199] The synthesised DHA specimens were identical with those synthesised previously[122,188] using acetylenic compounds and the Wittig reaction.



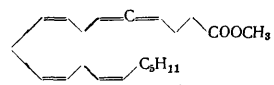
(XCVII)

Like 5,8,11,14-eicosatetraynoic acid, 5,6-dehydroarachidonic acid was synthesised by the authors of this review[197,203] from acetylenic derivatives by nucleophilic substitution at the terminal acetylenic carbon atom—a method proposed by Osbond and Wickens[204] and subsequently modified and improved by other workers.[205,206]

14,15-Dehydroarachidonic acid (14,15-DHA) (XCVII) was synthesised by arachidonic acid via the opening of the epoxy-ring[131] and the formation of a triple bond via a reaction involving ketobromides.[189]

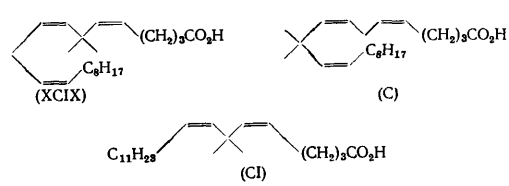
It has been shown[188,189,190] that 4,6-DHA and 14,15-DHA inhibit irreversibly only soya bean 5-LO and 15-LO respectively. A most effective inhibitor of the biosynthesis of prostaglandins is 11,12-DHA. 14,15-DHA can inhibit the formation of prostaglandins but at much higher concentrations than 11,12-DHA. 5,6-DHA and 8,9-DHA are not only inhibitors of the biosynthesis of prostaglandins but at higher concentrations can actually behave as substrates.

4,5-Dehydroarachidonic acid (4,5-DHA) (XCVIII), which is an irreversible and more selective inhibitor of the 5-LO from basophilic leukaemic rat cells,[207–209] the mechanism of the action of which on the enzyme is apparently different from that of 5,6-DHA, has been synthesised from 5,6-epoxyarachidonate (LIX).[131]



(XCVIII)

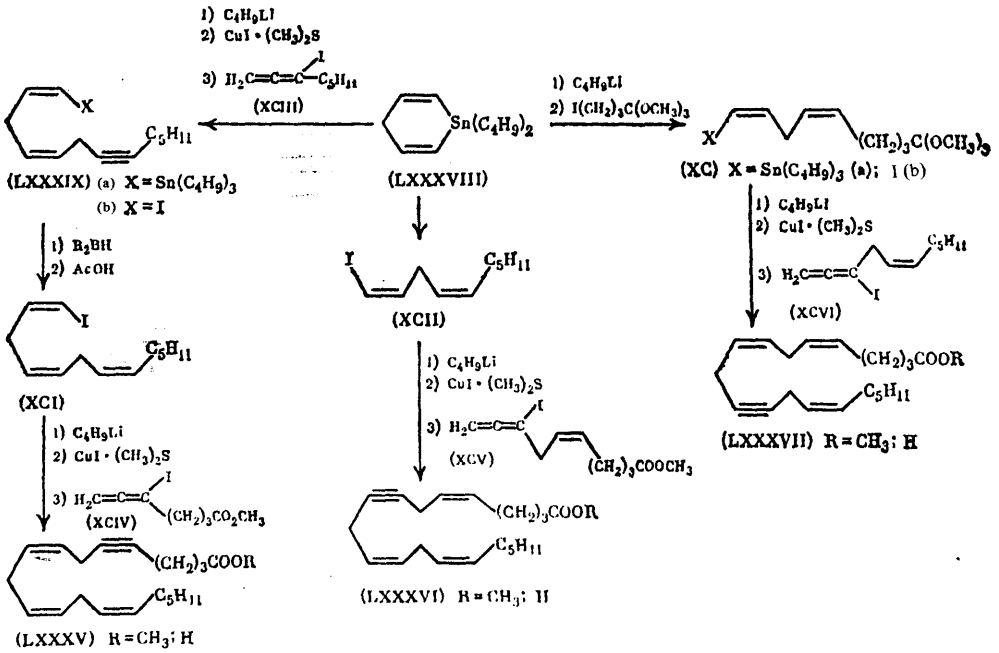
5-LO is inhibited by 7,7- and 10,10-dimethyl-5*Z*, 8*Z*, 11*Z*-eicosatrienoic acids (XCIX) and (C),[176] and also by 7,7-dimethyl-5*Z*, 8*Z*-eicosadienoic acid (CI),[191] which are derivatives of 5,8,11-eicosatrienoic acid—the substrate in the biosynthesis of series 3 luekotrienes.[8,41,122] The inhibitors (XCIX), (C), and (CI) have been synthesised from acetylenic compounds by means of the Wittig reaction.[176]



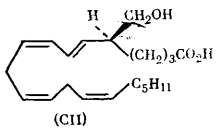
(XCIX) (C) (CI)

5,6-Methanolaukotriene A_4, the "carbo-analogue of LTA_4", (XLIXa),[117,118,210] the thio-analogue of LTA_4 (XLIXb),[122] and 5-hydroxymethyleicosatetraenoic acid (CII),[118] which are synthetic analogues of the selective inhibitors of the

Scheme 24



biosynthesis of leukotrienes, possess the properties of the latter.



