Regiospecific Opening of Glycidyl Derivatives Mediated by Boron Trifluoride. Asymmetric Synthesis of Ether-Linked Phospholipids

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A short, chiral synthesis of unnatural, cytotoxic ether-linked phospholipids is reported in which the key step is the very high regio- and stereospecific nucleophilic opening of the *p*-toluenesulfonate (**1a**, **1b**) or *tert*-butyldiphenylsilyl ether (**6a**, **6b**) derivatives of (*R*)- or (*S*)-glycidol with 1-hexadecanol using boron trifluoride etherate as catalyst. The enantiomeric excess of the ring-opened products was >94%, as judged by ^{1}H NMR and chiral HPLC analysis of the Mosher ester derivatives, indicating that ring opening of **1** and **6** proceeds without significant loss of optical purity. The synthetic strategy of using optically active glycidyl derivatives as the precursor of the glycerol backbone permits the desired enantiomers of 1(3)-*O*-2-*O*-methylphosphocholines (**5a**, **5b**) to be generated in good yield and high optical purity from the ring-opened intermediates (**2**, **7**) in three steps without the use of protecting groups.

Unnatural ether-linked phospholipids, often referred to as alkyl phospholipids (ALPs), represent an important group of biologically active molecules that act on cytoplasmic targets. The ALPs that contain a 16- or 18-carbon aliphatic chain at the *sn*-1 position[1] and an *O*-methyl group at the *sn*-2 position of glycerophosphocholine (GPC) have potent cytotoxic activity toward various tumor cells.[2] The cytotoxic ether phospholipids accumulate in membranes of tumor cells, where they may affect the structural order of membrane lipids and alter tumor cell invasion[3] or interfere with cellular phospholipid metabolism.[4] They may also activate tumor-specific cytotoxic macrophages in the host cells.[5] Since 1-*O*-alkyl-2-*O*-methyl-GPC is a structural analogue of the naturally occurring platelet activating factor (PAF), the possible involvement of ALP binding to a specific PAF membrane receptor has been considered in the mechanism of action of this class of new antitumor agents, particularly at the cell surface of macrophages.[6] Interaction of ALP or its metabolites with the phospholipid-requiring enzyme protein kinase C may also contribute to the mechanism of cytotoxic action.[7] With very few exceptions,[6,8] a racemic mixture of 1-*O*-alkyl-2-*O*-methyl-GPC (available commercially)[9] was used in the biochemical, biological, and pharmacological studies cited above. The development of methods to prepare optically pure isomers of ALP analogues would accelerate efforts to advance the understanding of the antitumor activity of synthetic tumoricidal ether lipids. Enantiomers **5a** and **5b** could be used, for example, to analyze whether conversion to metabolic products and/or binding to receptors in biological systems play important roles in the selective toxicity of **5** to tumor cells.

Epoxides have served as important synthetic intermediates because of their high chemical reactivity, ease of preparation, and availability in optically active form. In previous applications of epoxides as lipid precursors, (*S*)-glycidol has been used to prepare optically active triacylglycerols,[10] and *rac*-glycidol has been used to prepare *rac*-mono- and diacylglycerols[11] and phospholipids.[12] The discovery that Ti(O-*i*-Pr)$_4$ mediates the regioselective attack of a variety of nucleophiles at C$_3$ of 2,3-epoxy alcohols under mild experimental conditions[13] was the basis for the Ti(O-*i*-Pr)$_4$-assisted opening of (*S*)-glycidol with stearic acid, which gave (*S*)-glycidyl stearate in low yield.[14] Recent advances in asymmetric epoxidation of low molecular weight allylic alcohols by the use of catalytic amounts of Ti(O-*i*-Pr)$_4$ and tartrate ester in the presence of molecular sieves, followed by in situ derivatization of the epoxide formed,[15] offer a convenient synthetic route to optically active lipids. We demonstrate here the use of the *p*-toluenesulfonate and *tert*-butyldiphenylsilyl ether (TBDPS) derivatives of (*R*)- and (*S*)-glycidol (**1** and **6**) as

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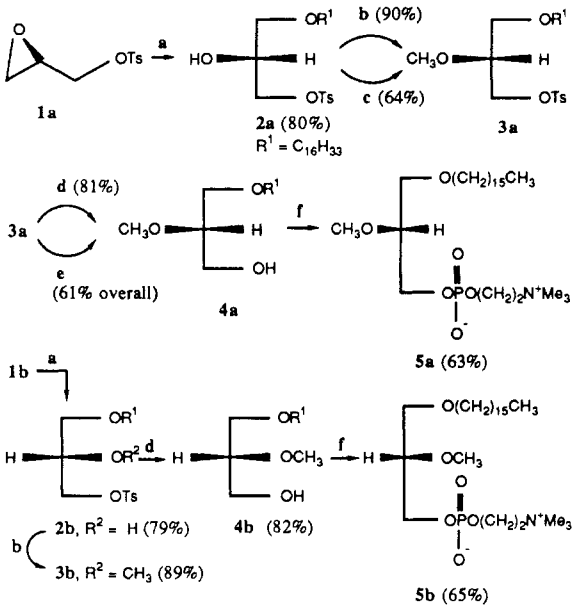
precursors in a short synthesis of both enantiomeric forms of 1-*O*-alkyl-2-*O*-methyl-3-GPC (**5a**) and 3-*O*-alkyl-2-*O*-methyl-1-GPC (**5b**).[16] The key carbon–oxygen bond-forming step is the regio- and stereospecific nucleophilic opening of glycidyl derivatives **1** and **6** with a long-chain alcohol using BF_3 etherate as a catalyst. Although BF_3-mediated opening reactions of epoxides using organometallic reagents[17] and acetone[18] have been reported, to our knowledge BF_3-mediated nucleophilic opening of glycidyl derivatives has not yet been reported.[19] In this paper we show that BF_3 etherate is a much better Lewis acid than Ti(O-*i*-Pr)$_4$ for ether lipid synthesis, probably because a nonnucleophilic molecule (ether) is displaced during ring opening; on the other hand, the nucleophilic species (2-propanol) liberated when excess Ti(O-*i*-Pr)$_4$ is used to mediate the ring opening[13] would be expected to compete with the long-chain alcohol. Furthermore, our BF_3-mediated procedure for opening of epoxide derivatives with a long-chain alcohol provides ether-linked lipids in much higher yield and optical purity than the Ti(O-*i*-Pr)$_4$-mediated opening of glycidol with a long-chain fatty acid.[14]

