eochemistry. The accuracy of a model can be determined from the quality of the fit of calculated and observed values. For the alkaloids used in these studies, the solution and the solid-state structures appeared to be closely similar, since the relaxation data determined in solution could be accurately modelled using previously reported crystal structure coordinates. These studies serve to demonstrate that the approach is valid, and that it can provide insights into the solution structure of alkaloids.

Experimental Section

All spectra were measured at 400 MHz at ambient temperature (about 20 °C) on a Bruker WH-400 spectrometer at the Montreal Regional High Field NMR Laboratory. Solutions were 0.1 M in deuterated solvent and were not degassed, since highly accurate experimental R_1 values were not required. All relaxation data were, however, corrected for contributions from dissolved oxygen, as described elsewhere.[11,35]

^1H R_1 values were measured by nonlinear regression analysis or by the null point method,[10] by using the standard inversion-recovery technique[46] with careful calibration of pulse lengths. NOE enhancements were measured by the difference technique,[14] as described elsewhere.[9] Interproton distances for calculation of R_1 values were obtained from crystal structure coordinates of morphine,[20] codeine,[21] heroin,[22] cinchonine, and quinidine[36] and from molecular models. R_1 values were calculated by using a Hewlett-Packard 1000 computer.

Samples used in this study were obtained from the following suppliers: Aldrich, tropine; Baker, quinine; BDH, cocaine and codeine; F. E. Cornell, heroin and morphine; Endo, naloxone and naltrexone; Fisher, cinchonine; Frosst, nalorphine; Sigma, cinchonidine, quinidine, and scopolamine; and T. and H. Smith, thebaine. The samples were dried before use.

Acknowledgment. This work was supported by an operating grant from the Natural Sciences and Engineering Research Council of Canada (NSERC), who also supplied funding toward the purchase of the 400-MHz spectrometer. W.J.C. thanks the Ministry of Education, Province of Quebec, and NSERC for postgraduate fellowships. We are indebted to Dr. Z. Amit and Mr. F. Rogan, Centre for Studies in Behavioral Neurobiology, Concordia University, for their collaboration.

Registry No. 1·HCl, 52-26-6; 2·H_3PO_4, 52-28-8; 3·HCl, 1502-95-0; 4·HCl, 57-29-4; 5·HCl, 850-57-7; 6·HCl, 357-08-4; 7·HCl, 16676-29-2; 8·HCl, 524-57-2; 9·HCl, 130-89-2; 10·HCl, 5949-11-1; 11·HCl, 1668-99-1; 12, 120-29-6; 13, 51-55-8; 14, 51-34-3; 15, 50-36-2.

(46) Vold, R. L.; Waugh, J. S.; Klein, M. P.; Phelps, D. E. *J. Chem. Phys.* **1968**, *48*, 3831.

A Chemoenzymatic Synthesis of Leukotriene B_4

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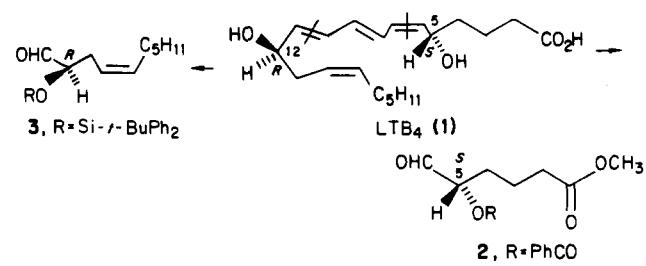
A total synthesis of leukotriene B_4 (1) is accomplished by the assembly of the key chirons 2 and 3, which are prepared via enzymatic methods.

The dihydroxy acid leukotriene B_4 (LTB_4, 1) is biosynthesized from arachidonic acid via the 5-lipoxygenase pathway.[1] Studies on the biological properties of LTB_4 have shown it to be one of the most potent chemotactic factors known for neutrophils.[2] The perceived importance of LTB_4 in allergic and inflammatory states[3] and the difficulty in isolating LTB_4 in quantity from biological sources prompted several groups to embark on the synthesis of this compound. Several elegant total syntheses of LTB_4 have now appeared.[4] With one exception,[4b] LTB_4 was constructed by the successive assembly of prefabricated chirons of carbohydrate origin that possess the stereochemical configuration corresponding to C-5 and C-12 of LTB_4. In this paper, we wish to report an alternative strategy of LTB_4 synthesis that utilizes enzymatic methods for the preparation of the key chiral fragments 2 and 3. The experimental details leading to a convergent synthesis of LTB_4 are described below.

Retrosynthetic analysis of the LTB_4 molecule (Scheme I) reveals that it could be conveniently constructed from two chirons, 2 and 3, each of which possesses the key chiral centers (C-5 and C-12) of the target molecule as shown.

Scheme I



We envisaged that 2 may be conveniently prepared by an enantioselective yeast reduction of the ketone 4 to yield the (5*S*)-carbinol 7, which may then be transformed into 2 using conventional methods.

4, R = CH_3
5, R = *t*-Bu
6, R = H

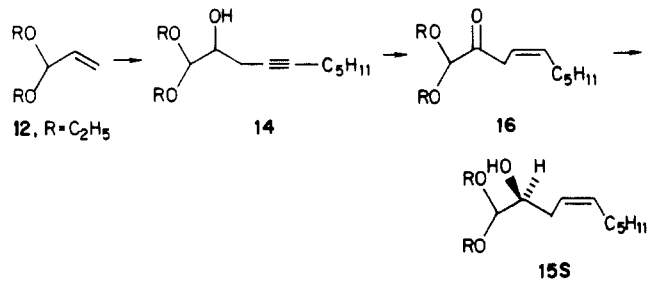
7, $R_1 = CH_3$; $R_2 = H$
8, R_1 = *t*-Bu; $R_2 = H$
9, $R_1 = R_2 = H$
10, R_1 = *t*-Bu; R_2 = PhCO
11, $R_1 = CH_3$; R_2 = PhCO

Reaction of the sodium salt of monomethyl glutarate with 2 equiv of 2-lithio-1,3-dithiane[5] afforded the acid 6 (78% yield), which was refluxed with 2,2-dimethoxy-

(1) Borgeat, P.; Samuelsson, B. *J. Biol. Chem.* **1979**, *254*, 2643.
(2) For reviews, see: (a) Borgeat, P.; Sirois, P. *J. Med. Chem.* **1981**, *24*, 121. (b) Ford Hutchinson, A. W. J. *R. Soc. Med.* **1981**, *74*, 831. (c) Bailey, D. M.; Casey, F. B. *Annu. Rep. Med. Chem.* **1982**, *17*, 203.
(3) Goetzl, E. J. *New Engl. J. Med.* **1980**, *303*, 822.
(4) See: (a) Rokach, J.; Adams, J. *Acc. Chem. Res.* **1985**, *18*, 87 and references cited therein. (b) Nicolaou, K. C.; Zipkin, R. E.; Dolle, R. E.; Harris, B. D. *J. Am. Chem. Soc.* **1984**, *106*, 3548.
(5) Seeback, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231.

