# Synthesis of Leukotrienes and Lipoxygenase Products

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Following extensive work on the cyclooxygenase pathways of arachidonic acid metabolism,[1] which give rise to the prostaglandins, Samuelsson and collaborators[2] discovered the first example of a lipoxygenase-derived product, 12-HPETE, in mammalian systems. Prior to this discovery, lipoxygenases had been found only in plant tissues. This finding by the Karolinska group was destined to open up a whole new and exciting area of arachidonic acid metabolism[3] which is still under vigorous investigation. Probably the single most exciting development in this area was the discovery in 1979 by Murphy, Hammarström, and Samuelsson[4] that the long-known[5] but very elusive "slow-reacting substance of anaphylaxis" (SRS-A)[6] was in fact a proudct of the mammalian lipoxygenase pathway of arachidonic acid metabolism.

Because of their great biological importance and the difficulty in isolating them in quantity from natural sources, a considerable chemical effort has been carried out to synthesize these new compounds arising from the lipoxygenase metabolism of arachidonic acid. The major synthetic efforts have been carried out in the laboratories of Professor E. J. Corey at Harvard University and in the laboratories of Merck Frosst Canada in Montreal, with a number of significant contributions from many other laboratories.[7]

Two general remarks concerning the synthetic efforts in this area are worth making. First, since none of the natural products in question has yet been obtained crystalline, no X-ray structural verification has been possible. Consequently, classical structural verification by total synthesis and comparison of the natural with the synthetic materials has been far from an academic exercise. Second, because of the instability of many of the leukotienes, they are in many cases unavailable from natural sources (e.g., the $LTA_4$-type leukotrienes). Since others have been isolated only in microgram quantities from cellular sources, by far the main source of leukotrienes today is from synthetic materials. The most important and extensive series of products discovered to date are those derived from the lipoxygenase-initiated reaction at position 5 of arachidonic acid.

A note on nomenclature in this field is in order. Leukotrienes A–F are referred to as $LTX_4$, where LT refers to leukotriene and X denotes the specific leukotriene. $LTA_4$ is the triene 5(*S*),6(*S*)-epoxide, and $LTB_4$, the enzymatic hydrolysis product of $LTA_4$, is the 5-(*S*),12(*R*)-dihydroxy triene. $LTC_4$, -$D_4$, -$E_4$, and -$F_4$ refer to the peptidoleukotrienes which adorn the fatty acid chain through a cysteinyl sulfide linkage at $C_6$. The subscript "4" refers to the total number of double bonds in the $C_{20}$ chain. The acronym HPETE describes the hydroperoxyeicosatetraenoic acid product that results from lipoxygenase enzymes. A HETE is a monohydroxy eicosanoid.

These natural products are the subject of intense studies by the scientific community. The relative importance of these metabolites, the intricate ways by which they exert their bilogical action, and the control they provide at the cellular level of the various steps of the metabolism of arachidonic acid are far from being understood. There is, however, some knowledge of their action that has emerged over the past few years. SRS-A, which is considered now to be a mixture of $LTC_4$, $LTD_4$, and $LTE_4$, the relative amounts of which vary with the cellular system and the tissue from which they are isolated, is a potent contractile substance of smooth muscle. It is, for example, 3000 times more potent than histamine. It is considered at present to be released in an anaphylactic reaction and may be a prime mediator in allergic diseases such as asthma, allergic rhinitis, etc. $LTC_4$, $LTD_4$, and $LTE_4$ also cause important changes in vascular permeability.

$LTB_4$ has been shown to be one of the most potent chemotactic factors (attracts white blood cells across membranes) known for leukocytes. In the normal state, it is presumed that $LTB_4$ attracts polymorphonuclear leukocytes (PMNs) to the site of inflammation and helps clean up the inflammation. In disease states, it

(1) See various authors in: "Advances in Prostaglandin and Thromboxane Research"; Samuelsson, B., Paoletti, R., Eds.; Raven Press: New York, 1976; Vol. 1.

(2) Hamberg, M.; Samulesson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1972**, *71*, 3400.

(3) For reviews, see: (a) Samuelsson, B. *Pure Appl. Chem.* **1981**, *53*, 1203. (b) Marx, J. L. *Science (Washington, D.C.)* **1982**, *215*, 1380. (c) See varius authors, in: "Advances in Prostaglandin, Thromboxane, and Leukotriene Research"; Samuelsson, B., Paoletti, R., Eds.; Raven Press: New York, 1982; Vol. 9. (d) Bailey, D. M.; Casey, F. B. *Annu. Rep. Med. Chem.* **1982**, *17*, Chapter 21.

(4) Murphy, R. C.; Hammarström, S.; Samuelsson, B. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 4275.

(5) (a) Feldberg, W.; Kellaway, C. H. *J. Physiol. (London)* **1938**, *94*, 187. (b) Kellaway, C. H.; Trethewie, E. R. *Q. J. Exp. Physiol. Cogn. Med. Sci.* **1940**, *30*, 121.

(6) Orange, R. P.; Austen, K. F. *Adv. Immunol.* **1969**, *10*, 105.