Results

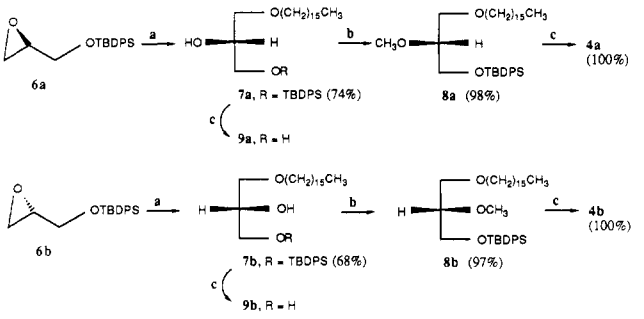
Epoxide Opening. Attempts to effect base-induced opening of TBDPS ether **6** with the sodium salt of 1-hexadecanol in DMF were unsuccessful. Reaction of the alkoxide ion with **6** resulted in attack on silicon, giving *n*-hexadecyl *tert*-butyldiphenylsilyl ether as the sole product. Alkoxide ion attack on glycidyl tosylate **1** is also not suitable for the preparation of chiral products **5a** and **5b**; alkoxide attack is known to give direct displacement of the tosyl group together with ring opening followed by internal displacement of the tosyl group, forming partially racemized product.[20] It is known, however, that Ti(O-*i*-Pr)$_4$ mediates the opening of glycidol by thiophenol and *N*-isopropylbenzylamine with high regioselectivity[21] and the opening of glycidyl *p*-nitrobenzoate by a variety of nucleophiles.[22] In the present paper, BF_3 etherate is shown to be the Lewis acid of choice for opening of glycidyl derivatives with 1-hexadecanol. In fact, glycidyl derivatives **1** and **6** did not react with 1-hexadecanol when Ti(O-*i*-Pr)$_4$ was used in either catalytic or stoichiometric amounts. Use of $TiCl_4$, $SnCl_4$, and $ZnCl_2$ as potential catalysts resulted in attack by chloride ion with only small amounts of attack by the long-chain alcohol. However, we found that when BF_3 etherate was used as the catalyst, ring-opened products **2** and **7** were obtained in good yields. Excellent regioselectivities were realized in this reaction. Attack of 1-hexadecanol on tosylate **1** gave regioisomer **2** exclusively, whereas attack on TBDPS ether **6** resulted in a 9:1 ratio of the desired regioisomer **7** (C_3 attack) to the undesired positional isomer (C_2 attack). Furthermore, ring opening proceeded with very high stereoselectivity (see Evaluation of Optical Purity). We also found that the *p*-toluenesulfonate and TBDPS ether derivatives **1** and **6** were far superior as C3 synthons compared with the *p*-nitrobenzoate ester of glycidol. The latter compound gave *n*-hexadecyl *p*-nitrobenzoate as the major product when treated with 1-hexadecanol and BF_3 etherate.

Scheme I[a]



[a] (a) $CH_3(CH_2)_{15}OH$, BF_3·Et_2O, $CHCl_3$; (b) CH_3OTf, 2,6-di-*t*-C_4H_9-4-CH_3-pyr, CH_2Cl_2, reflux; (c) CH_2N_2, SiO_2, Et_2O; (d) KO_2, 18-crown-6, Me_2SO/DMF/DME, 1:1:1; (e) i, NaI, Me_2CO, reflux; ii, MCPBA, CH_2Cl_2; (f) i, 2-chloro-2-oxo-1,3,2-dioxaphospholane, Et_3N, C_6H_6, 0 °C; ii, Me_3N, CH_3CN, 65–70 °C.

Scheme II[a]



[a] (a) $CH_3(CH_2)_{15}OH$, BF_3·Et_2O, CH_2Cl_2; (b) CH_3I, NaH, C_6H_6; (c) $(n\text{-}C_4H_9)_4N^+F^-$, THF.

Synthesis. Scheme I shows the conversion of (*R*)- and (*S*)-glycidyl tosylates (**1a**, **1b**) into the desired enantiomers of *O*-hexadecyl-2-*O*-methyl-GPC (**5a**, **5b**). Mild conditions were required for the conversion of ring-opened product **2** into *O*-methyl compound **3** to avoid epoxide formation. Methylation using diazomethane in the presence of excess silica gel[23] gave **3** in only 64% yield. Better results were obtained by methylating **2** with methyl triflate in the presence of the hindered 2,6-di-*tert*-butyl-4-methylpyridine in refluxing dichloromethane, giving **3** in 90% yield. The latter method has been applied to the methylation of carbohydrates under mild conditions.[24] Conversion of

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(23) Ohno, K.; Shiyama, H.; Nagase, H. *Tetrahedron Lett.* **1979**, 4405–4406.

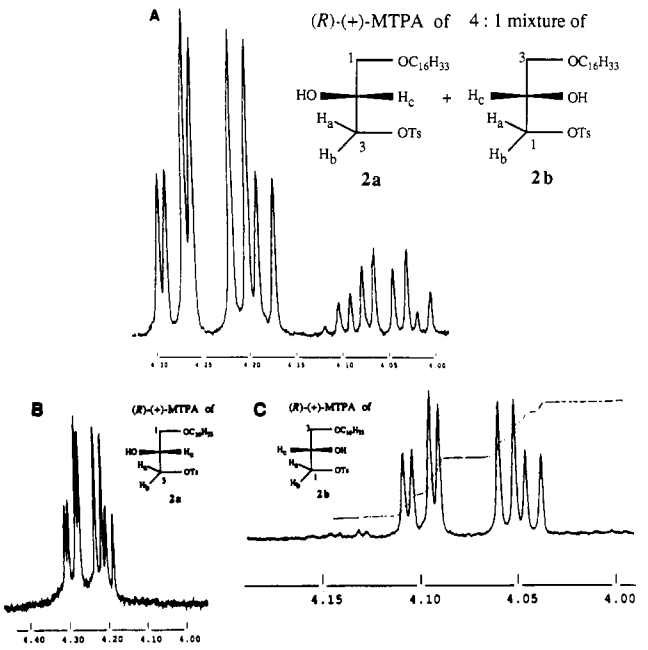

Figure 1. ^{1}H NMR spectra (400 MHz) of the (*R*)-(+)-MTPA esters of tosylate **2** corresponding to the CH_2OTs protons (H_a, H_b) at C_3 of (−)-**2a** and C_1 of (+)-**2b**: (A) 4:1 mixture of (−)-**2a**/(+)-**2b**; (B) (−)-**2a**; (C) (+)-**2b**.

