Asymmetrization of Tetrahydrofuran-2,2-dimethanol: Synthesis of the Enantiomers of SRI 62-834†

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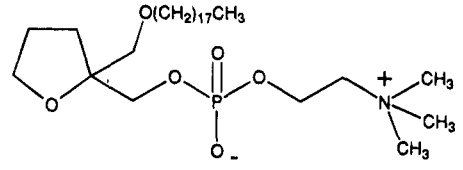
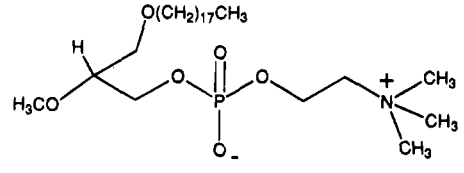
SRI 62-834 (**1**), a racemic cyclic ether analog of the antitumor agent ET-18-OCH_3, in which the oxygen atom at carbon atom 2 has been incorporated into a five-membered heterocycle, was synthesized by Houlihan and Lee[1] starting from 2-furoic acid. During our studies on



SRI 62-834 (1)

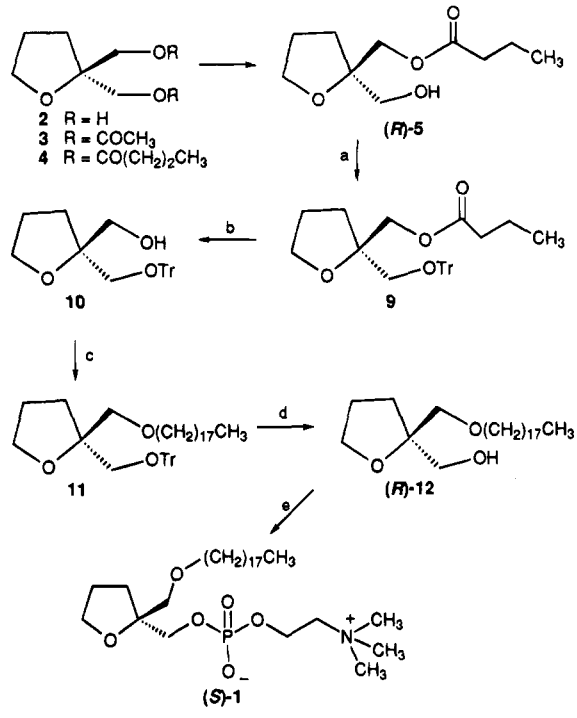


ET-18-OCH_3

the use of prochiral or meso substrates for preparing chiral intermediates,[2,3] we became interested in the asymmetrization of prochiral tetrahydrofuran-2,2-dimethanol (**2**) with the objective of making the enantiomers of **1**. The results of the investigation are presented in this note.

Tetrahydrofurandimethanol **2**, readily available following the literature method,[1] was converted into di-O-acyl derivative **3** or **4** (Scheme 1) using the corresponding acid chloride in >90% yield. The enzymatic hydrolysis of these acyl derivatives was carried out by vigorously stirring the substrate and an appropriate enzyme in pH 7 buffer at an effective concentration of 0.05–0.1 M, while maintaining the pH by the addition of 2 M NaOH with an automatic pH titrator. After the standard workup, the optical purity (ee) of the resultant monoester was measured by ^{31}P NMR using a chiral diazaphospholidine.[4] The results of enzymatic hydrolysis of dibutyrate **4** are summarized in Table 1.

Scheme 1[a]



[a] (a) TrCl, pyridine, CH_2Cl_2, rt; (b) K_2CO_3, MeOH, rt; (c) $C_{18}H_{37}Br$, *n*-Bu_4NI, NaH, THF, reflux; (d) TFA/H_2O, CH_2Cl_2, rt; (e) $POCl_3$, Et_3N, THF, rt; pyridine, rt, $HO(CH_2)_2N^+(CH_3)_3 \cdot TsO^-$.

