Enantioselective Syntheses of 1-*O*-Benzyl-*sn*-glycerol and 1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol via Asymmetric Dihydroxylation of Allyl 4-Methoxyphenyl Ether. Use of AD-Mix Supplemented with Potassium Persulfate

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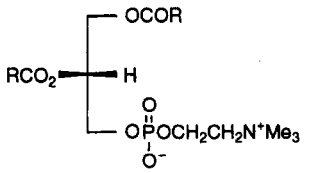
Diacylphosphatidylcholine (1) is one of the major components of membranes and is used widely in physical studies of membrane structure and function and for drug delivery in liposomes. Unnatural ether-linked phospholipids that contain a 16- or 18-carbon aliphatic chain at the *sn*-1 position and an *O*-methyl group at the *sn*-2 position of glycerophosphocholine (2) have potent cytotoxic activity toward various tumor cells.[1] We report a large scale preparation of 1-*O*-benzyl-*sn*-glycerol (**3a**) and 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**4a**), as well as the preparation of their enantiomers **3b** and **4b**, which are precursors of the phospholipids 1 and 2.



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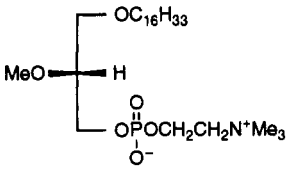

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The asymmetric dihydroxylation of olefins via osmylation in the presence of a chiral ligand provides enantiomerically enriched diols. Several osmylation procedures have been reported for the conversion of olefins to chiral 1,2-diols using stoichiometric amounts of osmium tetraoxide and a chiral ligand.[2] A catalytic asymmetric dihydroxylation reaction has been developed recently.[3] Sharpless and co-workers have shown recently that the dihydroxylation of aryl allyl ether using AD-mix-α or AD-mix-β generates substituted glycerols in high enantiomeric purity. The catalytic asymmetric dihydroxylation method is convenient for only small-scale syntheses of 1,2-diols, since 10 mL of *tert*-butyl alcohol and water (1:1 v/v) is used for a 1-mmol scale reaction. In large-scale preparations prohibitively large volumes of solvents and mechanical stirring would be required. We present herein a simple modification for the scale-up of the asymmetric dihydroxylation procedure that allows use of only small amounts of AD-mix supplemented with stoichiometric amounts of the cooxidant potassium persulfate, which promotes the catalytic reaction. Under these conditions, a large excess of solvents is not needed; for example, 0.2 mol of allyl 4-methoxyphenyl ether was dihydroxylated in only 400 mL of *tert*-butyl alcohol/water (1:1). In this paper, this modified asymmetric dihydroxylation procedure was applied to the synthesis of the important C_3 synthon 1-*O*-benzyl-*sn*-glycerol (**3a**) and to the antitumor phospholipid precursor, 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**4a**). The enantiomers of **3b** and **4b** are readily obtained by substituting AD-mix-β for AD-mix-α.

O-Benzylglycerol is one of the important building blocks for the synthesis of a variety of phospholipids[4] and biologically important natural products.[5] *O*-Benzylglycerol has been prepared from D-mannitol,[6] *O*-benzyl-L-serine,[7a] 3-(benzoyloxy)-1-hydroxypropanone,[7b] L-ascorbic acid,[7c] D-isoascorbic acid,[7c] and L-serine.[7d] The unnatural 1-*O*-benzyl-*sn*-glycerol (**3b**) has been prepared by bismesylation of **3a**, followed by inversion with acetate ion at C-2 and hydrolysis.[8] We now report a very short and highly enantioselective synthesis of **3a** or **3b** in 55% overall yield starting from aryl diol **5**. In addition, we show that alkylation of diol **5** with hexadecyl bromide via a cyclic stannoxane intermediate, followed by *O*-methylation and deprotection, provides access to multigram quantities of crystalline, optically pure 1-*O*-hexadecyl-2-*O*-methylglycerol (**4a** or **4b**).

