Total Synthesis of Leukotriene B_4

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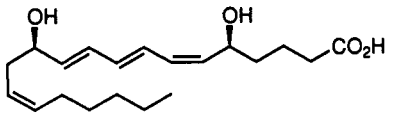
A new, efficient, and stereocontrolled total synthesis of leukotriene B_4 (1) has been developed. The convergent route employs a stereospecific Horner–Wadsworth–Emmons coupling of propargylic phosphonate **2** and aldehyde **3** to provide the essential carbon framework in 77% yield. The requisite phosphonate **2** containing the C_1–C_8 fragment was readily prepared in 47% yield from methyl 4-(chloroformyl)butyrate via an enantioselective reduction of alcohol **4** while the chiral aldehyde **3** which comprises the C_9–C_{20} skeleton of the eicosanoid was synthesized in 52% yield from optically active (2*R*)-(−)-glycidyl 4-nitrobenzoate.

There has been considerable interest recently in the scientific community regarding the arachidonic acid cascade. One of the biosynthetic products of this pathway, leukotriene B_4 (LTB_4, 1), has been implicated as an



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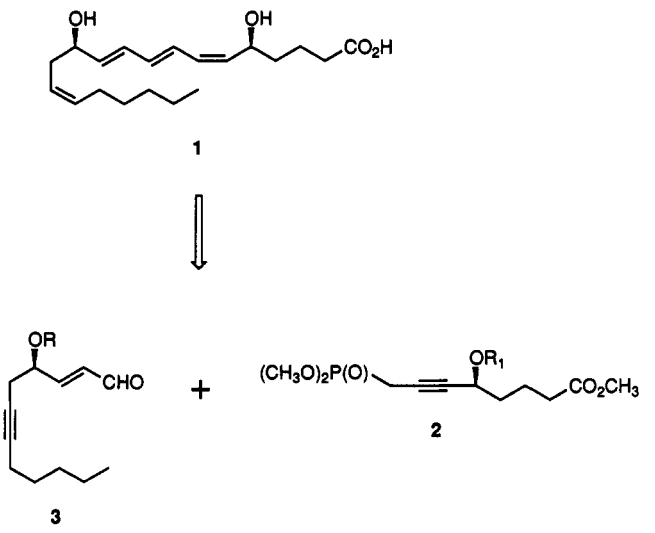
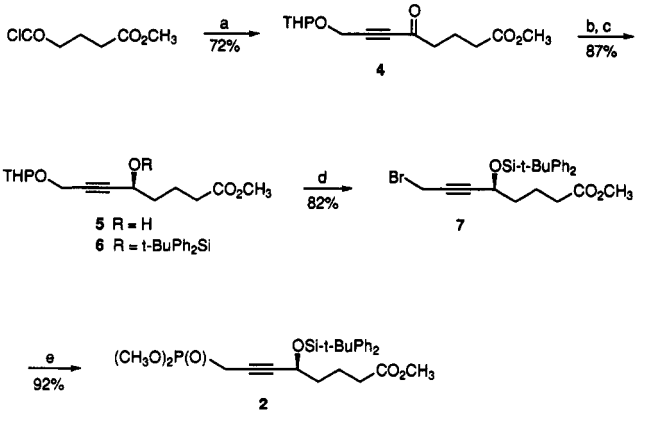
important mediator in inflammation and allergic reactions. It has been shown that this particular eicosatetraenoic acid exhibits potent chemotactic properties, induces vascular permeability, increases intracellular levels of calcium, and facilitates adhesion of neutrophils to the endothelium.[1] As a result of its physiological importance and limited availability from biological sources, several groups have reported elegant syntheses of the molecule.[2] We present herein a new, efficient, and stereocontrolled synthesis of leukotriene B_4.

Our synthetic strategy involving the preparation of LTB_4 was based on the retrosynthetic analysis shown in Scheme I. In a departure from the published procedures, we disconnected the compound at the C_8 double bond into propargylic phosphonate **2** and aldehyde **3** precursors. This approach offered several advantages including the incorporation of chiral centers, simultaneous generation of the two *cis* double bonds by a controlled hydrogenation, high degree of control of the geometry of the two *trans* double bonds by Wittig couplings, and finally flexibility to construct other novel and potentially useful analogues.

Scheme I



Scheme II[a]



[a] (a) $THPOCH_2C{\equiv}CLi$, CuCl, THF; (b) *S*-Alpine-borane, THF; (c) *t*-$BuPh_2SiCl$, imidazole, DMF; (d) $Ph_2P(CH_2)_2PPh_2$, $2Br_2$, CH_2Cl_2; (e) $HP(O)(OMe)_2$, NaN(TMS)$_2$, THF.