0022-3263/86/1951-1253$01.50/0

Scheme II

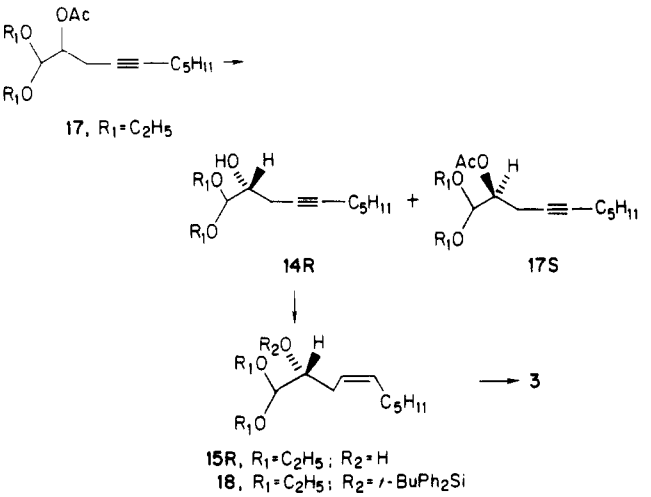


propane in methanol (*p*-TsOH) for 3 h to yield **4** (98% yield). Unexpectedly, when **4** was exposed to bakers' yeast,[6] the methyl ester grouping was rapidly hydrolyzed by the esterase of bakers' yeast to yield **6**, and very little reduction of the carbonyl group was observed. To block the esterase activity, **6** was treated with isobutylene (BF_3·OEt_2/−78 °C) to give the *tert*-butyl keto ester **5**. When it was incubated with bakers' yeast in tap water for 70 h, the chiral (*S*)-carbinol **8** was obtained in 65% yield. ^1H analysis of its (−)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA) ester revealed that the optical purity of (−)-**8** was greater than 97% enantiomeric excess (ee). Treatment of **8** (benzoyl chloride, pyridine, 0 °C) afforded **10**, which was transformed into the methyl ester **11**[7] (*p*-TsOH, benzene; CH_2N_2, ether, 92%) as a colorless oil. Deprotection of the thioacetal proceeded smoothly to give **2** (CH_3I, $CaCO_3$, aqueous acetone, 66%).

Our initial intended strategy for the preparation of the chiron **3** also entailed the use of bakers' yeast to introduce the chiral center via an enantioselective reduction of **16** as shown in Scheme II. The stereochemical course of the reduction of β-keto carboxylic acid derivatives can now be predicted with reasonable accuracy.[8] In contrast, no corresponding systematic studies have been conducted with α-keto carbonyl derivatives. Hence, it is not possible at this stage to predict with any degree of accuracy the sense of chirality and the extent of asymmetric reduction in the bakers' yeast reduction of **16**.

The following sequence of reactions was employed for the preparation of **16**: acrolein diethyl acetal (**12**) was converted to the epoxide **13** (MCPBA, 25 °C, 52%), which was smoothly converted into **14** (1-heptyne, *n*-BuLi, −78 °C, 95%). Hydrogenation of **14** gave **15** (H_2, Lindlar catalyst, 96%) followed by mild oxidation[9] to **16** (Py_2-(CrO_3), 50%).

Unfortunately, when **16** was exposed to bakers' yeast, it was transformed into the undesired (*S*)-carbinol **15** in only 10% chemical yield and 88:12 enantiomeric ratio. The low chemical yield is attributed to the instability of **16**, which undergoes facile isomerization to the α,β-unsaturated ketone; the latter stabilized ketone is then resistant to enzymatic reduction.[10] The instability of **16** detracted us from examining it further as a possible substrate for enantioselective reduction by growing cultures of other microorganisms. This unsuccessful approach prompted us to embark on the utilization of an alternative enzymatic method for the synthesis of chiron **3**. Thus, **14** was acetylated to **17** (Ac_2O, pyridine, DMAP, 87%) and subjected to a kinetic resolution using a microbial esterase. Although a variety of microorganisms were capable of cleaving the acetoxy group of **17** with varying degrees of stereospecificity, the most suitable one was found to be *Klebsiella pneumoniae* (4-10T).[11] By determining the enantiomeric excess (ee) of the substrate remaining fraction and the product fraction, one can calculate the extent of conversion (*c*), which then allows one to calculate the enantiomeric ratio (*E*,[12] which was 146:1 for this system. The absolute configuration of the resulting carbinol was shown to be 2*R*. This was achieved by its conversion into **3** via the following reaction sequence: the chiral carbinolic product, **14R**, was hydrogenated to yield **15R** (H_2; Lindlar catlyst, quinoline, 96%), which was then followed by protection of the hydroxyl group leading to **18** (*t*-$BuPh_2SiCl$, imidazole, THF, 96%). Cleavage of the acetal afforded the known aldehyde **3**[13] [$(CH_3)_3SiI$, 78%]. This correlation established that the microbial esterase preferentially cleaved the *R*-acetoxy group of **17**.



In accordance with the procedure developed by Rokach,[13] **3** was treated with 1.2 equiv of (formylmethylene)triphenylphosphorane in benzene to afford the *E* aldehyde **19** (90%), which upon reaction with excess ethyl (diethoxyphosphinyl)acetate (NaH, benzene) gave the diene ester **20** (76%). In turn, it was transformed into the phosphonium salt **23** as follows: reduction of **20** yielded the alcohol **21** (AlH_3, THF, 0 °C, 81%), which was converted into the highly sensitive bromide **22** (CBr_4, Ph_3P, 0 °C, 100%); the phosphonium salt **23** was generated via treatment of **22** with triphenylphosphine in acetonitrile (56%).

The chiral fragment **23** was coupled with **2** (*n*-BuLi, THF, HMPA), affording after workup and chromatographic puirification product **24** (30%) as a 5:1 *Z*–*E* mixture (as revealed by HPLC analysis). The pure *Z* isomer **24** (15%) was obtained after HPLC purification using a

(6) Although **11** may be prepared by enantioselective reduction of **4** using the microorganism *Kloeckera corticis* ATCC 20109, the yield of this transformation is only 40%. Further, the use of bakers' yeast obviates the need of fermentation equipment. See: Takaishi, Y.; Yang, Y. L.; DiTullio, D.; Sih, C. J. *Tetrahedron Lett.* **1982**, *52*, 5489.

(7) Because of the instability of LTB_4 to acid, the *tert*-butyl ester group was converted to the methyl ester at this stage.

(8) Sih, C. J.; Chen, C. S. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 570.

(9) Collins, J. C.; Hess, W. W.; Frank, F. J. *Tetrahedron Lett.* **1958**, *30*, 3363.

(10) Sih, C. J.; Rosazza, J. P. In "Applications of Biochemical Systems in Organic Chemistry" Jones, J. B., Sih, C. J., Perlman, D., Eds.; Wiley: New York, 1976; Part I, Chapter 3.

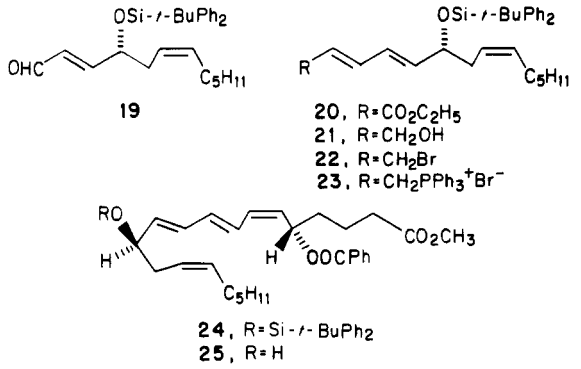
(11) This microorganism was isolated from soil by using the technique described by: Sih, C. J.; Chen, C. S.; Girdaukas, G.; Zhou, B. N. In "Basic Biology of New Developments in Biotechniology"; Hollaender, A., Laskin, A. I., Rogers, P., Eds.; Plenum Press: New York, 1983; Vol. 25, p 215.

