calcium carbonate (1.4 g, 14 mmol) in aqueous acetonitrile (18 mL, 20% H_2O). The mixture was stirred at room temperature for 4 h, and the solvent was removed in vacuo. A small sample purified by flash chromatography (ethyl acetate + 5% Et_3N) gave the pure α,β-unsaturated aldehyde: ^1H NMR ($CDCl_3$) δ 9.85 (s, H_9), 6.95 (d, J = 1.7 Hz, H_2), 4.70 (dm, J = 19 Hz, H_3), 4.61 (m, H_8), 4.30 (dt, J = 10.4, 7.4 Hz, H_7), 3.98 (dm, J = 19 Hz, H_3'), 3.31 (br s, OH), 2.86 (AB q, J = 15.6, 10.9 Hz, H_6), 2.07 (ABq, J = 15.6, 8.0 Hz, H_6'). The remaining crude hydrolysis product was suspended in tetrahydrofuran (18 mL), to which lithium aluminum hydride solution (10 mL, 2.5 M in THF) was added dropwise under argon. The reaction mixture was heated at reflux for 18 h and then after cooling to room temperature quenched by the slow addition of water and sodium sulfate dodecahydrate. The precipitate was removed by filtration through Celite/K_2CO_3, and the filter cake was washed with tetrahydrofuran containing 10% triethylamine. Concentration and flash chromatography ($CHCl_3$:MeOH:NH_4OH = 10:4:1) afforded 174 mg (64%) of (+)-heliotridine: mp 115-117 °C [lit.[1c] mp 116-118 °C]; $[\alpha]^{25}_D$ +30.3° (c 1.6, MeOH) [lit.[18b] $[\alpha]^{20}_D$ + 31° (10% in MeOH); lit.[18a] $[\alpha]_D$ +30.4° (EtOH)]; ^{13}C NMR ($CDCl_3$) 141.6, 123.0, 80.3, 75.0, 62.4, 59.6, 54.4, 33.8; MS, m/e (relative intensity) 155 (M^+, 16), 111 (58), 94 (15), 80 (100).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.02; H, 8.39; N, 8.94.

Other spectral data and chromatographic mobility (R_f 0.23, $CHCl_3$:CH_3OH:NH_4OH = 10:4:1) are identical with an authentic sample of heliotridine.

Acknowledgment. We are grateful to the National Institutes of Health (GM 30073) for financial support and to Professor Dave Evans for helpful advice. We also thank Professor Gary Keck for providing the sample of authentic heliotridine.

Registry No. 5, 520-63-8; **12**, 85319-59-1; **13**, 85319-60-4; **14** (isomer 1), 85319-61-5; **14** (isomer 2), 85319-65-9; **15**, 85319-62-6; **16**, 85319-63-7; **17**, 85335-11-1; **11** acetate, 85319-64-8; malic acid, 6915-15-7; acetyl chloride, 75-36-5; 2-(3-hydroxypropylidene)-1,3-dithiane, 83177-74-6.

Total Synthesis of Leukotriene E_4, a Member of the SRS-A Family

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Contribution from the Research and Development Division, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. *Received September 7, 1982*

Abstract: Leukotriene E_4 and two analogues homo-LTE_4 and nor-LTE_4 have been prepared via the intermediate epoxides. The epoxides were formed by the coupling of a polyenyne sulfonium salt with the required aldehyde–ester in a biphasic reaction system employing aqueous sodium hydroxide as the base for the generation of the ylide. Reduction of the acetylene bonds yielded the desired polyene epoxides which on treatment with L-cysteine methyl ester gave a 1:1 mixture of diastereomers from which the 5*S*,6*R* isomers were separated.

The slow-reacting substance of anaphylaxis (SRS-A), once thought to be a single entity, is a family of compounds belonging to a group of chemical mediators involved in the phenomenon of immediate-type hypersensitivity. These materials are apparently synthesized de novo by several cell types on antigen challenge and have been something of a mystery for the past 50 years.[1]

Samuelsson et al.[2] was the first to propose a gross structure for one of the members of the SRS family. Based on his pioneering work in the area of arachidonic acid metabolism, and skilfully using the clues left by past investigators, Samuelsson showed that SRS-A was a lipoxygenase-derived metabolite of arachidonic acid.

After this disclosure, other work showed[3] that SRS was a family of related compounds derived from the primary addition product **3** of glutathione and the polyene epoxide **1** (Figure 1). Subsequent enzymatic degradation of this primary adduct then yields the cysteinylglycine and cysteine derivatives **4** and **5**, respectively.[4] These SRS's were named leukotrienes because they contain the characteristic conjugated triene chromophore and were originally isolated from leukocytes.[5] Thus, the primary glutathione adduct **3** is called leukotriene C_4 (LTC_4), while the cysteinylglycine and cysteine derivatives are LTD_4 and LTE_4, respectively. All three products are potent bronchoconstrictive agents; LTD_4 and LTE_4 also have the ability to increase vascular permeability. Both of these features suggests that these mediators may play an important role in asthma and other diseases of the respiratory system. As in the case of the prostaglandins, the leukotrienes are found widely distributed in the body and comprise another important branch of the arachidonic acid cascade. The actual role of these materials in inflammation and asthma will have to await further studies.

As part of a program in the bronchopulmonary area, we have devised a synthesis of LTE_4 for the purpose of developing meaningful animal test systems to detect SRS antagonists of potential use in asthma therapy. While LTE_4 is not the principal SRS formed in human lung, it has a very similar activity profile in the established animal tests to date.[6]

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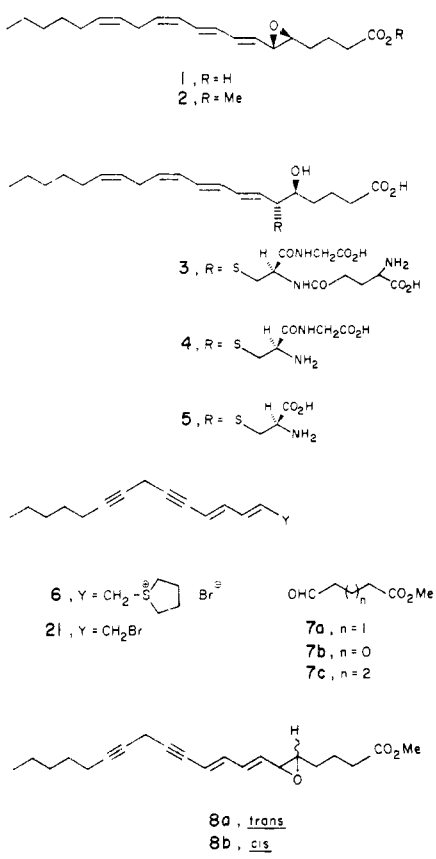

Figure 1.

Results

All syntheses of LTC_4, $-D_4$, and $-E_4$ are keyed to the epoxide **2**, which on exposure to the desired amino acid (e.g., glutathione) yields the required SRS.[7] From our past experience with polyene sulfonium salts,[8] we chose to construct **2** by the union of the ylide derived from **6**[9] and the five-carbon unit **7a**. Reduction of the triple bonds in **8a** would then give the desired cis olefins, and the addition of the chiral amino acid would then yield a mixture of diastereomers from which the natural SRS could be obtained.