(7) Other important contributors include: (a) Corey, E. J. *Experientia* **1982**, *38*, 1259. (b) Gleason, J. G.; Bryan, D. B.; Kinzig, C. M. *Tetrahedron Lett.* **1980**, *21*, 1129. (c) Green, R. H.; Lambeth, P. F. *Tetrahedron Lett.* **1983**, *24*, 1687. Buck, J. C.; Ellis, F.; North, P. C. *Tetrahedron Lett.* **1982**, *23*, 4161. (d) Just, G.; Luthe, C. *Tetrahedron Lett.* **1982**, *23*, 1331. (e) Hougham, J.; Pai, J.-K.; Atrache, V.; Sok, D.-E.; Sih, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **1980**, *77*, 5688. Atrache, V.; Pai, J.-K.; Sok, D.-E.; Sih, C. J. *Tetrahedron Lett.* **1981**, *22*, 3433. (f) Ernest, I.; Main, A. J.; Menassé, R. *Tetrahedron Lett.* **1982**, *23*, 167. (g) Rosenberger, M.; Newkom, C.; Aig, E. R. *J. Am. Chem. Soc.* **1983**, *105*, 3656. Cohen, N.; Banner, B. L.; Lopresti, R. L.; Wong, F.; Rosenberger, M.; Lin, Y.-Y.; Thom, E.; Liebman, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661. (h) Chiral epoxidation to make intermediate **10**: Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 464.

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Julian Adams was born in Quebec City, Canada, in 1954. He received his B.Sc. from McGill University, Montreal (1977), and his Ph.D. from M.I.T. in 1981. After spending a year on a postdoctoral fellowship at Columbia University, New York, he joined Merck Frosst Canada Inc. in 1982 as a Senior Research Chemist.

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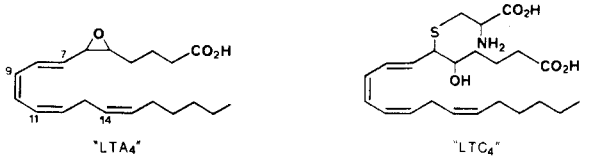
Chart I
Originally Proposed Structures for $LTA_4$ and $LTC_4$




is speculated that the PMNs degranulate and release their contents (e.g., lysosomal enzymes) at the site of inflammation and cause serious tissue damage that can be exacerbated by further amounts of $LTB_4$ released. $LTC_4$, $LTD_4$, $LTE_4$, and $LTB_4$ have now been shown to be produced by various cells (platelets, neutrophils, macrophages, mast cells, etc.) on stimulation. They are produced in varying amounts depending on the source of the stimulus and the type of cell.[3]

Because of their perceived key roles in a number of disease states, we embarked upon a program of total synthesis of the major leukotrienes immediately following Samuelsson's structure proposal in May 1979. This ongoing program has had the objective of making this interesting class of compounds readily available in order to fully characterize their biological properties. This knowledge should improve the ability of the medical community to treat the disease states in which they are implicated and facilitate the development of drugs for the treatment of these maladies.

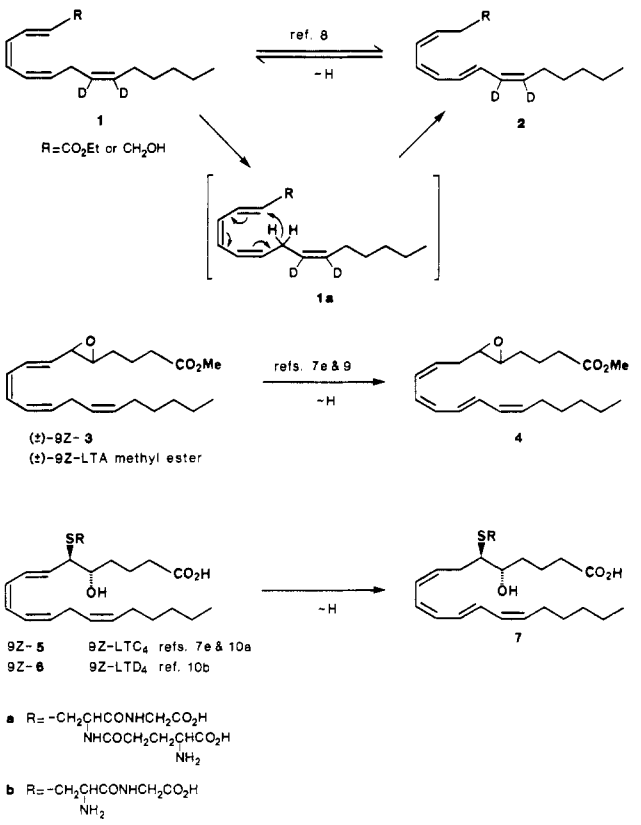
## First Synthesis of $LTA_4$, $LTC_4$, $LTD_4$, and $LTE_4$ and the Problem of Double-Bond Stereochemistry in the Leukotrienes

The history of the structure assignments for the leukotrienes is somewhat unusual in modern natural products chemistry as the complete structures were only assigned after comparison with totally synthetic material of known relative and absolute stereochemistry. In his original proposal of structures for $LTA_4$ and $LTC_4$, Samuelsson pointed out that there remained several areas of uncertainty in the structures.[4] The structures he suggested were as shown in Chart I, and the areas of uncertainty were (a) the relative and absolute stereochemistry at $C_5$ and $C_6$, (b) whether or not the cysteine unit was further derivatized, and (c) the geometry of the double bonds at $C_7$ and $C_9$.