Propargylic phosphonate **2** was synthesized as outlined in Scheme II. Addition of the lithium acetylide of 1-(tetrahydro-2-pyranoxy)-2-propyne to commercially available methyl 4-(chloroformyl)butyrate in the presence of 0.1 equiv of copper(I) chloride afforded propargylic ketone **4** (72%). Other conditions and variations were tried but were not successful. For instance, when glutaric anhy-

(1) For a review, see Rokach, J.; Guindon, Y.; Young, R. N.; Adams, J.; Atkinson, J. G. In *The Total Synthesis of Natural Products*; Apsimon, J., Ed.; Wiley: New York, 1987; Vol. 7, 141.

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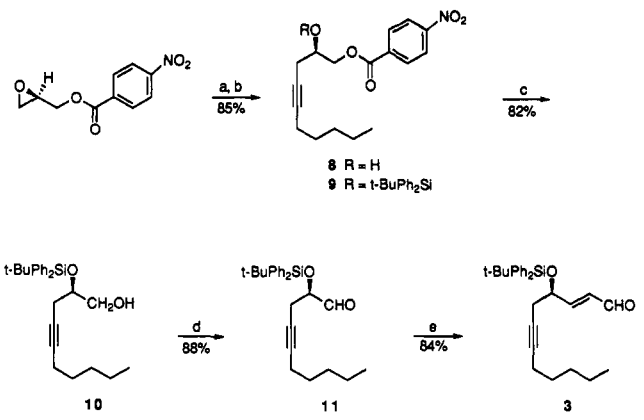
Scheme III[a]



[a] (a) $C_5H_{11}C{\equiv}CLi$, BF_3-Et_2O, THF; (b) *t*-$BuPh_2SiCl$, imidazole, DMF; (c) LiOH, MeOH; (d) TPAP, CH_2Cl_2; (e) $Ph_3P{=}CHCHO$, C_6H_6.

dride[3] was substituted for the chloroformate, the diaddition product, 5,5-bis[3-(tetrahydro-2-pyranoxy)-1-propyn]-5-hydroxypentanoic acid, was obtained in 91% yield. Replacement of copper(I) chloride with copper(I) iodide resulted in a substantial loss of the hydroxyl protecting group.

Enantioselective reduction of **4** with *S*-Alpine-borane (derived from (−)-α-pinene) afforded **5** in 88% yield and 94% ee as determined by ^1H NMR spectroscopy of its Mosher[4] derivative (the α-methoxy-α-(trifluoromethyl)-phenylacetic acid ester). The use of (−)-9-pinanyl-BBN[5] gave similar results. The alcohol **5** was treated with *tert*-butyldiphenylsilyl chloride to provide the silyl ether **6** and then subjected to 1,2-bis(diphenylphosphino)ethane tetrabromide[6] in methylene chloride to afford the bromo ester **7** directly. Not only did the reagent deprotect and halogenate in one step but it also facilitated purification since the diphenylphosphino monoxide produced by the reaction was easily removed by filtration. The bromo ester **7** was then readily transformed into the phosphonate **2** by alkylation with dimethyl phosphite. The use of trimethyl phosphite under more strenuous conditions gave inferior results. The phosphonate **2** was obtained in an overall yield of 47% from methyl 4-(chloroformyl)butyrate.

Having prepared the phosphonate, our attention turned toward the synthesis of the requisite aldehyde **3** as summarized in Scheme III. The commercially available and optically active (2*R*)-(−)-glycidyl 4-nitrobenzoate was stereoselectively combined with lithium heptynyl trifluoroborate[7] in tetrahydrofuran at −80 °C to afford the alcohol **8**. The alcohol **8** was treated with *tert*-butyldiphenylsilyl chloride to give protected alcohol **9**. Controlled hydrolysis of **9** in methanol containing lithium hydroxide afforded the alcohol **10** in high yield. We also utilized as starting materials the corresponding THP ether and butyl ester analogs of **8**. The THP group was effectively removed in 80% yield by acetic acid in a solution of tetrahydrofuran/water at 45 °C while the butyrate was removed in 58% yield in the presence of the *tert*-butyldimethylsilyl ether by enzyme hydrolysis utilizing the lipase from *Candida cylindracea* in a potassium phosphate buffer of pH 7.8 (maintained at that pH by the addition of 1 M NaOH) at 30 °C.[8] The use of the more stable and bulkier *tert*-butyldiphenylsilyl protecting group as opposed to the *tert*-butyldimethylsilyl group was generally preferred to prevent 1,2-silyl migration of the *tert*-butyldimethylsilyl group. With *tert*-butyldimethylsilyl as the secondary alcohol protecting group, hydrolysis with lithium hydroxide in 2-propanol/water at 23 °C proceeded with concomitant 1,2-silyl migration in 70% yield.