tosylate **3** into alcohol **4** was first attempted by displacement with iodide followed by MCPBA oxidation,[25] affording the alcohol in 61% overall yield. We improved the yield of this step to 81% by carrying out the reaction of **3** with potassium superoxide in the presence of 18-crown-6. These conditions have been reported to accomplish the direct displacement of tosylates to form alcohols.[26] In the final step, the phosphocholine moiety was introduced by reaction of alcohol **4** with 2-chloro-2-oxo-1,3,2-dioxaphospholane, followed by reaction of the cyclic phosphate intermediate with dry trimethylamine.[27]

Scheme II shows the conversion of (*R*)-(+)- and (*S*)-(−)-oxiranemethanol *tert*-butyldiphenylsilyl ethers ((+)-**6a** and (−)-**6b**), which were prepared by trapping glycidol with *tert*-butyldiphenylsilyl chloride,[15] into alcohols (−)-**4a** and (+)-**4b**. Although the regioselectivity of the ring-opening reaction of **6** → **7** was not quite as high as that of **1** → **2**, the desired regioisomer **7** was obtained in high yield. The sodium salt of **7** was methylated by using methyl iodide in benzene, giving **8** in almost quantitative yield. Desilylation using tetrabutylammonium fluoride[28] gave alcohol **4** in quantitative yield.

Evaluation of Optical Purity. To determine the enantiomeric excess (ee) of the ring-opened products **2** and **7**, we prepared their (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-(+)-MTPA) esters.[29] The diastereomeric ratio of the resulting mixture was analyzed by two methods: 400-MHz ^{1}H NMR and HPLC on a chiral stationary phase. Figure 1A shows the ^{1}H NMR spectrum (δ 4.0–4.3) of a mixture prepared from 80% of

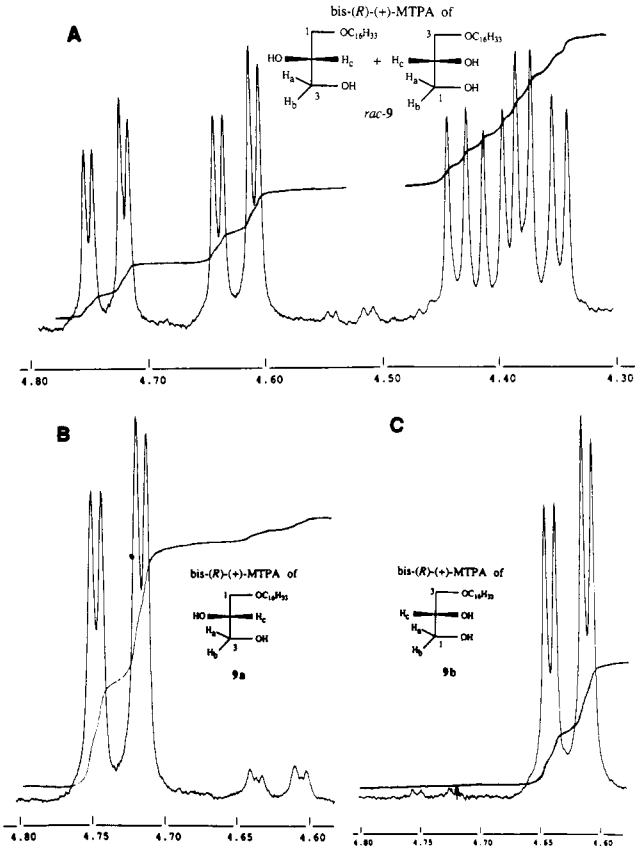

Figure 2. ^{1}H NMR spectra (400 MHz) of the bis-(*R*)-(+)-MTPA esters of *rac*-**9**, (−)-**9a**, and (+)-**9b** corresponding to the CH_2OMTPA protons (H_a, H_b) at C_3 of (−)-**9a** and C_1 of (+)-**9b**: (A) *rac*-**9**; (B) (−)-**9a**; (C) (+)-**9b**.

(−)-**2a** and 20% of (+)-**2b**. Integration of the two doublets of AB quartets on an expanded scale indicated a 4:1 ratio of the areas of the signals at δ 4.15–4.3 vs those at δ 4.0–4.1. The individual diastereotopic protons of CH_2OTs in each enantiomer show base-line separation. The lower field doublet of doublets (δ 4.28) is assigned to H_a of stereoisomer (−)-**2a** (see Figure 1B), and the other doublet of doublets (δ 4.20) of (−)-**2a** is assigned to H_b. Enantiomer (+)-**2b** has a low-field doublet of doublets at δ 4.09 (H_a of (+)-**2b**) and a higher field doublet of doublets at δ 4.04 (H_a of (+)-**2b**; Figure 1C). The absence in Figure 1B of the signals at δ 4.09 and 4.04 and the absence in Figure 1C of the signals at δ 4.28 and 4.20 indicate that the optical purities of (−)-**2a** and (+)-**2b** are >99% (the limits of detection).

We were unable to determine the optical purities of (+)-**7a** and (−)-**7b** directly by 400-MHz ^{1}H NMR because the diastereotopic protons of the OCH_2 signals of their Mosher esters overlapped. Therefore, (+)-**7a** and (−)-**7b** were desilylated, and the bis-(*R*)-MTPA esters were prepared from 1-*O*-hexadecyl- and 3-*O*-hexadecyl-*sn*-glycerol ((−)-**9a** and (+)-**9b**, respectively). Figure 2A shows that the two CH_2OMTPA signals exhibited by the bis-Mosher ester of *rac*-**9** are base-line separated in the region δ 4.3–4.8. The A proton doublet (split by the methine proton) of the AB quartet of each diastereoisomeric CH_2OMTPA group is clearly visible, with base-line separation in the region δ 4.58–4.75. The B segments are not so readily separable, and our estimation of enantiomeric purity was thus based only on the A segments. The integrated ratio of the signals centered at δ 4.73:4.62 in Figure 2B (on an expanded scale) indicated 96% ee for (−)-**9a**. Similarly, Figure 2C was analyzed to give 98% ee for (+)-**9b**. Thus we conclude that the optical purities of the precursors of (−)-**9a** and (+)-**9b**,

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i.e. (+)-**7a** and (−)-**7b**, are of the same magnitude. (Note that the specific rotations of (−)-**9a** (+)-**9b** are higher than those reported in the literature.)