(CII)

VI. THE BIOLOGICAL ROLES UF LEUKOTRIENES

The leukotrienes C_4, D_4, F_4, and B_4 are of considerable interest as a new class of natural physiologically active bioregulators.[6,8,59,111,138,144,192,210–222] Leukotrienes have been identified both in leukocytes and in a series of other sources, which indicates their wide distribution.[6,8,144,211,212]

Purified SRS-A, isolated from natural sources, and the synthetic LTC_4, LTD_4, and LTE_4 are as a rule tested for their ability to contract the smooth muscle tissue in guinea-pig intestines in the presence of histamine antagonists.[8] The studies of the action of leukotrienes on the guinea-pig aorta,[118] bronchi,[99] and trachaea[92] and human bronchi *in vitro*[8,211,212] have shown that LTC_4 and LTD_4 increase microvascular permeability and are powerful spasmogenic agents in relation to bronchi, acting on the smooth muscle tissue in peripheral air pathways.[8,94,96,183,212] LTC_4 and LTD_4 make the main contribution to the biological activity of SRS-A.[192] The leukotriene F_4 is 282 times less active than LTD_4.[143] LTD_4 contributes more than 90% of the biological hypersensitivity of human lungs. Leukotriene D_4 is 1000 times more active than LTC_4.[143,213] Since leukotrienes are secreted in the course of immunological action, it is extremely probable that cells serving as receptors of immunoglobulins E (or G in guinea-pigs) serve as sources of leukotrienes.[6] It has been suggested that SRS is liberated together with other mediators (histamine and chemotactic factors).[6,8]

The study of the action of LTD_4 as a function of concentration in the presence and absence of selective inhibitors of the biosynthesis of leukotrienes[8] has confirmed the existence of two separate receptors in peripheral airways. The study of the effects of LTC_4 and LTD_4 on pulmonary mechanics and the arterial blood pressure[93,213] has shown that both leukotrienes can contract human bronchi[23,214] (1000 times more actively than histamine)[8,213] and has confirmed the fact that LTC_4 and LTD_4 act as mediators in the bronchial spasm in bronchial asthma[93,138] and other instant hypersensitive responses.[211] The discovery of the biological activity of LTC_4 and LTD_4, which is comparable to the activity of histamine, explained why the attempts to alleviate the symptoms of bronchial asthma by antihistamine preparations were unsuccessful.[8] The fact that their precursor, arachidonic acid, can be converted into both prostaglandins and leukotrienes, explained the unfavourable effect of non-steroid anti-inflammatory agents on asthmatic symptoms in aspirin-sensitive patients.[211,212] Thus the arachidonic acid balance, disturbed by cyclo-oxygenase inhibitors, increases the concentration of leukotrienes with a corresponding increase of the intensity of the bronchial spasm. It has been possible to account for the successful treatment with corticosteroids in asthma therapy. These substances block the action of phospholipase A_2, which is involved in the cleavage of phospholipids and the secretion of arachidonic acid, which ultimately reduces the degree of biosynthesis of leukotrienes.[8] Studies on the possibility of the contraction of smooth muscles by a series of LTC_4 and LTD_4 analogues made it possible to formulate a structural requirement which must be met by compounds in order that they can manifest such biological activity.[8] Positional isomers with peptide substituents at sites other than C(6) exhibit a weak ability to contract smooth muscles.[23,93,94,102,104,146,213,214] It has been shown that the 5(*S*),6(*R*)-configuration of the substituents must be maintained.[102,215] Diastereoisomers are less active by two orders of magnitude. The fully saturated analogues of LTC_4, LTD_4, and LTE_4 are in essence inactive.[140] The change in the geometry of the

double bond from 11*Z* to 11*E* results in a significant loss of activity.[75,212] The biological activity of the 7-*cis*-isomer of LTD_4 amounts to only 1/10 of the activity of the natural LTC_4.[99] The results obtained in the study of 38 analogues of leukotrienes have shown[146,147] that their hydrophobic component and their stereochemical features influence the manifestation of their activity. Analogues lacking the natural structure of the hydrophobic component of the leukotriene molecule are much less active. The terminal amino-group in the peptide side chain, the carboxy-group of glycine, and the C(5)-hydroxy-group[114] are extremely important for the manifestation of the maximum biological activity. On the other hand, the carboxy-group at C(1) is not an important component. Changes in the aminoacid residue present in LTD_4 entail some loss of biological activity. These results have led to the conclusion that the receptor for LTD_4 as regards its binding and the generation of the response[114] must consist of a broad hydrophobic binding site, adjoining a multicomponent active section, which should bind the non-ionised C(1)-carboxy-group, the C(5)-hydroxy-group, and the peptide functional group containing a non-protonated amino-group.[114]