Before this approach could be put into practice, several important questions had to be answered. (i) Does the sulfur ylide generated from a sulfonium salt such as **9** retain the integrity of the trans double bond? (ii) Can the acetylene function be reduced to a cis olefin without destruction of the epoxide? (iii) What are the regio- and stereochemical consequences of adding a thiol to a system such as **13**? (iv) What is the absolute stereochemistry of the thiol addition products?

To answer these questions a series of model experiments employing the salt **9** were carried out as follows. Addition of 1-heptyne to acrolein gave the alcohol **10** which on exposure to phosphorus tribromide furnished a mixture of bromides in which the trans isomer **11** predominated. The trans-bromide was converted into the sulfonium salt **9** with tetrahydrothiophene in aqueous methanol. Subsequent condensation of this salt with methyl 4-formylbutyrate, in a two-phase system with aqueous sodium hydroxide solution as base, gave a mixture of epoxides.[10] This mixture contained *only* the *trans*- and *cis*-epoxides **12a** and **12b**, both compounds retaining the trans double bond originally present in the bromide **11**. Hydrogenation of the *trans*-epoxide (major isomer), with a poisoned palladium catalyst in hexane, yielded the desired (*E*,*Z*)-diene epoxide **13** (see Figure 2). The major byproducts from this reduction were overreduced materials and hydrogenolysis products formed by cleavage of the allylic epoxide.

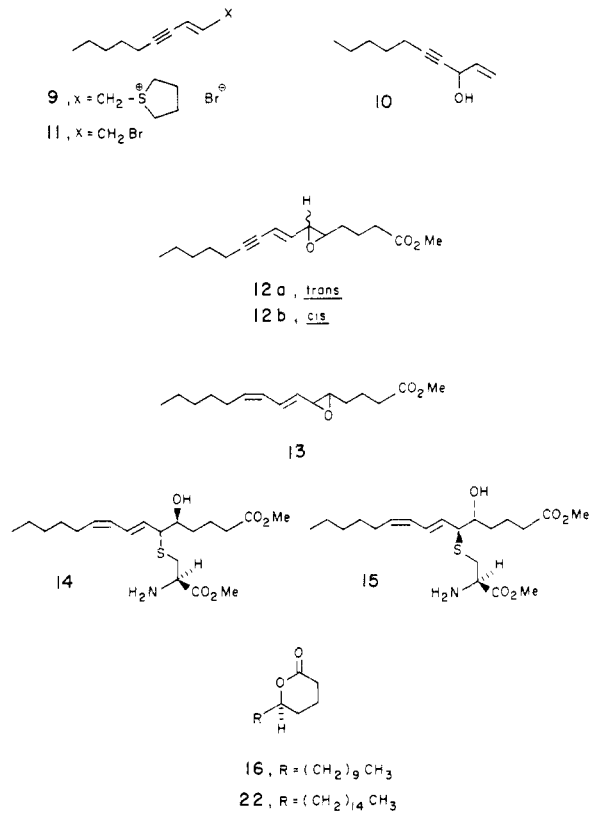

Figure 2.

Addition of L-cysteine methyl ester to the diene epoxide proved to be a very clean reaction when carried out in aqueous methanol containing triethylamine.[11] Only *one* mixture of diastereomers resulted and this mixture could be separated by preparative high performance liquid chromatography. Interestingly, these cysteine adducts **14** and **15** were far less stable than the corresponding derivatives formed from **12a**. The integrity of the diene system and the regiochemistry of the cysteine adducts was clear from the ^1H NMR spectra. The absolute stereochemistry of the hydroxyl function was determined as follows. Exposure of the cysteine methyl ester adduct to Raney nickel in refluxing ethanol resulted in removal of the cysteinyl unit and partial reduction of the diene system. Hydrolysis of the ester group with base and subsequent lactonization of the resulting hydroxy acid under acidic conditions yielded a δ-lactone (IR), reaffirming the regiochemistry of cysteine addition. Hydrogenation of this δ-lactone mixture yielded a lactone with a fully saturated side chain. Employing the cysteine adduct with the longer retention volume (HPLC), the δ-lactone showed a positive specific rotation, clearly identifying it as the 5*R* isomer

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(9) Dimethyl sulfonium salts suffer ylide equilibration–rearrangement: Trost, B. M.; Melvin, L. S., Jr. "Sulfur Ylides", Organic Chemistry; Academic Press: New York, 1975; Vol. 31.

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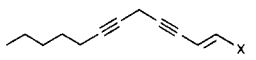

17, X = $CH_2OCH(CH_3)OC_2H_5$
18, X = CH_2OH
19, X = CHO
20, X = CH(OH)$CH=CH_2$

Figure 3.

of **16**.[12] Assuming the addition of the cysteine methyl ester to the epoxide is a pure S_N2 process, then the absolute stereochemistry of this diastereomer would be as shown in **14**, which corresponds to the natural stereochemistry of LTE_4. The other isomer, with the shorter retention volume, would then have structure **15**. The lactone **16** was also employed to estimate the purity of the cysteine adducts by treatment with (2*R*,3*R*)-butanediol, followed by analysis of the resulting ortho ester mixture by GLC.[13] In this way, the diastereomer **14** was shown to have a stereochemical purity of at least 90%.

Following these encouraging results, we turned our attention toward the synthesis of LTE_4 via the salt **6** which was prepared as follows. The copper-catalyzed coupling of 1-bromo-2-octyne[14] and the ethyl vinyl ether adduct of (*E*)-1-hydroxy-2-penten-4-yne[15] gave **17** and subsequently the alcohol **18** after acid hydrolysis. Oxidation of this material with aqueous chromic acid[16] gave the aldehyde **19** which was immediately converted into the carbinol **20** with vinylmagnesium chloride (Figure 3). Exposure of **20** to phosphorus tribromide in ether gave the *all-trans*-bromide[17] **21** which on treatment with tetrahydrothiophene yielded the desired salt **6**. Condensation of the crude sulfonium salt with an excess of aldehyde **7a** as before yielded the mixture of epoxides **8a** and **8b** in which the trans isomer predominated.[18] As in the case of the model reactions, the original trans–trans diene system of the bromide was retained throughout the reaction sequence and the epoxides formed were only isomeric about the oxirane junction. Hydrogenation of **8a**, as in the case of **12a**, gave a complex mixture of reduction products from which the desired racemic tetraene **2** could be isolated in 30–40% yield. Addition of L-cysteine methyl ester to racemic **2** furnished a mixture of diastereomers from which LTE_4 dimethyl ester was isolated by chromatography.[19] As in the case of **14** and **15**, the adduct with the natural 5*S*,6*R* configuration had the longer retention volume on HPLC and yielded the 5*R* lactone **22** after treatment with Raney nickel as before. When the same set of reactions was carried out with the aldehydes **7b** and **7c**,[20] the corresponding nor- and homo-LTE_4's were readily available, and again the isomers with the longer retention volumes were found to have the "natural" 5*S*,6*R* stereochemistry. When the *cis*-epoxide **8b** was reduced and then converted into the corresponding threo adducts with L-cysteine methyl ester, the isomer with the shorter retention volume had the "natural" 5*S*[21] configuration.[22]

Table I

Compound	Salt	EC_{50} M x 10^{-9}
(5S,6R)-LTE_4	K	1-4
(5R,6S)-LTE_4	K	8
(5S,6S)-LTE_4	K	1000
(5S,6R)-Homo-LTE_4	K	1
(5S,6R)-Nor-LTE_4	K	1000

Hydrolysis of the dimethyl esters of LTE_4 to the dicarboxylic acids has presented a problem in the past for some authors.[23] With carefully purified materials, free of L-cysteine methyl ester, we have found that the esters are rapidly hydrolyzed with potassium hydroxide in aqueous methanol with very little isomerization of the polyene system. The methyl ester at the terminus of the eicosatetraene chain is instantly hydrolyzed, possibly because of anchimeric assistance of the hydroxyl at C_5, while the amino acid methyl ester is removed at a slower rate. To what degree the cysteinyl fragment is *racemized* has not been clarified so far and would not be evident from the biological test results.[24] The hydrolysis products as the monopotassium salts are readily purified by reverse-phase or ion-exchange chromatography and are stable as freeze-dried powders, if stored at −80 °C under argon in the dark.

