(ddd, 1, J = 2, 11, 13 Hz), 3.45 (s, 3), 2.58 (d, 1, J = 14 Hz), 2.32 (d, 1, J = 14 Hz), 2.55 (m, 1), 2.5 (m, 1), 1.85 (ddd, 1, J = 2, 11, 15 Hz); isomer D 6.69 (d, 1, J = 10 Hz), 6.01 (d, 1, J = 10 Hz), 3.83 (s, 3), 3.44 (s, 3), 3.30 (m, 1), 3.01 (m, 1), 2.65 (m, 1), 2.5 (d, 1, J = 14 Hz), 2.36 (d, 1, J = 14 Hz), 2.11 (m, 1); $^{13}C(^1H)$ NMR δ 174.7, 174.4, 174.2, 174.0, 166.70, 166.69, 166.63, 135.3, 135.1, 134.5, 134.2, 133.6, 133.4, 132.9, 131.0, 103.4, 103.1, 103.0, 53.62, 53.58, 53.52, 53.42, 53.38, 45.8, 45.1, 45.0, 44.5, 44.0, 43.9, 43.8, 43.6, 42.9, 41.3, 41.4, 25.8, 25.2, 23.3, 22.4; ^{13}C(DEPT δ 135.3 (d), 135.1 (d), 134.5 (d), 134.2 (d), 133.6 (d), 133.4 (d), 132.9 (d), 131.0 (d), 53.62 (q), 53.58 (q), 53.52 (q), 53.42 (q), 53.38 (q), 45.8 (t), 45.1 (t), 45.0 (t), 43.8 (t), 43.6 (t), 42.9 (t), 41.8 (t), 41.4 (t), 25.8 (t), 25.2 (t), 23.3 (t), 22.4 (t); HRMS calcd for $C_{11}H_{14}O_6S$ m/z 274.049, found 274.051.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]deca-5,8-diene-3-carboxylate (18). To a solution of 29 mg (0.11 mmol) of sulfoxide **17** and 41 μL (0.23 mmol) of ethyldiisopropylamine in 0.5 mL of CH_2Cl_2 at 0 °C and under nitrogen was added 41 μL (0.21 mmol) of trimethylsilyl trifluoromethanesulfonate dropwise, and the solution was stirred under nitrogen at 0 °C for 2 h. The mixture was diluted with 10 mL of dichloromethane and washed with 2 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated. The residue was chromatographed (3:1 hexane/EtOAc) to afford 9.6 mg (34% yield) of the didehydro derivative **18** as a clear oil: ^1H NMR δ 6.42 (dd, 1, J = 10, 2.6 Hz), 6.35 (dd, 1, J = 10, 2.6 Hz), 5.76 (dd, 1, J = 10, 1.8 Hz), 5.47 (dd, 1, J = 10, 1.8 Hz), 3.86 (s, 3), 3.47 (s, 3), 2.55 (d, 1, J = 14 Hz), 2.37 (d, 1, J = 14 Hz); ^{13}C NMR δ 174.7, 167.3, 121.6, 120.1, 119.6, 118.7, 103.3, 53.4, 53.2, 49.6, 45.3.

Methyl 1-Oxo-3-methoxy-2-oxa-7-thiaspiro[4.5]deca-5,8-diene-3-carboxylate (19). To a solution of 3.6 mg (.014 mmol) of diene **18** in 250 μL of CH_2Cl_2 under nitrogen at −78 °C was added a solution of 2.9 mg (.017 mmol) of *m*-chloroperbenzoic acid in 200 μL of CH_2Cl_2 dropwise, and the solution was stirred at −78 °C for 25 min and then allowed to warm to 21 °C. After dilution with 4 mL of CH_2Cl_2, the mixture was washed with 0.5 mL each of saturated $NaHCO_3$ and brine, dried, and evaporated to afford 3.9 mg of sulfoxide **19** as a 2:1 mixture of sulfoxide isomers contaminated with 16% of the sulfone arising from overoxidation: ^1H NMR δ isomer A 6.95 (dd, 1, J = 2.6, 10 Hz), 6.85 (dd, 1, J = 2.6, 10 Hz), 6.45 (dd, 1, J = 1.3, 10 Hz), 6.08 (dd, 1, J = 1.3, 10 Hz), 3.92 (s, 3), 3.50 (s, 3), 2.83 (d, 1, J = 14 Hz), 2.78 (d, 1, J = 14 Hz); isomer B δ 6.80 (dd, 1, J = 3.2, 11 Hz), 6.73 (dd, 1, J = 3.2, 11 Hz), 6.61 (dd, 1, J = 2.6, 11 Hz), 6.27 (m, 1), 3.92 (s, 3), 3.53 (s, 3), 2.74 (d, 1, J = 14 Hz), 2.70 (d, 1, J = 14 Hz); sulfone δ 6.91 (dd, 1, J = 2.6, 9 Hz), 6.85 (m, 1), 6.49 (dd, 1, J = 1.3, 10 Hz), 6.27 (m, 1), 3.90 (s, 3), 3.52 (s, 3), 2.54 (d, 1, J = 14 Hz), 2.40 (d, 1, J = 14 Hz). This material was not further characterized in view of the fact that no defined compound could be isolated from its hydrolysis product(s).

Enzyme Assays. Prephenate Purity. Purity of the prephenate employed (Sigma) was determined by conversion to phenylpyruvate according to the method of Zalkin.[21]

Enzyme Purification and Assay. The procedures of Davidson[18] were employed for the purification and assay of chorismate mutase/prephenate dehydratase. The enzyme was isolated from *E. coli*, strain JP492, which was a gift from Professor John F. Morrison (Canberra).

Preincubation Studies. Stock enzyme solution (in 20 mM Tris pH 8.2, 1 mM EDTA, 1 mM dithioerythritol, 0.02% sodium azide) was diluted with an equal amount of 20 mM inhibitor solution (in 20 mM Tris pH 8.2, 20 mM mercaptoethanol, 1 mM EDTA, 0.01% bovine serum albumin) and incubated at 37 °C. Aliquots were removed at 15-min intervals over the course of 1.5 h and assayed for activity. A control in which enzyme was diluted with buffer solution containing no inhibitor was also incubated alongside the inhibitor solution.

Competitive Inhibition Studies. Stock substrate solution (1 mM prephenate in 20 mM Tris pH 8.2, 1 mM EDTA, 0.01% bovine serum albumin, 40 mM mercaptoethanol) was diluted with an equal amount of inhibitor solutions of varying concentrations (in 20 mM Tris pH 8.2, 1 mM EDTA, 0.01% bovine serum albumin) and equilibrated at 37 °C for 5 min. Enzyme was added and the solution was incubated an additional 5 min before being quenched with hydroxide. Two inhibitor incubations were run along with a blank to which no enzyme was added.

Acknowledgment. We thank Professor John F. Morrison (Australian National University, Canberra) for a gift of the *E. coli* strain JP492. Support for this work was provided by the National Institutes of Health (grant no. GM-28965).

Registry No. **4**, 119948-17-3; **5**, 119948-18-4; **6**, 119948-19-5; **7**, 119948-20-8; **8**, 119948-21-9; **9**, 4469-60-7; **10**, 119948-04-8; **11**, 119948-05-9; **12**, 119948-06-0; **13**, 119948-07-1; **14**, 119948-08-2; *trans*-**15**, 119948-09-3; *cis*-**15**, 119948-13-9; *cis*-**16**, 119948-10-6; *trans*-**16**, 119948-16-2; **17** (isomer 1), 119948-03-7; **17** (isomer 2), 120020-84-0; **17** (isomer 3), 120020-85-1; **17** (isomer 4), 120020-86-2; **18**, 119948-11-7; *cis*-**19**, 119948-12-8; *trans*-**19**, 119948-14-0; **19** sulfone, 119948-15-1; K_2S, 1312-73-8; prephenate dehydratase, 9044-88-6; α-ketoglutamic acid, 328-50-7; 2-(2-iodoethoxy)tetrahydropyran, 96388-83-9; dihydropyran, 110-87-2; 2-iodoethanol, 624-76-0.

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Total Synthesis of Leukotriene B_4 [(+)-LTB_4] and Homo-LTB_4 from D-Mannitol

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A convergent total synthesis of leukotriene B_4 and its homo analogue has been carried out via enantiomerically pure α-hydroxy aldehydes, chiral key intermediates obtained from D-mannitol and connected at a four carbon atom interval by Wittig reactions.

In the last few years, there has been considerable interest in hydroxylated eicosatetraenoic acids derived from arachidonic acid by lipoxygenase metabolic pathways. Leukotriene B_4 biosynthetized via the 5-lipoxygenase pathway[1] is one of the most potent chemotactic agents produced by human polymorphonuclear leukocytes. Implicated as mediator in inflammation and allergic reactions,[2] LTB_4 is also supposed to play an important role in immunobiological reactions.[3]

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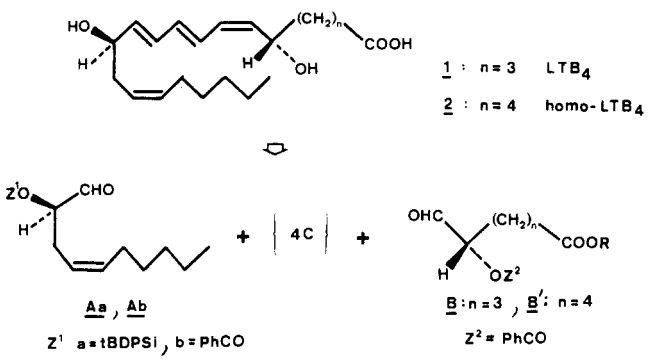
0022-3263/89/1954-2409$01.50/0

Scheme I



The perceived importance of leukotriene B_4 and the difficulty in isolating LTB_4 in quantity from biological sources prompted several groups to embark on the synthesis of this compound.[4] In order to determine the structural requirement for chemotactic activity of leukotriene B_4, the synthesis of structural analogues of LTB_4 is also a prime target for biological investigations. Thus, we developed total syntheses of leukotriene B_4 (1) and its homo analogue 2 to examine the role of the chain length on activity.

Retrosynthetic analysis (Scheme I) reveals that the α-hydroxy aldehydes A (*R*) and B (*S*) or B′ (*S*) are convenient chiral building blocks for LTB_4 (1) and homo-LTB_4 (2) construction.

We prepared these enantiomerically pure α-hydroxy aldehydes of *R* or *S* configuration from D-mannitol, a unique, inexpensive chiral compound. The strategy is based on nucleophilic opening of diastereoisomeric diepoxides according to the following general approach, depicted in Scheme II. Each molecule of D-mannitol leads via diepoxide without wastage of carbons to two molecules of enantiomerically pure α-hydroxy aldehyde with various side chains. Indeed the molecule of D-mannitol has a 2-fold axis of symmetry. If this symmetry is preserved during chemical transformations and, consequently, if there is control of the configuration of asymmetric carbons, then C-2 and C-5 will have identical absolute configuration and the cleavage of the C-3–C-4 bond will lead to two identical chiral molecules. Starting from D-mannitol, we prepared the "D-mannitol diepoxide" 3[5] with retention of configuration at C-2 and C-5. Regiospecific nucleophilic ring opening introduced various R groups at C-1 and C-6; deprotection and cleavage of the glycol led to two molecules of the (*R*)-α-hydroxy aldehyde. Always starting from D-mannitol, but now with inversion of configuration at C-2 and C-5, we prepared the "L-iditol diepoxide" 4,[5] and following the same reaction sequence, we obtained the enantiomerically pure (*S*)-α-hydroxy aldehyde.