Leukotriene B_4 induces the contraction of various preparations of the smooth muscle of the guinea-pig.[8,144,211-216] The duodenum is the organ most sensitive to the action of LTB_4, but the greater stability of the parenchymal§ component of the lung renders this tissue more suitable for biological tests. Leukotriene B_4 is closely associated with inflammatory processes and behaves as a chemotactic[146,154,156] and chemokinetic factor for neutrophil and eosinophil, which arise in large amounts (at a concentration of 3×10^{-9} M) in inflammatory states.[162-166,212] This activity is greater by 2–3 orders of magnitude than the activity of mono-HETE. An increase of the content of LTB_4 has been observed in the synovial fluid of patients suffering from inflammatory diseases.[212,217] In combination with vasodilators of the type of PGE_2, leukotriene B_4 increases vascular permeability.[212,218] Prostaglandins synergise this effect, increasing the blood flow.[165,211,212] The release of lysozyme by the products of the metabolism of arachidonic acid[211,212,219] and apparently LTB_4 has been described. Even low concentrations of hydroxyeicosatetraenoic acids increase the content of cyclic guanosine monophosphate (c-GMP),[220] which is believed to promote, in its turn, the release of lysozyme[211] in phagocytotic processes. A change in the geometry of the double bonds of the conjugated triene[51,149,153] and of the configuration of the C(12)-hydroxy-group[156] in the natural structure lead to an appreciable decrease of the biological activity of LTB_4.[154,156] The unique lipoprotein nature of leukotrienes and their close relation with a whole series of pathological states underlying many diseases[8,211,212] [bronchial asthma, Quincke's (angioneurotic) oedema, vasomotor rhinitis, rheumatoid arthritis, psoriasis, etc.] and their role as long-acting regulators of nerve excitability by allergic reactions[211,212] have given rise to the question how molecules of these compounds function in the organism and how they are deactivated biochemically.[144] The answers to these questions can apparently be provided by a detailed study of the biological role of leukotrienes. Analogues and antogonists of leukotrienes, the inhibitors of their biosynthesis, the synthesis and study of the properties of which accelerate the search for effective antiallergic preparations, are of great interest for this purpose.

§ Parenchyma consists of a set of cellular elements of the organ which effects its specific functions. It can be made up of various types of tissue: blood generating tissue (spleen), epithelium (glands), nerve cells (nerve ganglia), etc.

REFERENCES

1. L.S.Wolfe, J.Neurochem., 1982, **38**, 1.
2. N.A.Nelson, R.C.Kelly, and R.A.Johnson, Chem. Eng.News. 1982, **60**, 30.
3. B.Samuelsson, M.Goldyne, E.Granström, M.Hamberg, S.Hammerström, and C.Malmsten, Ann.Rev.Biochem., 1978, **47**, 997.
4. B.Samuelsson, P.Borgeat, S.Hammarström, and R.C.Murphy, Prostaglandins, 1979, **17**, 785.
5. B.Samuelsson and S.Hammarström, Prostaglandins, 1980, **19**, 645.
6. P.Borget, J.Medicin.Chem., 1981, **24**, 121.
7. W.Dawson, Nature, 1980, **285**, 68.
8. R.H.Green and P.F.Lambeth, Tetrahedron, 1983, **39**, 1687.
9. E.J.Corey, Experientia, 1982, **38**, 1259.
10. W.Feldberg and C.H.Kellaway, J.Physiol., 1938, **94**, 187.
11. C.H.Kellaway and E.R.Trethewie, Quart.J.Exp. Physiol., 1940, **30**, 121.
12. W.E.Brocklehurst, J.Physiol., 1953, **120**, 16P.
13. W.E.Brocklehurst, J.Physiol., 1960, **151**, 416.
14. E.Anggärd, U.Bergvist, B.Högberg, K.Johansson, L.-L.Thon, and B.Uvnäs, Acta Physiol.Scand., 1963, **59**, 97.
15. B.Uvnäs, Biochem.Pharmacol., 1963, **12**, 439.
16. J.A.Grant and L.M.Lichtenstein, J.Immunol., 1974, 112, 897.
17. K.F.Austen, R.P.Orange, and D.J.Stechschulte, J.Immunol., 1970, **105**, 1087.
18. M.K.Bach and J.R.Brashler, J.Immunol., 1974, **113**, 2040.
19. E.G.Moore and R.P.Orange, J.Immunol., 1976, **116**, 392.
20. W.E.Brocklehurst, Prog.Allergy, 1962, **6**, 539.
21. M.K.Bach, J.R.Brashler, and R.R.Gorman, Prostaglandins, 1977, **14**, 21.
22. P.J.Piper, J.R.Tippins, H.R.Morris, and G.W.Taylor, Agents and Actions Suppl., 1979, **4**, 37.
23. T.J.Sullivan and C.W.Parker, J.Immunol., 1979, 122, 431.
24. B.A.Jakschik, S.Falkenhein, and C.W.Parker, Proc.Nat.Acad.Sci.USA, 1977, **74**, 4577.
25. P.Sirois, Clin.Res., 1978, **26**, 881.
26. P.Sirois, E.G.Moore, and R.P.Orange. Agents and Actions, 1979, **9**, 337.
27. B.A.Jackshik, A.Kuczycki, H.M.MacDonald, and C.W.Parker, J.Immunol., 1977, **119**, 618.
28. H.R.Morris, P.J.Piper, G.W.Taylor, and A.B.Tippins, J.Pharmacol., 1979, **67**, 179.
29. H.R.Morris, G.W.Taylor, P.J.Piper, P.Sirois, and A.B.Tippins, FEBS Letters,1978, **87**, 203.
30. R.C.Murphy, S.Hammarström, and B.Samuelsson, Proc.Nat.Akad.Sci.USA, 1979, **76**, 4275.
31. D.M.Engineer, H.R.Morris, P.J.Piper, and P.Sirois, Brit.J.Pharmacol., 1978, **64**, 211.
32. R.T.Holman, P.O.Egwin, and W.W.Christie, J.Biol. Chem., 1969, **224**, 1149.
33. R.P.Orange, R.C.Murphy, and K.F.Austen, J.Immunol., 1973, **113**, 316.
34. W.Dawson, R.I.Lewis, and R.Tomlinson, J.Physiol. (London), 1975, **247**, 37.
35. E.G.Moore and R.P.Orange, J.Immunol., 1976, **116**, 392.
36. M.K.Bach and J.R.Brasher, Life Sci., 1978, **23**, 2119.
37. H.R.Morris, G.W.Taylor, P.J.Piper, and J.R.Tippins, Agents and Actions Suppl., 1979, **6**, 27.