Results and Discussion

Modified Chiral Dihydroxylation. The catalytic asymmetric dihydroxylation of 4-methoxyphenyl allyl ether using AD-mix-α or -β provides substituted glycerol derivatives.[3a,c] In this study, 4-methoxyphenyl allyl ether was used as the starting material to prepare glycerol derivatives because (i) 4-substituted-aryl allyl ethers on asymmetric dihydroxylation gave higher enantioselectivity than the 2-substituted- or unsubstituted-aryl allyl ethers[3a] or allyl benzyl ether[3c] or allyl triphenylmethyl ether,[3c] and (ii) the 4-methoxyphenyl group is easy to remove by using CAN.[9] 4-Methoxyphenyl allyl ether (0.2 mol) was dihydroxylated by using a small amount of AD-mix-α or -β

(1) (a) Munder, P. G.; Modolell, M.; Bausert, W.; Oettgen, H. F.; Westphal, O. In *Augmenting Agents in Cancer Therapy*; Hersh, E. M., Chirigos, M. A., Mastrangelo, M. J., Eds.; Raven Press: New York, 1981; pp 441–458. (b) Berdel, W. E.; Andreesen, R.; Munder, P. G. In *Phospholipids and Cellular Regulation*; Kuo, J. F., Ed.; CRC Press: Boca Raton, FL, 1985; Vol. 2, pp 41–73.

(2) Hanessian, S.; Meffre, P.; Girard, M.; Beaudoin, S.; Sancéau, J.-Y.; Bennani, Y. *J. Org. Chem.* **1993**, *58*, 1991–1993, and references cited therein.

(3) (a) Wang, Z.-M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267–2270. (b) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771, and references cited therein. (c) Vilchèze, C.; Bittman, R. *J. Lipid Res.* **1994**, *35*, 734–738.

(4) (a) For a recent review, see Bittman, R. In *Phospholipids Handbook*; Cevc, G., Ed.; Marcel Dekker: New York, 1993; pp 141–232. (b) Duclos, R. I., Jr.; Makriyannis, A. *J. Org. Chem.* **1992**, *57*, 6156–6163. (c) Young, R. C.; Downes, C. P.; Eggleston, D. S.; Jones, M.; Macphee, C. H.; Rana, K. K.; Ward, J. G. *J. Med. Chem.* **1990**, *33*, 641–646. (d) Abdelmageed, O. H.; Duclos, R. I., Jr.; Griffin, R. G.; Siminovitch, D. J.; Ruocco, M. J.; Makriyannis, A. *Chem. Phys. Lipids* **1989**, *50*, 163–169. (e) Hirth, G.; Barner, R. *Helv. Chim. Acta* **1982**, *65*, 1059–1084.

(5) (a) Burgess, K.; Ho, K-K.; Ke, C-Y. *J. Org. Chem.* **1993**, *58*, 3767–3768. (b) Saite, S.; Hamano, S.; Moriyama, H.; Okada, K.; Monibrake, T. *Tetrahedron Lett.* **1988**, *29*, 1157–1560. (c) Bauer, F.; Rueβ, K.-P.; Liefländer, M. *Liebigs Ann. Chem.* **1991**, 765–768.

(6) (a) Jurzak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447–488. (b) Golding, B. T.; Ioannou, P. V. *Synthesis* **1977**, 423–424, and references cited therein.

(7) (a) De Witt, P.; Misiti, D.; Zappia, G. *Tetrahedron Lett.* **1989**, *30*, 5505–5506. (b) Aragozzini, F.; Maconi, E.; Potenza, D.; Scolastico, C. *Synthesis* **1989**, 225–227. (c) Mikkilineni, A. B.; Kumar, P.; Abushanab, E. *J. Org. Chem.* **1988**, *53*, 6005-6009. (d) Hirth, G.; Saroka, H.; Bannwarth, W.; Barner, R. *Helv. Chim. Acta* **1983**, *66*, 1210–1240.

(8) Takano, S.; Seya, K.; Goto, E.; Hirama, M.; Ogasawara, K. *Synthesis* **1983**, 116–117.

(9) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *22*, 3627–3629.