Initial attempts to asymmetrize diacetate **3** using assorted enzymes were not successful; the optical purity of the product was low. Enzymatic asymmetrization studies with dibutyrate **4**, however, were more successful (see Table 1). Hydrolysis of **4** with lipase from porcine pancreas was found to be the method of choice, and the monobutyrate **5** was isolated with 98% optical purity. These conditions (PPL, 10 mmol scale), however, on a 5-fold larger scale afforded the product with only 86% ee. One of the reasons for such a decrease in optical purity was assumed to be due to racemization of the monoacylated product via intramolecular transacylation[5] (Scheme 2). In order to overcome this problem by sequestering the product as it is formed into an organic phase, the enzymatic hydrolysis was carried out in the presence of an equal volume of hexane. Interestingly, the optical purity of the product was improved to 94%. These conditions were found to be highly reproducible on the plant scale. An additional advantage of using hexane as a cosolvent is the increased rate of hydrolysis which is attributable to efficient emulsion formation, as pancreatic lipases are known to act at the interface between hydrophobic and aqueous phases.[6]

Having achieved an efficient asymmetrization of **2**, we turned our attention to establishing the absolute stereochemistry of the product **5**. As there was no possibility of a chemical correlation, we pursued the preparation of a crystalline derivative of **5** with which we hoped to obtain an X-ray analysis for establishing the absolute stereochemistry. Most ester derivatives were found to be either oils or amorphous solids. However, the (+)-camphorsulfonic acid derivative **8** made in three steps

† The authors have deposited atomic coordinates for compound **8** with the Cambridge Crystallographic Data Centre, and the details can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.

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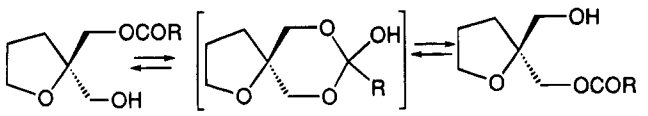
Table 1. Enzymatic Hydrolysis of 4[a]

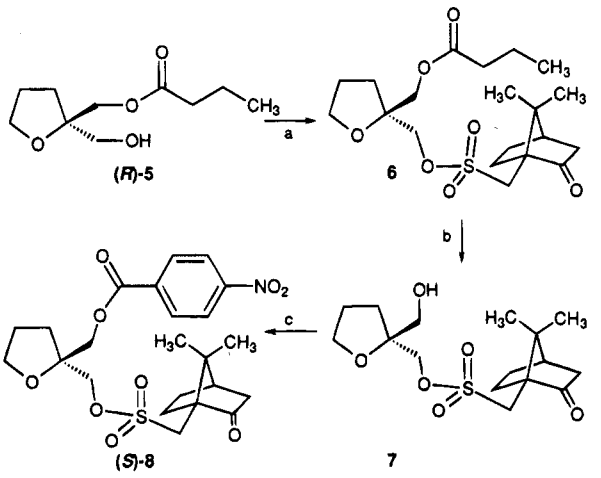
enzyme (amount)	reaction time (h)	consumption of NaOH (equiv)	yield (%)	ee (%)	remarks
CCL (100 mg)	2	1.30	54	48	10 mmol
PLE (50 mg)	1.75	1.50	35	36	10 mmol
α-chym (100 mg)	29	0.27	10		10 mmol
LMJ (19 mg)	5.5	0.69	64		10 mmol
PPL (100 mg)	1	1.00	89	>98	10 mmol
PPL (0.5 g)	1	1.00	91	86	50 mmol
PPL (2.2 g)	0.75	0.98	90	94	100 mmol + equal volume of hexane

[a] The enzymes that were used are abbreviated as follows: CCL = lipase type VII from *Candida cylindracea* (Sigma), PLE = esterase type 1 from porcine liver (Sigma), α-chym = α-chymotrypsin (Sigma), LMJ = lipase from *Mucor javanicus* (Fluka), and PPL = porcine pancreas lipase (Sigma).