38. P.Borgeat, M.Hamberg, and B.Samuelsson, J.Biol. Chem., 1976, **251**, 7816.
39. P.Borgeat and B.Samuelsson, J.Biol.Chem., 1979, **254**, 7865.
40. P.Borgeat and B.Samuelsson, Proc.Nat.Acad.Sci. USA, 1979, **76**, 3213.
41. S.Hammarström, J.Biol.Chem., 1981, **256**, 2275.
42. S.Hammarström, J.Biol.Chem., 1980, **255**, 7095.
43. S.Hammarström, Biochem.Biophys.Acta, 1981, **663**, 575.
44. I.Orning, K.Bergström, and S.Hammarström, Eur.J. Biochem., 1981, **120**, 41.
45. E.J.Corey, D.A.Clark, A.Marfat, and G.Goto, Tetrahedron Letters, 1980, **21**, 3143.
46. E.J.Corey, A.E.Barton, and D.A.Clark, J.Amer. Chem.Soc., 1980, **102**, 4278.
47. S.R.Baker, J.R.Boot, and S.E.Morgan, Tetrahedron Letters, 1983, **24**, 4469.
48. S.Hammarström, J.Biol.Chem., 1981, **256**, 7712.
49. S.Dahlen, P.Hedquist, and S.Hammarström, Europ. J.Pharmacol., 1983, **86**, 207.
50. A.W.Ford-Hutchinson, M.A.Bray, M.V.Doig, M.E.Shipley, and M.J.Smith, Nature, 1980, **286**, 264.
51. E.J.Corey, A.Marfat, G.Goto, and F.Brion, J.Amer. Chem.Soc., 1980, **102**, 7984.
52. P.Borget and B.Samuelsson, J.Biol.Chem., 1979, **254**, 7865.
53. O.Rädmark, C.Malmsten, B.Samuelsson, D.A.Clark, G.Goto, A.Marfat, and E.J.Corey, Biochem.Biophys. Res.Comm., 1980, **92**, 954.
54. E.J.Corey, J.O.Albright, A.E.Barton, and S.-i.Hashimoto, J.Amer.Chem.Soc., 1980, **102**, 1435.
55. O.Rädmark, C.Malsten, B.Samuelsson, G.Goto, A.Marfat, and E.J.Corey, J.Biol.Chem., 1980, **255**, 1182.
56. E.J.Corey, A.Yoshinobu, and C.Mioskowski, J.Amer.Chem.Soc., 1979, **101**, 6748.
57. E.J.Corey, D.A.Clark, G.Goto, A.Marfat, C.Mioskowski, B.Samuelsson, and S.Hammarström, J.Amer.Chem.Soc., 1980, **102**, 1436.
58. A.L.Maycock, M.S.Anderson, D.M.Desousa, and F.A.Kuehe Jr., J.Biol.Chem., 1982, **257**, 13911.
59. N.Cohen, B.L.Banner, R.J.Lopresti, F.Wong, M.Rosenberger, Y.-Y.Lin, E.Thom, and A.A.Loebman, J.Amer.Chem.Soc., 1983, **105**, 3661.
60. P.Borgeat and B.Samualsson, Proc.Nat.Acad.Sci. USA, 1979, **76**, 2148.
61. S.Hammarström, R.C.Murphy, B.Samuelsson, D.A.Clark, C.Mioskowski, and E.J.Corey, Biochem. Biophys.Res.Comm., 1979, **91**, 1266.
62. S.Hammarström, B.Samuelsson, D.A.Clark, G.Goto, C.Mioskowski, and E.J.Corey, Biochem.Biophys.Res. Comm., 1980, **92**, 946.
63. O.Rädmark, C.Malmsten, and B.Samuelsson, Biochem.Biophys.Res.Comm., 1980, **96**, 1679.
64. C.W.Parker, M.M.Huber, M.K.Hoffman, and S.F.Falkenhein, Prostaglandins, 1979, **18**, 673.
65. H.Ohnishi, H.Kosuzume, Y.Kitamura, K.Yamaguchi, M.Nobuhara, and Y.Suzuki, Prostaglandins, 1980, **20**, 655.
66. Y.Girard, M.Larue, T.Jones, and J.Rokach, Tetrahedron Letters, 1982, **23**, 1023.
67. R.C.Murphy, W.R.Mathews, J.Rokach, and C.Fenselau, Prostaglandins, 1982, **23**, 201.
68. D.A.Clark, G.Goto, A.Marfat, E.J.Corey, S.Hammarström, and B.Samuelsson, Biochem. Biophys.Res.Comm., 1980, **94**, 1133.