The Merck Frosst group first noted something unexpected in the behavior of compounds in which the conjugated triene unit in the Leukotrienes possessed the *E–Z–Z* stereochemistry, as depicted in Chart I. In the early stages of our first synthesis of the Leukotrienes,[8] compound **1** (R = $CO_2Et$ or $CH_2OH$, Scheme I) underwent a [1,7]-sigmatropic hydrogen migration and rearranged spontaneously at room temperature over a 24-h period to a 1:2 mixture of **1** and **2**. We concluded that as there was no obvious reason why the structures of $LTA_4$ and $LTC_4$, as depicted in Chart I, should not undergo a similar rearrangement, Samuelsson's tentatively proposed stereochemistry required revision. Samuelsson's evidence for the *Z* geometry of the $C_{11}$ and $C_{14}$ double bonds being based on solid grounds,[4] it was most reasonable to suppose that the $C_9$ double bond must have *E* stereochemistry rather than *Z*. With *E* geometry at $C_{9,10}$ it becomes sterically impossible for the

(8) Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Holme, G. *Tetrahedron Lett.* **1980**, *21*, 1485.

Scheme I
[1,7]-Hydrogen Migrations in Leukotriene-like Structures




molecule to assume a cyclic transition state, such as **1a**, which is necessary for the [1,7]-hydrogen migration to occur. This till left open the question of the correct geometry at the $C_7$ double bond, but we assumed that the thermodynamically more favorable *E* configuration was most probable. Subsequent synthesis and comparison with the natural products then confirmed the proposed revision of the stereochemistry of the $C_9$ double bond.

Subsequently, a group at the Lilly Research Centre[9] and Sih and co-workers[7e] prepared the (±)-$LTA_4$ isomer (±)-(9*Z*)-**3** (Scheme I) with the originally proposed 9*Z* geometry (Chart III). Both groups confirmed our predictions and found that it rearranged readily at room temperature to the conjugated tetraene **4**. Both groups also prepared the 9*Z* isomers of $LTC_4$ and $LTD_4$ and found that these functionalized leukotrienes also underwent the same [1,7]-hydrogen migration to produce the conjugated tetraene.

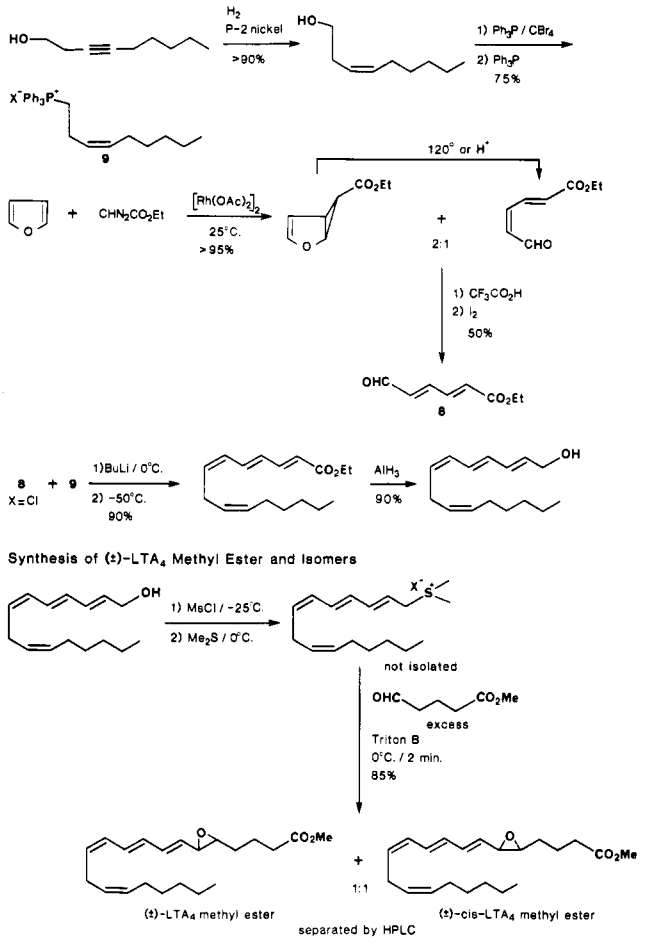
## Synthesis of $LTA_4$

Scheme II shows the details of our first synthesis of $LTA_4$.[8] The $LTA_4$ obtained this way is a racemic mixture of the cis and trans isomers. It is a very efficient synthesis and lends itself well to large-scale synthesis. The muconic acid semialdehyde **8** was a key intermediate in this synthesis. It has the attribute of readily differentiated functionality on either end of the diene unit. It was originally prepared photochemically,

(9) Baker, S. R.; Jamieson, W. B.; McKay, S. W.; Morgan, S. E.; Rackham, D. M.; Ross, W. J.; Shrubsall, P. R. *Tetrahedron Lett.* **1980**, *21*, 4123.

(10) (a) Baker, S. R.; Jamieson, W. B.; Osborne, O. J.; Ross, W. J. *Tetrahedron Lett.* **1981**, *22*, 2505. (b) Baker, S. R.; Boot, J. R.; Osborne, W. B.; Osborne, D. J.; Swentman, W. J. F. *Biochem. Biophys. Res. Commun.* **1981**, *103*, 1258.

Scheme II
Preparation of Intermediates for (±)-$LTA_4$ Synthesis




but a major improvement was made with the finding that the addition of ethyl diazoacetate to furan can be catalyzed very efficiently by rhodium acetate.

A bad step in the original report was the use of LDA for the condensation of the sulfonium ylide with methyl 4-formylbutyrate. This has been improved since, and Triton B was found to be the base of choice, yielding 85% of the desired products.