Scheme 2



Scheme 3[a]

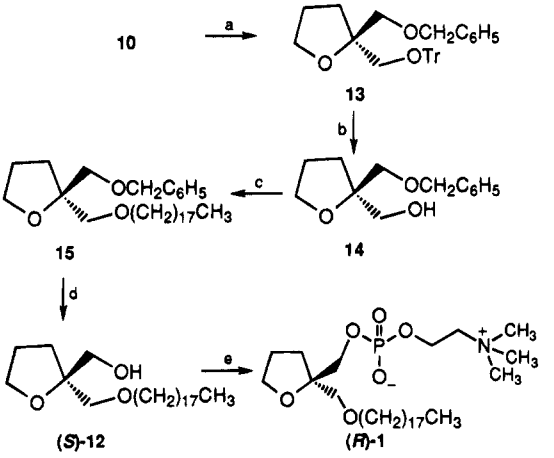


[a] (a) (+)-Camphorsulfonyl chloride/pyridine, CH_2Cl_2; (b) K_2CO_3, CH_3OH, rt; (c) *p*-nitrobenzoyl chloride/pyridine, CH_2Cl_2, rt.

(Scheme 3) from **5** gave a single crystal suitable for X-ray analysis.[7] On the basis of this study, **8** was assigned the *S* configuration at the newly formed stereogenic center. Accordingly, the stereogenic center in **5** was assigned the *R* configuration (note the change in priority of the groups attached to the stereogenic carbon).

With enantioenriched synthon **5** in hand, the remaining task, i.e., the synthesis of the enantiomers of **1**, was achieved in a straightforward manner (Scheme 1). Compound **5** on tritylation with trityl chloride/pyridine followed by transesterification with methanol in the presence of K_2CO_3 gave alcohol **10**. O-Alkylation of **10** with 1-bromooctadecane and detritylation with aqueous trifluoroacetic acid gave **12**. At this stage the enantiomeric purity was enriched to >99% by recrystallization from hexane. Conversion of **12** to phospholipid (*S*)-**1** was achieved by conventional methodology using phosphorus oxychloride followed by treatment with choline tosylate. For the synthesis of enantiomer (*R*)-**1**, a transposition of the enantiotopic hydroxymethyl groups was needed, and this was accomplished (Scheme 4) by benzylating the free hydroxy group of **10** and removing the trityl group to give **14**. Alkylation with 1-bromooctadecane and debenzylation with 10% Pd/C under hydrogen afforded alcohol (*S*)-**12** which was converted into (*R*)-**1** as described in the case of (*S*)-**1**.

Scheme 4[a]



[a] (a) BnBr, NaH, THF, *n*-Bu_4NI, reflux; (b) TFA/H_2O, CH_2Cl_2, rt; (c) $C_{18}H_{37}Br$, *n*-Bu_4NI, NaH, THF, reflux; (d) 10% Pd/C, H_2, EtOH, rt; (e) $POCl_3$, Et_3N, THF, rt; pyridine, rt, $HO(CH_2)_2$-$N^+(CH_3)_3$·TsO^-.

In summary, we have achieved an asymmetrization of tetrahydro-2,2-dimethanol by the enantiotopos-differentiating hydrolysis of dibutyrate **4** to give enantioenriched synthon **5** which was then used as a common intermediate for making enantiopure phospholipids (*S*)- and (*R*)-**1**.

Experimental Section

The optical purity of alcohols **5**, **10**, **12**, **14**, and (*S*)-**12** was determined by ^{31}P NMR using a diazaphospholidine described in the literature,[4] and the optical purity of phospholipids (*S*)- and (*R*)-**1** was determined by HPLC using a Chiracel OG column (column temperature 40 °C, detector temperature 40 °C, Waters 410 RI detector) using hexane (80):MeOH (7):*i*-PrOH (20):AcOH (0.5):triethylamine (0.5) at a flow rate of 1 mL/min. Commercially available compounds from Aldrich were used in this work.

Tetrahydro-2,2-bis[(butyryloxy)methyl]furan (4). To a solution of 13.2 g (0.1 mol) of diol **2** in 100 mL of CH_2Cl_2 at rt was added 23.4 g (0.22 mol) of butyryl chloride. After 16 h, the reaction was quenched with aqueous Na_2CO_3. The resulting layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was distilled (127–128 °C/0.4 mmHg) affording 25.41 g (93%) of dibutyrate **4**: ^1H NMR ($CDCl_3$) δ 4.07 (s, 4H), 3.90 (t, J = 6.5 Hz, 2H), 2.32 (t, J = 7.4 Hz, 4H), 2.02–1.09 (m, 2H), 1.82 (t, J = 7.2 Hz, 2H), 1.72–1.59 (m, 4H), 0.95 (t, J = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.16, 81.67, 68.78, 65.39, 35.94, 30.78, 25.70, 18.27, 13.48; IR (neat) 1741 cm^{-1}; MS *m*/*z* 273 $(MH)^+$.