(12) The enantiomeric ratio (*E*) is calculated from

$$E = \frac{\ln [(1 - c)(1 - ee_s)]}{\ln [(1 - c)(1 + ee_s)]}$$

where $c = ee_s/(ee_s + ee_p)$. For a comprehensive treatment of the principles involved in kinetic resolutions, see: Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294 and ref 8.

(13) Zamboni, R.; Rokach, J. *Tetrahedron Lett.* **1982**, *23*, 2631.



μPorasil column. The silyl ether protecting group was cleaved (Bu_4NF, THF, 25 °C, 48%) and the ester groupings of the resulting alcohol **25** were simultaneously hydrolyzed (K_2CO_3, 25 °C) to afford LTB_4, (1) (68%). The purity of the product was shown to be ≥98% by HPLC (reverse-phase C_{18} column) analysis.

The above strategy provides a facile alternative route to the key chiral fragments of LTB_4. These methods also can be applied to the preparation of chirons for the chiral synthesis of other members of the leukotriene family.

Experimental Section

^1H NMR spectra were recorded on a Varian EM-390 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Chemical shifts are reported in δ (peak multiplicity, coupling constant if appropriate, number of protons). When peak multiplicities are reported, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ^{13}C NMR spectra were obtained on a Jeol FX-90Q spectrometer operating at a frequency of 22.5 MHz. Infrared spectra were obtained on a Perkin-Elmer Model 599B spectrophotometer. Data are given in cm^{-1} by using the following convention: w, weak; m, medium; s, strong. Ultraviolet spectra were recorded in methanol on a Cary 14 UV–vis spectrophotometer. High-resolution mass spectroscopy was performed by the Analytical Instrument Center of Ohio State University, Columbus, OH. Carbon–hydrogen analyses were performed by Galbraith Laboratories. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in the indicated solvents.

All solvents were purified before use. Thin-layer chromatography (TLC) was performed on plates coated with 0.25-mm thickness of silica gel 60F-254 (E. Merck). Column chromatography was performed by using MN-Kieselgel 60 (0.05–0.2 mm/70–270 mesh ASTM, Brinkman Instruments, Inc.).

5-Oxo-5-(1,3-dithian-2-yl)pentanoic Acid (6). To a solution of 28.8 g (0.24 mol) of 1,3-dithiane in 600 mL of dry THF was slowly added 150 mL of *n*-BuLi (1.6 M/L, 0.239 mol) at −40 °C. The resulting clear pale yellow solution was continuously stirred at −25 °C for 3 h.

A 2-L flask was charged under N_2 with 5.26 g of NaH (60% oil dispersion, 0.13 mol, prewashed with dry THF twice) and 200 mL of dry THF. To the slurry was added 17.5 g (0.12 mol) of monomethyl glutarate slowly, and the resulting mixture was stirred at room temperature for 1 h. After the mixture was cooled to −78 °C, the 2-lithio-1,3-dithiane solution was transferred to this 2-L flask. The temperature was raised to −30 °C for 2 h and then to −20 °C for 4 h. After the mixture was stirred at room temperature for an additional 8 h, ether and water were added. The aqueous phase was acidified with HCl and extracted with ether. The ethereal extracts were washed successively with water, brine, and then dried over anhydrous Na_2SO_4. The solvent was removed in vacuo to yield 30.2 g of an orange-colored crude product. Crystallization from ethyl acetate–hexane afforded 21.86 g (78%) of **6** as colorless needles: ^1H NMR δ 1.90–2.10 (m, 4 H), 2.43 (t, 2 H), 2.59 (m, 2 H), 2.77 (t, 2 H), 3.22 (m, 2 H), 4.23 (s, 1 H), 10.80 (br, 1 H); ^{13}C NMR δ 18.98, 25.16, 26.24, 32.80, 38.75, 46.83, 179.01, 201.82.

Anal. Calcd for $C_9H_{14}O_3S_2$: C, 46.13; H, 6.02. Found: C, 46.32; H, 6.09.

***tert*-Butyl 5-Oxo-5-(1,3-dithian-2-yl)pentanoate (5).** To a stirred solution of 17.34 g (0.074 mol) of **6** in 140 mL of CH_2Cl_2 was rapidly added 70 mL of liquefied isobutylene, followed by the dropwise addition of 1.6 mL of phosphoric acid (prepared by dissolving 5 g of P_2O_5 in 11 mL of 85% H_3PO_4) in 10 mL of CH_2Cl_2 and 3.5 mL of boron trifluoride etherate. After the mixture was stirred at −78 °C for 2 h and at 0 °C for 24 h, ice–water and 200 mL of saturated aqueous solution of $NaHCO_3$ were added. The aqueous phase was then extracted with CH_2Cl_2, and the combined extracts were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was chromatographed over 1000 g of silica gel. Elution of the column with hexane–ethyl acetate (5:1) gave 15.7 g (73%) of *tert*-butyl ester **5**: TLC (5:1 hexane–ethyl acetate) R_f 0.35; ^1H NMR δ 1.43 (s, 9 H), 1.90–2.10 (m, 4 H), 2.25 (t, 2 H), 2.59 (m, 2 H), 2.73 (t, 2 H), 3.24 (m, 2 H), 4.23 (s, 1 H); ^{13}C NMR δ 19.41, 25.10, 26.18, 28.03, 34.31, 38.86, 46.88, 80.14, 201.93.

Anal. Calcd for $C_{13}H_{22}O_3S_2$: C, 53.76; H, 7.63. Found: C, 53.86; H, 7.76.

***tert*-Butyl 5(*S*)-Hydroxy-5-(1,3-dithian-2-yl)pentanoate (8).** To a suspension of 960 g of bakers' yeast (Red Star) in 1920 mL of water was added 16 g of **5**. After the mixture was incubated on a rotary shaker (250 rpm, 2-in. stroke) for 70 h at 25 °C, the contents were extracted with ethyl acetate (4 × 1000 mL). The organic layer was separated from the aqueous layer by centrifugation, washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, under vacuum, the crude product was purified by silica gel column chromatography. Elution of the column with ethyl acetate–Skelly B (1:5) afforded 10.4 g (65%) of pure **8** as an oil: TLC (3:1 hexane–ethyl acetate) R_f 0.19; $[\alpha]^{25}_D$ −21.96° (*c* 3.5, $CHCl_3$); IR ($CHCl_3$) 3450 (w), 2973 (s), 2930 (m), 2900 (m), 1715 (s), 1455 (w), 1440–1415 (w), 1390 (w), 1365 (m), 1275–1200 (m), 1150 (s), 1080 (w), 970 (w), 905 (w), 845 (w) cm^{-1}; ^1H NMR δ 1.43 (s, 9 H), 1.60–2.20 (m, 6 H), 2.30 (t, 2 H), 2.58–3.1 (m, 4 H), 3.7–4.0 (m, 2 H).