Since NMR analysis of the (*R*)-(+)-MTPA ester of **2** indicated a higher ee than that reported[15] for epoxide 1,[30] we reevaluated the ee of the MTPA esters derived from **2** by chiral HPLC. The percent ee values of the (*R*)-(+)-MTPA esters of (−)-**2a** and (+)-**2b** were 94.0 and 95.7, respectively.[31] Moreover, three recrystallizations of (−)-**2a** from ether–hexanes prior to conversion to the MTPA derivative enriched its chiral purity to 97.7% ee. Although the (*R*)-(+)-MTPA esters of (+)-**7a** and (−)-**7b** were not suitable for ee determination by NMR, chiral HPLC analysis was successful. The values obtained (93.8 and 95.3% ee, respectively)[32] are consistent with the higher optical purity estimated by comparing the specific rotation of (*S*)-**6b** with the literature[15] value. Thus, chiral HPLC analysis indicated that the ring opening of **1** and **6** by 1-hexadecanol proceeded without any significant loss of chiral purity.

Discussion

We have shown that BF_3 etherate serves as an excellent catalyst for the opening of glycidyl derivatives **1** and **6**, giving monoprotected diols **2** and **7** in high yield, regioselectivity, and optical purity. Our synthesis of the cytotoxic phospholipid 1-*O*-alkyl-2-*O*-methyl-GPC (**5a**) from glycidyl synthons **1a** and **6a** is short and efficient. Enantiomer **5b**, which has not been reported previously in pure form,[33] has been prepared by the same methodology from **1b** and **6b**. The enantiomerically pure compounds **5a** and **5b** will be useful for the study of the mechanism of cytotoxic activity and tumor specificity of these antineoplastic agents.

Previous syntheses of **5a** used natural sources as starting materials, such as D-mannitol,[34] L-glyceric acid,[35] and L-tartaric acid.[36] The previous synthetic routes involve many steps and require the extensive use of protection–deprotection reactions. Since these published routes rely on a natural source, the stereochemistry of the product is limited to the chirality of the starting material. In contrast, our asymmetric synthesis proceeds from inexpensive starting materials, which are prepared by asymmetric epoxidation of allyl alcohol followed by in situ sulfonation or silylation. Our synthesis of glycerolipids is short since no protecting groups are required. This methodology is flexible and can, therefore, be applied to prepare related analogues of ALPs. For example, the Lewis acid catalyzed ring-opening reaction (**1** → **2**, **6** → **7**) can be carried out with various aliphatic alcohols. Oleyl and petroselinyl [(*Z*)-9- and (*Z*)-6-octadecen-1-yl, respectively] groups were introduced at the *sn*-1 position of **2**[37a] and **7**[37b] in very high regio- and stereospecificity by use of the unsaturated alcohols as nucleophiles. These ring-opened intermediates can be converted into unsaturated long-chain ALP analogues of **5** by the same procedures used for the hexadecyl derivative. A variety of alkyl groups can be introduced at the 2 position by carrying out the O-alkylation of **2** and **7** with long-chain alkyl triflates or short-chain alkyl iodides (unpublished results). Such analogues are useful for examining the relationship between ALP structure and antitumor activity. The ability to prepare both enantiomers of ALPs and its analogues in high enantiomeric excess is expected to facilitate the study of the molecular mechanisms of action of ALPs, especially the possible involvement of a stereospecific receptor in the cellular responses elicited by these compounds.

Experimental Section

General Procedures. Melting points are uncorrected. Silica gel G TLC plates of 0.25-mm thickness (Analtech, Newark, DE) were used to monitor reactions, with 10% sulfuric acid in ethanol and/or short-wavelength ultraviolet light to visualize the spots. E. Merck silica gel 60 (230–400 ASTM mesh) was used for flash chromatography. Solvents were dried as follows: chloroform, dichloromethane, dimethyl sulfoxide (Me_2SO), dimethylformamide (DMF), and acetonitrile were distilled from calcium hydride and stored over type 3A molecular sieves; benzene and hexane were distilled from and stored over sodium; tetrahydrofuran was refluxed over sodium benzophenone ketyl for several hours and then used immediately; acetone was stored over calcium sulfate for at least 1 week. (*R*)-Glycidyl tosylate ((*R*)-oxiranemethanol 4-methylbenzenesulfonate, (−)-**1a**) was purchased from Aldrich Chemical Co. (*S*)-Glycidyl tosylate ((+)-**1b**) was prepared in 40% yield as described by Gao et al.;[15] $[\alpha]^{25}_D$ +17.1° (*c* 2.75, $CHCl_3$). In later experiments, commercially available (+)-**1b** was used (Aldrich). 1-Hexadecanol and (*R*)-(+)-MTPA were purchased from Aldrich.

1-*O*-Hexadecyl-*sn*-glycerol 3-*O*-*p*-Toluenesulfonate ((−)-2a). To 1.0 g (4.4 mmol) of (−)-**1a** and 1.5 g (6.2 mmol) of 1-hexadecanol in 25 mL of alcohol-free chloroform was added 3 drops (~5 mol %) of freshly distilled BF_3 etherate. After the mixture was stirred for 24 h under nitrogen, the solvent was removed under reduced pressure to give a residue that gave 1.65 g (80%) of (−)-**2a** after flash chromatography (elution with 5:1 hexane/EtOAc, R_f 0.25): mp 68.0–69.0 °C (lit.[38] mp 68.0–69.0 °C); TLC (20% ethyl acetate–hexanes) R_f 0.30; $[\alpha]^{25}_D$ −6.24° (*c* 5.0, C_6H_6) (lit.[38] $[\alpha]^{25}_D$ −5.55° (*c* 5.0, C_6H_6)); 94.0% ee,[31] 97.7% ee after three recrystallizations from ether–hexanes; IR (KBr) 3600, 1360, 1182, 1130, 1102, 846, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 8.5 Hz, 2H), 4.05 (m, 3 H, CH_2OTs and CH_2CHCH_2), 3.44 (d, *J* = 5.0 Hz, 2 H, $CH_2OC_{16}H_{33}$), 3.39 (t, *J* = 7.0 Hz, 2 H, OCH_2CH_2), 2.45 (s, 3 H, $CH_3C_6H_4$), 2.15 (s, 1 H, OH), 1.29 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.91 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{26}H_{45}O_5S$: C, 66.41; H, 9.89; S, 6.86. Found: C, 66.49; H, 9.66; S, 6.83.