Suitably protected α-hydroxy aldehyde Aa (Scheme III), which is a necessary synthon for the construction of both LTB_4 and homo-LTB_4, resulted from nucleophilic opening of the "D-mannitol diepoxide" 3 by lithium heptynide followed by silylation in situ, controlled hydrogenation of the triple bonds, removal of the acetonide group, and oxidative cleavage of the 3,4-diol. In the presence of the bulky *tert*-butyldiphenylsilyl (tBDPSi) protecting group, hydrolysis of the acetonide using trifluoroacetic acid was not complete at 0 °C and silicon–oxygen bond cleavage occurred at higher temperatures. Indeed, the glycol deprotection by transthioketalization[6] afforded crude diol. Aldehyde Aa was obtained in 33% overall yield from diepoxide.

We have also used benzoates as temporary protective groups for the alcohol functions in C-2 and C-5 positions. Then acetonide hydrolysis was carried out in 90% aqueous trifluoroacetic acid, and the resulting diol was cleaved by $Pb(OAc)_4$, leading to the aldehyde Ab (Z = COPh) in 57% overall yield from diepoxide 3.[5a] This benzoate protective group will be replaced by a silyl protective one during the synthesis.

The α-hydroxy aldehyde B preparation (Scheme IV) requires the introduction of a three carbon atom chain bearing a carboxylic acid functionality. Nucleophilic opening of the "L-iditol diepoxide" 4 by ethyl lithiopropiolate (large excess) in the presence of boron trifluoride etherate at −78 °C followed by diol benzoylation, triple-bond reduction, acetonide hydrolysis, and cleavage of the 3,4-diol led to aldehyde B in 47% overall yield from diepoxide.

Application of the previous strategy to obtain aldehyde B′ necessary for the synthesis of homo-LTB_4 requires opening of the diepoxide by a four carbon atom nucleophile having a carboxylic acid functionality. We preferred to investigate a new way, starting from D-mannitol (Scheme V), via the (*R*)-glyceraldehyde acetonide. The introduction of the side chain occurs on the D-mannitol skeleton at C-3 and C-4 (instead of C-1 and C-6 previously) while aldehyde functionality is now on C-1 and C-6 (instead of C-3 and C-4 previously). Thus, an α-hydroxy aldehyde of the *S* configuration is obtained without implication of C-2 and C-5 of D-mannitol.

The four carbon atom chain was introduced in two steps by vinyl Grignard condensation[7] on (*R*)-glyceraldehyde acetonide[7,8] followed by Claisen orthoester rearrangement,[7] the carboxylic acid functionality being formed simultaneously (Scheme VI). Reduction of the double bond followed by acetonide hydrolysis, protection of the alcohols, selective deprotection of the primary alcohol without intramolecular transesterification,[9] and finally oxidation[10] led to (*S*)-α-hydroxy aldehyde B′.

In the second part of the synthesis of LTB_4 and homo-LTB_4 (Scheme VII), a four carbon atom junction between the two aldehydes Aa and B or B′ was realized by successive Wittig condensations according to a scheme previously described.[4d] We have modified some experi-

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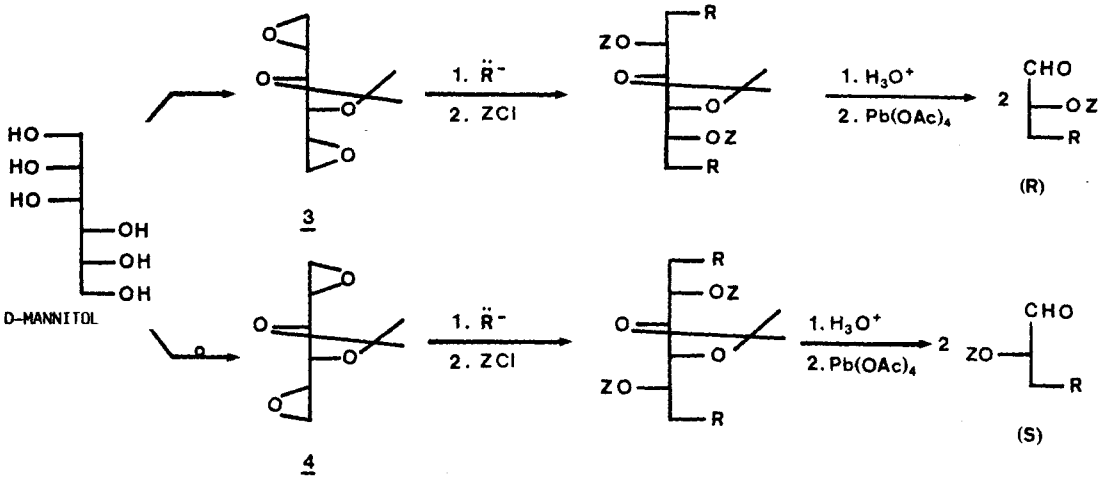
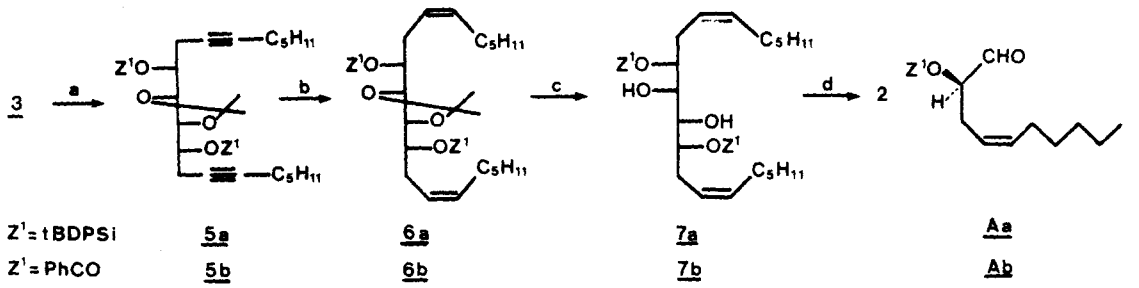
Scheme II



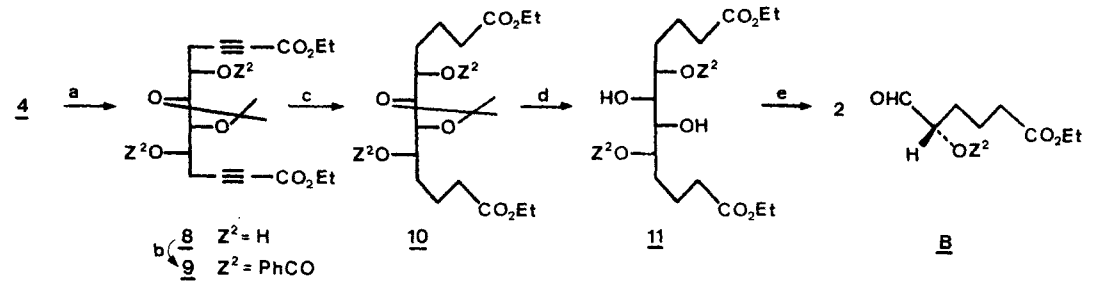
Scheme III[a]



a Z¹ = tBDPSi 5a 6a 7a Aa
b Z¹ = PhCO 5b 6b 7b Ab

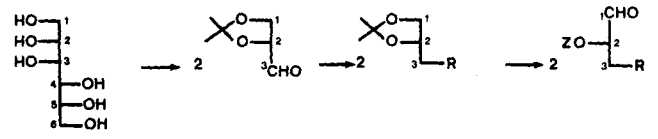
[a] (a) $C_5H_{11}C{\equiv}CLi$/THF/HMPA, 65 °C, 3.5 h, then tBDPSiCl, DMAP, 65 °C, 17 h → **5a**, or PhCOCl, pyridine, room temperature, 2 h → **5b**. (b) Lindlar catalyst, H_2, C_6H_6. (c) **6a** → **7a**: $(CH_2SH)_2$, TsOH, $CHCl_3$, 60 °C, 3 h, **6b** → **7b**: TFA, H_2O, 0 °C, 3 h. (d) $Pb(OAc)_4$, C_6H_6, room temperature, 1 h.

Scheme IV[a]



[a] (a) LiC≡CCOOEt, $BF_3{\cdot}OEt_2$, THF, −78 °C, 2 h. (b) PhCOCl, pyridine, room temperature, 2 h. (c) H_2, PtO_2, EtOH. (d) TFA, H_2O, −5 °C, 3.5 h. (e) $Pb(OAc)_4$, CH_2Cl_2, −10 °C, 1 h.

Scheme V



mental conditions. In particular, during the Horner–Wadsworth–Emmons reaction (**19** → **20**), we used conditions more appropriate for base-sensitive aldehydes.[11] For the transformation of allylic alcohol into bromide, use of DIPHOS ($[Ph_2PCH_2]_2$) instead of triphenylphosphine facilitates purification, since "diphosmonoxide" is more easily separated than triphenylphosphine oxide.

In the case of the benzoylated aldehyde Ab (Z^1 = PhCO), two Wittig reactions involving the same reagents as for the silyl aldehyde Aa (Z^1 = tBDPSi) led to the dienic ester **20b** (Z^1 = PhCO). It was then necessary to change the benzoyl for a silyl group insensitive to reduction. Thus the benzoate group removal was carried out by K_2CO_3–EtOH and afforded the ester–alcohol **20c** (Z^1 = H). This alcohol was then silylated to give the silyl ester **20a** (Z^1 = tBDPSi). The overall yield in both series (Z^1 = PhCO or tBDPSi) from the diepoxide **3** to the dienic ester **20a** was almost the same.

The last Wittig reaction involving the aldehyde B led to a mixture of the two double-bond isomers $\Delta^{6,7}$ cis and $\Delta^{6,7}$ trans (7:3) of the fully protected LTB$_4$. These compounds were easily separated by HPLC and fully characterized. Each isomer of LTB$_4$ was then deprotected, and the potassium salt of (+)-LTB$_4$ obtained is identical (HPLC, UV) with a sample supplied by Dr. J. Rokach.

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The study of LTB_4 metabolism[12] by different systems showed that the metabolic profile obtained was superposable on the one obtained from Rokach's sample of LTB_4.