Anal. Calcd for $C_{13}H_{24}O_3S_2$: C, 53.39; H, 8.27. Found: C, 53.16; H, 8.40.

***tert*-Butyl 5(*S*)-(Benzoyloxy)-5-(1,3-dithian-2-yl)pentanoate (10).** To a stirred solution of 7.4 g (0.025 mol) of the hydroxy ester **8** in 15 mL (14.8 g, 0.19 mol) of pyridine was added 35 mL (42.4 g) of benzoyl chloride at 0 °C. After the resulting mixture was stirred for 16 h at 25 °C, the contents were diluted with 100 mL of ether. The ethereal solution was washed with aqueous hydrochloric acid (2 N) and brine and dried over anhydrous Na_2SO_4. The solution was concentrated in vacuo, and the residue was chromatographed over a silica gel column. Elution of the column with hexane–ethyl acetate (6:1) yielded 8.53 g (86%) of **10** as a colorless oil: TLC (3:1 hexane–ethyl acetate) R_f 0.41; $[\alpha]^{25}_D$ +2.21° (*c* 4.0, $CHCl_3$); IR ($CHCl_3$) 2980 (s), 2950–2900 (m), 1720–1710 (s), 1600 (w), 1585 (w), 1450 (m), 1425 (w), 1390 (w), 1365 (m), 1315 (w), 1265 (s), 1220–1200 (w), 1175 (s), 1110 (s), 1070 (m), 1020 (w), 850 (w), 700 (m) cm^{-1}; ^1H NMR δ 1.40 (s, 9 H), 1.55–2.20 (m, 6 H), 2.30 (t, J = 6.3 Hz, 2 H), 2.60–3.10 (m, 4 H), 4.20 (d, J = 6.2 Hz, 1 H), 5.27–5.50 (m, 1 H), 7.45 and 8.75 (m, 5 H).

Anal. Calcd for $C_{20}H_{28}O_4S_2$: C, 60.57; H, 7.12. Found: C, 60.30; H, 7.01.

Methyl 5(*S*)-(Benzoyloxy)-5-(1,3-dithian-2-yl)pentanoate (11). A reaction mixture containing the *tert*-butyl ester **10** (9.52 g, 23.8 mmol) and *p*-toluenesulfonic acid monohydrate (950 mg) in 95 mL of benzene was refluxed under N_2 for 1.5 h. After cooling, the solvent was removed in vacuo. The residue was dissolved in ether and treated with an ethereal solution of diazomethane. After the organic layer was washed with saturated aqueous solution of $NaHCO_3$ and brine, it was dried over Na_2SO_4. Evaporation of the solvent afforded an oily residue, which was chromatographed over a silica gel column. Elution of the column with hexane–ethyl acetate (6:1) gave 7.8 g (92%) of the methyl ester **11** as a colorless oil: TLC (3:1 hexane–ethyl acetate) R_f 0.30; $[\alpha]^{25}_D$ +3.59° (*c* 5, $CHCl_3$); IR ($CHCl_3$) 3020–2980 (m), 2900 (m), 1725–1710 (s), 1600 (w), 1582 (w), 1450 (m), 1435 (m), 1420 (w), 1380–1340 (w), 1315 (w), 1265 (s), 1220–1200 (m), 1175 (m), 1110 (s), 1070 (m), 1025 (m), 700 (s) cm^{-1}; ^1H NMR δ 1.60–2.10 (m, 6 H), 2.33 (t, J = 6 Hz, 2 H), 2.66–3.10 (m, 4 H), 3.66 (s, 3 H), 4.23 (d, J = 6.2 Hz, 1 H), 5.30–5.60 (m, 1 H), 7.50 and 8.12 (m, 5 H).

Anal. Calcd for $C_{17}H_{22}O_4S_2$: C, 57.60; H, 6.26. Found: C, 57.36; H, 6.43.

Methyl 5(*S*)-(Benzoyloxy)-5-formylpentanoate (2). To a stirred solution of 6 g (0.017 mmol) of the thioacetal **11** in 250 mL of acetone–water (4:1) containing 6 g of $CaCO_3$ ws added 15 mL (34.2 g, 0.24 mol) of methyl iodide at room temperature. After the resulting mixture was stirred for 7 h at 65 °C, removal of the acetone and excess methyl iodide gave a slurry, which was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4, and then concentrated under reduced pressure to dryness. The residue was chromatographed over a silica gel column. Elution of the column with hexane–ethyl acetate (5:1) gave 2.96 g (66%) of the aldehyde **2** as a sticky oil: TLC (3:1 hexane–ethyl acetate) R_f 0.27; $[\alpha]^{25}_D$ −41.8°; IR ($CHCl_3$) 3020 (m), 2950 (m), 2820 (w), 1740–1710 (s), 1600 (m), 1582 (w), 1490 (w), 1450 (m), 1435 (m), 1315 (w), 1265 (s), 1170 (m), 1110 (s), 1067 (m), 1022 (m), 705 (s), 608 (w) cm^{-1}; ^1H NMR δ 1.66–2.10 (m, 4 H), 2.36 (t, J = 6 Hz, 2 H), 3.66 (s, 3 H), 5.23 (m, 1 H), 7.50 and 8.12 (m, 5 H), 9.66 (s, 1 H).

Exact mass calcd for (M^+ − CHO) $C_{13}H_{15}O_4$: 235.0970. Found: 235.0986.

2,3-Epoxypropionaldehyde Diethyl Acetal (13). To a mechanically stirred solution of 108 g (0.83 mol) of acrolein diethyl acetal (**12**) in 1800 mL of CH_2Cl_2 was added at 25 °C in small portions 186 g (0.87 mol, 80–85% pure) of *m*-chloroperbenzoic acid. After the reaction mixture was stirred at room temperature for 3 days, the resulting precipitate was removed by filtration, and the filtrate was concentrated in vacuo to 500 mL. After the newly formed solid was again removed by filtration, the solution was diluted with ether, washed with 1 N NaOH, water, and brine, and then dried over $MgSO_4$. Removal of the solvent yielded a pale yellow oil. Distillation of the residue at aspirator pressure (explosion was observed when MCPBA is not completely removed) gave 63 g (52%) of the epoxide **2** as a colorless oil: bp 82 °C (15 mm); IR ($CHCl_3$) 3002 (M), 2980 (m), 2930–2880 (m), 1482 (w), 1445 (w), 1390 (w), 1372 (w), 1345 (w), 1325 (w), 1298 (w), 1250–1200 (w), 1160 (w), 1115 (m), 1055 (s), 1020 (sh), 930 (m), 858 (m) cm^{-1}; ^1H NMR δ 1.22 (t, J = 7.5 Hz, 3 H), 1.24 (t, J = 7.5 Hz, 3 H), 2.75 (d, J = 3.3 Hz, 2 H), 3.1 (dt, J = 4.5 Hz, J = 3.3 Hz, 1 H), 3.67 (m, 4 H), 4.33 (d, J = 4.5 Hz, 1 H); ^{13}C NMR δ 15.03, 43.47, 51.56, 62.10, 62.64, 101.43.