(7) M. D. Walkinshaw and J. J. Bolsterli, Sandoz Ltd., Basel, Switzerland.

(*R*)-Tetrahydro-2-[(butyryloxy)methyl]-2-(hydroxymethyl)furan (5). A flask, equipped with an automatic pH titrator for continuous addition of NaOH to maintain pH, was charged with 1 L of a 1 M $NaOH/KH_2PO_4$ buffer solution (pH 7), 1 L of hexane, and 2.2 g of porcine pancreas lipase type II (Sigma). The solution was mixed vigorously, the pH titrator was turned on, and 27.2 g (100 mmol) of **4** was added. After the consumption of 49 mL of 2 M NaOH, the mixture was immediately diluted with 1 L of EtOAc, and the layers were separated. The organic layer was dried with $MgSO_4$ and concentrated and the residue distilled on a short path to give 18.18 g (90%) of oily **5**: $[\alpha]^{25}_D = +18.1°$ (c = 1.00, toluene); 94% ee; ^1H NMR ($CDCl_3$) δ 4.12 (q, J = 11 Hz, 1H), 4.06 (q, J = 11 Hz, 1H), 3.89 (t, J = 6.5 Hz, 2H), 3.54 (q, J = 11 Hz, 1H), 3.49 (q, J = 11 Hz, 1H), 2.33 (t, J = 7.5 Hz, 2H), 2.17 (br, 1H), 2.00–1.90 (m, 1H), 1.90–1.80 (m, 1H), 1.80–1.70 (m, 1H), 1.70–1.60 (m, 3H), 0.96 (t, J = 7.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.76, 83.63, 68.85, 65.52, 36.13, 30.24, 26.11, 18.43, 13.63; IR (neat) 3650–3300, 1739 cm^{-1}; MS m/z 203 $(MH)^+$.

(*S*)-Tetrahydro-2-[(*S*)-[(10-camphorylsulfonyl)oxy]methyl]-2-[(butyryloxy)methyl]furan (8). To a solution of 1.01 g (5 mmol) of **5** in 10 mL of CH_2Cl_2 at 0 °C was added 0.43 g (5.5 mmol) of pyridine followed by 1.38 g (5.5 mmol) of (+)-camphor-10-sulfonyl chloride (Fluka) in 5 mL of CH_2Cl_2. After 16 h at rt, the mixture was refluxed for 1 h and then diluted with 10 mL of 2 N HCl. The resulting layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts, after washing with aqueous $NaHCO_3$, were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was flash chromatographed on SiO_2 using hexane/EtOAc (1:1) to afford 1.8 g (87%) of **6** which was used in the following step. A solution of 1.66 g (4 mmol) of **6** in 5 mL of MeOH, 5 mL of water, and 0.53 g of Na_2CO_3 was stirred at rt for 4 h. The mixture was diluted with 50 mL of EtOAc and 30 mL of water. The resulting layers were separated, and the aqueous layer was extracted twice with 50 mL of EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue after flash chromatography on SiO_2 using hexane/EtOAc (1:2) gave 1.14 g (83%) of **7**. To a solution of 1.11 g (3.2 mmol) of **7** in 5 mL of CH_2Cl_2 at 0 °C was added 0.28 g (3.52 mmol) of pyridine followed by 0.71 g (3.4 mmol) of *p*-nitrobenzoyl chloride in 5 mL of CH_2Cl_2. After 2 h at room temperature, the mixture was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue on two recrystallizations from EtOAc/hexane gave 1.1 g (72%) of **8** as a colorless solid: mp 88.5–89.5 °C; $[\alpha]^{25}_D = +22.8°$ (c = 1.1, acetone); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.18, 164.33, 158.76, 135.22, 130.90, 123.63, 81.70, 77.20, 70.28, 69.18, 66.48, 57.99, 46.87, 47.31, 42.84, 42.55, 31.84, 26.92, 25.76, 25.83, 19.77, 19.69.