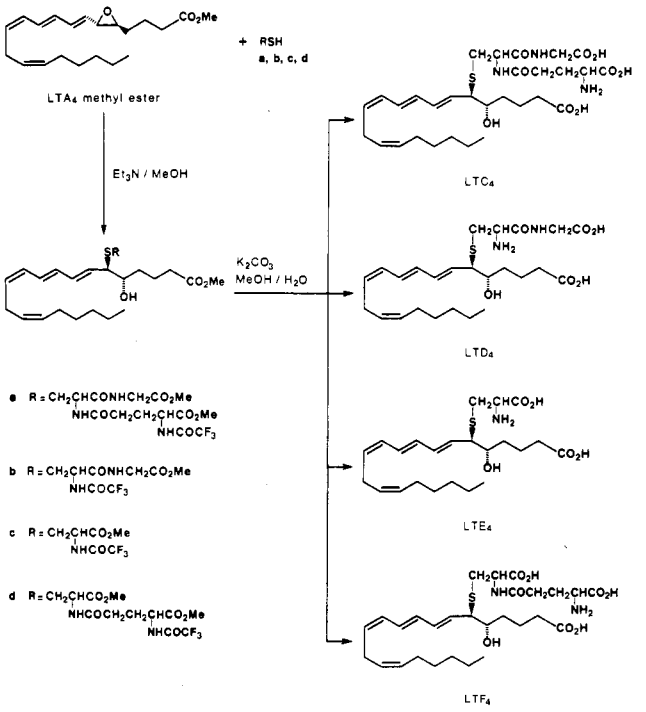
## Synthesis of $LTC_4$, $LTD_4$, and Isomers

We have performed the ring opening of the racemic *cis*- and *trans*-$LTA_4$ with glutathione, cysteinyl-glycine, and cysteine to yield a total of four diastereoisomers in each case. Scheme III illustrates the transformations leading to $LTC_4$, $LTD_4$, $LTE_4$, and $LTF_4$ starting with optically pure $LTA_4$. The natural isomers (5*S*,6*R*)-$LTC_4$, -$LTD_4$, and -$LTE_4$ are much more potent in their biological activities than the nonnatural isomers. The stereochemistry of the isomers has been assigned unambiguously by the stereospecific syntheses of the four isomers of $LTA_4$ described later.

The first preparation of $LTC_4$, $LTD_4$, and $LTE_4$ was performed by reaction with the corresponding trimethylsilyl sulfides.[8,11] The base-catalyzed ring opening gives cleaner reaction products and is the method used subsequently in all such transformations. We found that the unprotected peptides glutathione, cysteinyl-glycine, and cysteine, as well as their methyl

(11) Guindon, Y.; Young, R. N.; Frenette, R. *Synth. Commun.* **1981**, *11*, 391.

Scheme III
Synthesis of $LTC_4$, $LTD_4$, $LTE_4$, and $LTF_4$ from Optically Active $LTA_4$




esters can also be used for the reaction with $LTA_4$ and isomers. The unprotected peptides, however, gave consistently lower yields of products.

The biochemical conversions of $LTC_4$ to $LTD_4$ by the enzyme γ-glutamyl transpeptidase and $LTD_4$ to $LTE_4$ by a protease have been described. Thus, depending on the availability of these enzymes in various tissues and cells, one or more of the three leukotrienes are obtained as a mixture. As was mentioned earlier, the slow-reacting substance of anaphylaxis (SRS-A) is now considered to be a mixture of $LTC_4$, $LTD_4$, and $LTE_4$. $LTF_4$ has not yet been shown to be a natural product. It is a weak agonist on the guinea pig ileum and is at present under further investigation.[12]

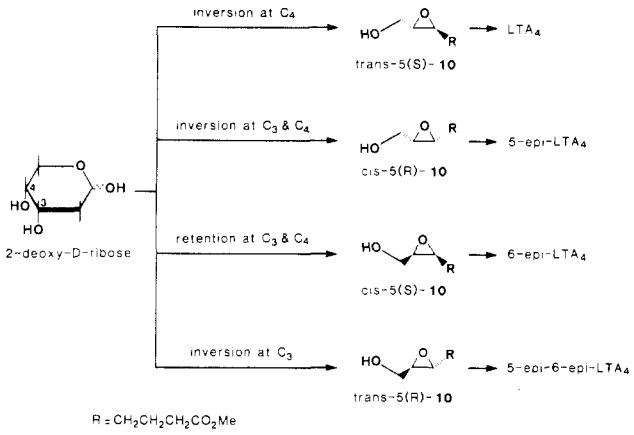
All the syntheses reported by our group and others for the leukotriene components of SRS-A, namely $LTC_4$, $LTD_4$, and $LTE_4$, used $LTA_4$ as starting material. Hence for all intents and purposes all the various syntheses we have devised for the preparation of $LTA_4$ have served for the preparation of the various leukotrienes using one or more of the simple methods described here. Likewise, with the same methodology, all the isomers of $LTA_4$ later were converted to the various isomers of $LTC_4$, $LTD_4$, $LTE_4$, and $LTF_4$. In all cases the ring opening by the sulfur nucleophiles of all the various triene epoxy derivatives occurs at $C_6$ with inversion of configuration at that center.