69. H.R.Morris, G.W.Taylor, P.J.Piper, M.N.Samhoun, and J.R.Tippins, Prostaglandins, 1980, **19**, 185.
70. H.R.Morris, G.W.Taylor, J.Rokach, Y.Girard, P.J.Piper, J.R.Tippins, and M.N.Samhoun, Prostaglandins, 1980, **20**, 601.
71. L.Orning, S.Hammarström, and B.Samuelsson, Proc.Nat.Acad.Sci.USA, 1980, **77**, 2014.
72. H.R.Morris, G.W.Taylor, P.J.Piper, and J.R.Tippins, Nature, 1980, **285**, 104.
73. J.L.Fox, Chem.Eng.News, 1979, **57**, 19.
74. R.A.Lewis, K.F.Austen, J.M.Drazen, D.A.Clark, A.Marfat, and E.J.Corey, Proc.Nat.Acad.Sci.USA, 1980, **77**, 3710.
75. R.A.Lewis, J.M.Drazen, K.F.Austen, D.A.Clark, and E.J.Corey, Biochem.Biophys.Res.Comm., 1980, **96**, 271.
76. J.Houglum, I.-K.Pai, V.Atrache, D.E.Sok, and C.J.Sih, Proc.Nat.Acad.Sci.USA, 1980, **77**, 5688.
77. C.W.Parker, S.F.Falkenheim, and M.M.Huser, Prostaglandins, 1980, **20**, 863.
78. M.K.Bach and J.R.Brashler, Biochem.Biophys.Res. Comm., 1980, **93**, 1121.
79. M.K.Bach, J.R.Brashler, C.D.Brooks, and A.J.Neerken, J.Immunol., 1979, **122**, 160.
80. M.K.Bach, J.R.Brashler, S.Hammarström, and B.Samuelsson, J.Immunol., 1980, **125**, 115.
81. W.Jubiz, O.Rädmark, J.A.Lingren, C.Malmsten, and B.Samuelsson, Biochem.Biophys.Res.Comm., 1981, **99**, 976.
82. U.Lundberg, O.Rädmark, C.Malsten, and B.Samuelsson, FEBS Letters, 1981, **126**, 127.
83. R.L.Maas, A.R.Brash, and J.A.Oates, Proc.Nat. Acad.Sci.USA, 1981, **78**, 5523.
84. S.Narumiya, J.A.Salmon, F.II.Cottee, B.C.Weatherley, and R.J.Flower, J.Biol.Chem., 1981, **256**, 9583.
85. D.E.Sok, C.-O.Hau, W.-R.Shieh, B.-N.Zhou, and C.J.Sih, Biochem.Biophys.Res.Comm., 1982, **104**, 1363.
86. C.P.A.Van Os, G.P.M.Rijke-Schilder, H.Van Halbeek, J.Verhagen, and J.F.G.Viliengenthart, Biochim.Biophys.Acta, 1981, **663**, 177.
87. J.R.Falck and S.Manna, Tetrahedron Letters, 1982, **23**, 1755.
88. E.Oliw, J.A.Lawson, A.R.Brash, and J.A.Oates, J.Biol.Chem., 1981, **256**, 9924.
89. S.Manna, J.R.Falch, N.Chacos, and J.Capdevila, Tetrahedron Letters, 1983, **24**, 33.
90. J.Ackroyd and F.Scheinmann, Chem.Soc.Rev., 1982, **11**, 321.
91. E.J.Corey and G.Schmidt, Tetrahedron Letters, 1979, **5**, 399.
92. J.Rokach, Y.Girard, Y.Guindon, G.Atkinson, M.Larue, R.N.Young, P.Masson, and G.Holme, Tetrahedron Letters, 1980, **21**, 1485.
93. M.Rosenberger and C.Neukom, J.Amer.Chem.Soc., 1980, **102**, 5425.
94. M.Rosenberger, C.Neukom, and E.R.Aig, J.Amer. Chem.Soc., 1983, **105**, 3656.
95. J.G.Gleasson, B.D.Bryan, and C.M.Kinzig, Tetrahedron Letters, 1980, **21**, 1129.
96. S.R.Baker, W.B.Jamieson, S.W.McKay, S.E.Morgan, D.M.Rackham, W.J.Ross, and P.R.Shrubshall, Tetrahedron Letters, 1980, **21**, 4123.
97. E.J.Corey, A.Marfat, and G.Goto, J.Amer.Chem. Soc., 1980, **102**, 6607.
98. R.H.Wollenberg, Tetrahedron Letters, 1978, **19**, 717.
99. J.Ernest, H.J.Main, and R.Menasse, Tetrahedron Letters, 1982, **23**, 167.