All the cysteine adducts mentioned above were agonists in the guinea pig ileum test system (Table I) and showed the slow, long-acting contraction so characteristic of the SRS-A family. Clearly the *relative* stereochemistry of the polar groups in the "head" of LTE_4 and a minimum separation of the 5-hydroxyl group and the terminal carboxyl function are critical for agonist activity [cf. Table I (5*S*,6*S*)-LTE_4[25] and nor-LTE_4].

In summary, the work described makes LTE_4 and its unnatural isomers readily available in gram quantities in very few steps from commercially available starting materials. With this important biological probe in hand, one now has the opportunity of establishing meaningful animal test systems for the screening of specific SRS antagonists.

Experimental Section[26]

(*E*)-1-Bromo-2-decen-4-yne (11). A solution of *n*-butyllithium (46 mL, 2.18 M hexane) was added to cold tetrahydrofuran (50 mL, −60°), and the resulting mixture was then treated with 1-heptyne (9.6 g, 0.1 mol) followed, after 5 min, by a solution of freshly distilled acrolein (5.6 g, 0.1 mol) dissolved in tetrahydrofuran (8 mL). The reaction mixture was warmed to room temperature and treated with ether (200 mL) and water (20 mL). The organic phase was dried ($MgSO_4$) and concentrated

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(14) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: Amsterdam, 1971.

(15) Available from Farchan, Division Chemsampco, Inc.; see also ref 14.

(16) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952. Manganese dioxide or pyridinium dichromate (Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399) gave similar yields but were less convenient to work up.

(17) Some 7,8-*cis*-bromide is also formed, and if this is not removed (HPLC) the final epoxide **2** is contaminated by the 7,8-*cis* isomer; cf. ref 6n.

(18) These epoxides are base labile because of the skipped diyne system; e.g., aqueous potassium carbonate solution in methanol rapidly forms allenic products from **8a**.

(19) Similarly, the addition of glutathione gave a 1:1 mixture of diastereomers. These were separable by analytical HPLC but resisted preparative HPLC (i.e., 100-mg quantities).

(20) The aldehydes **7a–c** were unpredictable materials and sometimes trimerized rapidly. They were always freshly prepared for these coupling reactions.

(21) Corey, E. J.; Goto, G. *Tetrahedron Lett.* **1980**, *21*, 3463.

(22) This HPLC behavior has held true for *all* the mixtures of diastereomers we have made in which the polar head has remained constant (i.e., LTE_4 type) and the "tail" has been modified (e.g., saturated chains, etc.).

(23) Atrache, V.; Sok, D. E.; Pai, J. K.; Sih, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 1523.

(24) The 1:1 mixture of diastereomers formed from **2** and D-cysteine was a potent spasmogen (as the ammonium salt, $EC_{50} = 5 \times 10^{-9}$ M in the guinea pig ileum assay) after hydrolysis.

(25) Lewis, R. A.; Drazen, J. M.; Austen, K. F.; Toda, M.; Brion, F.; Marfat, A.; Corey, E. J. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 4579.

(26) All reactions were carried out under an atmosphere of argon. Temperatures are in °C. The organic extracts were concentrated with a Büchi Rotavapor at 45 °C and 20 mm pressure and finally at room temperature at 0.5 mm pressure. Thin layer chromatograms were run on Brinkmann silica gel G plates[27] with UV indicator, and the spots were made visible with UV light or spraying with a 10% solution of phosphomolybdic acid in methanol and a 2% ceric sulfate solution in 5% aqueous sulfuric acid followed by heating to 120°. Preparative high performance liquid chromatography (HPLC) was performed using a Waters LC Prep 500 employing one or two deactivated silica columns with a flow rate of 250 mL/min. The fresh columns were deactivated with a methanol–acetone–ethyl acetate wash cycle and stored in hexane under pressure.[27b] Varian HA100, T60, XL100, and XL200 spectrometers were employed to record proton magnetic resonance spectra (^1H NMR) and the chemical shifts are relative to tetramethylsilane as an internal standard. Ultraviolet (UV) spectra were recorded on a Carey Model 14M and Perkin-Elmer 202 spectrophotometers. The LTE_4 potassium salts were desalted by reverse-phase chromatography on Waters Prep Pak-500/C_{18} packing.

to yield the crude alcohol (13.8 g, 90%) as an oil: ^{1}H NMR ($CDCl_3$) δ 5.9 (ddd, 1, J = 16, 12, 6 Hz, H-2), 5.4 (d, 1, J = 16 Hz, trans H-1), 5.05 (d, 1, J = 12 Hz, cis H-1), 4.8 (m, 1, H-3), 3.6 (s, 1, OH), 2.2 (m, 2, H-6), 0.9 (distorted t, 3, H-10). A solution of the crude alcohol (30 g, 0.197 mol) in ether (500 mL) was cooled to −40° and treated with a solution of phosphorus tribromide (20 mL, 0.211 mol) in ether (100 mL) and then warmed to room temperature. After stirring for a further 15 min, the mixture was poured onto ice; the ether extract was washed ($NaHCO_3$), dried ($MgSO_4$), and concentrated. Distillation of the residue gave the mixture of bromides (32.3 g, 76%): bp 70–85° (0.75 mm). Purification by HPLC (hexane) gave the pure *trans*-bromide **11**, (17.8 g), bp 80–85° (0.5 mm): ^{1}H NMR (CCl_4) δ 6.0 (dt, 1, J = 15, 7 Hz, H-2), 5.4 (dt, 1, J = 15, 2 Hz, H-3), 3.9 (d, 2, J = 7 Hz, H-1). Anal. ($C_{10}H_{15}Br$) C, H, Br. The *cis*-bromide had the longer retention volume (6.45 g), bp 65–70° (0.75 mm): ^{1}H NMR (CCl_4) δ 6.0 (dt, 1, J = 11, 8 Hz, H-2), 3.5 (dt, 1, J = 11, 2 Hz, H-3), 4.1 (d, 2, J = 8 Hz, H-1). Anal. ($C_{10}H_{15}Br$) C, H, Br. The 3-bromo compound related to **10** was also isolated.