In the same way, the last Wittig reaction involving the aldehyde B′ led to a mixture of two diastereoisomers, $\Delta^{7,8}$ cis and $\Delta^{7,8}$ trans (7:3). The homo-LTB_4 was then deprotected and purified by reverse-phase HPLC. Concerning chemotactism, it has been shown that increasing the chain length between the first hydroxyl group and the carbonyl group decreases potency but not activity.[13]

Experimental Section

Tetrahydrofuran (THF) and ether were distilled from sodium–benzophenone immediately prior to use. Hexamethylphosphoramide (HMPA) and dichloromethane were distilled from CaH_2 and stored under a nitrogen atmosphere. NMR spectra were recorded in $CDCl_3$ (unless indicated), and NOE experiments have been carried out in almost all cases to attribute coupling constants of protons. High-resolution mass spectra (HRMS) were performed by D. Gaudin of Centre d'Etudes Nucléaires. All reactions were carried out under an inert atmosphere of nitrogen or argon and were monitored by thin-layer chromatography with E. Merck 60F-254 precoated silica (0.2 mm) on glass. Flash chromatography was performed with Merck Kieselgel 60 (230–400 mesh ASTM) silica.[14] The chemical names given follow IUPAC rules. Satisfactory spectroscopic (^1H and ^{13}C NMR, MS) and/or analytical data were obtained for all new compounds, using chromatographically homogeneous samples.

9(*R*),12(*R*)-Bis[(*tert*-butyldiphenylsilyl)oxy]-10(*S*),11-(*S*)-*O*-(1-methylethylidene)-6,14-icosadiyne-10,11-diol (5a). To a stirred solution of 1-heptyne (4.67 mL, 35.8 mmol) in THF (36 mL) at 0 °C was dropwise added *n*-butyllithium (1 M in hexanes, 32.8 mL, 32.8 mmol). After the mixture was stirred for 30 min at 0 °C, the diepoxide **3** (2.77 g, 14.9 mmol) and HMPA (5.75 mL, 32.8 mmol) were successively added and the mixture was refluxed for 3.5 h. The resulting alcoholate functions were protected in situ by addition of both *tert*-butylchlorodiphenylsilane (15.7 mL, 59.6 mmol) and (*N*,*N*-dimethylamino)pyridine (7.27 g, 59.6 mmol). The solution was then refluxed for 17 h. The reaction was quenched, at 5 °C, by the addition of ice–water (30 mL) and ether (180 mL). After extraction, the organic layer was washed with brine and dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography. Elution of the column with (1:1) CH_2Cl_2–hexane (R_f 0.35) afforded a pale yellow crystalline solid. Recrystallization from ethanol gave 7.64 g (60%) of the dialkyne silylated **5a** as white prisms: mp 73 °C; $[\alpha]_D$ −26.2° (*c* 1.2, CH_2Cl_2); IR (neat) 3070, 3040, 1590, 1110, 825 cm^{-1}; ^1H NMR (90 MHz)[15] δ 0.85 (t, 6 H, *J* = 6, H-1), 1.00 (s, 18 H, tBu), 1.15 (s, 6 H, $C(Me)_2$), 1.25–2.20 (m, 20 H, H-2–5,8), 3.70 (m, 2 H, H-9), 4.25 (m, 2 H, H-10), 7.20–7.90 (2 m, 20 H, Ph); ^{13}C NMR[15] δ 14.2 (C-1), 19.6 (tBu), 27.2, 28.3 ($C(Me)_2$, tBu), 19.1, 22.5, 22.9, 28.8, 31.4 (C-2–5,8), 71.3, 79.1 (C-9,10), 76.4, 82.4 (C-6,7), 109.0 ($C(Me)_2$), 127.2, 127.3, 129.4, 133.2, 133.5, 135.8 (Ph).

9(*R*),12(*R*)-Bis[(*tert*-butyldiphenylsilyl)oxy]-10(*S*),11-(*S*)-*O*-(1-methylethylidene)-6(*Z*),14(*Z*)-icosadiene-10,11-diol (6a). Lindlar catalyst (palladium on calcium carbonate, poisoned with lead: 0.47 g) in benzene (45 mL) was stirred under 1 atm of H_2 at room temperature until catalyst was entirely hydrogenated. Then, the dialkyne **5a** (2.77 g, 3.2 mmol) was added in benzene (22 mL); the progress of hydrogenation was monitored by the volume of hydrogen absorbed. Filtration and evaporation in vacuo of the filtrate gave 2.78 g (100%) of the dialkene **6a** as a white viscous residue: $[\alpha]_D$ +2.3° (*c* 1.4, CH_2Cl_2); ^1H NMR[15] (250 MHz) δ 0.90 (t, 6 H, *J* = 7, H-1), 1.00 (s, 18 H, tBu), 1.10–1.30 (m, 12 H, H-2–4), 1.30 (s, 6 H, $C(Me)_2$), 1.65–1.80 (m, 6 H, H-5,8), 2.25 (ddd, 2 H, $J_{8',8}$ = 15, $J_{8',9}$ = 6, $J_{8',7}$ = 7, H-8′), 3.60 (t, 2 H, $J_{9,8}$ = $J_{9,8'}$ = 6, H-9), 4.00 (br s, 2 H, H-10), 5.15–5.40 (m, 4 H, $J_{6,7}$ = 11, H-6,7), 7.20–7.90 (3 m, 20 H, Ph); ^{13}C NMR[15] δ 14.3 (C-1), 19.6 (tBu), 22.8, 27.4, 29.3, 30.0, 31.6 (C-2–5,8), 27.3, 28.2 ($C(Me)_2$, tBu), 72.6, 79.8 (C-9,10), 108.7 ($C(Me)_2$), 125.3, 131.5 (C-6,7), 127.2, 127.3, 129.4, 133.5, 133.8, 135.9 (Ph).

9(*R*),12(*R*)-Bis[(*tert*-butyldiphenylsilyl)oxy]-6(*Z*),14-(*Z*)-icosadiene-10(*S*),11(*S*)-diol (7a). To a solution of the acetonide **6a** (2.91 g, 3.4 mmol) in chloroform (90 mL) were added both ethanedithiol (1.99 mL, 23.7 mmol) and *p*-toluenesulfonic acid[6] (0.12 g, 0.7 mmol), and the mixture was refluxed. At 1-h intervals, twice over, ethanedithiol (1.99 mL, 23.7 mmol) and *p*-toluenesulfonic acid (0.12 g, 0.7 mmol) were added while refluxing was wholly maintained for 3 h. After cooling to 0 °C, the reaction mixture was poured into ice–water (100 mL). The aqueous phase was extracted with $CHCl_3$, and the organic extracts were successively washed with 5% aqueous $NaHCO_3$ and brine and then dried over $MgSO_4$. Evaporation of the solvent in vacuo afforded the diol **7a**, which was directly used for the subsequent reaction. A sample (0.94 g) was purified by flash chromatography (CH_2Cl_2), yielding 0.63 g (70%) of the diol **7a**: IR (neat) 3470 cm^{-1}; ^1H NMR[15] (90 MHz) δ 0.80 (t, 6 H, *J* = 6, H-1), 1.00–1.25 (m, 12 H, H-2–4), 1.05 (s, 18 H, tBu), 1.60 and 2.00 (2 m, 8 H, H-5,8), 3.85 (m, 4 H, H-9,10), 5.10 (m, 4 H, H-6,7), 7.25–7.60 (2 m, 20 H, Ph); ^{13}C NMR[15] δ 14.2 (C-1), 19.7, 27.3 (tBu), 22.7, 27.3, 29.1, 29.3, 31.6 (C-2–5,8), 70.2, 76.1 (C-9,10), 123.6, 132.3 (C-6,7), 127.3, 127.4, 129.5, 129.6, 132.6, 133.7, 135.7, 136.0 (Ph).

2(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]dec-4(*Z*)-enal (Aa). To a solution of the crude diol **7a** (3.4 mmol) in benzene (25 mL) was added lead tetraacetate (1.65 g, 3.7 mmol). After stirring for 1 h at room temperature, filtration and evaporation in vacuo afforded crude aldehyde Aa. Distillation under reduced pressure yielded 1.50 g (55% from dialkene **6a**) of the aldehyde Aa: bp 168 °C (0.05 mm, Büchi); $[\alpha]_D$ −14.5° (*c* 2.2, $CHCl_3$) (lit.[4d] $[\alpha]_D$ −18° (*c* 2.0, $CHCl_3$), lit.[4h] $[\alpha]_D$ −16.5° (*c* 3.0, $CHCl_3$)); ^1H NMR[15] (250 MHz) δ 0.85 (t, 3 H, *J* = 6.25, H-20), 1.10 (s, 9 H, tBu), 1.15–1.40 (m, 6 H, H-17–19), 1.90 (m, 2 H, H-16), 2.40 (m, 2 H, H-13), 4.05 (dt, 1 H, $J_{12,13}$ = 6, $J_{12,11}$ = 1.85, H-12), 5.25–5.55 (m, 2 H, H-14,15), 7.40–7.70 (2 m, 10 H, Ph), 9.50 (d, 1 H, $J_{11,12}$ = 1.85, H-11); ^{13}C NMR[15] δ 14.1 (C-20), 19.4, 27.0 (tBu), 22.6, 27.3, 29.1, 31.1, 31.5 (C-13,16–19), 77.7 (C-12), 122.3, 133.0 (C-14,15), 127.4, 129.6, 132.6, 132.8, 135.4 (Ph), 202.2 (C-11); MS NH_3 chemical ionization 426 (M^+ + 18), 409 (M^+ + 1); HRMS calcd for $C_{22}H_{27}O_2Si$ 351.1779, found 351.1773 (M^+ − tBu).

2(*R*)-(Benzoyloxy)dec-4(*Z*)-enal (Ab). To the lithium heptynide solution (32.8 mmol) in THF (36 mL), prepared as above, were added the diepoxide **3** (2.77 g, 14.9 mmol) and HMPA (5.75 mL, 32.8 mmol) at 0 °C. The mixture was refluxed for 3.5 h, and the resulting alcoholate functions were protected in situ by addition of benzoyl chloride (4.67 mL, 40 mmol). After stirring for 30 min at room temperature, the reaction was quenched by the addition of ice water and the mixture was worked up in the usual manner. Flash chromatography (CH_2Cl_2:hexane = 4:1) of the crude mixture afforded 7.85 g (90%) of the dialkyne **5b** as an oil.

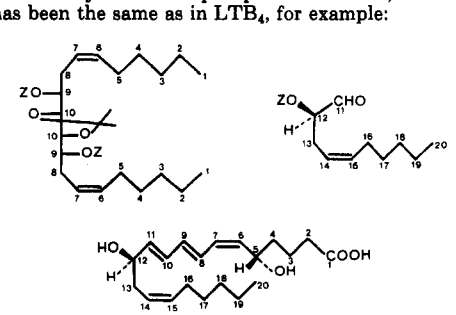
Compound **5b** (1.06 g, 1.8 mmol) was hydrogenated as previously described for **5a**, to give 1.05 g (98%) of **6b**: $[\alpha]_D$ 20.6° (*c* 1.1, CH_2Cl_2). The acetonide **6b** (5.56 g, 9.4 mmol) in 90% aqueous trifluoroacetic acid (110 mL) was stirred for 3 h at 0 °C. The reaction mixture was then extracted with CH_2Cl_2, and the mixture

(12) The metabolization of LTB_4 into ω-OH- and ω-COOH-LTB_4 in human polymorphonuclear leukocytes and into ω-OH-LTB_4 in hepatic microsomes of phenobarbitol-induced rats and rabbits has been studied. In both cases, the retention times in reverse-phase HPLC, the UV spectra, and the amounts of metabolites formed are superposable on those obtained from Rokach's sample.