Mild oxidation of alcohol **10** with tetra-*n*-propylammonium perruthenate (TPAP)[9] gave the aldehyde **11**. Pyridinium dichromate[10] and Swern[11] oxidations were also used (no significant amount of racemization of the resultant α-hydroxy aldehyde was detected) but gave slightly lower yields. The aldehyde **11** was then homologated with (formylmethylene)triphenylphosphorane to the α,β-unsaturated aldehyde **3**. The aldehyde **3** was obtained in an overall yield of 52% from the (*R*)-glycidyl 4-nitrobenzoate.

With the required precursors in hand, the synthesis of leukotriene B_4 proceeded as follows (Scheme IV). Generation of the anion of **2** by treatment with lithium bis(trimethylsilyl)amide in tetrahydrofuran at −78 °C followed by the addition of the aldehyde **3** at −78 °C and stirring at that temperature for 8 h followed by warming to 23 °C afforded, after workup and isolation, the product **12** as a 9/1 E/Z mixture at the newly formed double bond in 85% yield. Repeated flash chromatography or HPLC gave the pure *trans* compound **12** (77%). Controlled hydrogenation (constant monitoring) of the diacetylene **12** using 5% Pd/C poisoned with a 10-fold amount of quinoline in ethyl acetate at 23 °C gave the tetraene **13** in 88% yield. The ratio of quinoline to catalyst as well as the solvent system employed was crucial to insure a high yield of product and avoid overreduction. Finally, all three protecting groups were removed by treatment of **13** with excess tetra-*n*-butylammonium fluoride in tetrahydrofuran to provide, after workup and flash column chromatography, LTB_4 (**1**). It has been hypothesized[2f] that under these conditions, the 5-hydroxy group internally assists in the hydrolysis of the methyl ester. The eicosanoic acid could also be prepared in approximately 80% yield from **13** in a two-step reaction sequence involving (a) desilylation with hydrogen fluoride pyridine/tetra-*n*-butylammonium fluoride and (b) hydrolysis of the resulting methyl ester with lithium hydroxide. The spectral and optical data of **1** were in good agreement with reported values[2] while RP-HPLC analysis of an analytical sample showed it to have a chemical purity of >95%.

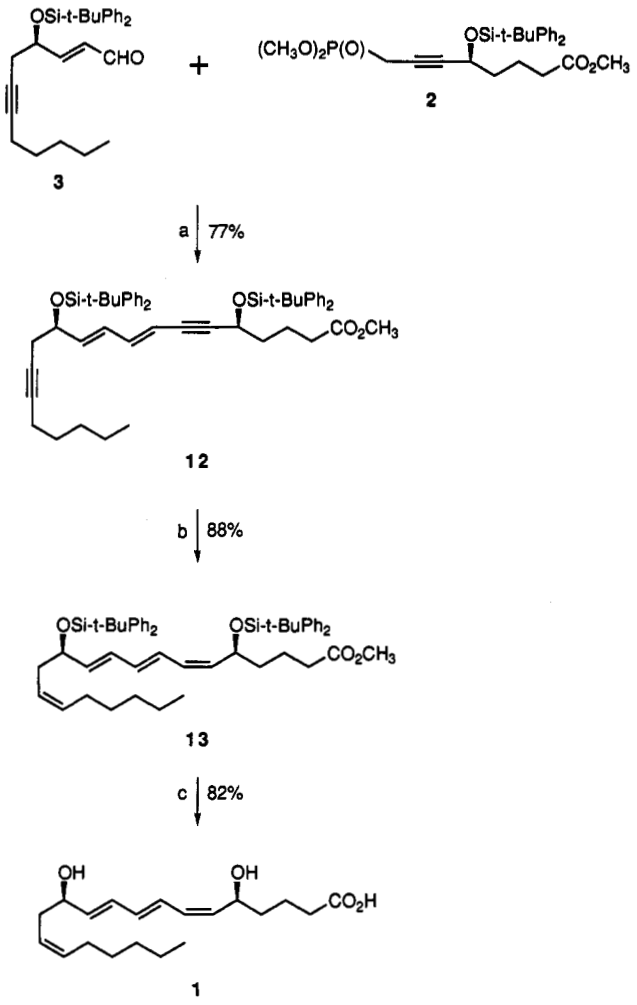
In conclusion, we have succeeded in developing an efficient and stereoselective synthesis of LTB_4. This new flexible process should be easily applicable to the synthesis of a wide variety of structural analogs.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether were distilled from

(3) Brown, H. C.; Racherla, U. S.; Singh, S. M. *Tetrahedron Lett.* **1984**, 2411.
(4) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(5) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1982**, *47*, 1606.
(6) Schmidt, S. P.; Brooks, D. W. *Tetrahedron Lett.* **1987**, 767.
(7) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.*, **1983**, 391.
(8) The lipase from porcine pancreas and the esterase from porcine liver gave inferior yields of product.
(9) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.
(10) Herscovici, J.; Egron, M. J.; Antonakis, K. J. *Chem. Soc. Perkin Trans. 1* **1982**, 1967.
(11) Mancuso, A. J.; Huang, S. L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