***rac*,*trans*-(*E*)-3-(1-Tetradecen-3-ynyl)oxiranebutanoic Acid Methyl Ester (12a) and the Cis Isomer (12b).** Pure *trans*-bromide **11** (13 g, 60.5 mmol) was dissolved in a mixture of tetrahydrothiophene (10 mL) and aqueous methanol (1.5:20, 21.5 mL) and stirred at room temperature for 1 h (clear and homogeneous after 5 min). The solvents were then removed (40°, 20 mm), and the residue was washed with hexane (2 × 25 mL by decantation) and dried at room temperature (0.5 mm) for 30 min to yield the crude salt as a colorless liquid (19.4 g): ^{1}H NMR ($CDCl_3$) δ 6.4 (dt, 1, J = 14, 2 Hz, H-3), 6.0 (dt, 1, J = 14, 7 Hz, H-2), 4.6 (d, 2, J = 7 Hz, H-1). The crude salt was dissolved in dichloromethane (100 mL) containing methyl 4-formylbutyrate (7.1 g, 54.6 mmol) and benzyltriethylammonium chloride (1 g) and cooled to −20°. Cold aqueous sodium hydroxide solution (80 mL, 10 M, 5°) was then added rapidly (1–3 min) and the mixture was stirred for a further 5 min at 0°. Ether and water were added and the organic phase was dried ($MgSO_4$) and concentrated to give the crude reaction product (20 g). Purification by HPLC (10% ethyl acetate–hexane) gave the pure *trans*-epoxide **12a** (8.3 g, 57%), *cis*-epoxide **12b** (2.2 g, 15%), and the epoxide rearrangement product 5-oxo-7-pentadecen-9-ynoic acid methyl ester (1 g, 7%). The rearrangement product can be avoided in this separation by employing 1% triethylamine in 9:1 hexane–ethyl acetate as the solvent mixture.

***trans*-Epoxide**: ^{1}H NMR (CCl_4) δ 5.8 (ddd, 2, J = 15 Hz, H-1 and H-2), 3.6 (s, 3, OCH_3), 3.0 (m, 1, J = 2 Hz, H-3), 2.65 (dt, 1, J = 6, 2 Hz, H-2), 0.85 (t, 3, H-9). Anal. ($C_{16}H_{24}O_3$) C, H. ***cis*-Epoxide**: ^{1}H NMR (CCl_4) δ 5.8 (ddd, 2, J = 15 Hz, H-1 and H-2), 3.6 (s, 3, OCH_3), 3.3 (dd, 1, J = 6, 4 Hz, H-3), 2.85 (dt, 1, J = 6, 4 Hz, H-2), 0.85 (t, 3, H-9). Anal. ($C_{16}H_{24}O_3$) C, H. The isomer had the following characteristics: UV max (ethanol) 229 nm (ϵ 14 000); IR (film) 2215 (C≡C), 1740 (ester C=O), 1720 (C=O) cm^{-1}; ^{1}H NMR (CCl_4) δ 6.0 (dt, 1, J = 16, 6 Hz, H-7), 5.5 (dt, 1, J = 16, 2 Hz, H-8), 3.55 (s, 3, OCH_3), 3.1 (d, 2, J = 6 Hz, H-6), 0.9 (t, 3, H-15). Anal. ($C_{16}H_{24}O_3$) C, H.

***rac*,*trans*-(1*E*,3*Z*)-3-(1,3-Tetradecadienyl)oxiranebutanoic Acid Methyl Ester (13).** A solution of the epoxide **12a** (8.1 g, 30.5 mmol) in hexane (100 mL) was treated with a Lindlar catalyst (1 g), stirred for 5 min, and filtered; the hexane solution was then treated with fresh catalyst (1 g) and hydrogenated. After 22 mL of hydrogen had been consumed, the reaction stopped owing to catalyst poisoning and the solids were filtered off. Fresh catalyst (1.2 g) was added and hydrogenation was continued at room temperature and pressure. A smooth and rapid uptake of hydrogen followed (no break in the curve); after approximately 1.2 equiv of hydrogen had been consumed (960 mL), the solids were filtered off and the crude hydrogenation product was purified by HPLC (9:1 hexane–ethyl acetate containing 1% triethylamine) to yield the pure diene epoxide **13** (5.1 g, 62%): ^{1}H NMR ($CDCl_3$) δ 6.7 (dd, 1, J = 15, 11 Hz, H-2), 5.98 (t, 1, J = 11 Hz, H-3), 5.47 (dt, 1, J = 11, 8 Hz, H-4), 5.35 (dd, 1, J = 15, 8.5 Hz, H-1), 3.68 (s, 3, OCH_3), 3.16 (dd, 1, J = 8.5, 2 Hz, H-2), 2.87 (dt, 1, J = 6, 2 Hz, H-3), 0.89 (t, 3, H-9). Anal. ($C_{16}H_{26}O_3$) C, H.

[5*S*-[5*R,6*S**(*R**),7*E*,9*Z*]]-5-Hydroxy-6-[(2-amino-3-methoxy-3-oxopropyl)thio]-7,9-dodecadienoic Acid Methyl Ester (14) and the (5*R*,6*S*) Diastereomer (15).** Cysteine methyl ester hydrochloride (5 g, 29 mmol) was dissolved in a mixture of methanol and water (20 mL, 4:1) and adjusted to pH 9 with triethylamine. This mixture was then added to the epoxide **13** (5 g), and the clear solution was left at room temperature for 2 h. The solvents were then removed (20 mm, 40°); the residue was treated with ethyl acetate and filtered. The combined ethyl acetate extracts were then washed with water (4 × 25 mL), dried ($MgSO_4$), and concentrated. Purification of the residue by HPLC (2.5% methanol in ethyl acetate and a second time with 5% methanol in 1:1 hexane–ethyl acetate) yielded the pure isomers **14** (1.3 g) and **15** (1.1 g). **Isomer 14**: $[\alpha]^{20}_D$ −27.7° (c 1.5, dioxane); ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, 1, J = 15, 11 Hz, H-8), 6.0 (t, 1, J = 11 Hz, H-9), 5.6 (dd, 1, J = 15, 8 Hz, H-7), 5.45 (dt, 1, J = 8, 6 Hz, H-10), 3.76 and 3.68 (2 s, 6, CO_2CH_3), 3.4 (dd, 1, J = 8, 4 Hz, H-6), 2.85 (ddd, 2, J = 14, 8, 5 Hz, $-SCH_2-$), 0.89 (t, 3, H-15). Anal. ($C_{20}H_{35}NO_5S$) C, H, N, S.

Isomer 15: $[\alpha]^{20}_D$ +20° (*c* 1.67, dioxane); ^{1}H NMR ($CDCl_3$) δ 6.45 (dd, 1, J = 15, 11 Hz, H-8), 6.0 (t, 1, J = 11 Hz, H-9), 5.5 (m, 2, H-7 and H-10), 3.75 and 3.68 (2 s, 6, CO_2CH_3), 3.45 (m, 1, H-6), 2.9 (ddd, 2, J = 14, 5, 5 Hz, $-SCH_2-$), 0.89 (t, 3, H-15). Anal. ($C_{20}H_{35}NO_5S$) C, H, N, S.