Anal. Calcd for $C_7H_{14}O_3$: C, 57.51; H, 9.65. Found: C, 57.61; H, 9.79.

2-Hydroxydec-4-yn-1-al Diethyl Acetal (14). To a stirred solution of 28.8 g (0.30 mol) of 1-heptyne in 400 mL of dimethyl ether at −78 °C was added 180 mL (0.29 mol) of *n*-butyllithium in hexane (1.6 M) via a syringe. After the mixture was stirred for 2.5 h at −78 °C, to that clean solution was added 29.6 g (0.20 mol) of the epoxide **13** in 100 mL of dimethyl ether. The mixture was stirred for 16 h while the temperature was raised from −78 to 25 °C. After the reaction mixture was refluxed for 20 h, 300 mL of ether was added, and the reaction was quenched by the addition of 500 mL of ice–water. The aqueous phase was acidified with 5 N H_2SO_4 and extracted with ether (200 mL). The combined organic layer was washed successively with water and brine. After drying over Na_2SO_4, the solution was concentrated in vacuo to give 49 g of crude product as a yellow oil. Distillation under reduced pressure yielded 46 g (95%) of the alcohol **14** as a colorless oil: TLC (5:1 hexane–ethyl acetate) R_f 0.44; IR ($CHCl_3$) 3560 (m), 3000 (m), 2972 (w), 2958 (w), 2930 (s), 2870 (w), 2860 (w), 1470–1420 (w), 1374 (w), 1335 (w), 1282 (w), 1240 (w), 1130 (s), 1060 (s) cm^{-1}; ^1H NMR δ 0.87 (t, 3 H), 1.20 (m, 12 H), 2.15 (m, 2 H), 2.40 (m, 2 H), 3.63 (m, 5 H), 4.43 (d, 1 H).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 39.38; H, 10.81. Found: C, 69.59; H, 10.78.

2-Acetoxydec-4-yn-1-al Diethyl Acetal (17). To the stirred mixture of 88 mL (95 g, 0.93 mol) of acetic anhydride and 71 mL (69.4 g, 0.88 mol) of pyridine were added 94 g (0.40 mol) of the alcohol **14** and a catalytic amount of DMAP. After the solution was stirred overnight at 25 °C, 500 mL of ether were added, followed by 500 mL of water, and the contents were extracted with ether (5 × 250 mL). The combined ethereal extracts were washed successively with water, 5 N H_2SO_4, $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was distilled at reduced pressure to give 98 g (87%) of the acetate **17** as a colorless oil: TLC (5:1 hexane–ethyl acetate) R_f 0.63; IR 3000 (s), 2972 (w), 2955 (w), 2930 (m), 2870 (w), 2860 (w), 1735 (s), 1470–1430 (w), 1375 (m), 1245 (s), 1210 (sh), 1120 (m), 1065 (s); ^1H NMR δ 0.91 (t, 3 H), 1.24 (m, 12 H), 2.03 (s, 3 H), 2.04 (m, 2 H), 2.56 (m, 2 H), 3.62 (m, 4 H), 4.59 (d, 1 H), 4.97 (m, 1 H).

Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.93. Found: C, 67.98; H, 10.12.

2(*R*)-Hydroxydec-4-yn-1-al Diethyl Acetal (14R). Bacteria 4-10T (*Klebsiella pneumoniae*) was grown on nutrient agar slants and stored at 3°. A loop of this organism from a refrigerated slant was transferred to a 125-mL Erlenmeyer flask containing 25 mL of Difco nutrient broth (NB). The flask was incubated at 25 °C on a rotary shaker (180 cycles/min, 2-in. radius) for 24 h, after which a 5% volume transfer was made to each of 20 2-L Erlenmeyer flasks containing 500 mL of NB. After 24 h of incubation on a rotary shaker, to each flask was added 10 mL of emulsion of ester **17** (1 mg/mL). The emulsion was made from 10 g of **17** and 200 mL of aqueous 3% Tween 80 (50 mg/mL). After incubation for an additional 5 days under the conditions used in the previous incubation, the flask contents were continuously extracted with chloroform for 4 days. After evaporation of the chloroform in vacuo, 14 g of crude residue was obtained. This residue was chromatographed over a column containing 500 g of silica gel. Elution of the column with hexane–ethyl acetate (7:1) afforded 2.4 g (25%) of the chiral alcohol **14R** as a colorless oil: TLC (5:1 hexane–ethyl acetate) R_f 0.44; $[\alpha]^{25}_D$ +16° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3560 (m), 3000 (m), 2972 (w), 2958 (w), 2930 (s), 2870 (w), 2860 (w), 2860 (w), 1470–1420 (w), 1374 (w), 1335 (w), 1282 (w), 1240 (w), 1130 (s), 1060 (s) cm^{-1}; ^1H NMR δ 0.87 (t, 3 H), 1.20 (m, 12 H), 2.15 (m, 2 H), 2.40 (m, 2 H), 3.63 (m, 5 H), 4.43 (d, 1 H).

Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.38; H, 10.81. Found: C, 69.22; H, 10.89.

Comparison of the ^1H NMR spectra of MTPA esters of **14R** and racemic **14** showed the purity ≥98%.

2(*R*)-Hydroxydec-4(*Z*)-enal Diethyl Acetal (15R). A mixture containing 8.51 g (0.035 mol) of **14R** and 3.8 g Lindlar catalyst in 300 mL of absolute ethanol containing 0.8 mL of 5% quinoline in absolute ethanol was hydrogenated under 1 atm of H_2 for about 40 min. The progress of hydrogenation was monitored by both the volume of hydrogen absorbed and TLC (5:1 hexane–ethyl acetate). The reaction mixture was filtered, and the filtrate was evaporated in vacuo to yield an oily residue, which was chromatographed over 1000 g of silica gel. Elution of the column with hexane–ethyl acetate (10:1) afforded 8.23 g (96%) of **15R**: TLC (5:1 hexane–ethyl acetate) R_f 0.41; $[\alpha]^{25}_D$ +6.7° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3560 (w), 3000 (m), 2970 (m), 2950 (m), 2920 (s), 1465–1445 (w), 1375 (w), 1280–1200 (w), 1120 (m), 1059 (s); ^1H NMR δ 0.88 (t, 3 H), 1.28 (m, 12 H), 2.20 (m, 5 H), 3.68 (m, 5 H), 4.31 (d, 1 H), 5.50 (m, 2 H).

Anal. Calcd for $C_{14}H_{28}O_3$: C, 68.81; H, 11.55. Found: C, 69.06; H, 11.55.

2-Oxodec-4(*Z*)-enal Diethyl Acetal (16). Dipyridine–chromium(VI) oxide complex was prepared by addition of 240 mg (2.40 mmol) of chromium trioxide to 380 mg (4.81 mmol) of anhydrous pyridine with stirring at room temperature. The complex was washed with petroleum ether and dried under vacuum. To a solution of 620 mg (2.4 mmol) of dipyridine–chromium(VI) oxide in 12 mL of dichloromethane was added 100 mg (0.41 mmol) of the alcohol **15**. After the reaction mixture was stirred at room temperaturte for 30 min, 1 mL of isopropyl alcohol and 10 mL of ether were added. The polymeric chromium reduction product was removed by filtration through a short silica gel column. Evaporation of solvent afforded an oil of the ketone **16** (48 mg), which was immediately used for the bakers' yeast reduction.