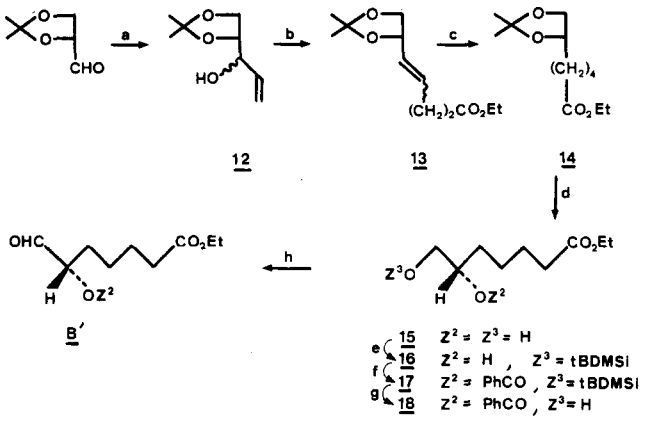
(13) Hoffstein, S. T.; Manzi, R. M.; Razgaitis, K. A.; Bender, P. E.; Gleason, J. *Prostaglandins* **1986**, *31*, 205.

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

(15) To facilitate the notation of ^1H and ^{13}C NMR data in the Experimental Section, only half of each symmetrical molecule is numbered, and from the aldehyde A to the phosphonium salt **23**, the numbering of carbons has been the same as in LTB_4, for example:



Scheme VI[a]



[a] (a) CH_2=CHMgBr, THF, 60 °C, 2 h. (b) $CH_3C(OEt)_3$, EtCOOH, 137 °C, 2 h. (c) H_2, 10% Pd/C, CH_3COOEt. (d) H_2SO_4, EtOH, 0 °C, 4 h. (e) tBDMSiCl, imidazole, DMF, room temperature, 4 h. (f) PhCOCl, pyridine, room temperature, 1 h. (g) TFA, H_2O, 0 °C, 2 h. (h) DMSO, TFA, DCC, C_6H_6, pyridine, room temperature, 2.5 h.

was worked up in the usual manner. Flash chromatography (CH_2Cl_2) of the crude mixture afforded 4.67 g (90%) of the diol **7b**: $[\alpha]_D$ +25.4° (*c* 1.4, CH_2Cl_2). Oxidative cleavage of the diol **7b** (3.11 g, 5.65 mmol) with lead tetraacetate (2.76 g, 6.2 mmol) in benzene (25 mL) was carried out as previously described for **7a**. Distillation under reduced pressure afforded 2.01 g (65%) of the aldehyde Ab: bp 138 °C (0.02 mm); $[\alpha]_D$ +17° (*c* 1.39, CH_2Cl_2); ^1H NMR[15] (250 MHz) δ 0.90 (t, 3 H, J = 6.5, H-20), 1.15–1.45 (m, 6 H, H-17–19), 2.1 (m, 2 H, H-16), 2.70 (t, 2 H, $J_{2,3}$ = 6.5, H-13), 5.25 (t, 1 H, $J_{2,3}$ = 6.5, H-12), 5.45 (m, 1 H, H-14), 5.60 (m, 1 H, H-15), 7.40–8.20 (2 m, 5 H, Ph), 9.65 (d, 1 H, $J_{1,2}$ < 1, H-11); ^{13}C NMR[15] δ 14.2 (C-20), 22.7, 27.4, 27.5, 29.2, 31.6 (C-13,16–19), 78.3 (C-13), 121.6, 134.3 (C-14,15), 128.3, 129.3, 129.6, 133.3 (Ph), 165.7 (PhCO), 197.8 (C-11). Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.4; H, 8.0.

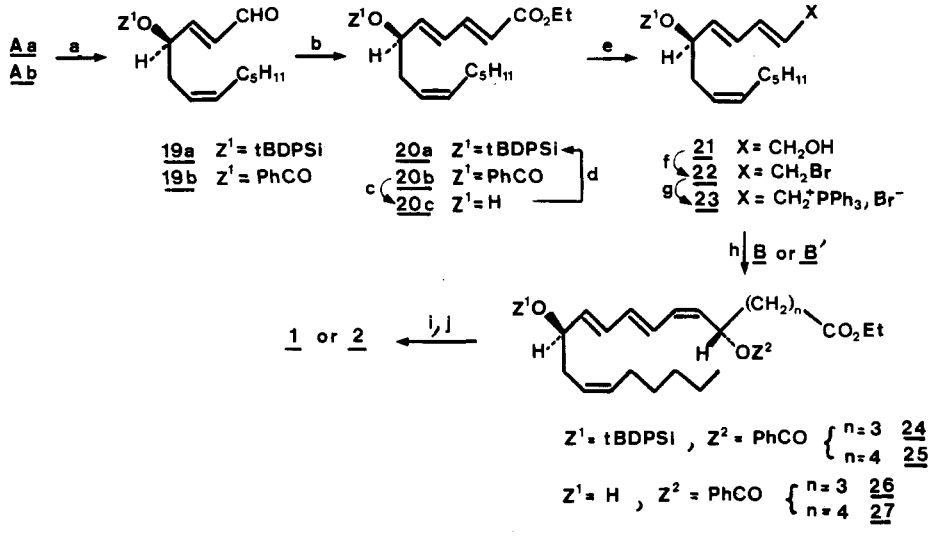
Diethyl 5(*S*),6(*R*),7(*R*),8(*S*)-Tetrahydroxy-6,7-*O*-(1-methylethylidene)-2,10-dodecadiynedioate (8). To a stirred solution of ethyl propiolate (2.94 g, 30 mmol) in THF (30 mL) at −78 °C was dropwise added nBuLi (1.55 M in hexanes, 19.35 mL, 30 mmol). The resulting red solution was stirred at −78 °C for 1 h. Then, the diepoxide **4** (0.93 g, 5 mmol) in THF (20 mL) and boron trifluoride etherate (3.75 mL, 30 mmol) were successively added. After stirring for 2 h at −78 °C, the reaction was quenched at −78 °C by the addition of a saturated aqueous solution of NH_4Cl (30 mL), and then the temperature was allowed to warm to 20 °C. After ether extraction (2 × 100 mL), the combined organic layers were washed with brine (2 × 100 mL) and dried over $MgSO_4$. Evaporation of the solvent gave a syrup (2.40 g), which was used without further purification: ^1H NMR[15] (90 MHz) δ 1.30 (t, 6 H, J = 7.5, OEt), 1.45 (s, 6 H, $C(Me)_2$), 2.70 (d, 4 H, $J_{4,5}$ = 6.75, H-4), 3.90 (m, 2 H, H-5), 4.15 (m, 2 H, H-6), 4.30 (q, 4 H, J = 7.5, OEt).

Diethyl 5(*S*),8(*S*)-Bis(benzoyloxy)-6(*R*),7(*R*)-dihydroxy-6,7-*O*-(1-methylethylidene)-2,10-dodecadiynedioate (9). To a stirred solution of crude **8** (5 mmol) in pyridine (16 mL 0.2 mol) at 0 °C was slowly added benzoyl chloride (1.45 mL, 12.5 mmol). After being stirred for 0.5 h at 0 °C and then 2 h at room temperature, the reaction mixture was poured into a cold aqueous HCl solution (6 N, 32 mL), pH = 3. The aqueous phase was extracted with ether (3 × 50 mL), and the organic extracts were successively washed with 3% aqueous $NaHCO_3$ and brine, then dried over $MgSO_4$, and evaporated in vacuo. Flash chromatography (CH_2Cl_2, R_f 0.25) afforded 2.40 g (80% from diepoxide **4**) of **9**: ^1H NMR[15] (90 MHz) δ 1.15 (t, 6 H, J = 7.5, OEt), 1.45 (s, 6 H, $C(Me)_2$), 2.90 (d, 4 H, $J_{4,5}$ = 6.75, H-4), 4.10 (q, 4 H, J = 7.5, OEt), 4.30 (m, 2 H, $J_{6,5}$ = 1.5, H-6), 5.50 (m, 2 H, $J_{5,4}$ = 6.75, $J_{5,6}$ = 1.5, H-5), 7.50–8.10 (2 m, 10 H, Ph).

Diethyl 5(*S*),8(*S*)-Bis(benzoyloxy)-6(*R*),7(*R*)-dihydroxy-6,7-*O*-(1-methylethylidene)dodecanedioate (10). Platinum oxide (0.35 g, PtO_2, 80%, Merck) in ethanol (270 mL) was entirely hydrogenated under 1 atm of H_2 at room temperature. Then dialkyne **9** (1.90 g, 3.2 mmol) in ethanol (10 mL) was added, and the progress of hydrogenation was monitored by the volume of hydrogen absorbed. Filtration and evaporation of the filtrate in vacuo afforded 1.92 g (100%) of the saturated compound **10** as an oil: ^1H NMR[15] (90 MHz) δ 1.20 (t, 6 H, J = 7.5, OEt), 1.40 (s, 6 H, $C(Me)_2$), 1.75 (m, 8 H, H-3,4), 2.35 (t, 4 H, J = 6.75, H-2), 3.95 (m, 2 H, H-6), 4.10 (q, 4 H, J = 7.5, OEt), 5.35 (m, 2 H, H-5), 7.50–8.10 (2 m, 10 H, Ph).

Diethyl 5(*S*),8(*S*)-Bis(benzoyloxy)-6(*S*),7(*S*)-dihydroxydodecanedioate (11). The acetonide **10** (1.71 g, 2.9 mmol) in 90% aqueous trifluoroacetic acid (22.9 mL) was stirred for 3.5 h at 0 °C. The reaction mixture was then diluted with CH_2Cl_2 (80 mL) and water (80 mL) and extracted with CH_2Cl_2 (5 × 40 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. Evaporation gave 1.39 g (87%) of the diol **11** as an oil. It was used without further purification: IR (neat) 3600–3300, 1740, 1720 cm^{-1}; ^1H NMR[15] (90 MHz) δ 1.20 (t, 6 H, J = 7.5, OEt), 1.80 (m, 8 H, H-3,4), 2.35 (t, 4 H, $J_{2,3}$ = 6.0, H-2), 3.85 (m, 2 H, H-6), 4.10 (q, 4 H, J = 7.5, OEt), 5.40 (m, 2 H, H-5), 7.40–8.00 (2 m, 10 H, Ph).

Scheme VII[a]



[a] (a) Ph_3P=CHCHO, C_6H_6, 80 °C, 6 h. (b) $(EtO)_2POCH_2COOEt$, LiCl, DBU, room temperature, 1 h. (c) K_2CO_3, EtOH, 45 °C, 22 h. (d) tBDPSiCl, DMF, imidazole, 65 °C, 22 h. (e) AlH_3, THF, 0 °C, 2.5 h. (f) CBr_4, DIPHOS, CH_2Cl_2, −35 °C, 2.5 h. (g) Ph_3P, CH_3CN, 20 °C, 1.5 h. (h) BuLi, THF, −100 °C, then B or B′, HMPA, −100 °C to room temperature. (i) nBu_4NF, THF, room temperature, 15 h. (j) K_2CO_3, MeOH, H_2O, room temperature, 7.5 h.