(5*R*)-5-Hydroxypentadecanoic Acid Lactone (16). The cysteine derivative **14** (0.4 g) was dissolved in ethanol (50 mL) containing Raney nickel (wet slurry 1 mL), heated under reflux for 1 h, and then filtered. Removal of the solvents yielded the crude product which was dissolved in methanol (15 mL), treated with potassium hydroxide (0.2 g) in water (5 mL), and left at room temperature for 1 h. Water was then added followed by aqueous sulfuric acid (2 N) until strongly acid. Extraction with dichloromethane yielded the crude hydroxy acid (150 mg) which was dissolved in benzene (10 mL) containing *p*-toluenesulfonic acid (0.05 g) and kept at room temperature for 1 h. Hexane–ethyl acetate (4:1, 20 mL) was then added and the mixture was washed ($NaHCO_3$, brine), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography[28] on silica gel, and the lactone mixture (100 mg) was then dissolved in ethyl acetate and hydrogenated at room temperature and pressure in the presence of a palladium catalyst (0.03 g, 10% on carbon). After the uptake of hydrogen stopped the solids were filtered off, the solvents were removed in vacuo, and the residue was purified by flash chromatography on silica gel (heptane and heptane–ethyl acetate 3:1) to yield the chemically pure lactone (0.067 g), $[\alpha]^{20}_D$ +30.7° (*c* 3.38, dioxane). The optical purity of this material was determined as follows. A solution of the lactone (0.067 g) in benzene (30 mL) containing (2*R*,3*R*)-butanediol (0.1 g) and *p*-toluenesulfonic acid (0.01 g) was heated under reflux in conjunction with a Dean–Stark trap for 2 h. The mixture was then cooled and chromatographed (neutral Alox III, 5 mL, made up in heptane). Elution with heptane and heptane–ether mixtures yielded the mixture of orthoesters (0.0785 g). GLC analysis (glass column, 1 m × 4 mm, 10% OV-17 on GCQ 100–120, 2°/min, 80–260°) showed the material to be a 90:10 mixture of diastereomers.

***rac*-(*E*)-4-Methyl-3,5-dioxa-7-decen-9-yne.** A mixture of ethyl vinyl ether (150 mL) and ether (150 mL) was cooled to 0° and treated with *p*-toluenesulfonic acid (0.2 g). To this cooled mixture was added, over 30 min, a solution of (*E*)-2-penten-4-yn-1-ol (100 g, 1.22 mol) dissolved in ether (150 mL). After complete addition the mixture was stirred for 20 min at room temperature and quenched with triethylamine (3 mL). More ether (300 mL) was then added and the mixture was washed with aqueous sodium bicarbonate solution ($NaHCO_3$) and brine and then dried ($MgSO_4$). Removal of the solvents and distillation of the residue yielded the pure material (185 g, 98%), bp 82–85° (18 mm).

1-Bromo-2-octyne. A solution of 2-octyn-1-ol (252 g, 2 mol) in ether (1 L) containing pyridine (20 mL) was cooled to −35° and treated with phosphorus tribromide (67.6 mL, 0.712 mol); the mixture was then stirred for 1 h at −30°, 18 h at room temperature, and $^1/_2$ h at 40°. The reaction mixture was cooled, poured onto ice, and extracted with more ether. The combined ether extracts were washed ($NaHCO_3$, brine), dried ($MgSO_4$), and concentrated; the residue was distilled to yield the pure bromide (338 g, 89%), bp 103–108° (16 mm).

(*E*)-4-Methyl-3,5-dioxa-7-octadecene-9,12-diyne (17). A solution of *rac*-(*E*)-4-methyl-3,5-dioxa-7-decen-9-yne (100 g, 0.65 mol) in tetrahydrofuran (100 mL) was added to a solution of ethylmagnesium bromide in tetrahydrofuran (562 mL, 1.27 M, 0.714 mol) at 30°. After complete addition the reaction mixture was heated at 60° for 45 min, cooled to room temperature, treated with anhydrous cuprous bromide (3.5 g), and then stirred for a further 10 min. A solution of 1-bromo-2-octyne (122.7, 0.649 mol) in tetrahydrofuran (100 mL) was then added at such a rate as to maintain the reaction temperature between 30 and 33°. After complete addition the reaction mixture was heated at 60° for 45 min, cooled to room temperature, and then poured into a saturated ammonium chloride solution (500 mL). The organic materials were extracted into ether and the combined extracts were washed (brine), dried ($MgSO_4$), and concentrated to yield the crude coupled product (169 g). A sample of this material purified by HPLC (3% ethyl acetate–hexane) yielded the analytical sample: ^{1}H NMR (CCl_4) δ 6.05 (dt, 1, J = 16, 5 Hz, H-7), 5.6 (d, 1, J = 16 Hz, H-8), 4.6 (q, 1, H-4), 3.9 (broad d, 2, J = 5 Hz, H-6), 3.4 (m, 2, H-2), 3.1 (q, 2, J = 2 Hz, H-11), 2.0 (m, 2, H-14), 1.2–0.8 (1 d, 2 t, 9, C_4-CH_3, H-1, H-18). Anal. ($C_{17}H_{26}O_2$) C, H.

(27) (a) Before chromatographing the allylic epoxides, the silica plates were dipped in a 3% triethylamine–hexane mixture. (b) HPLC columns were also pretreated with 5% triethylamine in ethyl acetate before the allylic epoxides were chromatographed.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(*E*)-2-Tridecene-4,7-diyn-1-ol (18). The crude acetal **17** (169 g) was dissolved in acetone (2 L), treated with aqueous sulfuric acid (120 mL, 0.5 N), and left at room temperature for 3 h. Half the acetone was then removed in vacuo (30°, 20 mm) and the residue was partitioned between ether and water. The combined ether extracts were then washed (H_2O, $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated. Purification of the residue (131 g) by HPLC (10% ethyl acetate–hexane) gave the pure alcohol **18** (103.5 g, 84% from 1-bromo-2-octyne): ^1H NMR (CCl_4) δ 6.15 (dt, 1, J = 16, 5 Hz, H-2), 5.6 (broad d, 1, J = 16 Hz, H-3), 4.05 (d, 2, J = 5 Hz, H-1), 3.5 (s, 1, OH), 3.2 (q, 2, J = 2 Hz, H-6), 0.9 (t, 3, H-13). Anal. ($C_{13}H_{18}O$) C, H.

(*E*)-2-Tridecene-4,7-diynal (19). A solution of the alcohol **18** (20 g, 105 mmol) in ether (200 mL) was cooled to −20° and treated over approximately 10 min with a cold (10°) solution of *freshly* prepared Jones chromic acid mixture (50 mL). After the solution was stirred for a further 10 min at −20°, water was added and the cold ether extract was washed (H_2O, $NaHCO_3$, brine), dried ($MgSO_4$), and concentrated to yield the aldehyde (16 g). This material can be purified by chromatography on silica gel *after* the adsorbent has been deactivated with a methanol wash. The crude aldehyde prepared in the above way is suitable for the next step. A sample was chromatographed to yield analytically pure material: ^1H NMR (CCl_4) δ 9.51 (d, 1, J = 6 Hz, H-1), 6.51 (broad d, 1, J = 15 Hz, H-3), 6.37 (dd, 1, J = 15, 7 Hz, H-2), 3.33 (q, 2, J = 2 Hz, H-6), 2.11 (m, 2, H-9), 0.9 (t, 3, H-13). Anal. ($C_{13}H_{16}O$) C, H.

***rac*-(*E*)-1,4-Pentadecadiene-6,9-diyn-3-ol (20).** A solution of vinylmagnesium chloride (75 mL, 2 M) in tetrahydrofuran was added to more tetrahydrofuran (250 mL), cooled to −60°, and treated with the crude aldehyde **19** (16 g) dissolved in tetrahydrofuran (100 mL), and then warmed to 10° over 30 min. After the mixture was stirred for a further 20 min at this temperature, it was cooled to −5°, treated with ether (500 mL) and saturated aqueous ammonium chloride solution (20 mL), and filtered. Removal of the solvents and purification of the residue by HPLC (10% ethyl acetate–hexane) gave the desired material **20** (16.2 g, 70%): ^1H NMR ($CDCl_3$) δ 6.04 (dd, 1, J = 16, 6 Hz, H-4), 5.66 (broad d, 1, J = 16 Hz, H-5); the characteristic ABX system of the terminal vinyl group was seen at 5.85, 5.11, 5.33, 4.59 (t, 2, J = 6 Hz, H-3), 0.85 (t, 3, H-15). Anal. ($C_{15}H_{20}O$) C, H.