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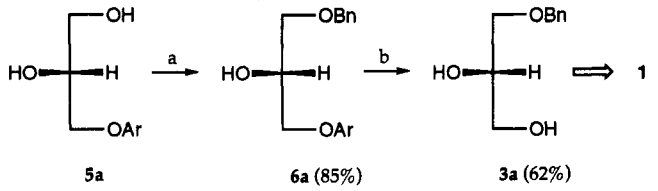
Scheme 1. Synthesis of 1-O-Benzyl-*sn*-glycerol (3a) (Ar = 4-methoxyphenyl)



5a 6a (85%) 3a (62%)

[a] Reagents: (a) (i) Bu_2SnO, $CHCl_3/CH_3OH$ (10:1 v/v), reflux; (ii) CsF, $C_6H_5CH_2Cl$, DMF, rt; (b) CAN, CH_3CN/H_2O (1:1), 0 °C.

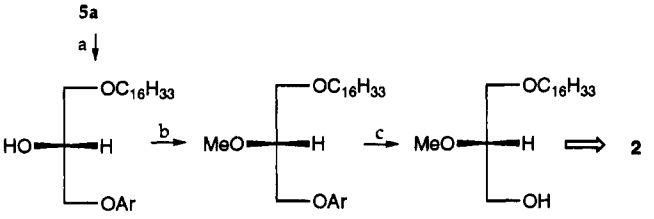
(<10% by weight of the olefin) in the presence of stoichiometric amounts of the cooxidant potassium persulfate. When only a small amount of AD-mix is used, the asymmetric dihydroxylation of olefins takes place slowly because the osmate content of commercial AD-mix is low. To speed up the dihydroxylation, the commercial AD-mix was supplemented with both osmate and the chiral dihydroquinine (DHQ) or dihydroquinidine (DHQD) phthalazine ligand. The role of the potassium persulfate and the potassium ferricyanide (present in AD-mix) is to reoxidize the osmium(IV) for further dihydroxylation in order to complete the reaction, so that large amounts of AD-mix were not required. The aryl diol **5** prepared by this process was similar with respect to physical properties with compound **5** prepared by using the unmodified[3a] asymmetric dihydroxylation reaction.[10]

Regioselective Monoetherification of 1,2-Diol. (a) *O*-Benzylation. The organotin-mediated benzylation of 1-phenylethanediol with benzyl bromide/iodide and benzyl chloride in DMF at room temperature is regioselective, giving the primary and secondary benzyl ethers in 9:1 and 7:1 ratio, respectively.[11] We have studied the reaction of 1-*O*-(4-methoxyphenyl)-*sn*-glycerol (**5a**) or 3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**5b**) with benzyl halides in various solvents in efforts to achieve high regioselectivity at the primary hydroxyl group. The reaction of the cyclic stannoxane derivative of **5a** with benzyl chloride and cesium fluoride in DMF at rt gave 1-*O*-benzyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**6a**) and 2-*O*-benzyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol in isolated yields of 85% and 9%, respectively (Scheme 1). **(b) *O*-Alkylation.** The reaction of the cyclic stannoxane of aryl diol **5a** with hexadecyl bromide in the presence of cesium fluoride in DMF at rt provided 1-*O*-hexadecyl-3-*O*-(4-methoxyphenyl)glycerol (**7a**) in 89% yield (Scheme 2).

2-*O*-Methylation and Deprotection of 4-Methoxyphenyl Group. Methylation of 1-*O*-hexadecyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**7a**) in the presence of sodium hydride in THF gave **8a** in quantitative yield. Oxidation of hydroquinone ether **8a** by reaction with CAN in aqueous acetonitrile afforded 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**4a**) in 95% yield. Similarly, deprotection of the 4-methoxyphenyl group from 1-*O*-benzyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**6a**) by reaction with CAN gave 1-*O*-benzyl-*sn*-glycerol (**3a**) in 62% yield. The only compound that required purification by column chromatography in the reaction sequence shown in Scheme 2 was 1-*O*-hexadecyl-2-*O*-methylglycerol (**4a**), which is a low-melting solid.