(*S*)-Tetrahydro-2-[(trityloxy)methyl]-2-(hydroxymethyl)furan (10). To a solution of 21.5 g (100 mmol) of **5** in 400 mL of CH_2Cl_2 at −30 °C was added 10.5 mL (130 mmol) of pyridine followed by 33.45 g (120 mmol) of trityl chloride dissolved in 100 mL of CH_2Cl_2. The temperature throughout the addition was maintained at −30 °C. The mixture was warmed to rt overnight, diluted with 400 mL of EtOAc, washed with 2 N HCl and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give crude **9** (48.82 g). Crude **9** was dissolved in 500 mL of MeOH, treated with 3.2 g of K_2CO_3, and stirred overnight. The mixture was diluted with 400 mL of EtOAc, washed with aqueous ammonium chloride, dried, and concentrated. Flash chromatography of the residue on SiO_2 using hexane/EtOAc (3:1) followed by hexane/EtOAc (1:1) gave 19.49 g (65%) of **10**: 92% ee; $[\alpha]^{25}_D = -3.85°$ (c = 1.04, MeOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.98, 128.82, 127.88, 127.08, 86.75, 84.77, 68.72, 66.47, 66.12, 30.49, 26.26. Anal. Calcd for $C_{25}H_{26}O_3$: C, 80.16; H, 7.00. Found: C, 80.07; H, 6.98.

(*S*)-Tetrahydro-2-[(octadecyloxy)methyl]-2-[(trityloxy)methyl]furan (11). To a mixture of 4.98 g (125 mmol) of NaH and 3.53 g (9.5 mmol) of tetrabutylammonium bromide in 105 mL of THF at 5 °C was added 27.5 g (73 mmol) of **10** in 105 mL of THF. The mixture was warmed to room temperature followed by the addition of 29.3 g (88 mmol) of octadecyl bromide in 105 mL of THF and then refluxed overnight. The reaction was quenched with 50 mL of 2-propanol, and 500 mL of ammonium chloride solution was added. The layers were separated, washed with brine, dried with $MgSO_4$, and concentrated to dryness. The residue was flash chromatographed on SiO_2, eluting first with hexane followed by hexane/EtOAc (6:1), to give 26.66 g (50%) of oily **11**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.32, 128.93, 127.74, 126.90, 86.45, 73.96, 72.03, 68.62, 65.66, 32.01, 30.83, 29.78, 29.74, 29.69, 29.63, 29.44, 26.22, 26.03, 22.77, 14.18. Anal. Calcd for $C_{43}H_{62}O_3$: C, 82.38; H, 9.97. Found: C, 81.89; H, 10.73.

(*R*)-Tetrahydro-2-[(octadecyloxy)methyl]-2-furanmethanol (12). To a solution of 26.65 g (64 mmol) of **11** in 500 mL of CH_2Cl_2 was added a precooled (5 °C) solution of 73.5 mL of trifluoroacetic acid in 230 mL of water. The two-phase mixture was stirred overnight at room temperature. The layers were separated, and the organic layer was washed with aqueous sodium bicarbonate solution, dried, and evaporated to dryness. Flash chromatography of the residue on SiO_2 using hexane/EtOAc (3:1) gave 10.37 g (64%) of **12** as an oil (92% ee). The product was dissolved in 90 mL of warm hexane, recrystallized at −10 °C with the aid of optically pure seed crystals of **12**, and filtered through a cold jacketed Buchner funnel to give, upon drying, 9.2 g (57%) of **12**: 98.5% ee; mp 36.5–37 °C; $[\alpha]^{25}_{365} = +4.28°$ (c = 1.00, MeOH); ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3H), 1.20–1.40 (m, 30H), 1.50–1.62 (m, 2H), 1.78–1.96 (m, 4H), 2.31 (t, J = 6.5 Hz, 1H), 3.35 (q, J = 9.4 Hz, 1H), 3.44 (q, J = 9.4 Hz, 1H), 3.38–3.50 (m, 2H), 3.53 (m, 1H), 3.59 (m, 1H), 3.86 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 83.99, 74.41, 72.06, 68.61, 66.59, 31.94, 30.54, 29.71, 29.68, 29.63, 29.61, 29.48, 29.37, 26.14, 26.12, 22.70, 14.12, 73.96, 72.03, 68.62, 65.66, 32.01, 30.83, 29.78, 29.74, 29.69, 29.63, 29.44, 26.22, 26.03, 22.77, 14.18; IR (KBr) 3600–3200 cm^{-1}; MS m/z 385 $(MH)^+$. Anal. Calcd for $C_{24}H_{48}O_3$: C, 74.94; H, 12.58. Found: C, 74.30; H, 12.90.