Scheme IV[a]



[a] (a) $LiN(TMS)_2$, THF; (b) H_2, $Pd/BaSO_4$, EtOAc; (c) nBu_4NF, THF.

sodium benzophenone immediately prior to use. N,N-Dimethylformamide (DMF) and methylene chloride were dried over calcium hydride. All reactions were carried out under an atmosphere of argon or nitrogen. ^1H NMR spectra were obtained on a General Electric QE-300 NMR instrument at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. ^1H NMR data are tabulated in the following order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. Mass spectra were recorded with an HP5985A spectrometer, and high-resolution mass spectra were obtained on a Kratos MS50 instrument. Optical rotations were obtained by using a Perkin-Elmer 481 polarimeter. High-performance liquid chromatography was done on a Beckman Model 420/110A liquid chromatograph. Merck TLC plates were used for analytical TLC and Merck Kieselgel 60 was used for column chromatography. All new compounds were characterized by full spectroscopic and analytical or exact mass data and yields refer to spectroscopically and chromatographically homogeneous materials. Microanalyses were performed by the Abbott Analytical Department. All products were obtained as colorless oils unless otherwise noted.

Methyl 5-Oxo-8-(tetrahydropyran-2-yloxy)-6-octynoate (4). *n*-Butyllithium (8.20 mL of a 2.5 M solution in hexane, 20.5 mmol) was slowly added dropwise at −78 °C under argon to a solution of 1-(tetrahydropyran-2-yloxy)-2-propyne (2.80 g, 20 mmol) in THF (30 mL). After stirring at −78 °C for 20 min, the resulting lithium acetylide solution was cannulated dropwise into a vigorously stirred mixture of methyl 4-(chloroformyl)butyrate (4.95 g, 30 mmol) and copper(I) chloride (0.20 g, 2 mmol) in THF (20 mL) at −78 °C with the copper(I) chloride added just prior to cannulation. The reaction mixture was stirred at −78 °C for 45 min and then allowed to warm to 5 °C. The solution was quenched with saturated sodium bicarbonate (40 mL) and extracted with ether (4 × 40 mL). The combined ether extracts were washed successively with saturated sodium bicarbonate (2 × 50 mL) and saturated sodium chloride (1 × 50 mL). The organic layer was dried ($MgSO_4$) and evaporated and the residue chromatographed (silica, pentane/ether 2/1) to afford **4** (2.92 g, 72%): ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (t, 1H, J = 7 Hz), 4.43 (s, 2H), 3.83 (m, 1H), 3.68 (s, 3H), 3.56 (m, 1H), 2.67 (t, 2H, J = 7 Hz), 2.37 (t, 2H, J = 7 Hz), 1.98 (m, 2H), 1.5–1.7 (m, 6H); HRMS calcd for $C_{14}H_{20}O_5$ (M^+) 268.1302, found 268.1298. Anal. Calcd: C, 62.66; H, 7.52. Found: C, 62.70; H, 7.49.

5(*S*)-Methyl 5-Hydroxy-8-(tetrahydropyran-2-yloxy)-6-octynoate (5). To *S*-Alpine-borane (5.7 mmol, 11.4 mL of 0.5 M solution in THF) at 0 °C under argon was added **4** (1.07 g, 4.0 mmol) dropwise, and the resulting light-yellow liquid allowed to warm to 23 °C. After stirring for 15 h, the reaction mixture was cooled to 0 °C and acetaldehyde added (1 mL). After 5 min at 0 °C, diethyl ether (10 mL) was added followed by the dropwise addition of ethanolamine (0.36 mL, 6.0 mmol). The resulting solution was diluted with ether (15 mL) and washed with saturated sodium chloride (3 × 30 mL). The ether portion was dried ($MgSO_4$), the solvent evaporated, and the residue chromatographed (silica, pentane/ether 2/3) to afford **5** (0.95 g, 88%) in 94% ee (determined by preparation of its Mosher ester and analyzing the ^1H NMR spectrum): ^1H NMR (300 MHz, $CDCl_3$) δ 4.80 (t, 1H, J = 3 Hz), 4.44 (m, 1H), 4.34 (m, 1H), 4.25 (m, 1H), 3.84 (m, 1H), 3.69 (s, 3H), 3.55 (m, 1 H), 2.39 (t, 2H, J = 7 Hz), 2.00 (d, 1H, J = 5 Hz), 1.4–1.9 (m, 10H); HRMS calcd for $C_{14}H_{22}O_5$ (M^+) 270.1470, found 270.1468. Anal. Calcd: C, 62.19; H, 8.21. Found: C, 62.24; H, 8.18.