2(*S*)-Hydroxydec-4(*Z*)-enal Diethyl Acetal (15S). To a suspension of 12 g of bakers' yeast (Red Star) in 24 mL of tap water was added 200 mg of **16**. After the mixture was incubated on a rotary shaker (250 rpm, 2-in. stroke) for 65 h at 25 °C, the contents were extracted with ethyl acetate (4 × 75 mL). The organic layer was separated from the aqueous layer by centrifugation, washed with brine, and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude residue was purified by silica gel column chromatography. Elution of the column with ethyl acetate–Skelly B (1:5) afforded 21 mg (10%) of **15S**, $[\alpha]^{23}_D$ −3.8° (*c*, 0.8, $CHCl_3$); HPLC analysis of its (+)-MTPA derivative revealed that its optical purity as enan-

tiomeric excess (ee) was 0.76 (10 μPorasil; 200:3 hexane–ether; 1.5 mL/min; 16 and 18 min).

2(*R*)-(*tert*-Butyldiphenylsiloxy)dec-4(*Z*)-enal Diethyl Acetal (18). To a solution of 6.1 g (0.025 mol) of alcohol **15R** and 3.33 g (0.05 mol) of imidazole in 84 mL of dry THF was added 9.54 g (0.035 mol) of *tert*-butyldiphenylsilyl chloride via syringe. After the reaction mixture was stirred at 25 °C for 8 h, the contents were diluted with 100 mL of ether, and the organic layer was washed with water and brine. After the organic layer was dried over Na_2SO_4, the solvents were concentrated in vacuo to give an oil, which was chromatographed over 600 g of silica gel. Elution of the column with hexane–ethyl acetate (10:1) afforded 11.6 g (96%) of the silyl ether **18**: TLC (5:1 hexane–ethyl acetate) R_f 0.55; $[\alpha]^{25}_D$ −16° (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 3060–3040 (w), 3000 (w), 2952 (m), 2924 (m), 2852 (m), 1470–1450 (w), 1425 (m), 1388–1360 (w), 1120 (s), 1060 (m), 1020–995 (w), 940 (w), 820 (m), 700 (s), 608 (m), 510–470 (w) cm^{-1}; ^1H NMR δ 1.10 (m, 24 H), 1.95 (m, 2 H), 2.30 (m, 2 H), 3.5 (b, 5 H), 4.24 (d, 1 H), 5.47 (m, 2 H), 7.35 and 7.73 (m, 10 H).

Anal. Calcd for $C_{30}H_{46}O_3Si$: C, 74.64; H, 9.60. Found: C, 74.73; H, 9.82.

2(*R*)-(*tert*-Butyldiphenylsiloxy)dec-4(*Z*)-enal (3). To a solution of propene in 125 mL of $CHCl_3$ (prepared by bubbling propene through $CHCl_3$) was added 2.6 mL (3.64 g, 0.019 mol) of trimethylsilyl iodide. The mixture was stirred for 10 min at 25 °C. To this HI-free solution was added 7.9 g (16.4 mmol) of diethyl acetal **18**. After the mixture was stirred for an additional 30 min, excess trimethylsilyl iodide was quenched with aqueous $NaHCO_3$ (5%), and the iodine color was removed by adding aqueous $Na_2S_2O_3$ (10%). The organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was chromatographed over a silica gel column. Elution of the column with hexane–ethyl acetate (10:1) afforded 5.2 g (78%) of the aldehyde **3** as an oil: TLC (5:1 hexane–ethyl acetate) R_f 0.53; $[\alpha]^{25}_D$ −16.5° (*c* 3.0, $CHCl_3$); IR ($CHCl_3$) 3070 (w), 3000 (w), 2950 (m), 2924 (s), 2856 (m), 1730 (s), 1470 (w), 1426 (m), 1390–1360 (w), 1060 (s), 820 (m), 700 (s), 680 (m) cm^{-1}; ^1H NMR δ 0.87 (t, 3 H), 1.10 (s, 9 H), 1.0–1.5 (m, 6 H), 1.6–2.1 (m, 2 H), 2.2–2.5 (m, 2 H), 4.08 (dt, *J* = 6.0 and 1.2 Hz, 1 H), 5.2–5.6 (m, 2 H), 7.3–7.5 (m, 6 H), 7.6–7.85 (m, 4 H), 9.6 (d, *J* = 1.2 Hz, 1 H).

Anal. Calcd for $C_{26}H_{36}O_2Si$: C, 76.42; H, 8.88. Found: C, 76.13; H, 8.95.

4(*R*)-(*tert*-Butyldiphenylsiloxy)dodeca-2(*E*),6(*Z*)-dienal (19). A 500-mL round-bottomed flask was charged under N_2 with 4.57 g (0.015 mol) of (formylmethylene)triphenylphosphorane, 5.33 g (0.013 mol) of **3**, and 120 mL of dry benzene. After the mixture was refluxed for 16 h, the benzene was removed in vacuo. The product was extracted with hexane–ethyl acetate (10:1) and the solid was removed by filtration. After the organic extracts were concentrated in vacuo, the resulting dark oil was chromatographed over 700 g of silica gel. Elution of the column with hexane–ethyl acetate (20:1) afforded 5.1 g (90%) of **19**: TLC (5:1 hexane–ethyl acetate) R_f 0.46; $[\alpha]^{25}_D$ −14.4° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3070–3000 (w), 2950 (m), 2924 (m), 2856 (m), 1735 (s), 1470 (w), 1460 (w), 1426 (m), 1390 (w), 1360 (w), 1110–1000 (s), 975 (m), 820 (m), 700 (s), 605 (w); ^1H NMR δ 0.86 (t, 3 H), 1.09 (s, 9 H), 1.10–1.15 (m, 6 H), 1.6–2.1 (m, 2 H), 2.2–2.5 (m, 2 H), 4.4 (m, 1 H), 5.1–5.4 (m, 2 H), 6.1–6.3 (m, 2 H), 7.3–7.5 (m, 6 H), 7.5–7.7 (m, 4 H), 9.45 (d, 1 H, CHO).

Exact mass calcd for (M^+ − $C(CH_3)_3$) $C_{24}H_{29}O_2Si$: 377.1937. Found: 377.1925.