Ethyl 5(*S*)-(Benzoyloxy)-5-formylpentanoate (B). To a stirred solution of the diol **11** (0.69 g, 1.2 mmol) in CH_2Cl_2 (18 mL) at −10 °C was added lead tetraacetate (0.57 g, 1.3 mmol). The reaction mixture was stirred for 1.25 h at −10 °C, filtered through a Celite pad, and evaporated. After purification by flash chromatography (CH_2Cl_2, R_f 0.26), 0.37 g (57%) of the aldehyde B was obtained: bp 100 °C (0.02 mm, Büchi); IR (neat) 2730, 1720, 1745–1730 cm^{-1}; $[\alpha]_D$ −39° (*c* 1.2, $CHCl_3$) (lit.[4c] $[\alpha]_D$ −46° (*c* 0.5, $CHCl_3$), lit.[16a] $[\alpha]_D$ −32.85° (*c* 0.5, $CHCl_3$), lit.[16b] $[\alpha]_D$ −35.7° (*c* 1.66, $CHCl_3$); ^1H NMR (90 MHz) δ 1.25 (t, 3 H, *J* = 7.5, OEt), 1.95 (m, 4 H, H-3,4), 2.40 (t, 2 H, $J_{2,3}$ = 7.25, H-2), 4.15 (q, 2 H, *J* = 7.5, OEt), 5.30 (t, 1 H, $J_{5,4}$ = 7.0, H-5), 7.60–8.15 (2 m, 5 H, Ph), 9.75 (s, 1 H, CHO); ^{13}C NMR δ 14.1 (OEt), 20.5 (C-3), 28.3 (C-4), 33.6 (C-2), 60.4 (OEt), 78.3 (C-5), 128.5, 129.1, 129.8, 133.5 (Ph), 165.9 (*C*OPh), 172.6 (C-1), 197.8 (CHO); MS *m/e* (relative intensity) 249 (M^+ − 29, 5), 145 (23), 128 (19), 105 (100), 99 (12), 77 (5), NH_3 chemical ionization 296 (M^+ + 18), 279 (M^+ + 1); HRMS calcd for $C_{14}H_{17}O_4$ 249.1126, found 249.1119 (M^+ − CHO).

1,2(*R*),3-Trihydroxy-1,2(*R*)-*O*-(1-methylethylidene)-4-pentene (12). To a stirred solution of vinylmagnesium bromide[7b] in THF (0.24 mol, 2 M) was dropwise added (*R*)-glyceraldehyde acetonide[8] (13.72 g, 0.11 mol) in THF (40 mL). The temperature was maintained at 20 °C with a water–ice bath during the addition. After being stirred for 3 h at room temperature, the reaction mixture was refluxed for 2 h. The reaction was then quenched by the addition of a cold saturated aqueous solution of NH_4Cl (200 mL). After ether extraction (4 × 50 mL), the combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation in vacuo and distillation afforded 13.09 g (79%) of **12** as a mixture of two diastereoisomers: bp 86–88 °C (10 mm); ^1H NMR (250 MHz) δ 1.40 (s, 6 H, $C(Me)_2$), 3.70–4.30 (m, 4 H, H-1–3), 5.25 (ddd, 1 H, $J_{5',4}$ = 10.5, $J_{5',5}$ = 1.5, $J_{5',3}$ = 1.5, H-5′), 5.40 (dd, 1 H, $J_{5,4}$ = 16.5, $J_{5,5'}$ = 1.5, $J_{5,4}$ = 1.5, H-5), 5.80 (m, 1 H, H-4); ^{13}C NMR δ 25.1, 25.2 ($C(Me)_2$), 64.9, 65.6 (C-1), 71.8, 73.8 (C-3), 78.0, 78.4 (C-2), 109.1, 109.4 ($C(Me)_2$), 116.2, 117.2 (C-5), 135.8, 135.9 (C-4). Anal. Calcd for $C_8H_{14}O_3$: C, 60.73; H, 8.93. Found: C, 60.7; H, 8.9.

Ethyl 6(*S*),7-Dihydroxy-6(*S*),7-*O*-(1-methylethylidene)-4(*E*)-heptenoate (13). A stirred solution of the alcohol **12** (6 g, 38.0 mmol) in ethyl orthoacetate (67 mL) in the presence of propanoic acid (0.17 g, 2.3 mmol) was heated at 137 °C for 2.5 h. After cooling to room temperature and removal of the solvent (distillation), distillation in vacuo afforded 7.34 g (84%) of **13**: bp 78 °C (0.3 mm); ^1H NMR (250 MHz) δ 1.25 (t, 3 H, *J* = 7.5, OEt), 1.33–1.37 (2 s, 6 H, $C(Me)_2$), 2.35 (m, 4 H, H-2,3), 3.50–4.00 (2 dd, 2 H, $J_{7,7'}$ = 8, $J_{7',6}$ = 8, $J_{7,6}$ = 6, H-7,7′), 4.08 (q, 2 H, *J* = 7.5, OEt), 4.41 (ddd, 1 H, $J_{6,7'}$ = 8, $J_{6,7}$ = 6, $J_{6,5}$ = 5.5, H-6), 5.45 (dd, 1 H, $J_{5,4}$ = 15.5, $J_{5,6}$ = 5.5, H-5), 5.75 (dt, 1 H, $J_{4,5}$ = 15.5, H-4); ^{13}C NMR δ 14.2 (OEt), 25.8, 26.6 ($C(Me)_2$), 27.4, 33.5 (C-2,3), 60.1 (OEt), 69.1 (C-7), 76.7 (C-6), 108.7 ($C(Me)_2$), 128.3 (C-4), 132.6 (C-5), 172.0 (C-1). Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.2; H, 8.9.

Ethyl 6(*S*),7-Dihydroxy-6(*S*),7-*O*-(1-methylethylidene)-heptanoate (14). A suspension of the alkene **13** (7.35 g, 32 mmol) and palladium on activated charcoal (10%) (0.57 g) in ethyl acetate (15 mL) was vigorously stirred under 1 atm of H_2. The progress of hydrogenation was monitored by the volume of hydrogen absorbed. Filtration, evaporation in vacuo, and distillation afforded 6.68 g (90%) of **14**: bp 61 °C (0.1 mm); ^1H NMR (90 MHz) δ 1.20 (t, 3 H, *J* = 7.5, OEt), 1.30–1.40 (2 s, 6 H, $C(Me)_2$), 1.50–1.70 (m, 6 H, H-3–5), 2.30 (t, 2 H, *J* = 7, H-2), 3.60 (m, 1 H, H-6), 3.90 (m, 2 H, H-7), 4.20 (q, 2 H, *J* = 7.5, OEt); ^{13}C NMR δ 14.2 (OEt), 24.4, 24.9 (C-3,4), 25.7, 26.9 ($C(Me)_2$), 33.2, 33.8 (C-2,5), 59.9 (OEt), 69.2 (C-7), 75.6 (C-6), 108.3 ($C(Me)_2$), 172.0 (C-1).

Ethyl 6(*S*),7-Dihydroxyheptanoate (15). A solution of the acetonide **14** (1.93 g, 8.35 mmol) and a 10% aqueous solution of sulfuric acid (3.5 mL) in ethanol (40 mL) was stirred at 0 °C for 4 h. The reaction mixture was then neutralized (saturated aqueous Na_2CO_3) and extracted with CH_2Cl_2 (8 × 25 mL). after drying ($MgSO_4$), removal of the solvent, and purification by flash chromatography (elution with ether to remove impurities, then ethanol), 1.10 g (66%) of diol **15** was obtained: ^1H NMR (90 MHz) δ 1.10–1.90 (m, 9 H, H-3–5, OEt), 2.35 (t, 2 H, *J* = 7, H-2), 3.30–3.90 (m, 3 H, H-6,7), 4.10 (q, 2 H, *J* = 7.5, OEt).

Ethyl 6(*S*)-Hydroxy-7-[(*tert*-butyldimethylsilyl)oxy]-heptanoate (16). To a stirred solution of the diol **15** (1.37 g, 7.2 mmol) in DMF (38.5 mL) at 20 °C were added both imidazole (1.08 g, 15.9 mmol) and *tert*-butylchlorodimethylsilane (1.30 g, 8.6 mmol). The reaction mixture was stirred for 4 h and then quenched with a saturated aqueous solution of NH_4Cl. After CH_2Cl_2 extraction (4 × 50 mL), the combined organic layers were washed with saturated aqueous NH_4Cl and dried ($MgSO_4$). Evaporation in vacuo afforded 2.19 g (100%) of **16**. It was then used without further purification: ^1H NMR (90 MHz) δ 0.10 (s, 6 H, SiMe), 0.90 (s, 9 H, tBu), 1.20 (t, 3 H, *J* = 7.5, OEt), 1.45 (m, 6 H, H-3–5), 2.25 (t, 2 H, H-2), 3.30–3.70 (m, 3 H, H-6,7), 4.10 (q, 2 H, *J* = 7.5, OEt).

Ethyl 6(*S*)-(Benzoyloxy)-7-[(*tert*-butyldimethylsilyl)-oxy]heptanoate (17). To a stirred solution of the alcohol **16** (1.00 g, 3.3 mmol) in pyridine (6 mL, 66 mmol) at 0 °C was added benzoyl chloride (0.46 mL, 4.0 mmol). After being stirred for 2 h at 0 °C and 1 h at room temperature, the reaction mixture was poured into cold (19%) aqueous HCl (12 mL) and extracted with ether (3 × 15 mL). Organic layers were washed successively with saturated aqueous solutions of $NaHCO_3$ and NaCl, dried ($MgSO_4$), filtered, and concentrated in vacuo. After purification by flash chromatography (R_f 0.3, CH_2Cl_2), 1.47 g (85% from diol **15**) of the protected diol **17** was obtained: $[\alpha]_D$ −13.6° (*c* 1.8, CH_2Cl_2); ^1H NMR (250 MHz) δ 0.01 (s, 6 H, SiMe), 0.85 (s, 9 H, tBu), 1.20 (t, 3 H, *J* = 7.25, OEt), 1.42–1.70 (2 m, 6 H, H-3–5), 2.28 (t, 2 H, *J* = 7, H-2), 3.75 (m, 2 H, H-7), 4.09 (q, 2 H, *J* = 7.25, OEt), 5.12 (m, 1 H, H-6), 7.49–8.05 (2 m, 5 H, Ph); ^{13}C NMR δ −5.4 (SiMe), 14.2 (OEt), 18.2 (tBu), 24.9, 25.0, 30.4 (C-3–5), 25.9 (tBu), 34.3 (C-2), 60.1 (OEt), 64.3 (C-7), 75.0 (C-6), 128.3, 128.4, 129.6, 132.7 (Ph), 166.2 (C-1), 173.4 (*C*OPh); MS *m/e* (relative intensity) 363 (M^+ − OEt, 1), 351 (2), 179 (84), 155 (20), 135 (15), 105 (100). Anal. Calcd for $C_{22}H_{36}O_5Si$: C, 64.67; H, 8.89. Found: C, 64.7; H, 9.0.