100. E.J.Corey, D.A.Clark, G.Goto, A.Marfat, C.Mioskowski, B.Samuelsson, and S.Hammarström, J.Amer.Chem.Soc., 1980, **102**, 3663.
101. E.J.Corey, H.Niwa, J.R.Falck, C.Mioskowsky, Y.Arai, and A.Marfat, in "Advances in Prostaglandin and Thromboxane Research" (Edited by B.Samuelsson and R.Paoletti), Raven, New York, 1980, Vol.6, p.19.
102. E.J.Corey and D.A.Clark, Tetrahedron Letters, 1980, **21**, 3547.
103. E.J.Corey, S.Hashimoto, and A.E.Barton, J.Amer. Chem.Soc., 1981, **103**, 721.
104. E.J.Corey, H.Niwa, and J.Knolle, J.Amer.Chem. Soc., 1978, **100**, 1942.
105. J.Rokach, R.W.Young, M.Kakushi, C.-K.Lau, R.Seguin, R.Frenette, and Y.Guindon, Tetrahedron Letters, 1981, **22**, 979.
106. J.Rokach, R.Zamboli, C.Lau, and Y.Guindon, Tetrahedron Letters, 1981, **22**, 2759.
107. J.Rokach, C.Lau, R.Zamboli, and Y.Guindon, Tetrahedron Letters, 1981, **22**, 2673.
108. K.C.Nicolaou, M.R.Pavia, and S.P.Seitz, Tetrahedron Letters, 1979, **20**, 2327.
109. K.M.Sun and B.Fraser-Reid, Canad.J.Chem., 1980, **58**, 2732.
110. B.M.Trost and D.P.Curran, Tetrahedron Letters, 1981, **22**, 1287.
111. D.P.Mariotti and J.R.Bentick, Tetrahedron Letters, 1981, **22**, 3657.
112. R.Zamboni, S.Milette, and J.Rokach, Tetrahedron Letters, 1983, **24**, 4899.
113. N.Cohen, B.L.Banner, and R.J.Lopresti, Tetrahedron Letters, 1980, **21**, 4163.
114. E.J.Corey and G.Goto, Tetrahedron Letters, 1980, **21**, 3463.
115. J.C.Buck, F.Ellis, and P.C.North, Tetrahedron Letters, 1982, **23**, 4161.
116. G.A.Tolstikov, M.S.Miftakhov, and A.G.Tolstikov, Izv.Akad.Nauk SSSR, Ser.Khim., 1984, 475.
117. K.C.Nicolaou, N.A.Petasis, and S.P.Seitz, J.Chem. Soc., Perkin Trans.I, 1981, 1195.
118. Y.Arai, M.Konno, K.Shimoji, Y.Konishi, H.Niwa, M.Toda, and M.Hayashi, Chem.Pharm.Bull., 1982, **30**, 379.
119. G.A.Tolstikov, M.S.Miftakhov, and A.G.Tolstikov, Zhur.Org.Khim., 1984, **20**, 2278.
120. G.A.Tolstikov, M.S.Miftakhov, and A.G.Tolstikov, Akad.Nauk Kazakh SSR, Ser.Khim., 1984(4), 41.
121. G.A.Tolstikov, M.S.Miftakhov, and A.G.Tolstikov, Izv. Akad.Nauk SSSR, Ser. Khim., 1983, 1452.
122. E.J.Corey, H.Park, A.Barton, and Y.Nii, Tetrahedron Letters, 1980, **21**, 4243.
123. R.Zamboni and J.Rokach, Tetrahedron Letters, 1983, **24**, 331.
124. S.Okuyama, S.Miyamoto, K.Shimoji, Y.Konishi, D.Fukushima, H.Niwa, Y.Arai, M.Toda, and M.Hayashi, Chem.Pharm.Bull., 1982, **30**, 2453.
125. E.J.Corey, J.Kang, and B.C.Laguzza, Tetrahedron Letters, 1983, **24**, 4913.
126. J.W.Patterson and D.V.K.Murthy, J.Org.Chem., 1983, **48**, 4413.
127. T.Katsuki and K.B.Sharpless, J.Amer.Chem.Soc., 1980, **102**, 5947.
128. B.E.Rossiter, T,Katsuki, and K.B.Sharpless, J.Amer.Chem.Soc., 1981, **103**, 464.
129. M.S.Miftakhov, A.G.Tolstikov, and G.A.Tolstikov, Zhur.Org.Khim., 1984, **20**, 678.