(2*E*,4*E*)-1-Bromo-2,4-pentadecadiene-6,9-diyne (21). Phosphorus tribromide (3.7 mL, 39 mmol) dissolved in ether (70 mL) was added to a solution of the alcohol **19** (8.5 g, 39.4 mmol) in ether (200 mL) at −40°. The mixture was then warmed to 0° over 1 h and then washed (ice water, Na_2CO_3 brine), dried ($MgSO_4$), and concentrated. The crude bromo compound was extracted into hexane, filtered rapidly through a silica gel plug (250 mL, 70–230 mesh, deactivated with 1:1 hexane–ethyl acetate), and subsequently purified by HPLC (hexane) to yield the pure bromide (7.8 g, 71%): UV max (ethanol) 275 nm (ϵ 27 400); IR (film) 2215 (C≡C), 1634 (C=C) cm^{-1}; ^1H NMR (CCl_4–C_6D_6) δ 6.44 (dd, 1, J = 15, 10 Hz, H-4), 6.12 (dd, 1, J = 14, 10 Hz, H-3), 5.79 (dt, 1, J = 14, 8 Hz, H-2), 5.55 (broad d, 1, J = 15 Hz, H-5), 3.84 (d, 2, J = 8 Hz, H-1), 3.18 (m, 2, H-8), 2.14 (m, 2, H-11), 0.91 (t, 3, H-15). Anal. ($C_{15}H_{19}Br$) C, H. This material is unstable and suffers extensive decomposition when chromatographed on active silica gel.

***rac-trans*-(2*E*,4*E*)-3-(1,3-Tetradecadiene-5,8-diynyl)oxiranebutanoic Acid Methyl Ester (8a) and the Cis Isomer (8b).** The bromo compound **21** (28.5 g, 102 mmol) was dissolved in tetrahydrothiophene (28 mL) and treated with a methanol–water mixture (9:1, 60 mL). After stirring for 5–10 min, a homogeneous reaction mixture was obtained. The mixture was left at room temperature for a further 30 min, concentrated (30°, 20 and 0.5 mm), washed with hexane as in the case of **9**, and dried (20°, 0.25 mm, 30 min) to yield the salt as a semicrystalline mass. This crude material was dissolved in a mixture of dichloromethane (200 mL), methyl 4-formylbutyrate (26 g, 200 mmol), and benzyltriethylammonium chloride (1 g) and cooled to −40°. Cold (−5°) aqueous sodium hydroxide solution (175 mL, 10 M) was then added rapidly over 1 min (exothermic) while the temperature was held below −25° with a dry ice–acetone bath. After complete addition, the dark-colored heterogeneous mixture was stirred for a further *3 min* at −25°, the stirring was stopped, and the reaction mixture was cooled to −70° and treated with ether (200 mL). The organic phase was decanted and the residue was treated with more ether (100 mL), warmed to form two mobile layers, stirred, refrozen, and decanted. This freeze–thaw cycle was repeated three times (100 mL of ether each time), and the combined organic extracts were then washed (H_2O, brine), dried (Na_2SO_4), and concentrated. The crude residue was extracted into hexane, filtered, and purified by HPLC (1% triethylamine in 5% ethyl acetate–hexane; the silica columns were first equilibrated with 5% triethylamine in ethyl acetate) to yield the pure *trans*-epoxide **8a** (13.6 g, 40%) and the *cis*-epoxide **8b** (3.2 g, 9%) and a mixed fraction (1.3 g). ***trans*-Epoxide 8a**: UV max (ethanol) 260, 272, 285 nm (ϵ 26 600, 35 500, 29 400); ^1H NMR (CCl_4) δ 6.46 (dd, 1, J = 15, 11 Hz, H-3), 6.3 (dd, 1, J = 15, 11 Hz, H-2), 5.52 (dd, 1, J = 15, 2 Hz, H-4), 5.37 (dd, 1, J = 15, 7.5 Hz, H-1), 3.58 (s, 3, OCH_3), 3.18 (m, 2, H-7), 2.93 (dd, 1, J = 7.5, 2 Hz, H-2), 2.67 (dt, 1, J = 8, 2 Hz, H-3), 0.9 (t, 3, H-14). Anal. ($C_{21}H_{28}O_3$) C, H. ***cis*-Epoxide 8b**: ^1H NMR (CCl_4) δ 6.54 (dd, 1, J = 16, 12 Hz, H-3), 6.32 (dd, 1, J = 16, 12 Hz, H-2), 5.67 (d, 1, J = 16 Hz, H-4), 5.54 (dd, 1, J = 16 and 4 Hz, H-1), 3.18 (s, 3, OCH_3), 3.26 (dd, 1, J = 8, 4 Hz, H-2), 3.18 (m, 2, H-7), 2.96 (dt, 1, J = 8, 4 Hz, H-3), 0.91 (t, 3, H-14).

***rac-trans*-(1*E*,3*E*,5*Z*,8*Z*)-(1,3,5,8-Tetradecatetraenyl)oxiranebutanoic Acid Methyl Ester (2).** The *trans*-epoxide **8a** (15 g, 45.2 mmol) was dissolved in hexane (200 mL; old samples often contained hexane-insoluble material) treated with a Lindlar catalyst (1 g) and Celite (5 g), stirred for 5 min, and filtered to give a clear, pale-yellow solution which was treated with more catalyst (1.5 g) and hydrogenated at room temperature and pressure until approximately 1.15 mol of hydrogen per triple bond had been consumed (2600 mL, 22°, 760 mm). The solids were filtered off and the mixture of reduction products was separated by HPLC (1% triethylamine in 5% ethyl acetate–hexane) to yield pure racemic **2** (4.3 g 28%) and some slightly impure material (1.2 g): UV max (hexane) 268, 279, 291 nm (ϵ 34 200, 42 900, 32 100); ^1H NMR (C_6D_6) δ 6.59 (dd, 1, J = 14, 12 Hz, H-4), 6.39 (dd, 1, J = 15, 8 Hz, H-2), 6.15 (dd, 1, J = 14, 11 Hz, H-3), 6.07 (dd, 1, J = 12 Hz, H-5), 5.47 (m, 3, H-6, H-8 and H-9), 5.34 (dd, 1, J = 15, 8 Hz, H-1), 3.36 (s, 3, OCH_3), 2.96 (m, 3, H-7 and H-3), 2.57 (dt, 1, J = 8, 2 Hz, H-2), 0.88 (t, 3, H-14). Anal. ($C_{21}H_{32}O_3$) C, H. Pure samples of this material have been stored under argon at −80° for 6 months with little apparent decomposition.