Evaluation of Optical purity. To determine the enantiomeric excess (ee) of benzyl glycerol (**3a** and **3b**) by 400-MHz ^1H NMR, we prepared their (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenyl acetic acid [(*R*)-(+)-(MTPA] esters. Integration of the two AB quartets of the (*R*)-MTPA esters derived from a racemic mixture of **3a** and **3b** on an expanded scale indicated a 1:1 ratio of the areas of the signals at δ 4.76–4.72 and 4.66–4.62. The individual diastereotopic protons of CH_2OMTPA in each enantiomer showed base-line separation. The lower-field AB quartet at δ 4.76 and 4.73 is assigned to the protons of CH_2OMTPA of the 3-*O*-benzyl-*sn*-glycerol (**3b**) bis-MTPA ester and the higher-field AB quartet at δ 4.66 and 4.62 corresponds to the protons of CH_2OMTPA of the 1-*O*-benzyl-*sn*-glycerol (**3a**) bis-MTPA ester. Integration of the signal at δ 4.66 and 4.62 vs δ 4.76 and 4.73 indicated an ee of 91%. A comparison of the optical rotations of the commercially available glycerol **3a** with our sample also indicated high optical purity. The specific rotation of **3a** prepared according to Scheme 1 was 3.95° in benzene, compared with 3.09° for commercially available **3a**.

Scheme 2. Synthesis of 1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol (4a) (Ar = 4-methoxyphenyl)



7a (89%) 8a (99%) 4a (95%)

[a] Reagents: (a) (i) Bu_2SnO, $CHCl_3/CH_3OH$ (10:1 v/v), reflux; (ii) CsF, $C_{16}H_{33}Br$, DMF, rt, overnight, then 90 °C for 2 h; (b) NaH, CH_3I, *n*-Bu_4NBr, THF, rt; (c) CAN, CH_3CN/H_2O (1:1), 0 °C to rt.

In summary, *O*-benzylglycerol (**3a,b**) and 1-*O*-hexadecyl-2-*O*-methylglycerol (**4a,b**) were prepared from aryl allyl diol **5a,b** in 55 and 84% overall yields, respectively, and in high chiral purity by using catalytic AD-mix-α or -β supplemented with potassium persulfate. Compounds **5**, **7**, and **8** are crystalline solids and were purified by recrystallization. The route to **4** shown in Scheme 2 offers the advantage that chromatography is not required until the final step.

Experimental Section

General Procedures. Melting points were taken on a capillary melting point apparatus (Thomas-Hoover) and are uncorrected. ^1H NMR spectra were recorded on an IBM-Bruker WP 200-MHz spectrometer except where otherwise indicated; chemical shifts are given as parts per million downfield from internal tetramethylsilane. IR spectra were recorded on a Perkin-Elmer FT-1600 spectrophotometer. Optical rotations were measured in a cell of 1-dm pathlength on a JASCO DIP-140 digital polarimeter. Elemental analyses were performed by Desert Analytics (Tucson, AZ). TLC was carried out with silica gel GF (250-μm thickness) glass plates from Analtech (Newark, DE). Visualization of the compounds was by charring with 10% sulfuric acid in ethanol or short-wavelength UV light. For flash chromatography, silica gel 60 (230–400 ASTM mesh) was used (purchased from Aldrich).

Chemicals. Solvents were dried as follows: THF was refluxed over sodium benzophenone ketyl for several hours and then distilled just before use; chloroform was distilled from P_2O_5; benzene was washed with concentrated sulfuric acid and water,

(10) Compound **5a**: mp 79–80 °C; $[\alpha]^{25}_D$ +2.27° (*c* 0.5, $CHCl_3$) and $[\alpha]^{25}_D$ +7.35° (*c* 1.5, CH_3OH) [lit.[3a] $[\alpha]_D$ +7.5° (*c* 1.1, CH_3OH)].
(11) Nagashima, N.; Ohno, M. *Chem. Lett.* **1987**, 141–144.

dried over calcium chloride, and then distilled over sodium metal. DMF was dried over barium oxide and distilled. AD-mix-α, AD-mix-β, $(DHQ)_2$-PHAL, $(DHQD)_2$-PHAL, potassium osmate(VI) dihydrate, potassium persulfate, methyl iodide, benzyl chloride, cesium fluoride, dibutyltin oxide, (*R*)-(−)-MTPA chloride, and ammonium cerium(IV) nitrate were from Aldrich.