130. E.J.Corey, E.J.Trubulski, L.S.Melvin, K.C.Nicolaou, J.A.Secrist, R.Lett, P.W.Sheldrake, J.R.Falck, D.J.Brunelle, M.F.Haslanger, S.Kim, and S.Yoo, J.Amer.Chem.Soc., 1978, **100**, 4618.
131. E.J.Corey, H.Niwa, and J.R.Falck, J.Amer.Chem. Soc., 1979, **101**, 586.
132. E.J.Corey and D.A.Clark, Tetrahedron Letters, 1979, 2875.
133. E.J.Corey, S.Iguchi, and J.O.Albright, Tetrahedron Letters, 1983, **24**, 37.
134. T.Fukuyama, K.Akasaka, D.S.Karenewsky, C.-L.J.Wang, G.Schmidt, and Y.Kishi, J.Amer. Chem.Soc., 1979, **101**, 262.
135. N.A.Porter, J.Logan, and V.Kontoyiannidou, J.Org.Chem., 1979, **44**, 3177.
136. V.Atrache, J.-K.Pai, D.-E.Sok, and C.J.Sih, Tetrahedron Letters, 1981, **22**, 3443.
137. E.J.Corey and A.E.Barton, Tetrahedron Letters, 1982, **23**, 2351.
138. S.R.Baker, W.B.Jamieson, D.J.Osborne, and W.J.Ross, Tetrahedron Letters, 1981, **22**, 2505.
139. B.Spur, A.Crea, W.Peters, and W.König, Tetrahedron Letters, 1983, **24**, 2135.
140. R.N.Young, W.Coombs, Y.Guindon, J.Rokach, D.Ethler, and R.Hall, Tetrahedron Letters, 1981, **22**, 4933.
141. L.Örning and S.Hammarström, FEBS Letters, 1983, **153**, 253.
142. E.J.Corey and D.J.Hoover, Tetrahedron Letters, 1982, **23**, 3463.
143. F.Ellis and P.C.North, Tetrahedron Letters, 1982, **23**, 3735.
144. E.J.Corey, H.Oh, and A.E.Barton, Tetrahedron Letters, 1982, **23**, 3467.
145. W.H.Pirkie and I.M.Finn, J.Org.Chem., 1981, **46**, 2935.
146. Y.M.Drazen, R.A.Lewis, K.F.Austen, M.Toda, F.Brion, A.Marfat, and E.J.Corey, Proc.Nat.Acad. Sci.USA, 1981, **78**, 3195.
147. R.A.Lewis, J.M.Drazen, K.F.Austen, M.Toda, F.Brion, A.Marfat, and E.J.Corey, Proc.Nat.Akad. Sci.USA, 1981, **78**, 4579.
148. R.M.Palmer, R.J.Stepney, G.A.Higgs, and K.E.Eakins, Prostaglandins, 1980, **20**, 411.
149. E.J.Corey, P.B.Hopkins, J.E.Munro, A.Marfat, and S.Hashimoto, J.Amer.Chem.Soc., 1980, **102**, 7986.
150. E.J.Corey, A.Marfat, J.Munroe, Kwan Soo Kim, P.B.Hopkins, and F.Brion, Tetrahedron Letters, 1981, **22**, 1077.
151. E.J.Corey, A.Marfat, and B.C.Laguzza, Tetrahedron Letters, 1981, **22**, 3339.
152. E.J.Corey, A.Marfat, and D.J.Hoover, Tetrahedron Letters, 1981, **22**, 1587.
153. P.Sirois, S.Poy, P.Borgeat, S.Picard, and E.J.Corey, Biochem.Biophys.Res.Comm., 1981, **99**, 385.
154. Y.Guindon, R.Zamboni, C.K.Lau, and J.Rokach, Tetrahedron Letters, 1982, **23**, 739.
155. J.Rokach, R.Zamboni, C.K.Lau, and Y.Guindon, Tetrahedron Letters, 1981, **22**, 2759.
156. R.Zamboni and J.Rokach, Tetrahedron Letters, 1982, **23**, 2631.
157. M.Y.H.Wong and G.R.Gray, J.Amer.Chem.Soc., 1978, **100**, 3548.
158. S.K.Chandhary and O.Hernandez, Tetrahedron Letters, 1980, **21**, 835.
159. L.S.Mills and P.C.North, Tetrahedron Letters, 1983, **24**, 409.
160. C.Funganti, S.Serri, and C.Zirotti, Tetrahedron Letters, 1983, **24**, 5285.