## Synthesis of $LTA_4$ and Its Chiral Epoxide Isomers from 2-Deoxy-D-ribose

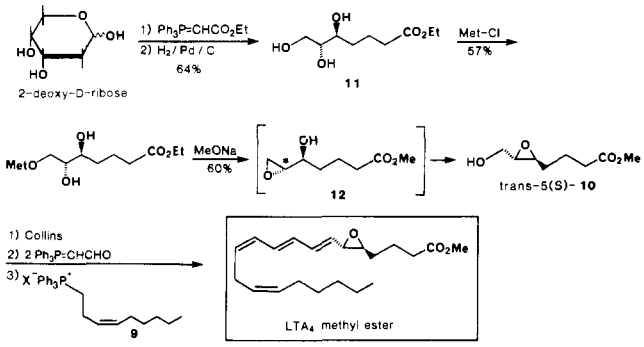
As would be expected, considerable effort has been put into developing syntheses for the naturally occurring, chirally pure form of $LTA_4$ both for the purpose of preparing $LTC_4$, $LTD_4$, and $LTE_4$ and in order to study its enzymatic conversion to these same com-

(12) Denis, D.; Charleson, S.; Rackham, A.; Jones, T. R.; Ford-Hutchinson, A. W.; Lord, A.; Cirino, M.; Girard, Y.; Larue, M.; Rokach, J. *Prostaglandins* **1982**, *24*, 801.

Chart II
Stereochemical Relationship between 2-Deoxy-D-ribose and $LTA_4$ Optical Isomers




Scheme IV
Synthesis of $LTA_4$ and Its Optical Isomers from 2-Deoxy-D-ribose

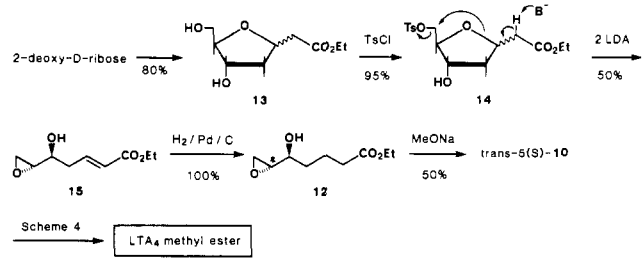



pounds and to $LTB_4$. In order to study the effect of the stereochemistry at $C_5$ and $C_6$ on biological activity, there has also been a need to obtain the three nonnatural stereoisomers (5-epi, 6-epi, and 5,6-diepi) of $LTC_4$, $LTD_4$, and $LTE_4$. As a result, considerable effort has gone into developing syntheses for the three nonnatural stereoisomers of $LTA_4$, which are the immediate precursors of the desired leukotriene stereoisomers.

The first complete study of the synthesis of $LTA_4$ and its three optical isomers (as their methyl esters) has been carried out by the group at Merck Frosst and has resulted in two syntheses of this series of key compounds.[13,14] The particularly successful and satisfying aspect of these syntheses is that from a single chiral starting material, 2-deoxy-D-ribose, by appropriate manipulation of its chiral centers, all four of the optically active isomers of $LTA_4$ were obtained.[15] The overall stereochemical relationship between the starting material and the various isomers of $LTA_4$ is illustrated schematically in Chart II. In each case, one of the series of epoxy alcohols **10** was first obtained and then elaborated to the corresponding $LTA_4$ isomer.

Scheme IV exemplifies the stereospecific total synthesis of natural $LTA_4$ from 2-deoxy-D-ribose.[13] The readily available triol ester **11** was regioselectively functionalized on the primary hydroxyl group by using

Scheme V
*C*-Glycoside Route to $LTA_4$, 5-*epi*-$LTA_4$ and 5-*epi*-6-*epi*-$LTA_4$




the sterically hindered mesitylenesulfonyl chloride (Met-Cl). Treatment with sodium methoxide in methanol then yielded the desired epoxy alcohol *trans*-(5S)-**10**. The terminal epoxide **12** is an intermediate in the reaction and undergoes epoxide transposition under the basic reaction conditions.

The asterisk in **12** and subsequent structures indicates the point of inversion, which is effected in order to achieve the desired stereochemistry as schematically indicated in Scheme IV. The epoxy alcohol was then oxidized to the epoxy aldehyde, which was extended by a double Wittig reaction with (formylmethylene)triphenylphosphorane. The final step of the synthesis was a Wittig reaction with the widely used triphenyl[(*Z*)-non-3-en-1-]phosphonium chloride (**9**, X = Cl). The three nonnatural isomers of $LTA_4$ were also prepared, by appropriate manipulations of the stereochemistry, by starting from 2-deoxy-D-ribose.[13]

In the second synthesis,[14] 2-deoxy-D-ribose was used to obtain the *C*-glycoside **13**.[16] The key to the *C*-glycoside synthesis was the finding that with a suitably located leaving group, these structures open upon base treatment, as illustrated in **14** (Scheme V), to yield unsaturated epoxy alcohols (**15**). The intermediate **12** (Scheme IV) was isolated prior to conversion to *trans*-(5*S*)-**10**.

## Synthesis of $LTB_4$

Of the more highly oxygenated products from arachidonic acid, the compound that has attracted the greatest attention both biologically and synthetically is leukotriene $B_4$ ($LTB_4$).