3-*O*-(4-Methoxyphenyl)-*sn*-glycerol [(+)-5a]. A mixture of AD-mix-α (2.8 g), $(DHQ)_2$-PHAL (1.55 g), $K_2OsO_2(OH)_4$ (0.15 g), K_2CO_3 (83 g), and $K_2S_2O_8$ (54 g, 0.20 mol) in *tert*-butyl alcohol (200 mL) and water (200 mL) was stirred for 30 min at rt. The mixture was cooled to 0 °C, and allyl 4-methoxyphenyl ether (32.84 g, 0.20 mol) was slowly added. After the mixture had stirred for 24 h sodium sulfite (30 g) was added, and the mixture was allowed to warm to rt. The product was extracted with ethyl acetate. The organic layers were washed with brine and dried over anhydrous sodium sulfate. Removal of the solvents under reduced pressure gave crude diol **5a**, which was dissolved in ethyl acetate/hexane (1:1) and filtered through a pad of silica gel. The filtrate was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate and hexane twice to give aryl diol **5a** as a white solid (33.2 g, 84%): mp 79–80 °C; $[\alpha]^{25}_D$ +2.27° (*c* 0.5, $CHCl_3$) and $[\alpha]^{25}_D$ +7.35° (*c* 1.5, CH_3OH) [lit.[3a] $[\alpha]_D$ +7.5° (*c* 1.1, CH_3OH)]; IR (KBr) 3319, 2931, 2907, 2860, 2837, 1507, 1284, 1237, 1108, 1037 cm^{-1}; ^{1}H NMR δ 7.26–6.69 (m, 4H), 4.09–4.02 (m, 1H), 3.94 (d, 2H, J = 5.0 Hz), 3.78–3.63 (m, 2H), 3.74 (s, 3H).

1-*O*-(4-Methoxyphenyl)-*sn*-glycerol [(−)-5b]. This compound was prepared by using AD-mix-β and $(DHQD)_2$-PHAL in 85% yield by the procedure described above; $[\alpha]^{25}_D$ −2.45° (*c* 0.5, $CHCl_3$) and $[\alpha]^{25}_D$ −7.40° (*c* 1.6, CH_3OH).

1-*O*-Benzyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol [(−)-6a]. A suspension of 1.99 g (10 mmol) of diol **5a** and 2.49 g (10 mmol) of dibutyltin oxide in 100 mL of chloroform–methanol (10:1) was refluxed for 3 h to give a clear solution. After the solvents were removed under reduced pressure to give a white solid, 2.9 g (19.1 mmol) of cesium fluoride was added. After the solid mixture was dried overnight under high vacuum, the mixture was suspended in 20 mL of DMF. To the suspension was added a solution of 1.26 mL (10.9 mmol) of benzyl chloride in 5 mL of DMF, and the mixture was stirred for 24 h at rt. After 50 mL of ethyl acetate and 1 mL of water were added, the mixture was stirred vigorously for 30 min and then filtered through a pad of silica gel to remove dibutyltin oxide. The filtrate was washed with water and then with brine. Removal of the solvents gave a residue that was purified by column chromatography on silica gel (elution with hexane/ethyl acetate 4:1) to give 2.45 g (85%) of **6a** as a colorless oil: $[\alpha]^{25}_D$ −2.44° (*c* 5.7, C_6H_6); IR (neat) 3436, 2919, 2860, 2837, 1507, 1225, 1120, 1037 cm^{-1}; ^{1}H NMR δ 7.44–7.31 (m, 5H), 6.93–6.86 (m, 4H), 4.66–4.63 (m, 2H), 4.21–4.26 (m, 1H), 3.98 (d, 2H, J = 5.0 Hz), 3.78–3.63 (m, 2 H), 3.74 (s, 3H). Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.47; H, 6.92.

3-*O*-Benzyl-1-*O*-(4-methoxyphenyl)-*sn*-glycerol [(+)-6b]. This compound was prepared in 82% yield by the procedure described above: $[\alpha]^{25}_D$ +2.35° (*c* 5.3, C_6H_6).