161. G.Hansson, L.A.Lindgren, S.-E.Dalen, P.Hedguist, and B.Samuelsson, FEBS Letters, 1981, **130**, 107.
162. J.Palmblad, A.-M.Uden, J.A.Lindgren, O.Rädmark, G.Hansson, and C.L.Malsten, FEBS Letters, 1982, **114**, 81.
163. S.J.Zamboni, J.A.Lindgren, H.-E.Claesson, C.Malsten, and B.Samuelsson, FEBS Letters, 1981, **23**, 4751.
164. S.J.Feinmark, J.A.Lindgren, H.-E.Claesson, C.Malsten, and B.Samuelsson, FEBS Letters, 1981, **136**, 141.
165. M.A.Bray, A.W.Ford-Hutchinson, and M.J.H.Smith, Prostaglandins, 1981, **22**, 213.
166. E.J.Goetzl and W.C.Pickett, J.Immunol., 1980, **125**, 1789.
167. A.L.Gemal and J.L.Luche, Tetrahedron Letters, 1981, **22**, 4077.
168. E.J.Corey, S.Pyne, and Su Wei-Guo, Tetrahedron Letters, 1983, **24**, 4883.
169. R.A.Murphy, W.C.Pickett, B.R.Culp, and W.R.Lands, Prostaglandins, 1981, **22**, 613.
170. E.J.Corey and J.Kang, J.Amer.Chem.Soc., 1982, **104**, 4724.
171. E.J.Corey, A.Marfat, J.R.Falck, and J.O.Albright, J.Amer.Chem.Soc., 1980, **102**, 1433.
172. J.Rokach, J.Adams, and R.Perrey, Tetrahedron Letters, 1983, **24**, 5185.
173. J.Turk, T.H.Rand, R.L.Maas, J.A.Lawson, A.R.Brash, L.J.Roberts, D.G.Colley, and J.A.Oates, Biochim.Biophys.Acta, 1983, **750**, 78.
174. J.R.Falck, S.Manna, A.K.Siddhanta, and J.Capdevila, Tetrahedron Letters, 1983, **24**, 5715.
175. J.R.Falck, S.Manna J.Capdevila, and J.D.Buynak, Tetrahedron Letters, 1983, **24**, 5719.
176. C.D.Perchonock, J.A.Finkelstein, I.Uzinskas, J.G.Gleason, H.M.Sarau, and B.L.Cieslinski, Tetrahedron Letters, 1983, **24**, 2457.
177. N.A.Porter, J.Logan, and V.Kontoyiannidou, J.Org.Chem., 1979, **44**, 3177.
178. N.A.Porter, R.A.Wolf, E.M.Yarbro, and H.Weenen, Biochem.Biophys.Res.Comm., 1979, **89**, 1058.
179. M.I.Thomas, J.T.O'Flaherty, S.Cousart, and C.E.McCall, Prostaglandins, 1982, **23**, 265.
180. A.J.Sbarra and M.L.Karnovsky, J.Biol.Chem., 1959, **234**, 1355.
181. J.E.Baldwin, N.V.Reed, and E.J.Thomas, Tetrahedron, 1981, Suppl.1, **37**, 263.
182. J.Corey and S.Hashimoto, Tetrahedron Letters, 1981, **22**, 299.
183. R.Zamboni and J.Rokach, Tetrahedron Letters, 1983, **24**, 999.
184. K.Eiter, F.Lieb, H.Disselnkotter, and H.Oediger, Annalen, 1978, 658.
185. E.J.Corey and J.Kang, J.Amer.Chem.Soc., 1981, **103**, 4618.
186. G.Just and C.Luthe, Tetrahedron Letters, 1981, **23**, 1331.
187. G.Just, C.Luthe, and P.Polvin, Tetrahedron Letters, 1982, **23**, 2285.
188. E.J.Corey and J.E.Munroe, J.Amer.Chem.Soc., 1982, **104**, 1752.
189. E.J.Corey and H.Park, J.Amer.Chem.Soc., 1982, **104**, 1750.
190. D.M.Bailey and L.W.Chakrin, Ann.Rep.Med.Chem., 1981, **16**, 213.
191. J.Ackroyd, A.Manro, and F.Scheinmann, Tetrahedron Letters, 1983, **24**, 5139.
192. E.J.Corey and P.T.Lansbury, J.Amer.Chem.Soc., 1983, **105**, 4093.
193. C.W.Parker and S.Aykent, Biochem.Biophys.Res. Comm., 1982, **109**, 1011.
194. E.J.Corey, M.M.Mehrotra, and J.R.Cashman, Tetrahedron Letters, 1983, **24**, 4917.
195. E.J.Corey and M.M.Mehrotra, Tetrahedron Letters, 1983, **24**, 4921.
196. S.Hammarström, Biochim.Biophys.Acta, 1977, **487**, 517.
197. G.I.Myagkova, L.A.Yakusheva, O.O.Bordyukova, V.B.Shatskaya, and R.P.Evstigneeva, Bioorg.Khim., 1982, **8**, 255.
198. L.A.Yakusheva, G.I.Myagkova, O.O.Bordyukova, and R.P.Evstigneeva, Bioorg.Khim., 1982, **8**, 422.
199. E.J.Corey and J.Kang, Tetrahedron Letters, 1982, **23**, 1651.
200. P.Jutzt and J.Baumgärtner, J.Organomet.Chem., 1978, **148**, 257.
201. E.J.Corey, D.Floyd, and B.Lipshutz, J.Org.Chem., 1978, **43**, 3418.
202. A.I.Rachlin, N.Wasyliw, and M.W.Goldberg, J.Org.Chem., 1961, **26**, 2688.
203. G.I.Myagkova, Yu.Yu.Belosludtsev, P.M.Demin, L.A.Yakusheva, and R.P.Evstigneeva, Bioorg. Khim., 1985, **12**, 1693.
204. J.M.Osbond and J.C.Wickens, Chem.Ind., 1959, 1288.
205. A.A.Kraveskii, Yu.B.Pyatnova, G.I.Myagkova, I.K.Sarycheva, and N.A.Preobrazhenskii, Dokl.Akad.Nauk SSSR, 1962, **146**, 1349.
206. R.I.Eryer, N.W.Gilman, and B.C.Holland, J.Org. Chem., 1975, **40**, 348.
207. E.J.Corey, S.S.Kantner, and P.T.Lansburg, Tetrahedron Letters, 1983, **24**, 265.
208. C.Walsh, Tetrahedron, 1982, **38**, 871.
209. P.Baret, E.Barreiro, A.E.Greene, L.-L.Luche, M.-A.Texeira, and P.Crabbe, Tetrahedron Letters, 1979, **35**, 2931.
210. Y.Arai, Shimojk, M.Konno, Y.Konishi, S.Okuyama, S.Iguchi, M.Hayashi, T.Miyamoto, and M.Toda, J.Med.Chem., 1983, **26**, 72.
211. J.L.Marx, Science, 1982, **215**, 1380.
212. P.J.Pipper, L.G.Lettes, M.N.Samhoun, and J.R.Tippins, Allergologie, 1982, **5**, 138.
213. J.M.Drazen, K.F.Austen, R.A.Lewis, D.A.Clark, G.Goto, A.Marfat, E.J.Corey, Proc.Nat.Acad. Sci.USA, 1980, **77**, 4354.
214. S.-E.Dahlen, P.Hedqvist, and B.Hammarström, Nature, 1980, **288**, 484.
215. B.S.Tsai, P.Bernstein, R.A.Macia, J.Conaty, and R.D.Krell, Prostaglandins, 1982, **23**, 489.
216. P.Sirois, P.Borget, and A.Jeanson, J.Pharm. Pharmacol., 1981, **83**, 466.
217. C.B.Klickstein, C.Shapleigh, and E.J.Goetzl, J.Clin.Invest., 1980, **66**, 1166.
218. M.A.Bray, F.M.Cunningham, A.W.Ford-Hutchinson, and M.J.H.Smith, Brit.J.Pharmacol., 1981, **72**, 483.
219. P.H.Naccache, H.J.Showell, E.L.Becker, and R.I.Shaafi, Biochem.Biophys.Res.Comm., 1979, **87**, 292.
220. E.J.Goetzl, New Eng.J.Med., 1980, **303**, 822.
221. B.Samuelsson, Angew.Chem.Int.Ed.Engl., 1983, **22**, 805.
222. E.G.Lapetina and W.Swiss, Life Sciences, 1983, **33**, 1011.
223. E.P.Frolov, I.A.Rudakov, and O.B.Svyatkina, Uspekhi Sov.Biol., 1984, **97**, 413.

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