5(*S*)-Methyl 5-[(*tert*-Butyldiphenylsilyl)oxy]-8-(tetrahydropyran-2-yloxy)-6-octynoate (6). A solution of *tert*-butyldiphenylsilyl chloride (0.99 g, 3.6 mmol) in DMF (3 mL) was added slowly to a slurry of **5** (0.90 g, 3.3 mmol) and imidazole (0.49 g, 7.2 mmol) in DMF (2 mL) at 0 °C under argon. After stirring at 23 °C for 2.5 h, the reaction mixture was quenched with water (20 mL) and extracted with diethyl ether (3 × 30 mL). The combined ether extracts were washed with saturated sodium chloride and dried ($MgSO_4$), and the solvent was evaporated to give **6** (1.66 g, 99%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.63 (m, 4H), 7.46–7.33 (m, 6H), 4.82 (m, 1H), 4.41 (m, 1H), 4.29 (m, 2H), 3.85 (m, 1H), 3.67 (s, 3H), 3.53 (m, 1H), 2.35 (t, 2H, J = 7 Hz), 1.5–1.9 (m, 10H), 1.08 (s, 9H); HRMS calcd for $C_{30}H_{40}O_5Si$ (M^+) 508.2645, found 508.2650. Anal. Calcd: C, 70.83; H, 7.93. Found: C, 70.79; H, 7.97.

5(*S*)-Methyl 8-Bromo-5-[(*tert*-butyldiphenylsilyl)oxy]-6-octynoate (7). Bromine (0.64 g, 4.0 mmol) in dry methylene chloride (3 mL) was added dropwise under argon to a cooled (ice bath) solution of 1,2-bis(diphenylphosphino)ethane (0.8 g, 2.0 mmol) in dry methylene chloride (5 mL). The THP ether **6** (0.76 g, 1.5 mmol) was then added. After stirring at 0 °C for 5 min, the reaction mixture was quenched by the addition of ether (10 mL) and pentane (20 mL). The white precipitate was allowed to settle and the liquid decanted and saved. The solid was redissolved under a stream of nitrogen in a minimum amount of methylene chloride. Ether (10 mL) was added to the vigorously stirred solution followed by the combined decants filtered through a 1-in. pad of silica gel 60 (40–63 μm). The filtrate was concentrated in vacuo and the clear liquid residue was chromatographed (silica, pentane/ether 9/1) to afford **7** (598 mg, 82%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.71–7.63 (m, 4H), 7.47–7.33 (m, 6H), 4.56 (t, 1H, J = 6 Hz), 4.05 (s, 2H), 3.68 (s, 3H), 2.32 (t, 2H, J = 7 Hz), 1.75–1.42 (m, 4H), 1.07 (s, 9H); HRMS calcd for $C_{25}H_{31}O_3SiBr$ (M^+) 486.1048, found 486.1041. Anal. Calcd: C, 61.72; H, 6.42; Br, 16.23. Found: C, 61.69; H, 6.46; Br, 16.18.

(5*S*)-Methyl 8-(Dimethylphosphono)-5-[(*tert*-butyldiphenylsilyl)oxy]-6-octynoate (2). To a stirred solution of $NaN(SiMe_3)_2$ in THF (1 M, 1.2 mL, 1.2 mmol) at −10 °C was added dimethyl phosphonate (132 mg, 1.2 mmol) in THF (0.4 mL). The solution was stirred for 15 min at −10 °C and then treated with bromide **7** (580 mg, 1.2 mmol) in THF (0.4 mL) maintaining the temperature at −10 °C. The mixture was stirred at −10 °C for 1 h, diluted with water (5 mL), and extracted with ethyl acetate (2 × 5 mL). The extract was washed with 10% HCl (5 mL),

water (5 mL), and dried ($MgSO_4$). The solvent was evaporated and the residue chromatographed (2% methanol in ether) to give **2** (0.57 g, 92%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.73–7.63 (m, 4H), 7.47–7.33 (m, 6H), 4.56 (t, 1H, J = 6 Hz), 3.75 (s, 3H), 3.71 (s, 3H), 3.68 (s, 3H), 2.71 (s, 2H), 2.32 (t, 2H, J = 7 Hz), 1.75–1.42 (m, 4H), 1.06 (s, 9H); HRMS calcd for $C_{27}H_{37}O_6SiP$ (M^+) 516.2097, found 516.2092. Anal. Calcd: C, 62.77; H, 7.22. Found: C, 62.82; H, 7.19.