(*S*)-[2-[[Hydroxy[[2-[(octadecyloxy)methyl]tetrahydrofuran-2-yl]methoxy]phosphinyl]oxy]ethyl-*N,N,N*-trimethylaminium Hydroxide Inner Salt ((*S*)-1). To a solution of 10.0 g (26 mmol) of **12** in 66 mL of THF was added at 3 °C 2.52 mL (27 mmol) of $POCl_3$ followed by the dropwise addition of 4.12 mL (29.6 mmol) of triethylamine. The reaction mixture was stirred at room temperature for 2 h followed by the addition of 9.3 g (33.8 mmol) of choline *p*-toluenesulfonate and 8.4 mL of pyridine. The mixture was warmed to 50 °C and stirred for 5 h, and then 10 mL of water was added followed by stirring at 55 °C for another 5 h. The solution was filtered through a column of 685 g of Amberlite MB-3 ion exchange resin, eluting with 10% water in THF. The product-containing fractions were combined, concentrated, and diluted with 80 mL of water. Further concentration to one-half the volume followed by freeze-drying gave 11.32 g (79%) of (*S*)-**1**: mp >250 °C; $[\alpha]^{25}_D = -1.9°$ (c = 1.00, EtOH); ee 97%; ^1H NMR (CD_3OD) δ 0.89 (3H, t, J = 7 Hz), 1.20–1.40 (30H, m), 1.56 (2H, m), 1.80–1.92 (4H, m), 3.22 (9H, s), 3.36–3.47 (4H, m), 3.63 (2H, m), 3.80–3.85 (4H, m), 4.27 (2H, m); ^{13}C NMR (75 MHz, CD_3OD) δ 85.47, 85.35, 74.45, 72.97, 69.85, 69.18, 69.10, 67.58, 60.38, 60.31, 54.79, 54.74, 54.69, 33.11, 31.14, 30.80, 30.65, 30.50, 27.31, 27.08, 23.76, 14.46; FABMS m/z 550.6 ($M = 1^+ + NH_3$). Anal. Calcd for $C_{29}H_{60}NO_6P \cdot 2.1H_2O$: C, 59.28; H, 11.01; N, 2.38. Found: C, 59.26; H, 11.25; N, 2.16.

(*S*)-Tetrahydro-2-[(benzyloxy)methyl]-2-[(trityloxy)methyl]furan (13). To a mixture of 9.86 g (246 mmol) of NaH (60% dispersion in mineral oil) and 6.96 g (19 mmol) of tetrabutylammonium iodide in 205 mL of THF at 5 °C was added 54.28 g (145 mmol) of **10** in 205 mL of THF. The mixture was warmed to room temperature followed by the addition of 20.7 mL (174 mmol) of benzyl bromide in 245 mL of THF and then refluxed overnight. The reaction was quenched with 100 mL of 2-propanol, and 1 L of ammonium chloride solution was added. The layers were separated, and the organic layer was washed with brine, dried with $MgSO_4$, and concentrated. The residue was flash chromatographed on SiO_2, eluting with hexane/EtOAc (95:5), to give 64.72 g (95%) of **13**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.28, 138.74, 128.95, 128.30, 127.79, 127.56, 127.41, 126.94, 86.52, 84.52, 73.58, 68.65, 65.73, 30.94, 26.02. Anal. Calcd for $C_{32}H_{32}O_3$: C, 82.73; H, 6.94. Found: C, 81.92; H, 7.26.