Ethyl 6(*S*)-(Benzoyloxy)-7-hydroxyheptanoate (18). A solution of **17** (0.70 g, 1.7 mmol) in 90% aqueous trifluoroacetic acid (15 mL) was stirred for 2 h at 0 °C. Water (20 mL) was then added, and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). Organic layers were washed with brine, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography (R_f 0.2, CH_2Cl_2:Et_2O = 90:10) afforded 0.43 g (85%) of the alcohol **18**: $[\alpha]_D$ −20.5° (*c* 1.7, CH_2Cl_2); ^1H NMR (250 MHz) δ 1.22 (t, 3 H, *J* = 7.5, OEt), 1.46 (m, 2 H, H-4), 1.72 (m, 4 H, H-3,5), 2.31 (t, 2 H, $J_{2,3}$ = 7.5, H-2), 3.84 (m, 2 H, H-7), 4.12 (q, 2 H, *J* = 7.5, OEt), 5.19 (m, 1 H, H-6), 7.46–8.07 (3 m, 5 H, Ph); MS *m/e* (relative intensity) 264 (M^+ − CH_2O, 37), 249 (M^+ − OEt, 25), 159 (12), 113 (18), 105 (100), 77 (26).

Ethyl 6(*S*)-(Benzoyloxy)-6-formylhexanoate (B′). To a stirred solution of the alcohol **18** (0.57 g, 1.9 mmol) in DMSO:benzene = 1:1 (16 mL) at room temperature were successively added trifluoroacetic acid (75 μL, 0.26 mmol), pyridine (0.17 mL, 2.1 mmol), and *N,N′*-dicyclohexylcarbodiimide (1.24 g, 6.0 mmol).[10] After being stirred for 2.5 h, the reaction mixture was filtered and the filtration cake was washed with water (10 mL) and ether (40 mL). After ether extraction, the organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The aldehyde B′, purified by flash chromatography (CH_2Cl_2:Et_2O = 9:1, R_f 0.48), was isolated in 93% (0.53 g) yield: bp 160 °C (0.03 mm, Büchi); $[\alpha]_D$ −28.0° (*c* 2.6, CH_2Cl_2); ^1H NMR (90 MHz) δ 1.25 (t, 3 H, *J* = 6.75, OEt), 1.45–2.10 (m, 6 H, H-3–5), 2.35 (t, 2 H, $J_{2,3}$ = 6.75, H-2), 4.10 (q, 2 H, *J* = 6.75, OEt), 5.15 (t, 1 H, $J_{6,5}$ = 6, H-6), 7.45–8.05 (2 m, 5 H, Ph), 9.55 (s, 1 H, CHO).

4(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]dodeca-2(*E*),6(*Z*)-dienal (19a). To a solution of the aldehyde Aa (0.68 g, 1.7 mmol) in benzene (28 mL) was added (formylmethylene)triphenylphosphorane (0.61 g, 2.0 mmol). The mixture was refluxed for 6 h, and benzene was removed under reduced pressure. The product was extracted with cold ether or hexane, and solid triphenylphosphine oxide was removed by filtration. After the organic extracts were concentrated in vacuo, the residue was purified by flash chromatography. Elution of the column with (1:1) CH_2Cl_2–hexane (R_f 0.26) gave 0.44 g (61%) of the aldehyde **19a**: bp 230 °C (0.03 mm, Büchi); IR (neat) 1695, 970 cm^{-1}; $[\alpha]_D$ −13° (*c* 1.6, $CHCl_3$) (lit.[4h] $[\alpha]_D$ −14.4° (*c* 2.0, $CHCl_3$); enantiomer of **19a** lit.[17] $[\alpha]_D$ +15.6° (*c* 3.0, $CHCl_3$)); ^1H NMR[15] (250 MHz)

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δ 0.90 (t, 3 H, J = 7, H-20), 1.10 (s, 9 H, tBu), 1.15–1.40 (m, 6 H, H-17–19), 1.85 (m, 2 H, H-16), 2.25 (m, 2 H, H-13), 4.45 (m, 1 H, H-12), 5.35 (m, 2 H, H-14,15), 6.2 (dd, 1 H, $J_{10,11}$ = 15, $J_{10,9}$ = 7.5, H-10), 6.7 (dd, 1 H, $J_{11,10}$ = 15, $J_{11,12}$ = 4.5, H-11), 7.40–7.70 (2 m, 10 H, Ph), 9.45 (d, 1 H, $J_{9,10}$ = 7.5, H-9); ^{13}C NMR[15] δ 14.0 (C-20), 19.4, 27.1 (tBu), 22.5, 27.4, 29.1, 31.5, 35.3 (C-13,16–19), 72.6 (C-12), 123.0, 133.4 (C-14,15), 130.3, 158.2 (C-10,11), 127.7, 129.6, 135.5 (Ph), 193.1 (C-9); MS m/e (relative intensity) 434 (M^+, <1), 377 (38), 323 (27), 199 (77), 197 (32), 183 (27), 160 (28), 139 (32), 125 (100); HRMS calcd for $C_{24}H_{29}O_2Si$ 377.1935, found 377.1903 (M^+ – tBu).

4(*R*)-(Benzoyloxy)dodeca-2(*E*),6(*Z*)-dienal (19b). Formyl olefination of Ab (0.97 g, 3.5 mmol) in benzene (60 mL) with (formylmethylene)triphenylphosphorane (1.29 g, 4.2 mmol) was carried out as previously described for Aa. Purification by flash chromatography (CH_2Cl_2:hexane = 9:1, R_f 0.27) gave 0.53 g (50%) of **19b** as a colorless oil: $[\alpha]_D$ –63° (*c* 0.93, CH_2Cl_2); ^1H NMR[15] (250 MHz) δ 0.9 (t, 3 H, J = 7, H-20), 1.2–1.45 (m, 6 H, H-17–19), 2.05 (m, 2 H, H-16), 2.65 (m, 2 H, H-13), 5.4–5.6 (2 m, 2 H, H-14,15), 5.8 (m, 1 H, H-12), 6.35 (ddd, 1 H, $J_{9,10}$ = 7.5, $J_{10,11}$ = 16, $J_{10,12}$ = 1.5, H-10), 6.9 (dd, 1 H, $J_{10,11}$ = 16, $J_{11,12}$ = 4.5, H-11), 7.45–8.2 (m, 5 H, Ph), 9.6 (d, 1 H, $J_{9,10}$ = 7.5, H-9); ^{13}C NMR[15] δ 14.2 (C-20), 22.7, 27.5, 29.2, 31.6, 31.9 (C-13,16–19), 72.3 (C-12), 121.9, 134.2 (C-14,15), 131.4, 153.1 (C-10,11), 128.2, 129.4, 133.1 (Ph), 165.0 (PhCO), 192.4 (C-9). Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 76.2; H, 8.1.

Ethyl 6(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-2(*E*),4(*E*),8-(*Z*)-tetradecatrienoate (20a). To a suspension of lithium chloride[11] (48 mg, 1.1 mmol) in acetonitrile (11 mL) at 20 °C were added ethyl (diethoxyphosphinyl)acetate (0.22 mL, 1.1 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.14 mL, 0.9 mmol), and finally the aldehyde **19a** (407 mg, 0.9 mmol). After stirring for 1 h at 20 °C, water was added and the aqueous mixture was extracted with ether. The combined organic layers were washed with brine and dried over $MgSO_4$. After concentration of the organic extracts in vacuo, the crude product was purified by flash chromatography. Elution of the column with (3:2) hexane–CH_2Cl_2 (R_f 0.18) afforded 284 mg (60%) of the dienic ester **20a**: $[\alpha]_D$ +43° (*c* 2.2, $CHCl_3$) (lit.[4d] $[\alpha]_D$ +45°, lit.[4h] $[\alpha]_D$ +40.6° (*c* 2.0, $CHCl_3$)); IR (neat) 1720 cm^{-1}; ^1H NMR[15] (250 MHz) δ 0.80 (t, 3 H, J = 7, H-20), 1.00 (s, 9 H, tBu), 1.10–1.20 (m, 6 H, H-17–19), 1.20 (t, 3 H, J = 7, OEt), 1.80 (m, 2 H, H-16), 2.20 (m, 2 H, H-13), 4.15 (q, 2 H, J = 7, OEt), 4.20 (m, 1 H, $J_{12,13}$ = 7.5, $J_{12,11}$ = 5.5, H-12), 5.30 (m, 2 H, H-14,15), 5.70 (d, 1 H, $J_{8,9}$ = 15.5, H-8), 6.10 (m, 2 H, $J_{10,11}$ = 15.5, H-10,11), 7.20 (dd, 1 H, $J_{9,8}$ = 15.5, $J_{9,10}$ = 9.5, H-9), 7.40–7.65 (2 m, 10 H, Ph); ^{13}C NMR[15] δ 14.2 (C-20), 14.5 (OEt), 19.5, 27.2 (tBu), 22.7, 27.4, 29.3, 31.6, 35.8 (C-13,16–19), 60.2 (OEt), 73.2 (C-12), 120.8, 123.6, 132.4, 143.7, 144.4 (C-8–11,14,15), 127.3, 129.5, 133.5, 133.8, 135.6 (Ph), 166.7 (COOEt); MS m/e (relative intensity) 504 (M^+, <1), 447 (40), 397 (63), 199 (100), 135 (98); HRMS calcd for $C_{28}H_{35}O_3Si$ 447.2353, found 447.2328 (M^+ – tBu).

The title compound **20a** was also obtained from the alcohol **20c** (see below for the preparation of **20c**): to a solution of this alcohol **20c** (82 mg, 0.3 mmol) in *N*,*N*-dimethylformamide (2.5 mL) were added *tert*-butylchlorodiphenylsilane (0.16 mL, 0.6 mmol) and imidazole (0.11 g, 1.5 mmol). The mixture was stirred at 65 °C for 22 h, it was then diluted with CH_2Cl_2, and the organic layer was washed with brine. After the usual workup and flash chromatography (CH_2Cl_2), 132 mg (85%) of the silyl ester **20a** was obtained.

Ethyl 6(*R*)-(Benzoyloxy)-2(*E*),4(*E*),8(*Z*)-tetradecatrienoate (20b). To a suspension of sodium hydride (0.13 g, 2.7 mmol) in benzene (3 mL) was dropwise added ethyl (diethoxyphosphinyl)acetate (0.65 g, 2.9 mmol), and the mixture was stirred for 1 h at room temperature. Then, the aldehyde **19b** (0.58 g, 1.9 mmol) in benzene was added, and after 4 h at room temperature, the reaction was quenched by addition of water. The mixture was worked up in the usual manner. Purification by flash chromatography (CH_2Cl_2) gave 0.47 g (65%) of **20b** as a colorless oil: $[\alpha]_D$ –62° (*c* 1.14, CH_2Cl_2); ^1H NMR[15] (250 MHz) δ 0.9 (t, 3 H, J = 6.7, H-20), 1.2–1.4 (m, 9 H, H-17–19, OEt), 2.1 (m, 2 H, H-16), 2.6 (m, 2 H, H-13), 4.2 (q, 2 H, J = 7, OEt), 5.45 (m, 1 H, H-14), 5.6 (m, 1 H, H-15), 5.7 (m, 1 H, H-12), 6.0 (d, 1 H, $J_{8,9}$ = 15, H-8), 6.2 (dd, 1 H, $J_{10,11}$ = 15, $J_{11,12}$ = 6, H-11), 6.5 (dd, 1 H, $J_{9,10}$ = 10.5, $J_{10,11}$ = 15, H-10), 7.3 (dd, 1 H, $J_{8,9}$ = 15, $J_{9,10}$ = 10.5, H-9), 7.4–8.2 (m, 5 H, Ph); ^{13}C NMR[15] δ 14.2, 14.4 (C-20, OEt), 22.7, 27.5, 29.3, 31.6, 32.4 (C-13,16–19), 60.3 (OEt), 73.5 (C-12), 122.3, 122.6, 128.1, 129.2, 129.4, 129.9, 132.8, 133.5, 139.1, 142.9 (Ph, C-8–11,14,15), 165.2, 166.3 (C-7, PhCO). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.56; H, 8.16. Found: C, 74.5; H, 8.1.