(2*R*)-2-Hydroxy-4-decynyl 4-Nitrobenzoate (8). *n*-Butyllithium (1 mL of 2.5 M solution in hexanes, 2.5 mmol) was slowly added dropwise to 1-heptyne (0.24 g, 2.5 mmol) in THF (21 mL) at −78 °C under nitrogen. After 40 min at −78 °C, the vigorously stirred solution was cooled to −90 °C and boron trifluoride etherate (0.35 g, 2.5 mmol) was slowly added dropwise. After stirring at −80 °C for 1 h, a solution of 98% ee (2*R*)-(−)-glycidyl 4-nitrobenzoate (0.55 g, 1.25 mmol) in THF (2 mL) was slowly added dropwise. The solution was stirred at −80 °C for 1 h and then quenched with saturated aqueous NH_4Cl (1 mL). The reaction mixture was warmed to 23 °C and the organic layer separated. The aqueous portion was extracted with ether and the combined organic extracts dried ($MgSO_4$). Removal of the solvent in vacuo and chromatography (silica gel, pentane/ether 1/1) gave **8** (0.686 g, 86%): $[\alpha]^{25}_D$ −38.4° (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.35–8.20 (m, 4H), 4.53–4.38 (m, 2H), 4.19–4.08 (m, 1H), 2.59–2.51 (m, 2H), 2.38 (d, 1H, J = 6 Hz), 2.20–2.10 (m, 2H), 1.53–1.42 (m, 2H), 1.40–1.25 (m, 4H), 0.90 (t, 3H, J = 7 Hz); HRMS calcd for $C_{17}H_{21}NO_5$ (M^+) 319.1420, found 319.1416. Anal. Calcd: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.88; H, 6.64; N, 4.35.

2(*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-4-decynyl 4-Nitrobenzoate (9). A mixture of **8** (0.67 g, 2.1 mmol), *tert*-butyldiphenylsilyl chloride (0.33 g, 2.2 mmol), and imidazole (0.3 g, 4.4 mmol) in dry DMF (4 mL) under argon was stirred at 23 °C for 2 h. The reaction mixture was poured into water (30 mL) and extracted with ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), the solvent removed, and the residue chromatographed (silica, pentane/ether 9/1) to afford **9** (1.16 g, 99%): ^1H NMR (300 MHz, $CDCl_3$) δ 8.30–8.08 (m, 4H), 7.68–7.55 (m, 4H), 7.40–7.25 (m, 6H), 4.53–4.42 (m, 2H), 4.38–4.3 (m, 1H), 2.59–2.51 (m, 2H), 2.15–2.08 (m, 2H), 1.50–1.41 (m, 2H), 1.38–1.24 (m, 4H), 1.07 (s, 9H), 0.88 (t, 3H, J = 7 Hz); HRMS calcd for $C_{33}H_{39}NO_5Si$ (M^+) 557.2598, found 557.2603. Anal. Calcd: C, 71.06; H, 7.05; N, 2.51. Found: C, 71.11; H, 7.01; N, 2.48.

(2*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-4-decyn-1-ol (10). To compound **9** (1.11 g, 2 mmol) in MeOH (50 mL) at 0 °C under argon was slowly added LiOH (80 mg) in water (5 mL) and the reaction monitored by TLC. After the starting material was consumed, saturated NH_4Cl (5 mL) was added. The solution was extracted with ether. The ether extracts were washed with brine and dried ($MgSO_4$). The solvent was removed and the residue chromatographed (silica, pentane/ether 4/1) to give **10** (669 mg, 82%): $[\alpha]^{25}_D$ −25.4° (*c* 0.1, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.64 (m, 4H), 7.48–7.33 (m, 6H), 3.93–3.84 (m, 1H), 3.63 (dd, 2H, J = 4 and 7 Hz), 2.46–2.22 (m, 2H), 2.11–2.01 (m, 2H), 1.83 (t, 1H, J = 7 Hz), 1.48–1.20 (m, 6H), 1.02 (s, 9H), 0.88 (t, 3H, J = 7 Hz); HRMS calcd for $C_{26}H_{36}O_2Si$ (M^+) 408.2485, found 408.2489. Anal. Calcd: C, 76.42; H, 8.89. Found: C, 76.38; H, 8.92.

(2*R*)-2-[(*tert*-Butyldiphenylsilyl)oxy]-4-decynal (11). Solid tetra-*n*-propylammonium perruthenate (0.2 g) was added in one portion to a stirred mixture of the alcohol **10** (612 mg, 1.5 mmol), *N*-methylmorpholine *N*-oxide (0.26 g, 2.25 mmol) and powdered 4-Å molecular sieves (1.5 g) in dichloromethane (5 mL) at 23 °C under argon. On completion, the reaction mixture was filtered through a pad of silica eluting with dichloromethane. The filtrate was evaporated and the residue chromatographed (silica gel) to afford **11** (536 mg, 88%): $[\alpha]^{25}_D$ −24.7° (*c* 0.03, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.62 (d, 1H, J = 1 Hz), 7.71–7.63 (m, 4H), 7.47–7.33 (m, 6H), 4.07 (dt, 1H, J = 1 and 6 Hz), 2.48 (dd, 2H, J = 1.5 and 6 Hz), 2.12–2.05 (m, 2H), 1.46–1.22 (m, 6H), 1.13 (s, 9H), 0.90 (t, 3H, J = 7 Hz); HRMS calcd for $C_{26}H_{34}O_2Si$ (M^+) 406.2328, found 406.2325. Anal. Calcd: C, 76.80; H, 8.44. Found: C, 76.75; H, 8.47.