3-*O*-Hexadecyl-*sn*-glycerol 1-*O*-*p*-Toluenesulfonate ((+)-2b). This title compound was prepared in 79% yield from (+)-**1b** by the same procedure used to prepare (−)-**2a**; mp 68.0–69.0 °C (lit.[38] mp 68.0–69.0 °C); $[\alpha]^{25}_D$ +6.37° (*c* 5.0, C_6H_6) (lit.[38] $[\alpha]^{25}_D$ +5.75° (*c* 5.0, C_6H_6)); 95.7% ee.[31] IR and ^1H NMR spectra were identical with those obtained for (−)-**2a**.

General Procedure for Preparation of Mosher Esters. To 1.5 g (6.4 mmol) of (*R*)-(+)-MTPA in 1 mL of hexane were added sequentially 1.67 mL (19.2 mmol) of oxalyl chloride and 1 drop of DMF. The mixture was stirred at room temperature for 30 min and then was refluxed for 3 h. After the volatiles were removed under reduced pressure, the Mosher chloride was distilled

(30) It should be noted that ref 18 shows that the ee of (*S*)-**1b** can be enhanced to 97% by several recrystallizations.

(31) The percent ee was determined by HPLC on a chiral stationary-phase column (Pirkle type IA, 4.6 × 250 mm, J. T. Baker) using a flow rate of 0.40 mL/min (elution with hexanes–*i*-PrOH 90:10). Under these conditions, base-line separation of the diastereomeric (*R*)-(+)-MTPA esters of (−)-**2a** and (+)-**2b** was achieved (R_t 17.2 and 19.0 min, respectively).

(32) The R_t values of the (*R*)-(+)-MTPA esters of (+)-**7a** and (−)-**7b** were 20.7 and 23.4 min, respectively (flow 0.45 mL/min, elution with hexanes–*i*-PrOH 100:0).

(33) The preparation of 3-*O*-octadecyl-2-*O*-methyl-1-GPC from 1,2-*O*-isopropylidene-*sn*-glycerol was outlined recently, but comparison of its specific rotation ($[\alpha]_D$ +1.7° (*c* 1, $CHCl_3$)) with that of its enantiomer ($[\alpha]_D$ −2.3° (*c* 1, $CHCl_3$)) indicates that partial racemization occurred: Hayashi, H.; Kudo, I.; Inoue, K.; Onozaki, K.; Tsushima, S.; Nomura, H.; Nojima, S. *J. Biochem.* **1985**, *97*, 1737–1745.

(34) Berchtold, R. *Chem. Phys. Lipids* **1982**, *30*, 389–392. In contrast to the $[\alpha]_D$ reported in ref 33, this ref reported 1-*O*-octadecyl-2-*O*-methyl-3-GPC to give $[\alpha]_D$ +2.8° (*c* 10, $CHCl_3$).

(35) Bhatia, S. K.; Hajdu, J. *Tetrahedron Lett.* **1987**, *28*, 271–274; *J. Org. Chem.* **1988**, *53*, 5034–5039.

(36) Ohno, M.; Fujita, K.; Nakai, H.; Kobayashi, S.; Inoue, K.; Nojima, S. *Chem. Pharm. Bull.* **1985**, *33*, 572–582.

(37) (a) Guivisdalsky, P. N.; Bittman, R. *J. Org. Chem.*, following paper in this issue. (b) Unpublished results.

(38) Hirth, G.; Barner, R. *Helv. Chim. Acta* **1982**, *65*, 1059–1084.

under vacuum (50 °C, 0.6 mmHg) (lit.[39] bp 50 °C, 0.6 mmHg). To a solution of 0.15 mmol of the alcohol [(−)-**2a**, (+)-**2b**, (+)-**7a**, (−)-**7b**] in 1 mL of pyridine was added 30 μL of neat (*R*)-(+)-MTPA chloride. The mixture was stirred until all of the starting material had been consumed (approximately 2 h), as monitored by TLC (hexane/EtOAc, 4:1 for (−)-**2a** and (+)-**2b**, 9:1 for (+)-**7a** and (−)-**7b**). Ether (50 mL) was added, the ether layer was washed with water (4 × 30 mL), dried (Na_2SO_4), filtered, and concentrated, affording the crude Mosher ester.

Mosher Ester of (−)-2a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2 H), 7.35–7.45 (m, 5 H), 7.31 (d, J = 8.5 Hz, 2 H), 5.38 (m, 1 H, CH_2CHCH_2), 4.28 (dd, J_{AC} = 3.0 Hz, J_{AB} = 11.5 Hz, 1 H), 4.20 (dd, J_{BC} = 7.5 Hz, J_{AB} = 11.5 Hz, 1 H), 3.52 (dd, J_{AC} = 5.4 Hz, J_{AB} = 10.3 Hz, 1 H), 3.51 (s, 3 H, CH_3O), 3.46 (dd, J_{BC} = 5.4 Hz, J_{AB} = 10.3 Hz, 1 H), 3.27 (t, J = 6.59 Hz, 2 H, OCH_2CH_2), 2.45 (s, 3 H, $CH_3C_6H_4$), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.88 (br t, 3 H, ω-CH_3).

Mosher Ester of (+)-2b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 2 H), 7.35–7.45 (m, 5 H), 7.31 (d, J = 8.5 Hz, 2 H), 5.41 (m, 1 H, CH_2CHCH_2), 4.09 (dd, J_{AC} = 3.66 Hz, J_{AB} = 10.74 Hz, 1 H), 4.04 (dd, J_{BC} = 6.35 Hz, J_{AB} = 10.74 Hz, 1 H), 3.31–3.59 (m, 4 H, $OCH_2(CH_2)_{14}CH_3$ and $CH_2OC_{16}H_{33}$), 3.49 (s, 3 H, CH_3O), 2.45 (s, 3 H, $CH_3C_6H_4$), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.88 (br t, 3 H, ω-CH_3).