(*R*)-Tetrahydro-2-[(benzyloxy)methyl]-2-furanmethanol (14). To a solution of 64.71 g (139 mmol) of **13** in 1.6 L of CH_2Cl_2 was added a precooled solution of 240 mL of trifluoroacetic acid in 750 mL of water. The solution was stirred overnight at room temperature. The layers were separated, and the organic layer was washed with aqueous sodium bicarbonate solution, dried, and evaporated to dryness. Flash chromatog-

raphy of the residue on SiO_2 using hexane/EtOAc (2:1) followed by hexane/EtOAc (3:2) gave 22.11 g (70%) of **14** as an oil (94% ee): ^1H NMR ($CDCl_3$) δ 7.23–7.40 (m, 2H), 4.57 (q, J = 12.1 Hz, 1H), 4.52 (q, J = 12.1 Hz, 1H), 3.85 (t, J = 6.2 Hz, 2H), 3.60 (dq, J = 11.4, 4.5 Hz, 1H), 3.55 (dq, J = 11.4, 4.5 Hz, 1H), 3.48 (q, J = 9.4 Hz, 1H), 3.39 (q, J = 9.4 Hz, 1H), 2.26–2.38 (br, 1H), 1.70–2.00 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.22, 128.37, 127.61, 127.57, 84.30, 73.57, 73.13, 68.64, 66.10, 30.40, 26.16; IR (neat) 3200–3680 cm^{-1}; MS m/z 223 $(MH)^+$. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.66; H, 8.20.

(*R*)-Tetrahydro-2-[(octadecyloxy)methyl]-2-[(benzyloxy)-methyl]furan (15). To a mixture of 6.76 g (169 mmol) of NaH (60% dispersion in mineral oil) and 4.77 g (12.9 mmol) of tetrabutylammonium iodide in 130 mL of THF at 5 °C was added 22.11 g (99.5 mmol) of **14** in 130 mL of THF. The mixture was warmed to room temperature followed by the addition of 39.79 g (119 mmol) of octadecyl bromide in 155 mL of THF and then refluxed overnight. The reaction was quenched with 50 mL of 2-propanol, and 500 mL of ammonium chloride solution was added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated to dryness. The residue was flash chromatographed on SiO_2, eluting first with hexane followed by hexane/EtOAc (6:1), to give 22.52 g (48%) of oily **15**: ^1H NMR ($CDCl_3$) δ 7.22–7.36 (m, 5H), 4.57 (q, J = 12.2 Hz, 1H), 4.55 (q, J = 12.2 Hz, 1H), 3.85 (t, J = 6.4 Hz, 2H), 3.35–3.48 (m, 6H), 1.78–1.94 (m, 4H), 1.40–1.60 (m, 32H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.49, 128.06, 127.30, 127.20, 83.94, 73.28, 73.17, 72.63, 71.68, 68.44, 31.75, 30.46, 29.53, 29.47, 29.32, 29.18, 25.98, 25.83, 22.51, 13.93; MS m/z 475 $(MH)^+$. Anal. Calcd for $C_{31}H_{54}O_3$: C, 78.43; H, 11.46. Found: C, 78.44; H, 11.60.

(*S*)-Tetrahydro-2-[(octadecyloxy)methyl]-2-furanmethanol ((*S*)-12). A solution of 22.52 g (47 mmol) of **15** in 250 mL of EtOH was hydrogenated overnight in a Parr bottle in the presence of 11.5 g of 10% Pd/C at 49 psi of H_2. The mixture was filtered over Celite and concentrated, and the residue was recrystallized from hexane in the presence of pure seed crystals as described for the enantiomer (*R*)-**12** to give 13.59 g (75%) of (*S*)-**12**: >99% ee; mp 36 °C; $[\alpha]^{25}_{365} = -4.38°$ (c = 1.00, MeOH); spectral data identical with those of (*R*)-**12**.

(*R*)-[2-[[Hydroxy[[2-[(octadecyloxy)methyl]tetrahydrofuran-2-yl]methoxy]phosphinyl]oxy]ethyl]-*N*,*N*,*N*-trimethylaminium Hydroxide Inner Salt ((*R*)-1). Utilizing the procedure as described with example (*S*)-**1**, the title compound was prepared in a similar yield. (*R*)-**1**: mp >250 °C; $[\alpha]^{25}_D$ = +2.0° (c = 1.00, EtOH); ee >99%; spectral data identical with those of (*S*)-**1**.

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Supporting Information Available: Spectroscopic data (^1H, ^{13}C, and ^{31}P NMR, IR, and MS) for all new compounds reported (21 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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