(2*E*,4*R*)-4-[(*tert*-Butyldiphenylsilyl)oxy]-2-dodecen-6-ynal (3). To a solution of aldehyde **11** (487 mg, 1.2 mmol) in dry benzene (10 mL) under argon was added (formylmethylene)-triphenylphosphorane (0.395 g, 1.3 mmol) and the resulting mixture stirred at 60 °C for 15 h. The reaction mixture was concentrated in vacuo and the residue chromatographed (silica, pentane/methylene chloride 5/2) to give **3** (436 mg, 84%): ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, 1H, J = 1 Hz), 7.71–7.63 (m, 4H), 7.47–7.33 (m, 6H), 6.82 (m, 1H), 6.28 (m, 1H), 4.11 (dt, 1H, J = 1 and 6 Hz), 2.48 (dd, 2H, J = 1.5 and 6 Hz), 2.12–2.05 (m, 2H), 1.46–1.22 (m, 6H), 1.13 (s, 9H), 0.90 (t, 3H, J = 7 Hz); HRMS calcd for $C_{28}H_{36}O_2Si$ (M^+) 432.2485, found 432.2491. Anal. Calcd: C, 77.73; H, 8.39. Found: C, 77.69; H, 8.41.

(5*S*,8*E*,10*E*,12*S*)-Methyl 5,12-Bis[(*tert*-butyldiphenylsilyl)oxy]-8,10-eicosadiene-6,14-diynoate (12). A solution of lithium bis(trimethylsilyl)amide (1.1 mL of 1.0 M solution in THF, 1.1 mmol) was added dropwise to a magnetically stirred solution of phosphonate **2** (567 mg, 1.1 mmol) in THF (8 mL) under argon at −78 °C. The reaction mixture was stirred for 1 min, and aldehyde **3** (432 mg, 1 mmol) in THF (2 mL) was added in one portion. The reaction mixture was stirred at −78 °C for 1 h, slowly warmed to −20 °C, kept at that temperature for 1 h, and then warmed to 0 °C and kept at that temperature for 1 h. Ether (10 mL) was added followed by aqueous NH_4Cl (10 mL), and the organic layer was washed with water, brine, and dried. The cis/trans isomers were separated by repeated flash chromatography (silica, 1% ethyl acetate in hexane) to afford the trans isomer **12** (633 mg, 77%): $[\alpha]^{25}_D$ −47.8° (*c* 0.01, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.79–7.61 (m, 8H), 7.45–7.29 (m, 12H), 6.19 (dd, 1H, J = 15 and 11 Hz), 5.94 (dd, 1H, J = 15 and 11 Hz), 5.77 (dd, 1H, J = 6 and 15 Hz), 5.30 (dd, 1H, J = 1 and 15 Hz), 4.52–4.45 (m, 1H), 4.32–4.20 (m, 1H), 3.65 (s, 3H), 2.37–2.25 (m, 4H), 2.13–2.03 (m, 2H), 1.85–1.64 (m, 4H), 1.47–1.20 (m, 6H), 1.10 (s, 18H), 0.88 (t, 3H, J = 7 Hz); HRMS calcd for $C_{53}H_{66}O_4Si_2$ (M^+) 822.4496, found 822.4488.

(5*S*,6*Z*,8*E*,10*E*,12*R*,14*Z*)-Methyl 5,12-Bis[(*tert*-butyldiphenylsilyl)oxy]-6,8,10,14-eicosatetraenoate (13). A suspension of $BaSO_4$/Pd (35 mg) and quinoline (0.35 mL) in ethyl acetate (50 mL) at 23 °C was magnetically stirred under a hydrogen atmosphere for 1 h. A solution of **12** (123 mg, 0.15 mmol) in ethyl acetate (1.5 mL) was then added. The reaction was constantly monitored and after the starting material and almost all the monoreduced material (approximately 4 h) was consumed the suspension was filtered and the solvent evaporated. The residue was chromatographed (silica, ethyl acetate/hexane 2/98) to provide **13** (109 mg, 88%): $[\alpha]^{25}_D$ +32.9° (*c* 0.02, CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74–7.58 (m, 8H), 7.44–7.25 (m, 12H), 5.93 (dd, 1H, J = 15 and 11 Hz), 5.87–5.56 (m, 4H), 5.46–5.17 (m, 3H), 4.54–4.42 (m, 1H), 4.23–4.12 (m, 1H), 3.61 (s, 3H), 2.30–2.08 (m, 4H), 1.87–1.77 (m, 2H), 1.62–1.37 (m, 4H), 1.32–1.12 (m, 6H), 1.10 (s, 9H), 1.05 (s, 9H), 0.85 (t, 3H, J = 7 Hz); HRMS calcd for $C_{53}H_{70}O_4Si_2$ (M^+) 826.4813, found 826.4824.