Hydrogenation of the *cis*-epoxide (9.7 g) in hexane (100 mL) as above yielded the racemic *cis*-epoxide corresponding to **2** (4.4 g, 44%): UV max (ethanol) 271, 281, 292 nm (ϵ 32 000, 40 000, 29 000); ^1H NMR (C_6D_6) 6.51 (dd, 1, J = 15, 12 Hz, H-4), 6.35 (dd, 1, J = 15, 11 Hz, H-2), 6.1 (dd, 1, J = 15, 11 Hz, H-3), 6.0 (t, 1, J = 12, 11 Hz, H-5), 5.4 (complex m, 4, H-8, H-9, H-6, and H-1), 3.4 (s, 3, OCH_3), 3.23 (dd, 1, J = 8, 4 Hz, H-3), 2.94 (m, 2, H-7), 2.83 (dt, 1, J = 6, 4 Hz, H-2), 0.9 (t, 3, H-14). Anal. ($C_{21}H_{32}O_3$) C, H.

[5*S*-[5*R,6*S**(*R**),7*E*,9*E*,11*Z*,14*Z*]]-5-Hydroxy-6-[(2-amino-3-methoxy-3-oxopropyl)thio]-7,9,11,14-eicosatetraenoic Acid Methyl Ester (LTE$_4$ Dimethyl Ester) and the 5*R*,6*S* Isomer.** A solution of L-cysteine methyl ester hydrochloride (4 g, 23.3 mmol) in methanol and water (50 mL, 6:1) was treated with triethylamine to pH 9. Racemic epoxide **2** (4 g, 12 mmol) was then added and the mixture was stirred at room temperature for 18 h (the reaction is nearly complete after 8 h). Most of the methanol was then removed (35°, 20 mm) and the residue was partitioned between ether and water. The ether extract was then washed (H_2O, brine), dried ($MgSO_4$), and concentrated. Purification of the residue by HPLC (ethyl acetate) gave the pure isomers. (5*R*,6*S*) Isomer (1.95 g): $[\alpha]^{20}_D$ −19.6° (*c* 3.245, dioxane); UV max (ethanol) 276, 282, 292 nm (ϵ 29 600, 37 100, 29 100). Anal. ($C_{25}H_{41}NO_5S$) C, H, N, S. (5*S*,6*R*) Isomer (1.8 g): $[\alpha]^{20}_D$ +35.2°; UV max (ethanol) 271, 281, 292 nm (ϵ 25 500, 36 300, 28 500); ^1H NMR ($CDCl_3$) δ 6.53 (dd, 1, J = 14.5, 10 Hz, H-10), 6.0 (t, 1, J = 10 Hz, H-11), 5.62 (dd, 1, J = 14.4, 9.6 Hz, H-7), 5.3 (m, 1, J = 10, 9 Hz, H-14), 3.71 and 3.62 (2 s, 6, CO_2CH_3), 3.65 (m, 1, H-5), 3.4 (m, 1, H-6), 2.95 (t, 2, J = 9 Hz, H-13), 2.02 (m, 2, H-16), 0.86 (t, 3, J = 6 Hz, H-20). Anal. ($C_{25}H_{41}NO_5S$) C, H, N, S.

Leukotriene E$_4$ Monopotassium Salt. A solution of the dimethyl ester (1.5 g, 3.2 mmol) in methanol (45 mL) was treated with cold (10°) potassium hydroxide (0.75 g, 13.4 mmol) in water (10 mL) and kept at room temperature for 90 min. Water (50 mL) was then added and the methanol was distilled off (25°, 20 mm); the aqueous solution was adjusted to pH 8.5 with phosphoric acid (0.5 N). This material was then absorbed onto a single C_{18} Waters Prep column and washed with water (4 L). Elution with methanol–water (4:1) yielded the desired material as an aqueous solution after removal of the methanol in vacuo. The aqueous solution was freeze-dried; the residue was dissolved in water, filtered, and freeze-dried a second time to yield the potassium salt of LTE$_4$ (1 g) as a pale-yellow powder contaminated by K_2HPO_4: UV max (methanol) 268, 279, 288 nm (ϵ 31 000, 38 800, 31 000) (92% purity based on an ϵ 280 of 42 000). This material showed the characteristic UV changes on degradation with soybean lipoxygenase, Sigma Type I. The powder is hygroscopic and rapidly degraded in air with the formation of polar products and destruction of the characteristic UV spectrum (the 280-nm triene system is replaced by a band at 245 nm).

(5*S*,6*S*)-LTE$_4$ Dimethyl Ester. The racemic *cis*-epoxide (1.5 g, 4.5 mmol) was treated with L-cysteine methyl ester (from 1.5 g of the hydrochloride salt) in aqueous methanol as before. After 16 h at room temperature the reaction was worked up as before, and the crude material (3 g) was purified by HPLC (ethyl acetate) to yield the (5*S*,6*S*) isomer (0.45 g), a mixed fraction (0.9 g), and the (5*R*,6*R*) isomer (0.1 g). (5*S*,6*S*) Isomer: $[\alpha]^{20}_D$ −24.6° (*c* 1.36, dioxane); UV max (ethanol) 273,

282, 291 nm (ε 29 200, 35 300, 28 300). The vinyl protons showed the same pattern in the ^{1}H NMR spectrum as LTE_4 dimethyl ester. Anal. ($C_{25}H_{41}NO_5S$) C, H, N, S. (5*R*,6*R*) Isomer: $[\alpha]^{20}_D$ +7.9° (*c* 0.47, dioxane). Anal. ($C_{25}H_4$;NO_5S) C, H, N.

Desulfurization of the (5*S*,6*S*) material gave a lactone with a *positive* rotation.

Hydrolysis with potassium hydroxide in aqueous methanol and purification by reverse phase chromatography as before yielded the monopotassium salt: UV max (methanol) 270, 279.5, 290 nm. Assuming an ε 280, 42 000, this material contained 85% LTE_4 equivalent.

(5*S*)-5-Hydroxyeicosanoic Acid Lactone (22). A solution of the dimethyl ester (5*R*,6*S* isomer, 1 g) in ethanol (30 mL) containing Raney nickel (5 mL, aqueous slurry) was stirred at room temperature for 2 h, filtered, and concentrated. The residue was dissolved in ethyl acetate (25 mL), dried ($MgSO_4$), stirred for 5 min with a palladium catalyst (5% on carbon, 500 mg), and filtered free of solids. The ethyl acetate solution was then treated with more of the same catalyst and hydrogenated at room temperature and pressure until the uptake of hydrogen stopped. The solids were then removed and the mixture was concentrated and the residue treated with base as in the case of **16**. The crude hydroxy acid was dissolved in dichloromethane (50 mL), treated with trifluoroacetic acid (0.1 mL), left at room temperature for 1 h, and then washed (Na_2CO_3, brine), dried ($MgSO_4$), and concentrated. Purification of the residue by HPLC (4:1 hexane-ethyl acetate) gave the *total* lactone fraction (100 mg). This material was dissolved in heptane and subjected to flash chromatography to yield the pure lactone (98.3 mg). This second purification step is needed to remove impurities carried over by the reagent grade hexane used in the HPLC purification: mp 52-56°; $[\alpha]^{20}_D$ -26° (*c* 2.07, dioxane). Anal. ($C_{20}H_{38}O_2$) C, H.

To estimate the optical purity of the lactone, the above sample was converted to the orthoester mixture as before. GLC indicated a 93:7 mixture of orthoesters.