Ethyl 6(*R*)-Hydroxy-2(*E*),4(*E*),8(*Z*)-tetradecatrienoate (20c). To the benzoate **20b** (0.34 g, 0.92 mmol) in ethanol (5 mL), was added potassium carbonate (13 mg, 0.09 mmol), and the reaction mixture was stirred at 45 °C for 22 h. After removal of the solvent, the residue was diluted with ether (50 mL) and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent and purification by flash chromatography (CH_2Cl_2:Et_2O = 95:5, R_f 0.3) gave 196 mg (80%) of the alcohol **20c**: $[\alpha]_D$ +10° (*c* 0.9, $CDCl_3$) (lit.[4c] $[\alpha]_D$ +11.4°); ^1H NMR[15] (250 MHz) δ 0.80 (t, 3 H, J = 7, H-20), 1.1–1.4 (m, 9 H, H-17–19, OEt), 2.00 (m, 2 H, H-16), 2.30 (dd, 2 H, $J_{12,13}$ = 6, $J_{13,14}$ = 6, H-13), 4.15 (q, 2 H, J = 7, OEt), 4.25 (m, 1 H, H-12), 5.30 (m, 1 H, H-14), 5.55 (m, 1 H, H-15), 5.85 (d, 1 H, $J_{8,9}$ = 15.5, H-8), 6.05 (dd, 1 H, $J_{10,11}$ = 15, $J_{11,12}$ = 6, H-11), 6.35 (dd, 1 H, $J_{10,11}$ = 15, $J_{9,10}$ = 11, H-10), 7.20 (dd, 1 H, $J_{8,9}$ = 15.5, $J_{9,10}$ = 11, H-9); ^{13}C NMR[15] δ 14.2 (C-20), 14.5 (OEt), 22.7, 27.6, 29.4, 31.6, 35.3 (C-13,16–19), 60.4 (OEt), 71.3 (C-12), 121.3, 123.4, 127.3, 134.1, 143.5, 143.9 (C-8–11,14,15), 166.6 (C-7); MS NH_3 chemical ionization 267 (M^+ + 1), 284 (M^+ + 18).

6(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-ol (21). To a solution of the dienic ester **20a** (0.25 g, 0.50 mmol) in dry THF (1.45 mL) was dropwise added a THF solution of aluminum hydride prepared from $LiAlH_4$ by addition of H_2SO_4[18] (1.2 M, 0.55 mL, 0.7 mmol). After stirring for 2.5 h at 0 °C, the reaction was quenched, at 0 °C, by addition of (1:1) ice–water:THF. The aqueous phase was extracted with ether, and the combined extracts were washed with a saturated aqueous solution of sodium and potassium tartrate. After drying over $MgSO_4$ and removal of the solvent, 0.23 g (100%) of the crude alcohol **21** was obtained as an oil: IR (neat) 3400 cm^{-1}; ^1H NMR[15] (250 MHz) δ 0.80 (t, 3 H, J = 6.25, H-20), 1.00 (s, 9 H, tBu), 1.10–1.35 (m, 6 H, H-17–19), 1.75 (m, 2 H, H-16), 2.15 (m, 2 H, H-13), 4.10 (d, 2 H, $J_{7,8}$ = 5.5, H-7), 4.20 (m, 1 H, H-12), 5.30 (m, 2 H, H-14,15), 5.70 (m, 2 H, H-8,11), 5.95–6.15 (2 dd, 2 H, $J_{8,9}$ = 15, $J_{9,10}$ = 10.5, $J_{10,11}$ = 15, H-10,11), 7.40–7.65 (2 m, 10 H, Ph); ^{13}C NMR[15] δ 14.1 (C-20), 19.4, 27.0 (tBu), 22.6, 27.3, 29.2, 32.4, 35.9 (C-13,16–19), 63.1 (C-7), 73.5 (C-12), 124.1, 128.7, 130.7, 131.0, 131.6, 135.9 (C-8–11,14,15), 127.0, 129.1, 135.5 (Ph); MS m/e (relative intensity) 462 (M^+, <1), 405 (2.7), 351 (30), 199 (100), 197 (25), 135 (70), 77 (25), NH_3 chemical ionization 463 (M^+ + 1), 480 (M^+ + 18).

1-Bromo-6(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-2(*E*),4-(*E*),8(*Z*)-tetradecatriene (22). To a solution of the alcohol **21** (124 mg, 0.27 mmol) and carbon tetrabromide (294 mg, 0.89 mmol) in CH_2Cl_2 (1.7 mL) at –35 °C was added ethylenebis(diphenylphosphine) (160 mg, 0.41 mmol) in small portions. The mixture was stirred for 2.5 h at –35 °C and then concentrated under reduced pressure while the temperature was allowed to slowly increase to 20 °C. To the resulting solid residue was added hexane, and after filtration and repeated washings with hexane, the filtrate was evaporated, yielding 108 mg (90%) of the labile bromide **22**, which was used without further purification: ^1H NMR[15] (90 MHz) δ 0.80 (t, 3 H, J = 7, H-20), 1.00 (s, 9 H, tBu), 1.10–1.30 (m, 6 H, H-17–19), 1.80 (m, 2 H, H-16), 2.20 (m, 2 H, H-13), 3.95 (d, 2 H, J = 7.5, H-7), 4.15 (m, 1 H, H-12), 5.30 (m, 2 H, H-14,15), 5.10–6.30 (m, 4 H, H-8–11), 7.40–7.65 (2 m, 10 H, Ph).

[6(*R*)-[(*tert*-Butyldiphenylsilyl)oxy]-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-yl]triphenylphosphonium Bromide (23). To a solution of the bromide **22** (108 mg, 0.21 mmol) in CH_3CN (4.5 mL) was added triphenylphosphine (65 mg, 0.25 mmol). The mixture was stirred for 1.5 h at 20 °C and concentrated under reduced pressure. After ether addition (3 × 1 mL), the solution was centrifuged and the supernatant was discarded. The resulting phosphonium salt was washed twice over with ether. Removal of the solvent in vacuo afforded 153 mg of **23** as a pale yellow foam in 80% overall yield from dienic ester **20a**: ^1H NMR[15] (250 MHz)

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δ 0.80 (t, 3 H, J = 6.25, H-20), 1.00 (s, 9 H, tBu), 1.05–1.30 (m, 6 H, H-17–19), 1.80 (m, 2 H, H-16), 2.20 (m, 2 H, H-13), 4.10 (m, 1 H, H-12), 4.70 (m, 2 H, H-7), 5.10–5.45 (m, 3 H, H-14,15,9(or 10), 5.55 (ddd, 1 H, $J_{11,10}$ = 15, $J_{11,12}$ = 6, $J_{11,9}$ = 2.5, H-11), 5.70–6.20 (2 m, 2 H, H-8,9(or 10), 7.30–7.80 (3 m, 25 H, Ph).

Ethyl 5(*S*)-(Benzoyloxy)-12(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-6(*Z*),8(*E*),10(*E*),14(*Z*)-icosatetraenoate (24). To a solution of the phosphonium salt **23** (133 mg, 0.17 mmol) in THF (1.5 mL), at −100 °C, was quickly added *n*-butyllithium (1.5 N in hexanes, 0.11 mL, 0.17 mmol), and the carmine red resulting solution was stirred at −100 °C for 2 min. Then, the aldehyde B (70 mg, 0.25 mmol) in THF (0.8 mL) was added, and the reaction mixture was stirred at −100 °C for 5 min before HMPA (0.15 mL, 0.85 mmol) addition. After the mixture was stirred at −100 °C for an additional 15 min, the temperature was slowly raised to room temperature. The reaction mixture was stirred for 1 h altogether, including 15 min at room temperature, after HMPA addition. Then, the mixture was poured into a 25% aqueous NH_4OAc solution (20 mL), ether (20 mL), and triethylamine (1.2 mL), pH 8–9. The aqueous phase was extracted with ether, and combined organic layers were washed with brine. After drying over $MgSO_4$ and evaporation in vacuo, the crude product was filtered over 6 g of silica gel neutralized with (4:1) hexane–Et_3N (20 mL). Elution with (7:3) hexane–AcOEt containing Et_3N (2%) gave 105 mg (88%) of a crude product containing a 7:3 *Z*:*E* mixture of **24** and some impurities. The separation of both isomers was carried out by HPLC chromatography through a μ-Porasil column (length 30 cm, i.d. 7.9 mm; eluent 98.5:1:0.5 hexane–Et_3N–AcOEt; flow rate 2.0 mL/min; retention time of *Z* isomer = 5.79 min; retention time of *E* isomer = 6.80 min). Compound **24** (15.7 mg) and its 6*E* isomer (7.0 mg) were obtained with a purity above 98% (experimental conditions have not been improved in order to prevent the partial decomposition of **24** during the HPLC chromatograhy). For **24**: UV (EtOH) λ max 263, 272, 283 nm (ε 34 000, 43 000, 34 000); ^{1}H NMR (250 MHz, C_6D_6)[19] δ 0.80 (t, 3 H, $J_{20,19}$ = 7.5, H-20), 0.90 (t, 3 H, J = 7, OEt), 1.10–1.40 (m, 15 H, H-17–19, tBu), 1.60 (m, 4 H, H-3,4), 1.85 (m, 2 H, H-16), 2.10 (m, 2 H, H-2), 2.35 (m, 2 H, H-13), 3.95 (q, 2 H, J = 7, OEt), 4.30 (m, 1 H, H-12), 5.30 (dd, 1 H, $J_{6,5}$ = 9.5, $J_{6,7}$ = 10.5, H-6), 5.40–5.60 (m, 2 H, $J_{14,15}$ = 11, H-14,15), 5.70 (dd, 1 H, $J_{11,10}$ = 14.5, $J_{11,12}$ = 7.2, H-11), 5.95 (dd, 1 H, $J_{10,11}$ = 14.5, $J_{10,9}$ = 10.2, H-10), 6.00 (dd, 1 H, $J_{7,8}$ = 11.5, $J_{7,6}$ = 10.5, H-7), 6.05 (m, 1 H, H-9), 6.10 (m, 1 H, $J_{5,4}$ = 5.5, H-5), 6.70 (dd, 1 H, $J_{8,9}$ = 14, $J_{8,7}$ = 11.5, H-8), 7.00–8.10 (2 m, 5 H, COPh), 7.20–7.80 (2 m, 10 H, SiPh); ^{13}C NMR δ 14.1 (C-20, OEt), 19.6, 27.3 (tBu), 20.9, 22.9, 27.8, 29.6, 31.8, 34.0, 34.7, 36.6 (C-2–4,13,16–19), 60.0 (OEt), 70.7 (C-5), 74.7 (C-12), 125.0, 128.2, 128.4, 128.9, 129.9, 130.7, 130.9, 132.3, 132.6, 135.3, 136.4, 137.6 (C-6–11,14,15, Ph), 165.6 (*C*OPh), 172.3 (*C*OOEt); MS m/e 661 (M^+ − OEt), 649 (M^+ − tBu), 601 (M^+ − COPh), 595 (M^+ − $CH_2CH{=}CHC_5H_{11}$), NH_3 chemical ionization 724 (M^+ + 18); HRMS calcd for $C_{30}H_{37}O_3Si$ 473.2509, found 473.2488 (M^+ − C_8H_{15} − PhCOOH). For the 6*E* isomer: UV (EtOH) λ_{max} 262, 270, 282 (ε 26 000, 47 000, 37 000); ^{1}H NMR (400 MHz, C_6D_6)[19] δ 0.80 (t, 3 H, $J_{20,19}$ = 7.5, H-20), 0.90 (t, 3 H, J = 7, OEt), 1.10–1.40 (m, 15 H, H-17–19, tBu), 1.60 (m, 4 H, H-3,4), 1.85 (m, 2 H, H-16), 2.05 (t, 2 H, $J_{2,3}$ = 7, H-2), 2.40 (m, 2 H, $J_{13,12}$ = 5.5, H-13), 3.90 (q, 2 H, J = 7, OEt), 4.40 (m, 1 H, H-12), 5.35–5.55 (m, 2 H, $J_{14,15}$ = 11, H-14,15), 5.50 (ddd, 1 H, $J_{6,7}$ = 14, $J_{6,5}$ = 7.5, $J_{6,8}$ = 2, H-6), 5.65 (m, 1 H, $J_{5,4}$ = 5.5, H-5), 5.70 (dd, 1 H, $J_{11,10}$ = 15, $J_{11,12}$ = 7, H-11), 5.95 (m, 1 H, H-8), 6.0 (m, 1 H, H-9), 6.10 (m, 1 H, $J_{10,11}$ = 15, $J_{10,9}$ = 9, H-10), 6.30 (ddd, 1 H, $J_{7,6}$ = 14, $J_{7,8}$ = 9.5, $J_{7,9}$ = 2.5, H-7), 7.05–8.20 (2 m, 5 H, COPh), 7.20–7.80 (2 m, 10 H, SiPh); ^{13}C NMR δ 14.3 (C-20, OEt), 19.6, 27.3 (tBu), 21.0, 23.0, 27.8, 29.6, 31.8, 33.9, 34.2, 36.6 (C-2–4,-13,16–19), 60.0 (OEt), 74.4, 74.6 (C-5,12), 124.9, 129.9, 130.4, 131.2, 131.8, 132.4, 132.8, 133.2, 133.8, 136.3, 137.0 (C-6–11,14,15, Ph), 165.3 (*C*OPh), 172.3 (*C*OOEt).