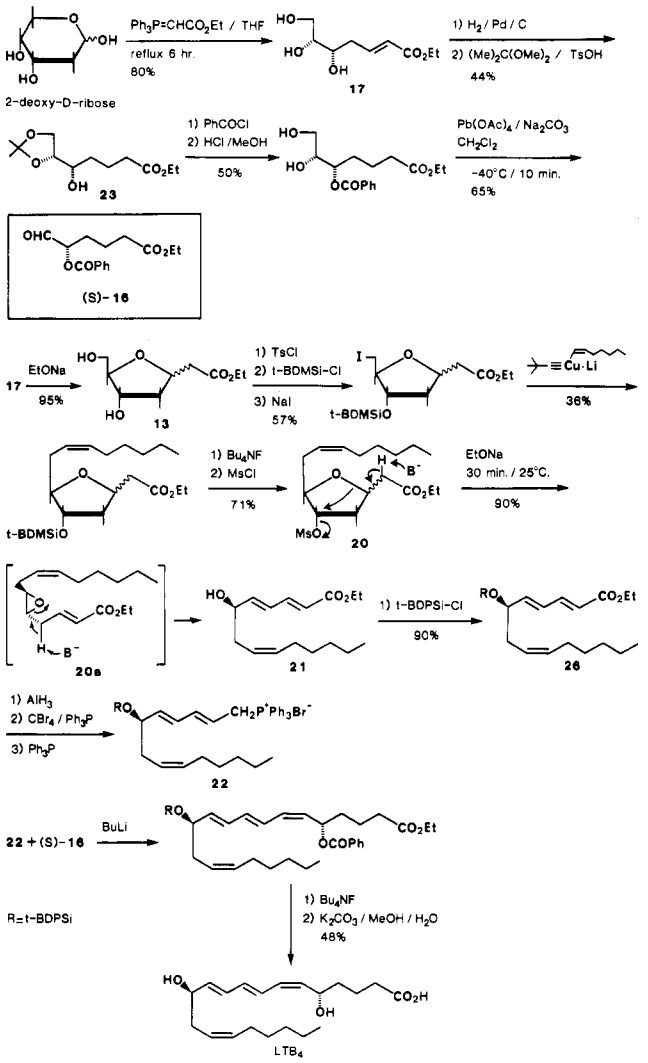
**Two Syntheses of $LTB_4$.** The *S* isomer of **16** has been used as a synthon in all our reported syntheses of $LTB_4$, isomers, and metabolites and a synthesis of 5(*R*)- and 5(*S*)-HETE.[18]

Drawing on our previous experience in the synthesis of $LTA_4$,[13] we developed a synthesis of the ethyl ester, (*S*)-**16**, from 2-deoxy-D-ribose (Scheme VI). The intermediate acetonide **23** served to protect the terminal diol unit and allow benzoylation to be effected on the desired hydroxyl group.

The first synthesis of $LTB_4$ from our laboratories[16] is outlined in Scheme VI. One key aspect of this synthesis is the fact that 2-deoxy-D-ribose serves as the source of chirality for both asymmetric centers of $LTB_4$, with $C_3$ becoming $C_5$ in $LTB_4$ ((*S*)-**16**) and $C_4$ becoming $C_{12}$ (**21**). The critical chemical step that made this synthesis possible was the novel finding that certain *C*-glycosides, containing a suitable leaving group in the

(13) Rokach, J.; Zamboni, R.; Lau, C.-K.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2759.
(14) Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2763.
(15) We have also prepared $LTA_4$ starting from L-arabinose. Rokach, J.; Young, R. N.; Kakushima, M.; Lau, C.-K.; Séguin, R.; Frenette, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 979.
(16) Guindon, Y.; Zamboni, R.; Lau, C.-K.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 739.
(17) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 2631.
(18) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1983**, *24*, 999.

Scheme VI
Synthesis of $LTB_4$




Scheme VII
Synthesis of $LTB_4$

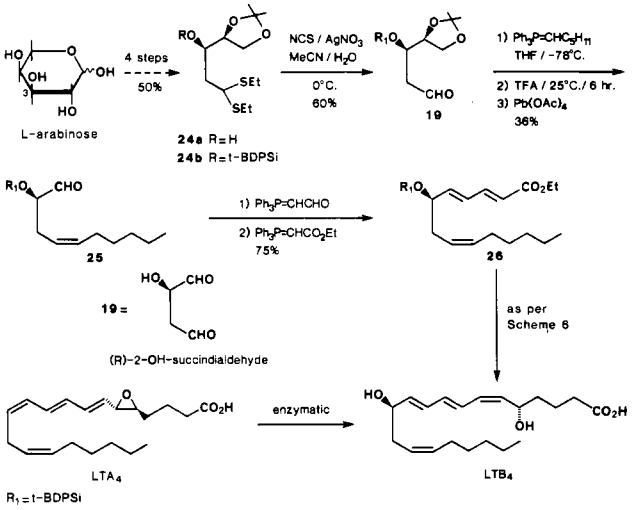
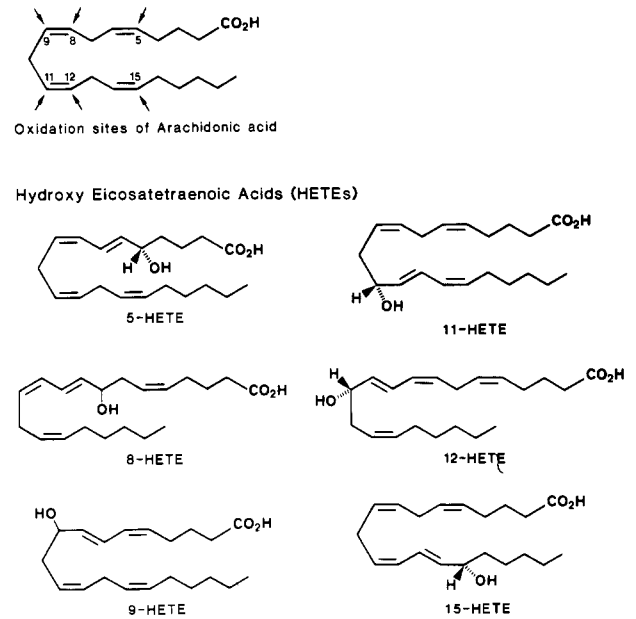



Chart III



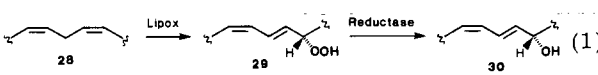

tetrahydrofuran ring, unravel completely upon base treatment, giving rise to a conjugated diene unit in high yield, as depicted in the sequence **20** → **20a** → **21**. The epoxide **20a** is considered to be true intermediate since in other cases it could be isolated.