Homo-LTE_4 Dimethyl Ester. The bromide **21** (14 g, 50 mmol) was converted into the salt as before and allowed to react with the aldehyde **7c** (14 g, 97 mmol, freshly distilled) as before to yield the pure *cis*-epoxide (2.4 g, 14%), a mixed fraction (1.5 g, mainly trans), and the pure *trans*-epoxide (4.9 g, 28%): UV max (hexane) 261, 273, 284 nm (ε 27 300, 34 100, 25 200); ^{1}H NMR (CCl_4) δ 6.48 (dd, 1, *J* = 15, 11 Hz, H-9), 6.32 (dd, 1, *J* = 15, 11 Hz, H-8), 5.54 (d, 1, *J* = 15 Hz, H-10), 5.42 (dd, 1, *J* = 15, 8 Hz, H-7), 3.62 (s, 3, OCH_3), 3.22 (m, 2, H-13), 2.99 (dd, *J* = 8, 2 Hz, H-6), 2.72 (m, 2, H-5). Anal. ($C_{22}H_{30}O_3$) C, H. Hydrogenation of this material (4.9 g, 14.3 mmol) in hexane (100 mL) followed by HPLC yielded the pure tetraene (1.7 g, 34%). The ^{1}H NMR (C_6D_6) showed the same features as in the case for racemic **2**. This epoxide (1.7 g, 4.9 mmol) was added to L-cysteine methyl ester (from the hydrochloride 1.7 g) in a mixture of methanol (8 mL) and water (2 mL) at pH 9 (triethylamine) and left at room temperature for 4 h. The solvents were then removed in vacuo and the residue was partitioned between ethyl acetate and water, and the crude cysteine derivatives were then purified by HPLC (5% methanol in 1:1 hexane-ethyl acetate). (6*R*,7*S*) isomer (0.8 g): $[\alpha]^{20}_D$ -12.6° (*c* 1.725, dioxane); UV max (ethanol) 272, 281, 290 nm (ε 26 500, 32 600, 26 400). Anal. ($C_{26}H_{43}NO_5S$) C, H, N, S. (6*S*,7*R*) Isomer (0.65 g): $[\alpha]^{20}_D$ +39.2° (*c* 2.42, dioxane); UV max (ethanol) 271, 281, 290 nm (ε 29 100, 36 000, 29 100); ^{1}H NMR ($CDCl_3$) δ 6.54 (dd, 1, *J* = 14, 11 Hz, H-4), 6.28 (m, 1, *J* = 14 Hz, H-2), 6.20 (m, 1, *J* = 14 Hz, H-3), 6.03 (ddt, 1, *J* = 11, 2 Hz, H-5), 5.64 (dd, 1, *J* = 14, 10 Hz, H-1), 3.76 and 3.67 (2 s, 6, CO_2CH_3), 2.95 (m, 2, H-7), 2.84 (ddd, 2, *J* = 12, 8, 5 Hz, SCH_2-). Anal. ($C_{26}H_{43}NO_5S$) C, H, N, S.

Nor-LTE_4 Dimethyl Ester. The bromide **21** (20 g, 71.7 mmol) was converted into the sulfonium salt and allowed to react with the aldehyde **7b** (25 g, 216 mmol, freshly distilled) as before. Purification by HPLC (2% triethylamine in 3:1 hexane-ether) gave the pure *cis*-epoxide (3.4 g, 15%) and the *trans*-epoxide (8.6 g, 37%). Crystallization of the trans isomer from hexane gave the analytical sample: mp 46-48°; UV max (hexane) 262, 272, 284 nm (ε 34 300, 44 000, 36 200); ^{1}H NMR ($CDCl_3$) δ 6.55 and 6.40 (2 dd, 2, *J* = 14.5, 11 Hz, H-2 and H-3), 5.61 (d, 1, *J* = 14.5 Hz, H-4), 5.45 (dd, 1, *J* = 14.5, 8 Hz, H-1), 3.69 (s, 3, CO_2CH_3), 3.29 (s, 2, H-7), 3.15 (dd, 1, *J* = 8, 2 Hz, H-3), 2.92 (dt, *J* = 6, 2 Hz, H-2). Anal. ($C_{20}H_{26}O_3$) C, H.

Hydrogenation of the *trans*-epoxide (8 g, 25.5 mmol) in hexane (150 mL) as before yielded the desired tetraene (3.5 g, 43%) after HPLC purification (2% triethylamine in 5% ethyl acetate-hexane): ^{1}H NMR (C_6D_6) δ 6.55 (dd, 1, *J* = 15, 11 Hz, H-4), 6.33 (dd, 1, *J* = 15, 11 Hz, H-2), 6.09 (dd, 1, *J* = 15, 11 Hz, H-3), 6.03 (t, 1, *J* = 11 Hz, H-5), 5.5 (m, 3, H-6, H-8, and H-9), 5.28 (dd, 1, *J* = 15, 8 Hz, H-1), 3.33 (s, 3, CO_2CH_3), 3.0 (m, 2, H-7), 2.96 (dd, 1, *J* = 8, 2 Hz, H-3), 2.7 (dt, 1, *J* = 8, 2 Hz, H-2). Anal. ($C_{20}H_{30}O_3$) C, H.

Cysteine methyl ester hydrochloride (2.4 g) was converted to the free amine in aqueous methanol as before and then allowed to react with the *trans*-epoxide (2.35 g, 7.4 mmol) for 1 h at room temperature. Workup as before and purification by HPLC (3% methanol in 1:1 hexane-ethyl acetate) yielded the pure (4*R*,5*S*) isomer (1 g) and the (4*S*,5*R*) isomer (1.25 g). The (4*S*,5*R*) diastereomer was contaminated by the γ-lactone which could be removed by repeated HPLC purification. (4*R*,5*S*) Isomer: $[\alpha]^{20}_D$ -19.5° (*c* 3.07, dioxane). Anal. ($C_{24}H_{39}NO_5S$) C, H, N, S. (4*S*,5*R*) Isomer: $[\alpha]^{20}_D$ +27° (*c* 3.14, dioxane). Anal. ($C_{24}H_{39}NO_5S$) C, H, N, S.

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Enantiospecific Syntheses of Leukotrienes C_4, D_4, and E_4 and [14,15-$^3H_2$]Leukotriene E_4 Dimethyl Ester

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Abstract: A "chiral-pool" approach was employed to synthesize various leukotrienes (slow-reacting substance of anaphylaxis, SRS-A) enantiospecifically. The pivotal (*S*,*S*)-*trans*-epoxy alcohol **9** was prepared by efficient and facile routes starting from erythorbic acid (*D*-araboascorbic acid, **13**). This epoxide could also be produced starting from D-glucose. The epimeric (*S*,*R*)-*cis*-epoxide **38** was obtained utilizing L-tartaric acid as the chiral starting material. Elaboration of **9** into leukotriene A_4 methyl ester (**5**) and the potassium salts of leukotrienes C_4 (**4a**), D_4 (**4b**), and E_4 (**4c**) was accomplished by standard methods. These salts exhibited potent contractile activities in the in vitro guinea pig ileum assay. Reduction of 14,15-dehydroleukotriene A_4 methyl ester (**44**) with tritium gas gave [14,15-$^3H_2$]-**5** and subsequently the dimethyl ester of [14,15-$^3H_2$]leukotriene E_4 having a high specific activity of 40 Ci/mmol.

Slow-reacting substance of anaphylaxis (SRS, SRS-A) is, along with histamine and certain chemotactic peptides, an important mediator of asthma and other conditions of hypersensitivity.[1] This factor has been isolated from a variety of mammalian cells upon

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