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(*p*-tolylsulfonyl)-*sn*-glycerol ((−)-3a). This compound was prepared by using two different procedures. **Procedure A**: To mixture of (−)-**2a** (235 mg, 0.5 mmol) in 15 mL of ether and 1.2 g (50 wt equiv based on substrate **2a**) of silica gel (Baker, 60–200 mesh, dried overnight at 120 °C) was added a solution of diazomethane (20 mol equiv based on substrate **2a**) in ether. The mixture was stirred at room temperature for 6 h, filtered, and washed with ether. The solvents were evaporated under vacuum, leaving a residue that was purified by flash chromatography (elution with 8:1 hexane/EtOAc) to give 155 mg (64%) of (−)-**3a**. **Procedure B**: A solution of (−)-**2a** (141 mg, 0.3 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (616 mg, 3.0 mmol) in dry dichloromethane (3 mL) was treated with methyl triflate (340 μL, 3.0 mmol). After the mixture was refluxed for 16 h under nitrogen, the solvents were evaporated. To the residue EtOAc (50 mL) and 2 N HCl (30 mL) were added. The organic phase was isolated and washed again with 30 mL of 2 N HCl. To recover the excess hindered pyridine, the combined aqueous phase was neutralized with 20% aqueous NaOH, and 2,6-di-*tert*-butyl-4-methylpyridine was extracted into dichloromethane. The EtOAc phase was washed with water, saturated $NaHCO_3$, and water and then dried (Na_2SO_4). Removal of the solvents gave a residue that was purified by flash chromatography (elution with 8:1 hexane/EtOAc) to yield 130 mg (90%) of (−)-**3a** as a yellow oil at room temperature: $[\alpha]^{25}_D$ −4.82° (*c* 5.0, $CHCl_3$); IR ($CHCl_3$) 1360, 1182, 1130, 846, 821 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.34 (d, J = 8.3 Hz, 2 H), 4.17 (dd, J_{AC} = 4.15 Hz, J_{AB} = 10.42 Hz, 1 H, C_3H_a), 4.05 (dd, J_{BC} = 5.6 Hz, J_{AB} = 10.42 Hz, 1 H, C_3H_b), 3.36 (s, 3 H, OCH_3), 3.33–3.53 (m, 5 H, CH_2OCH_2 and CH_2CHCH_2), 2.45 (s, 3 H, $CH_3C_6H_4$), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.88 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{27}H_{48}O_5S$: C, 66.90; H, 9.98; S, 6.61. Found: C, 66.98; H, 9.82; S, 6.58.

3-*O*-Hexadecyl-2-*O*-methyl-1-*O*-(*p*-tolylsulfonyl)-*sn*-glycerol ((+)-3b). This compound was prepared from (+)-**2b** in 89% yield by procedure B described above; $[\alpha]^{25}_D$ +4.80° (*c* 5.0, $CHCl_3$). IR and ^{1}H NMR spectra were identical with those obtained for (−)-**3a**.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((−)-4a). This compound was prepared by two procedures. **Procedure A**: To a mixture of potassium superoxide (42 mg, 0.6 mmol) and 18-crown-6 (159 mg, 0.6 mmol) in 3 mL of Me_2SO/DMF/1,2-dimethoxyethane (1:1:1) at room temperature under nitrogen was added 70 mg (0.15 mmol) of (−)-**3a**. After the mixture was stirred for 6 h, 2 mL of cold brine was added slowly and cautiously. The product was extracted with ether (2 × 30 mL), and the ether layer was washed with water (20 mL) and dried (Na_2SO_4). Removal of the solvents under vacuum gave a yellow residue that was purified by flash chromatography (elution with 4:1 hexane/EtOAc) to give 40 mg (81%) of (−)-**4a** as a low-melting solid, mp 29–30 °C (lit.[36] mp 30–31 °C); $[\alpha]^{25}_D$ −9.96° (*c* 1.64, $CHCl_3$); (lit.[36] $[\alpha]^{25}_D$ −9.95° (*c* 1.64, $CHCl_3$); IR (neat) 3370, 2930, 2840, 1640, 1460, 1375, 1190, 1060 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.38–3.85 (m, 10 H, CH_2OCH_2, CH_2OH, CH_2CHCH_2), 3.47 (s, 3 H, OCH_3), 1.26 (br s, 29 H, $CH_3(CH_2)_{14}$, OH), 0.89 (br t, 3 H, ω-CH_3). **Procedure B**: To a solution of (−)-**3a** (83 mg, 0.17 mmol) in 10 mL of dry acetone was added 51 mg (0.34 mmol) of sodium iodide. The mixture was refluxed for 24 h under nitrogen. The solvents were evaporated under reduced pressure, and dichloromethane was added to the residue. After the salts were removed by filtration, the filtrate was treated with 1.5 equiv of *m*-chloroperbenzoic acid (MCPBA) at 0 °C for 1 h and then was allowed to stir at room temperature for 24 h. The mixture was filtered, the filtrate was washed with 0.5 N NaOH, and the aqueous layer was extracted twice with dichloromethane. The combined organic phase was dried over Na_2SO_4, and the solvent was removed under vacuum to give a residue that was purified by flash chromatography (elution with 4:1 hexane/EtOAc), yielding 36 mg (61% overall) of (−)-**4a** as a low-melting solid with the same physical properties as described for the product obtained from procedure A.

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((+)-4b). This compound was prepared from (+)-(**3b**) in 89% yield by procedure A; mp 29–30 °C; $[\alpha]^{25}_D$ +9.92° (*c* 1.64, $CHCl_3$). IR and ^{1}H NMR spectra were identical with those obtained for (−)-**4a**.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycero-3-phosphocholine ((−)-5a). To a solution of 2-chloro-2-oxo-1,3,2-dioxaphospholane (51.3 mg, 0.36 mmol) in 3 mL of benzene at 0 °C was added slowly with stirring a mixture of 94 mg (0.30 mmol) of (−)-**4a** and 50 μL (0.36 mmol) of triethylamine in 3 mL of benzene. During a period of 2 h of stirring at room temperature the starting material (R_f 0.32) had completely disappeared as monitored by TLC (4:1 hexane/EtOAc). After the crystalline triethylamine hydrochloride was removed by filtration, the solvent was removed under vacuum to give 128 mg (100%) of the desired cyclic phosphate as a white solid, which was used as soon as possible in the next step. The cyclic phosphate (128 mg, 0.30 mmol) was transferred into a pressure bottle with 4 mL of dry acetonitrile. The mixture was cooled to −78 °C, and excess (approximately 0.5 mL) of dry trimethylamine (Fluka) was allowed to condense into the solution. The bottle was sealed and heated at 65–70 °C for 36 h. On cooling at −20 °C for 3 h, 152 mg of crystalline product was obtained. Flash chromatography ($CHCl_3/CH_3OH/H_2O$ 65:25:4) gave 94 mg (63% overall yield) of the product (−)-**5a**; $[\alpha]^{25}_D$ −5.41° (*c* 0.95, $CHCl_3/CH_3OH$ 1:1); (lit.[36] $[\alpha]^{25}_D$ −5.38° (*c* 0.95, $CHCl_3/CH_3OH$ 1:1)); IR (Nujol) 3385, 1220, 1080 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ 1:1) δ 3.38–3.85 (m, 10 H, CH_2OCH_2, CH_2OH, CH_2CHCH_2), 3.46(s, 3 H, OCH_3), 3.39 (s, 9 H, $N(CH_3)_3$), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.89 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{25}H_{54}O_6PN\cdot H_2O$: C, 58.45; H, 10.99; N, 2.73; P, 6.03. Found: C, 58.71; H, 10.86; N, 2.53; P, 5.98.