In our second synthesis was started from the known intermediate **24a** (Scheme VII), which is easily prepared from L-arabinose, in which $C_3$ becomes $C_{12}$ in $LTB_4$. The synthesis of Scheme VII converges with that of Scheme VI with the obtention of the protected ester **26**. It should be noted that the two-step chain elongation of **25** by four carbons to **26** was found to be superior in this instance to several one-step reactions investigated (2 equiv of $Ph_3P{=}CHCHO$, $Ph_3P{=}CHCH{=}CHCHO$, or $(EtO)_2PO{-}CH_2CH{=}CHCO_2C_2H_5$). The particular advantages of this synthesis lie in the fact that starting from D-arabinose, the same sequence of reactions has allowed a synthesis of the 12*S* isomer of $LTB_4$,[17] and starting from synthon **19**, the terminally oxygenated compounds 20-hydroxy-$LTB_4$ and 20-carboxy-$LTB_4$ have been prepared.

## Synthesis of HETEs and diHETEs. Control of Olefin Geometry in Leukotriene Synthesis

Arachidonic acid has been shown to produce six different possible monohydroxylated metabolites (HETEs) through a lipoxygenase pathway (see Chart III). The formation of these HETEs occurs presumably via the radical trapping by enzyme-bound molecular oxygen in the lipoxygenase system.

Upon closer examination of the process leading to the introduction of a hydroperoxy group by a lipoxygenase, it becomes apparent that regardless of the position involved, the net result in all cases is the transformation, shown in eq 1, in which a "skipped" diene from ara-

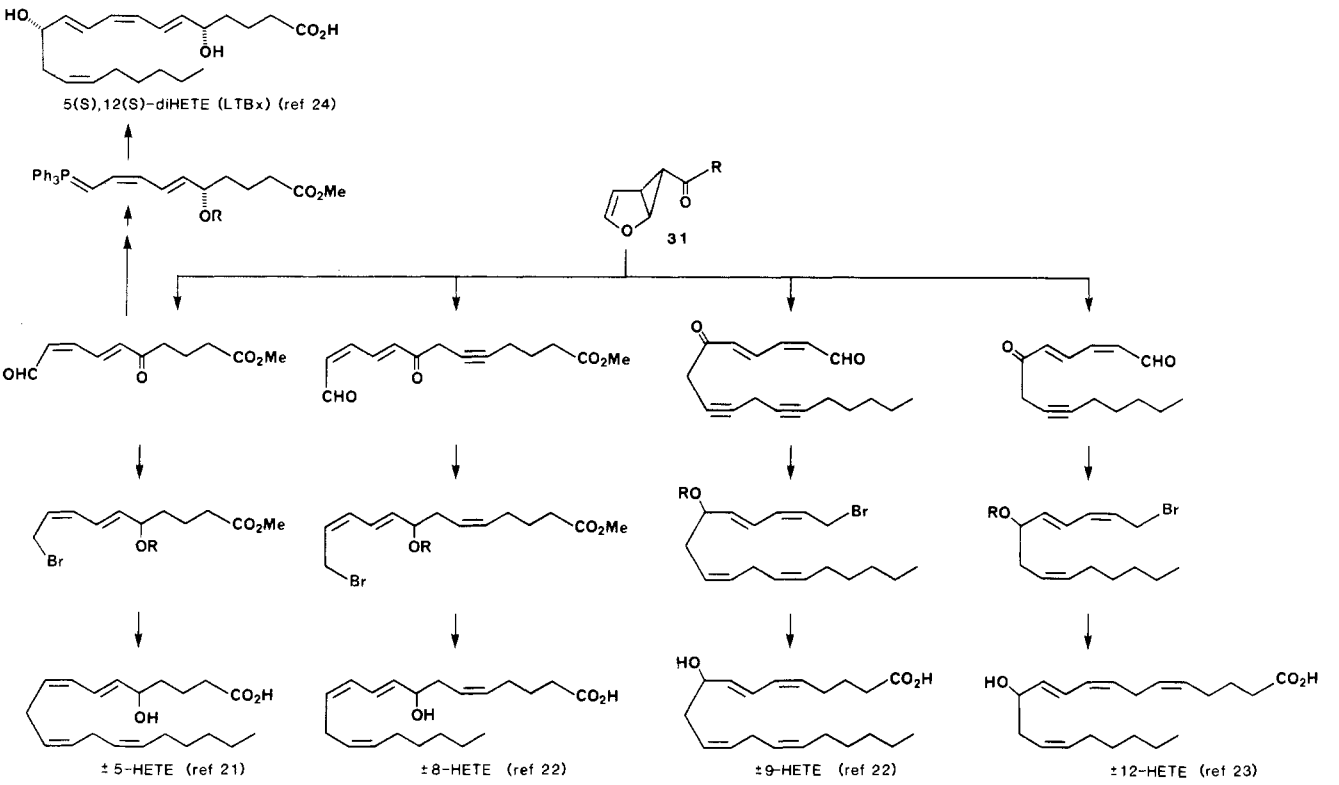


(1)

chidonic acid **28** is converted to a conjugated diene **29**, having a cis–trans olefin geometry, and the hydroperoxy group assumes the *S* configuration for 5, 12-, and 15-HPETEs.