Ethyl 6(*R*)-(*tert*-Butyldiphenylsiloxy)-2(*E*),4(*E*),8(*Z*)-tetradecatrienoate (20). A 100-mL flask was charged with 1.44 g (0.03 mol) of a 50% dispersion of sodium hydride in mineral oil and 12 mL of dry benzene. To this stirred mixture was added dropwise over a period of 1 h 6.72 g (0.03 mol) of ethyl (diethoxyphosphinyl)acetate at 0 °C; a vigorous evolution of H_2 was observed. After the addition was completed, the mixture was stirred for 1 h at 25 °C. To this clear solution was added dropwise over a 40 min period 4.3 g (0.01 mol) of aldehyde **19** at 0 °C. The progress of the reaction was monitored by TLC and the color of the spots after $CeSO_4$–H_2SO_4 spray. After completion of the reaction, water (12 mL) was then added, and the aqueous mixture was extracted with ether (3 × 25 mL). The combined organic layers were washed with water and brine. After the organic layer was dried over Na_2SO_4, the solvents were evaporated in vacuo to furnish an oil (8 g), which was chromatographed over 500 g of silica gel. Elution of the column with hexane–ethyl acetate (20:1) gave 3.6 g (76%) of the ester **20** as an oil: TLC (5:1 hexane–ethyl acetate) R_f 0.53; $[\alpha]^{25}_D$ +40.6° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3010 (w), 2960 (m), 2938 (m), 2862 (m), 1705 (s), 1605 (m), 1620 (m), 1470 (w), 1430 (m), 1370 (w), 1310 (m), 1270 (m), 1235–1220 (m), 1140 (m), 1110 (s), 1000 (s), 825 (m), 705 (s), 612 (w) cm^{-1}; ^1H NMR δ 0.87 (t, 3 H), 1.07 (s, 9 H), 1.24 (t, *J* = 6.6 Hz, 3 H), 1.10–1.33 (m, 6 H), 1.85 (m, 2 H), 2.22 (m, 2 H), 4.17 (q, *J* = 6.6 Hz, 2 H), 4.20 (m, 1 H), 5.27 (m, 2 H), 5.60–6.10 (m, 4 H), 7.37 and 7.65 (m, 10 H).

Exact mass calcd for (M^+ − $C(CH_3)_3$) $C_{28}H_{35}O_3Si$: 447.2356. Found: 447.2363.

6(*R*)-(*tert*-Butyldiphenylsiloxy)-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-ol (21). Lithium aluminum hydride (100 mL, 1.0 M) and 66.7 mL of dry THF were introduced into a 500-mL three-necked flask. To this solution was slowly added 5.15 g (0.05 mol) of 98% H_2SO_4 by means of a syringe under vigorous stirring conditions at 0 °C, while evolving H_2. After the mixture was stirred for an additional hour, it was allowed to stand at room temperature overnight to permit the lithium sulfate precipitate to settle. The clear supernatant of aluminum hydride solution (~0.50 M) was removed by a syringe and stored under N_2.

To a solution of 3.45 g (6.8 mmol) of ethyl ester **20** in 36 mL of dry THF was added 36 mL (0.5 m) of solution of aluminum hydride by means of a syringe during a period of 1 h at 0 °C, under vigorous stirring. After the clear solution was stirred at 0 °C for an additional 1.5 h, 250 mL of ether and 250 mL of ice–water were added to quench the reaction. The aqueous phase was extracted with ether (2 × 100 mL), and the combined extracts were washed with water and brine. After drying over $MgSO_4$, the solvent was removed in vacuo to give 2.93 g of alcohol **21** as a pale yellow oil, which was subjected to column chromatography on silica gel. Elution of the column with hexane–ethyl acetate (3:1) gave 2.55 g (81%) of the alcohol **21** as a colorless oil: TLC (5:1 hexane–ethyl acetate) R_f 0.23; $[\alpha]^{25}_D$ +22.5° (*c* 2.0, $CHCl_3$); IR ($CHCl_3$) 3600 (w), 3002 (w), 2955 (m), 2924 (m), 2855 (m), 1470–1453 (w), 1425 (m), 1360 (w), 1103 (m), 1075 (m), 987 (m), 819 (w), 695 (m), 605 (w) cm^{-1}; ^1H NMR δ 0.89 (t, 3 H), 1.10 (s, 9 H), 1.20–1.60 (m, 6 H), 1.85 (m, 2 H), 2.22 (m, 2 H), 4.15 (m, 3 H), 5.30 (m, 2 H), 5.60–6.10 (m, 4 H), 7.37 and 7.65 (m, 10 H).

Exact mass calcd for (M^+ − $C(CH_3)_3$ $C_{26}H_{33}O_2Si$: 405.2250. Found: 405.2250.

6(*R*)-(*tert*-Butyldiphenylsiloxy)-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-yl Bromide (22). To a solution of 662 mg (2.0 mmol) of carbon tetrabromide and 918 mg (2.0 mmol) of the alcohol **21** in 8 mL of CH_2Cl_2 was added 524 mg (2.0 mmol) of triphenylphosphine in small portions at 0 °C for 1 h. The resulting yellow solution was concentrated in vacuo, and the residue was chromatographed over 10 g of silica gel, which was deoxygenated and saturated with argon. Elution of the column with hexane–ethyl acetate (10:1) gave 1.04 g (100%) of the labile bromide **22** as a yellow oil: TLC (5:1 hexane–ethyl acetate) R_f 0.68; $[\alpha]^{25}_D$ +21.4° (*c* 2.2, $CHCl_3$); IR ($CHCl_3$) 3002 (w), 2955 (m), 2924 (s), 2855 (m), 1470–1460 (w), 1425 (m), 1360 (w), 1194 (w), 1100 (s), 1108 (s), 1055 (m), 987 (m), 819 (w), 695 (s), 655 (w), 610 (w) cm^{-1}; ^1H NMR δ 0.87 (t, 3 H), 1.04 (s, 9 H), 1.14–1.40 (m, 6 H), 1.60–2.00 (m, 2 H), 2.08–2.30 (m, 2 H), 3.90–4.30 (m, 3 H), 5.30 (m, 2 H), 5.60–6.30 (m, 4 H), 7.37 and 7.65 (m, 10 H).

[6(*R*)-(*tert*-Butyldiphenylsiloxy)-2(*E*),4(*E*),8(*Z*)-tetradecatrien-1-yl]triphenylphosphonium Bromide (23). To a stirred solution of 290 mg (1.11 mmol) of triphenylphosphine in 3 mL of dry CH_3CN was added 292 mg (0.56 mmol) of bromide **22** via a syringe at 0 °C. After the resulting yellow solution was stirred at 0 °C for 6 h, the solvent was removed in vacuo. The residue was first dissolved in a small amount of dry ether. After 10 mL of dry ether was added, the phosphonium salt was separated from the ethereal layer as a yellow oil, which was washed with ether (2 × 1 mL). Evaporation of the solvent in high vacuo afforded 248 mg (56%) of salt **23** as a pale yellow solid, which was directly used for the subsequent Wittig reaction with the aldehyde **2**.

Methyl 5(*S*)-(Benzoyloxy)-12(*R*)-(*tert*-butyldiphenylsiloxy)-6(*Z*),8(*E*),10(*E*),14(*Z*)-eicosatetraenoate (24). To a solution of 248 mg (0.315 mmol) of the phosphonium salt **23** in 1.5 mL of dry THF was added a 2.5 M solution of *n*-butyllithium

in hexane (126 μL, 0.315 mmol) dropwise at -78 °C. After the resulting dark red solution was stirred at -78 °C for 15 min, 200 μL of HMPA and 150 μL of the aldehyde **2** were added successively. The reaction mixture was stirred at -78 °C for 40 min, then warmed to -20 °C, and stirred at that temperature for 30 min. After the temperature was slowly raised to 25 °C, the reaction mixture was poured into ice-water. The aqueous phase was extracted by 3 × 2 mL of ether. The combined extracts were washed with brine, filtered through 1 g of deoxygenated silica gel, and dried over $MgSO_4$. After concentrating in vacuo, the yellow oily residue was chromatographed over 4 g of silica gel. Elution with hexane-ethyl acetate (10:1) resulted in a crude product (**24**) (30%) containing 5:1 Z-E mixture and some impurities.