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycero-1-phosphocholine ((+)-5b). This compound was prepared from (+)-**4b** in 65% overall yield; $[\alpha]^{25}_D$ +5.45° (*c* 0.95, $CHCl_3/CH_3OH$ 1:1).

(*R*)-(+)-Oxiranemethanol *tert*-Butyldiphenylsilyl Ether ((+)-6a). Epoxide (+)-**6a** was prepared in 45% yield by asymmetric epoxidation of allyl alcohol using the procedure of Gao et al.[15] with minor modification; $[\alpha]^{25}_D$ +2.40° (*c* 9.07, $CHCl_3$); IR ($CHCl_3$) 2968, 2962, 2940, 1365, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67–7.71 (m, 5 H), 7.35–7.45 (m, 5 H), 3.86 (dd, J = 2.9, 12.5 Hz, 1 H), 3.70 (dd, J = 4.4, 12.5 Hz, 1 H), 3.10–3.13 (m, 1 H), 2.73 (dd, J 3.3, 5.8 Hz, 1 H), 2.60 (dd, J = 3.3, 5.1 Hz, 1 H), 1.06 (s, 9 H).

(*S*)-(−)-Oxiranemethanol *tert*-Butyldiphenylsilyl Ether ((−)-6b). Epoxide (−)-**6b** was prepared in 49% yield as described above by using D-(−)-DIPT. GC/MS analysis of the oil obtained from vacuum distillation (138–140 °C, 0.1 mmHg) indicated the presence of 10% impurity (allyl *tert*-butyldiphenylsilyl) ether); therefore, (−)-**6b** was purified by flash chromatography (20:1 hexane/EtOAc); TLC (9:1 hexane/EtOAc) R_f 0.59; $[\alpha]^{25}_D$ −2.46° (*c* 9.07, $CHCl_3$); (lit.[15] $[\alpha]^{25}_D$ −2.28° (*c* 9.07, $CHCl_3$)).

1-*O*-Hexadecyl-3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol ((+)-7a). To a solution of 625 mg (2.0 mmol) of (+)-**6a** and 510 mg (2.1 mmol) of 1-hexadecanol in 12 mL of dry dichloromethane under nitrogen atmosphere were added catalytic amounts (2 drops,

(39) (a) Bosshard, H. H.; Mory, R.; Schmid, M.; Zollinger, H. *Helv. Chim. Acta* **1959**, *42*, 1653–1658. (b) Egawa, Y.; Suzuki, M.; Okuda, T. *Chem. Pharm. Bull.* **1963**, *11*, 589–596.

~5 mol %) of BF_3 etherate. After the mixture was stirred for 24 h, water (30 mL) was added and the products were extracted into dichloromethane (3 × 60 mL). The organic layer was dried (Na_2SO_4), and the solvents were removed under vacuum. TLC analysis (9:1 hexane/EtOAc) of the residue indicated the presence of a small amount of less polar material; flash chromatography (96:4 hexane/EtOAc) gave 819 mg (74%) of (+)-**7a** as an oil that crystallized on storing at −20 °C and 93 mg (8%) of the regioisomer. (+)-**7a**: $[\alpha]^{25}_D$ +2.56° (*c* 11.05, $CHCl_3$); 93.8% ee;[32] IR ($CHCl_3$) 3600, 2985, 2930, 1130, 1105 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (m, 5 H), 7.41 (m, 5 H), 3.86 (quintet, 1 H, CH_2CHCH_2), 3.69 (d, 2 H, CH_2OSi), 3.40–3.55 (m, 4 H, CH_2OCH_2), 2.15 (br s, 1 H, OH), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 1.05 (s, 9 H, $(CH_3)_3Si$), 0.89 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{35}H_{58}O_3Si$: C, 74.75; H, 10.54. Found: C, 74.79; H, 10.44.

3-*O*-Hexadecyl-1-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol ((−)-7b). The TBDPS ether (−)-**7b** was prepared from (−)-**6b** in 68% yield as described above; $[\alpha]^{25}_D$ −2.60° (*c* 11.05, $CHCl_3$); 95.3% ee.[32] IR and ^1H NMR spectra were identical with those obtained for (+)-**7a**. Anal. Calcd for $C_{35}H_{58}O_3Si$: C, 74.75; H, 10.54. Found: C, 74.80; H, 10.53.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol ((+)-8a). Sodium hydride (97%, 24 mg, 1.0 mmol) was added under a stream of dry nitrogen to a solution of 277 mg (0.5 mmol) of (+)-**7a** in dry benzene (5 mL) at room temperature. After the evolution of hydrogen had stopped, 0.4 mL (6.4 mmol) of methyl iodide was added, and the reaction mixture was stirred for 12 h at room temperature. Hexane (5 mL), ethanol (1 mL), and water (0.5 mL) were added successively, and the product was extracted with hexane (2 × 50 mL). The organic layer was dried over Na_2SO_4, and the solvents were evaporated under vacuum. The residue was purified by flash chromatography (97:3 hexane/EtOAc) to give 279 mg (98%) of (+)-**8a**; $[\alpha]^{25}_D$ +5.98° (*c* 4.09, $CHCl_3$); IR ($CHCl_3$) 2985, 2930, 1130, 1110 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.69 (m, 5 H), 7.39 (m, 5 H), 3.69 (d, 2 H, CH_2OSi), 3.40–3.65 (m, 5 H, CH_2OCH_2, CH_2CHCH_2), 3.38 (s, 3 H, OCH_3), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 1.05 (s, 9 H, $(CH_3)_3Si$), 0.89 (br t, 3 H, ω-CH_3). Anal. Calcd for $C_{36}H_{60}O_3Si$: C, 76.00; H, 10.63. Found: C, 76.16; H, 10.84.