Ethyl 6(*S*)-(Benzoyloxy)-13(*R*)-[(*tert*-butyldiphenylsilyl)oxy]-7(*Z*),9(*E*),11(*E*),15(*Z*)-henicosatetraenoate (25). According to the experimental procedure previously described for compound **24**, the same reaction involving now aldehyde B′ was carried out and afforded a mixture of the protected homo-LTB_4 **25** and its 7*E* isomer, respectively 7:3. They were separated by HPLC chromatography under the same conditions as previously (hexane:Et_3N:AcOEt = 98.5:1:0.5; flow rate 2 mL min^{-1}; retention time of **25** = 4.91 min; retention time of *E* isomer = 6.85 min). The ^{1}H NMR (250 MHz) spectra obtained for these compounds are almost superposable on those obtained for the protected LTB_4 **24** and its isomer, respectively. MS: m/e 675 (M^+ − OEt), 663 (M^+ − tBu), 615 (M^+ − COPh), 609 (M^+ − $CH_2CH{=}CHC_5H_{11}$), NH_3 chemical ionization 738 (M^+ + 18).

Ethyl 5(*S*)-(Benzoyloxy)-12(*R*)-hydroxy-6(*Z*),8(*E*),10(*E*),14(*Z*)-icosatetraenoate (26). To a stirred solution of the silyl ether **24** (3.3 mg, 4.7 μmol) in THF (500 μL) at room temperature was added a tetra-*n*-butylammonium fluoride solution (1 M in THF, 23 μL). After being stirred at room temperature for 15 h, the reaction mixture was quenched by the addition of brine (500 μL) and diluted with ether (5 mL). After ether extractions (5 × 2 mL), the organic layers were dried over $MgSO_4$ and concentrated in vacuo. The crude product was then purified on a Sep-Pak silica cartridge from Waters. Elution with hexane–AcOEt–Et_3N, 80:20:0.02 (TLC, same solvent, R_f 0.15), afforded 2.05 mg (61%) of **26**: ^{1}H NMR (250 MHz) δ 0.85 (t, 3 H, $J_{20,19}$ = 7, H-20), 0.90 (t, 3 H, J = 7, OEt), 1.15–1.40 (m, 6 H, H-17–19), 1.45–1.80 (m, 4 H, H-3,4), 2.10 (t, 2 H, $J_{2,3}$ = 7, H-2), 2.10 (m, 2 H, H-16), 2.25 (m, 2 H, H-13), 3.90 (q, 2 H, J = 7, OEt), 4.00 (m, 1 H, H-12), 5.35 (dd, 1 H, $J_{6,7}$ = 10.5, $J_{6,5}$ = 9.5, H-6), 5.40–5.55 (m, 2 H, $J_{14,15}$ = 11, H-14,15), 5.60 (dd, 1 H, $J_{11,10}$ = 15, $J_{11,12}$ = 6.25, H-11), 6.05 (dd, 1 H, $J_{7,8}$ = 11.5, $J_{7,6}$ = 10.5, H-7), 6.05–6.15 (m, 2 H, $J_{11,10}$ = 15, $J_{9,8}$ = 14.5, $J_{9,10}$ = 11, H-9,10), 6.20 (m, 1 H, $J_{5,6}$ = 9.5, H-5), 6.85 (dd, 1 H, $J_{8,9}$ = 14.5, $J_{8,7}$ = 11.5, H-8), 7.00–8.15 (2 m, 5 H, Ph).

5(*S*),12(*R*)-Dihydroxy-6(*Z*),8(*E*),10(*E*),14(*Z*)-icosatetraenoic Acid (LTB_4) (1). To a stirred solution of the diester **26** (0.5 mg, 1.1 μmol) in MeOH (160 μL) and H_2O (40 μL) was added potassium carbonate (2 mg, 14 μmol). After the mixture was stirred for 7.5 h at room temperature, the methanol was evaporated under reduced pressure, and the resulting mixture was then lyophilized. The sample was dissolved in water and applied on a C_{18} Sep-Pak cartridge from Waters. Elution with H_2O removed the excess salts, and then elution with MeOH:H_2O = 3:1 afforded LTB_4 (1) as a potassium salt: UV (CH_3CN:H_2O + 1% AcOH = 65:35) λ_{max} 260, 270.5, 281 nm; ^{1}H NMR (250 MHz, D_2O) δ 0.70 (m, 3 H, H-20), 1.00–1.25 (m, 6 H, H-17–19), 1.35–1.60 (m, 4 H, H-3,4), 1.85 (m, 2 H, H-16), 2.00 (m, 1 H, H-2), 2.15 (m, 2 H, H-13), 4.05 (m, 1 H, H-12), 4.60 (HOD, H-5), 5.25 (m, 2 H, H-6,14), 5.40 (m, 1 H, H-15), 5.65 (m, 1 H, H-11), 6.0 (m, 1 H, H-7), 6.15 (m, 2 H, H-9,10), 6.45 (m, 1 H, H-8). The retention time of LTB_4 (column Spherisorb ODS 2, eluent H_2O + 1% AcOH:CH_3CN = 80:20 to 10:90 in 40 min) was 25 min.

6(*S*),13(*R*)-Dihydroxy-7(*Z*),9(*E*),11(*E*),15(*Z*)-henicosatetraenoic Acid (Homo-LTB_4) (2). The silyl ether **25** was deprotected with a solution of tetra-*n*-butylammonium fluoride in THF in the same way as **24**, and then basic hydrolysis with potassium carbonate in MeOH–H_2O (4:1) afforded the potassium salt of homo-LTB_4 (**2**), which was then purified by HPLC chromatography on a Spherisorb ODS 2 column, eluent H_2O + 1% AcOH:CH_3CN = 80:20 to 10:90 in 40 min. The retention time of homo-LTB_4 (**2**) was 26.1 min, compared to 25 min for LTB_4 (1). UV (CH_3CN:H_2O + 1% AcOH = 65:35): λ_{max} 260, 270.5, 280 nm.

Registry No. **1**, 71160-24-2; **2**, 101705-33-3; **2**·K, 119414-23-2; **3**, 63700-05-0; **4**, 63699-97-8; **5a**, 119414-22-1; **5b**, 97579-27-6; **6a**, 109420-87-3; **6b**, 97579-31-2; **7a**, 109420-88-4; **7b**, 97579-33-4; **8**, 119392-28-8; **9**, 119392-29-9; **10**, 109458-67-5; **11**, 109420-89-5; (3*R*)-**12**, 18524-18-0; (3*S*)-**12**, 18524-19-1; **13**, 119392-30-2; **14**, 119392-31-3; **15**, 119392-32-4; **16**, 119392-33-5; **17**, 119392-34-6; **18**, 119392-35-7; **19a**, 100311-75-9; **19b**, 119392-37-9; **20a**, 82498-75-7; **20b**, 119392-38-0; **20c**, 82493-54-7; **21**, 82493-55-8; **22**, 101398-98-5; **23**, 82493-56-9; **24**, 82493-59-2; (6*E*)-**24**, 82493-61-6; **2k**, 119392-39-1; (7*E*)-**25**, 119413-60-4; **26**, 82493-60-5; **Aa**, 100428-42-0; **Ab**, 97579-36-7; *B*, 82493-58-1; *B*′, 119392-36-8; $C_5H_{11}C{\equiv}CH$, 628-71-7; $HC{\equiv}CCOOEt$, 623-47-2; $CH_3C(OEt)_3$, 78-39-7; $Ph_3P{=}CHCHO$, 2136-75-6; $(EtO)_2P(O)CH_2COOEt$, 867-13-0; D-mannitol, 69-65-8; (*R*)-glyceraldehyde acetonide, 15186-48-8.

(19) The chemical shifts and the coupling constants of each proton for both diastereoisomers have been determined by 2D chemical shift correlated spectroscopy (COSY) and NOE experiments, which were performed by Dr. J. P. Girault from our laboratory.