Further purification of the *Z* isomer was effected by either repeated flash column chromatography (silica gel; 20:1 hexane-ethyl acetate; *E* isomer, R_f 0.09; *Z* isomer, R_f = 0.06; on TLC plate) or HPLC (Alltech, 10 μPorsail, length 50 cm, i.d. 9.4 mm column; 988:2:10 hexane-ethyl acetate-Et_3N; flow rate 3 mL/min; retention time of *E* isomer = 17.7 min; *Z* isomer = 19.8 min) gave 32 mg (15%) of pure **24**: TLC (5:1 hexane-ethyl acetate) R_f 0.56; $[\alpha]^{25}_D$ +205° (*c* 2.1, $CDCl_3$); UV $(MeOH)_{max}$ 262, 272, 284 nm; IR ($CDCl_3$) 3000 (w), 2960 (m), 2930 (m), 2850 (m), 1740-1710 (s), 1450-1425 (w), 1310 (w), 1270 (s), 1105 (s), 1065 (w), 1020 (w), 990 (m), 700 (s) cm^{-1}; ^1H NMR δ 0.88 (t, 3 H), 1.10 (s, 9 H), 1.10-1.40 (m, 8 H), 1.76 (m, 4 H), 2.29 (m, 4 H), 3.60 (s, CH), 4.18 (m, 2 H), 5.28 (m, 2 H), 5.63-6.38 (m, 6 H), 7.30, (7.60, and 7.92 (m, 15 H).

Methyl 5(*S*)-(Benzoyloxy)-12(*R*)-hydroxy-6(*Z*),8,10-(*E*),14(*Z*)-eicosatetraenoate (25). To a stirred solution of 32 mg (0.046 mmol) of the silyl ether **24** in 0.6 mL of THF was added 400 μL of tetra-*n*-butylammonium fluoride at 25 °C. After the mixture was stirred for 5 h, 1.5 mL of water was added. The aqueous phase was extracted with ether (3 × 1 mL). The combined extracts were washed with water and concentrated in vacuo to yield 31 mg of crude product, which was chromatographed over 1.4 g of silica gel. Elution of the column with hexane-ethyl acetate (5:1) afforded 10 mg (48%) of the alcohol **25**: TLC (5:1 hexane-ethyl acetate) R_f 0.29; $[\alpha]^{25}_D$ +288.7° (*c* 0.75, $CDCl_3$); UV $(CH_3OH)_{max}$ 262, 271, 282; ^1H NMR δ 0.88 (t, 3 H), 1.30 (m, 8 H), 1.70 (m, 4 H), 2.00 (m, 2 H), 2.35 (m, 4 H), 3.68 (s, 3 H), 4.18 (m, 1 H), 5.28 (m, 2 H), 5.63-6.38 (m, 6 H), 7.92 and 7.60 (m, 5 H).

LTB_4 (1). A 1-mL reaction vial was charged with a solution of 10 mg (0.022 mmol) of the ester **25** in 200 μL of CH_3OH, 50 μL of water, and 24 mg (0.24 mmol) of K_2CO_3 at room temperature under argon. The reaction progress was monitored by TLC. After the starting material **25** was completely hydrolyzed (12 h), 200 μL of water was added. The pH was adjusted to pH 4 with 10% acetic acid and the aqueous phase was then extracted with ethyl acetate (5 × 300 mL). After concentration of the extracts, the residue was purified by column chromatography over 1 g of deoxygenated silica gel. The column was eluted with hexane-ethyl acetate (1:1) with 1% acetic acid, to yield 5 mg (68%) of LTB_4 (1). RP-HPLC (reversed-phase HPLC, using a C_{18} partisil 10/50 ODS Whatman column; 3:1 methanol-water, containing 0.01% acetic acid) showed ≥98% purity for the final product, 1: TLC (ethyl acetate), R_f 0.31; $[\alpha]^{25}_D$ +12.6° (*c* 0.46, $CDCl_3$); UV (CH_3OH) λ_{max} 260 270.5, 281 nm, (ε 43 000, 52 000, 42 000); ^1H NMR δ 0.91 (t, 3 H), 1.30 (m, 8 H), 1.69 (m, 4 H), 2.03 (m, 2 H), 2.35 (m, 4 H), 4.25 (m, 1 H), 4.66 (m, 1 H), 5.25-5.55 (m, 4 H), 5.68-5.98 (m, 1 H), 6.10-6.40 (m, 4 H).

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Synthesis of 9-[5-(Alkylthio)-5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenines as Potential Inhibitors of Transmethylation†

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Various methods have been examined for the conversion of suitably protected nucleoside 5'-aldehydes into the previously undescribed dithioacetals. Treatment with (alkylthio)trimethylsilanes in the presence of trimethylsilyl triflate and/or zinc iodide is effective in various series, and sequential formation of mixed dithioacetals can be achieved. Treatment of thioacetals of fully benzoylated adenosine derivatives with bromine and DBU leads to efficient elimination to provide, e.g., 9-[5-deoxy-5-(isobutylthio)-β-D-*erythro*-(*Z*)-pent-4-enofuranosyl]adenine (**20a**), a compound containing structural features of both the sinefungin analogue A9145C and SIBA. A comparable elimination in the uridine series can be accomplished with mercuric trifluoroacetate and lithium carbonate.

The importance of *S*-adenosylmethionine (AdoMet) mediated transmethylation in diverse biochemical processes has made this system an attractive target for medicinal intervention.[2] The byproduct of such transmethylation, *S*-adenosylhomocysteine (AdoHcy), is itself a potent inhibitor of the methyl transferases and plays a key regulatory role. The levels of AdoHcy are regulated by the enzyme AdoHcy hydrolase (EC 3.3.1.1), and the latter species has become a central target in the development of specific methylation inhibitors.[3]

Amongst the many compounds that have proved to suppress transmethylation via inhibition of AdoHcy hydrolase are the natural products sinefungin (1),[4] a recent synthetic target within this Institute,[5] and the related unsaturated nucleoside A9145C (**2**).[4] Also, a wide range of biological effects have been recorded by using 5'-deoxy-5'-(isobutylthio)adenosine (SIBA, **3**)[3a] a compound

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(2) See, e.g.: (a) "Transmethylations"; Usdin, E., Borchardt, R. T., Creveling, C. R., Eds.; Elsevier: New York, 1969. (b) "The Biochemistry of *S*-Adenosylmethionine and Related Compounds"; Usdin, E., Borchardt, R. T., Creveling, C. R., Eds.; Macmillan Press: London, 1982.

(3) See, e.g.: (a) Ueland, P. M. *Pharmacol. Rev.* **1982**, *34*, 223. (b) Houston, D. M.; Dolence, E. K.; Keller, B. T.; Patel-Thombre, U.; Borchardt, R. T. *J. Med. Chem.* **1985**, *28*, 467 and references therein.

(4) See: Suhadolnik, R. J. "Nucleosides as Biological Probes"; Wiley: New York, 1979; p 19.

(5) Mock, G. A.; Moffatt, J. G. *Nucleic Acids Res.* **1982**, *10*, 6223.

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