Leukotriene B_4 (1). Method A. *n*-Bu_4NF (3.75 mL of 1 M solution in THF, 3.75 mmol) was added to a magnetically stirred solution of **13** (310 mg, 0.375 mmol) in THF (3.75 mL) at 0 °C under an argon atmosphere. The reaction mixture was then stirred for 14 h at 23 °C and poured into a vigorously stirred and ice-cooled mixture of ether (40 mL) and McIlvaine's phosphate buffer solution (pH 5, 20 mL). The organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The residue was chromatographed (silica, deoxygenated ether and methanol mixture) to provide **1** (104 mg, 82%) as a colorless oil. RP-HPLC (reversed-phase HPLC, using a C_{18} partisil ODS Whatman column; mobile phase, MeOH/H_2O/AcOH 3/1/0.01 with UV detection at 270 nm) of an analytical sample found it to be >95%: TLC (ethyl acetate), R_f 0.31; $[\alpha]^{25}_D$ +12.6° (*c* 0.40, $CDCl_3$) (lit.[2g] $[\alpha]^{25}_D$ +12.6° (*c* 0.46, $CDCl_3$)); ^1H NMR (300 MHz, $CDCl_3$) δ 6.47 (dd, 1H, J = 14 and 12 Hz), 6.28 (m, 2H), 6.09 (t, 1H, J = 11 Hz), 5.78 (dd, 1H, J = 15 and 7 Hz), 5.65–5.25 (m, 4H), 4.62 (m, 1H), 4.23 (q, 1H, J = 7 Hz), 2.35 (m, 4H), 2.04 (m, 2H), 1.80–1.15 (m, 12H), 0.90 (t, 3H, J = 7 Hz); IR (film) ν_{max} 3360 (s), 3020 (w), 2970 (s), 2935 (s), 2860 (m), 1715 (s); UV max (CH_3OH) λ_{max} 260, 270, 281 nm (ϵ 43000, 52000, 42000).

Method B. To a suspension of hydrofluoric acid/pyridine complex (prepared from 1 equiv of 50% aqueous hydrofluoric acid and 1 equiv of pyridine, 0.72 mmol, 0.9 mL) in dry THF (0.3 mL) under argon was added **13** (99 mg, 0.12 mmol). n-Bu_4NF (0.24 mL of a 1 M solution in THF, 0.24 mmol) was added and the reaction mixture stirred for at 30 °C for 24 h. The reaction

mixture was quenched with water (2.5 mL) and extracted with ether (3 × 20 mL). The ether extracts were washed with water, 10% aqueous HCl, saturated aqueous $NaHCO_3$, brine, and dried ($MgSO_4$). Removal of solvent, followed by chromatography (methylene chloride/ether 2/1) afforded the methyl ester of 1 (39 mg, 81%): $[\alpha]^{20}_D$ +6.5° (c 1.8, CCl_4) (lit.[20] $[\alpha]^{25}_D$ +6.47° (c 1.8, CCl_4)); ^1H NMR (300 MHz, $CDCl_3$) δ 6.52 (dd, 1H, J = 14 and 12 Hz), 6.34 (dd, 1H, J = 15 and 11 Hz), 6.27 (dd, 1H, J = 14 and 11 Hz), 6.12 (t, 1H, J = 11 Hz), 5.81 (dd, 1H, J = 15 and 7 Hz), 5.66–5.57 (m, 1H), 5.50–5.36 (m, 2H), 4.62 (m, 1H), 4.25 (q, 1H, J = 7 Hz), 3.70 (s, 3H), 2.45–2.32 (m, 4H), 2.09 (m, 2H), 1.90–1.65 (m, 6H), 1.40–1.28 (m, 6H), 0.90 (t, 3H, J = 7 Hz). To a solution of the methyl ester of 1 (18 mg, 0.05 mmol) in 2-propanol (2.5 mL) under argon at 0 °C was added dropwise lithium hydroxide (11 mg, 0.25 mmol) in water (1.25 mL). The reaction mixture was allowed to warm to 23 °C and stirred at that temperature for 1 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (2.5 mL) and acidified to pH 3. The solution was extracted with ether, and the extracts were dried ($MgSO_4$). Removal of solvent and chromatography (silica, deoxygenated ether and methanol mixture) provided 1 (16 mg, 95%).

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Supplementary Material Available: ^1H NMR spectra of compounds 12 and 13 (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.