3-*O*-Hexadecyl-2-*O*-methyl-1-*O*-(*tert*-butyldiphenylsilyl)-*sn*-glycerol ((−)-8b). This compound was prepared from (−)-**7b** in 97% yield as described above; $[\alpha]^{25}_D$ −6.01° (*c* 4.09, $CHCl_3$). IR and ^1H NMR spectra were identical with those obtained for (+)-**8a**. Anal. Calcd for $C_{36}H_{60}O_3Si$: C, 76.00; H, 10.63. Found: C, 75.80; H, 10.75.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((−)-4a). To a solution of 256 mg (0.45 mmol) of (+)-**8a** in 5 mL of tetrahydrofuran was added 0.9 mL (0.90 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran. After the mixture was stirred for 2 h at room temperature, water was added and the product was extracted into ether (3 × 50 mL). The organic layer was dried over Na_2SO_4, and the solvents were removed under vacuum. The residue was purified by flash chromatography (4:1 hexane/EtOAc) to give 148 mg (100%) of (−)-**4a**: mp 29–30 °C (lit.[36] mp 29–30 °C); $[\alpha]^{25}_D$ −9.46° (*c* 1.64, $CHCl_3$), 97.5% ee based on lit.[36] $[\alpha]^{25}_D$ −9.92° (*c* 1.64, $CHCl_3$) and 97% ee based on ^1H NMR analysis of its (*R*)-(+)-MTPA ester. Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.80. Found: C, 72.49; H, 12.79.

Mosher Ester of (−)-4a. ^1H NMR (200 MHz, $CDCl_3$) δ 7.46 (m, 5 H), 4.52 (dd, J_{AC} = 3.8 Hz, J_{AB} = 11.6 Hz), 4.36 (dd, J_{BC} = 6.0 Hz, J_{AB} = 11.6 Hz, 1 H), 3.33–3.61 (m, 5 H, CH_2CHCH_2, $OCH_2(CH_2)_{14}CH_3$, and $CH_2OC_{16}H_{33}$), 3.56 (s, 3 H, CH_3O), 3.39 (s, 3 H, CH_3O), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.89 (br t, 3 H, ω-CH_3).

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol ((+)-4b). This compound was prepared from (−)-**7b** in 100% yield by using the same procedure as described for (−)-**4a**; $[\alpha]^{25}_D$ +9.51° (*c* 1.64, $CHCl_3$). Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.80. Found: C, 72.65; H, 13.08.

1-*O*-Hexadecyl-*sn*-glycerol ((−)-9a). A solution of 832 mg (1.50 mmol) of (+)-**7a** in 25 mL of tetrahydrofuran was treated with 3 mL (3.0 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran for 2 h at room temperature. Workup as described above for (−)-**4a** gave a white solid that was purified by flash chromatography (1:1 hexane/EtOAc), yielding 460 mg (97%) of (−)-**9a**: mp 63.0–64.0 °C (lit.[40] mp 62.5–63.5 °C); TLC (2:1 hexane/EtOAc) R_f 0.16; $[\alpha]^{25}_D$ −2.68° (*c* 3.5, THF), $[\alpha]^{25}_D$ −3.40° (*c* 1.0, $CHCl_3$) (lit.[40] $[\alpha]^{25}_D$ −3.20° (*c* 1.0, $CHCl_3$)).

3-*O*-Hexadecyl-*sn*-glycerol ((+)-9b). This compound was prepared from (−)-**7b** in 98% yield by using the same procedure as described for (−)-**9a**; mp 63.0–64.0 °C (lit.[40] mp 62.5–63.5 °C); TLC (2:1 hexane/EtOAc) R_f 0.16; $[\alpha]^{25}_D$ +2.69° (*c* 3.5, THF), $[\alpha]^{25}_D$ +3.50° (*c* 1.0, $CHCl_3$) (lit.[40] $[\alpha]^{25}_D$ +2.28° (*c* 3.5, THF), lit.[38] $[\alpha]^{25}_D$ +3.1° (*c* 1.0, $CHCl_3$)).

Bis-Mosher Ester of (−)-9a, (+)-9b, and *rac*-9. The MTPA chloride was prepared as described under General Procedure for Preparation of Mosher Esters. To a solution of the diol (0.15 mmol) in 2 mL of pyridine was added 60 μL of neat (*R*)-(+)-MTPA chloride. After the mixture had stirred overnight, TLC analysis (1:1 hexane/EtOAc) indicated the complete conversion of the diols into the corresponding bis-Mosher esters. Workup was as described above. ^1H NMR (400 MHz, $CDCl_3$) of bis-Mosher ester of (−)-**9a**: δ 7.45 (m, 10 H), 5.45 (m, 1 H, CH_2CHCH_2), 4.73 (dd, 1 H, J_{AB} = 12.45 Hz, J_{AC} = 2.93 Hz, H_a of C_3 of CH_2OH), 4.42 (dd, 1 H, J_{AB} = 12.45 Hz, J_{BC} = 6.34 Hz, H_b of C_3 of CH_2OH), 3.31–3.59 (m, 10 H, $CH_2OC_{16}H_{33}$, $OCH_2(CH_2)_{14}CH_3$, and two OCH_3), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.89 (br t, 3 H, ω-CH_3). ^1H NMR (400 MHz, $CDCl_3$) of bis-Mosher ester of (+)-**9b**: δ 7.45 (m, 10 H), 5.48 (m, 1 H, CH_2CHCH_2), 4.62 (dd, 1 H, J_{AB} = 12.45 Hz, J_{AC} = 3.40 Hz, H_a of C_1 of CH_2OH), 4.36 (dd, 1 H, J_{AB} = 12.45 Hz, J_{BC} = 5.08 Hz, H_b of C_1 of CH_2OH), 3.31–3.59 (m, 10 H, $CH_2OC_{16}H_{33}$, $OCH_2(CH_2)_{14}CH_3$, and two OCH_3), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.89 (br t, 3 H, ω-CH_3). ^1H NMR (400 MHz, $CDCl_3$) of bis-Mosher ester of *rac*-9: δ 7.45 (m, 10 H), 5.48 (m, 1 H, CH_2CHCH_2), 4.73 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{AC} = 2.93 Hz, H_a of C_3 of CH_2OH), 4.62 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{BC} = 3.40 Hz, H_b of C_1 of CH_2OH), 4.42 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{AC} = 6.34 Hz, H_a of C_3 of CH_2OH), 4.36 (dd, 0.5 H, J_{AB} = 12.45 Hz, J_{BC} = 5.08 Hz, H_b of C_1 of CH_2OH), 3.31–3.59 (m, 10 H, $CH_2OC_{16}H_{33}$, $OCH_2(CH_2)_{14}CH_3$, and two OCH_3), 1.26 (br s, 28 H, $CH_3(CH_2)_{14}$), 0.89 (br t, 3 H, ω-CH_3).

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