The 11-position gives rise to the *R* hydroperoxy group and can fall into the prostaglandin cascade. As yet both 8- and 9-HPETEs and -HETEs have not been fully characterized with regard to absolute stereochemistry. Hydroperoxide **29** is enzymatically reduced to produce the HETE **30**, which retains all the structural features of **29**. This structure is common to the primary lip-

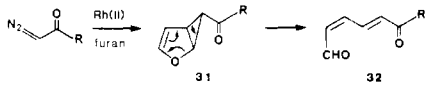
Scheme VIII
Cyclopropylfuran Route to HETEs and diHETE (LTBx)




oxygenase products identified from natural sources: namely, 5-, 8-, 9-, 11-, 12-, and 15-HPETEs and HETEs.

Most of the synthetic methodology to control olefin geometry in leukotriene synthesis relies heavily on the Wittig reaction (or modifications thereof). While this has been effective, it remains rather difficult to regulate olefin geometry of dienes functionalized at the allylic positions. We were looking for a method to prepare such dienes, specifically *cis,trans*-dienes, as required in the synthesis of HETEs.

The addition of diazo compounds to furans to form cyclopropyl adducts is well documented.[19] We have over the past few years developed a method to produce compounds of type **32** (eq 2) by the highly efficient




(2)

addition of $\alpha$-diazocarbonyl compounds to furan, catalyzed by rhodium acetate dimer. Initially the reaction forms the carbene addition product cyclopropylfuran **31**, which then undergoes electrocyclic ring opening to the cis–trans dicarbonyl compound.[20-23]

Considering the initial reaction product, **32**, one realizes that this synthon has the desired features necessary for the construction of HETEs. The ketone function can serve as the precursor to the OH group, the cis–trans olefin geometry is the desired one, and by varying the R group in the bicyclic system **31** to incorporate the necessary features and using the aldehyde as a handle to elaborate the rest of the carbon chain, one can synthesize any of the desired HETEs. Thus, structures of type **31** may be considered to be masked dienes of the correct geometry for HETEs. Scheme VIII summarizes our utilization of this methodology to synthesize a variety of HETEs.

For HETEs, in each case, the diene allylic bromide was coupled with the appropriate synthon to complete the $C_{20}$ carbon skeleton. Thus we have completed four of the possible six oxidative metabolites of arachidonic acid. Both 11-HETE and 15-HETE could be synthesized following a similar plan.

As shown in Scheme VIII, the precursor to (±)-5-HETE was also used to enter into the conjugated triene diHETE series, this being accomplished by using a stereoselective Wittig reaction. Thus the same methodology to form HETEs proves to be versatile in the preparation of compounds in the LTB family.

## Conclusion

In the last few years since the structure elucidation of SRS-A by Samuelsson, important progress has been made in the elucidation of the biosynthesis of the 5-lipoxygenase cascade. The implication of leukotrienes in pathophysiological diseases such as allergy, respiratory disease, and inflammation is strongly suggested by our own and other studies.[24]

Progress has also been made in the measurement and analysis of leukotrienes. High-pressure liquid chromatography has been the most important tool for isolation, purification, and characterization of leukotrienes. However, HPLC sensitivity is still not high enough for assaying leukotrienes in clinical situations. For this

(19) For example, see: Wenkert, E.; Bakuzis, M. L. F. *Synth. Commun.* **1981**, *11*, 533.
(20) Rokach, J.; Adams, J.; Perry, R. *Tetrahedron Lett.* **1983**, *24*, 5185.
(21) Adams, J.; Rokach, J. *Tetrahedron Lett.* **1984**, *25*, 35.
(22) Adams, J.; Pérez, F.; Rokach, J., unpublished results.
(23) Adams, J.; Leblanc, Y.; Rokach, J. *Tetrahedron Lett.*, in press.

(24) References in: (a) "SRS-A and Leukotrienes"; Piper, P. J., Ed.; Wiley: New York, Chichester, Brisbane, and Toronto, 1981. (b) Ford-Hutchinson, A. W.; Bray, M. A.; Doig, M. V.; Shipley, M. E.; Smith, M. J. H. *Nature (London)* **1980**, *286*, 264.

purpose, we have developed radioimmune assays for $LTB_4$, $LTC_4$, and $LTD_4$. This involved attaching the leukotriene to a protein and raising specific antibodies that are used in the radioimmune assay to measure levels of leukotrienes as low as $10^{-13}$ g/mL.[25]

Clearly, the next major contribution to the field will be the development of specific leukotriene antagonists and biosynthesis inhibitors which should prove useful in the clinical setting as new therapy for various diseases.

Possibly another important area that requires a more sustained attention is the 12- and 15-lipoxygenase pathways. Beyond the identification of a few metabolites, not much is known about the physiological importance of these pathways. Another hurdle to be overcome is the isolation and purification of the various enzymes that control lipoxygenase metabolism.

(25) Hayes, E. C.; Lombardo, D. L.; Girard, Y.; Maycock, A. L.; Rokach, J.; Rosenthal, A. S.; Young, R. N.; Egan, R. W.; Zweerink, H. J. *J. Immunol.* **1983**, *131*, 429.