1-*O*-Benzyl-*sn*-glycerol [(−)-3a]. 1-*O*-Benzyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (1.0 g, 3.47 mmol) was dissolved in a mixture of acetonitrile (12.5 mL) and water (5.5 mL) and cooled in an ice/water bath. Ceric ammonium nitrate (4.75 g, 8.66 mmol) was added in portions with vigorous stirring. After 30 min, 1.5 g of sodium chloride was added to give two layers. The organic layer was separated, and the aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (elution with 8:1 hexane/ethyl acetate) to give 0.39 g (62%) of **3a** as a colorless oil: $[\alpha]^{25}_D$ −3.95° (*c* 6.0, C_6H_6); the commercially available Sigma sample gave $[\alpha]^{25}_D$ −3.09° (*c* 3.75, C_6H_6); IR (neat) 3436, 2919, 2860, 2837, 1507, 1225, 1120, 1037 cm^{-1}; ^{1}H NMR δ 7.39–7.25 (m, 5H), 4.54 (s, 2H), 3.88–3.53 (m, 5H), 2.72 (br s, 2 H). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.92; H, 7.74. Found: C, 65.98; H, 7.68.

3-*O*-Benzyl-*sn*-glycerol [(+)-3b]. This compound was prepared in 67% yield by the procedure described above; $[\alpha]^{25}_D$ +3.90° (*c* 6.0, C_6H_6).

Procedure for Preparation of the Bis-MTPA Ester of 1-*O*-Benzyl-*sn*-glycerol. To a solution of 8.5 mg (46.7 μmol) of *O*-benzylglycerol **3** and 12.0 mg (98.2 μmol) of *N,N*-(dimethylamino)pyridine in 1 mL of dichloromethane was added 25 mg (98.9 μmol) of (*R*)-(−)-MTPA chloride. The mixture was stirred overnight at rt, the solvent was removed under reduced pressure, and the residue was suspended in ether and filtered through a pad of silica gel. The filtrate was concentrated to give 18 mg (100%) of bis-MTPA ester as a colorless oil. **Bis-MTPA ester of 1-*O*-benzyl-*sn*-glycerol (3a):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.21 (m, 15H), 5.52–5.48 (m, 1H), 4.76 and 4.73 (AB q, 1H, J = 11.92, 12.3 Hz), 4.48–4.36 (m, 5H), 3.46 (s, 3H), 3.38 (s, 3H). **Bis-MTPA ester of 3-*O*-benzyl-*sn*-glycerol (3b):** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.25 (m, 15H), 5.55–5.50 (m, 1H), 4.65 and 4.63 (AB q, 1H, J = 11.8, 12.3 Hz), 4.51–4.36 (m, 5H), 3.46 (s, 3H), 3.40 (s, 3H).

1-*O*-Hexadecyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (7a). A mixture of dibutylstannoxane derivative and 28.8 g (0.19 mol) of cesium fluoride was prepared by the same procedure described for **6a** using 19.9 g (0.10 mol) of diol **5a** and 24.9 g (0.10 mol) of dibutyltin oxide. This mixture was suspended in 50 mL of DMF, and 34 mL (0.11 mmol) of hexadecyl bromide was added. The mixture was stirred for 24 h at rt and then at 90 °C for 2 h. The reaction mixture was cooled and 200 mL of ethyl acetate and 10 mL of water were added. The mixture was stirred vigorously for 30 min and filtered through a pad of silica gel to remove dibutyltin oxide. The filtrate was washed with water and then with brine. Removal of the solvent gave a residue that was purified by crystallization with hexane–ethyl acetate to give 37.6 g (89%) of **7a**[12] as a white solid: mp 64–65 °C; IR (KBr) 3436, 2919, 2837, 1507, 1231, 1131, 1038 cm^{-1}; ^{1}H NMR δ 7.30–6.80 (m, 4H), 4.08–4.09 (m, 1H), 3.97 (d, 2H, J = 4.59 Hz), 3.77 (s, 3H), 3.53–3.64 (m, 2H), 3.48 (t, 3H, J = 6.65 Hz), 1.54–1.58 (m, 2H), 1.26 (br s, 26H), 0.88 (t, 3H, J = 5.96 Hz). Anal. Calcd for $C_{26}H_{46}O_4$: C, 73.89; H, 10.97. Found: C, 73.88; H, 11.13.

3-*O*-Hexadecyl-1-*O*-(4-methoxyphenyl)-*sn*-glycerol (7b). This compound was prepared in 90% yield by the procedure described above.

1-*O*-Hexadecyl-2-*O*-methyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (8a). To a suspension of 4.25 g (141 mmol, 80% in white oil, washed with dry hexane twice) of sodium hydride in 200 mL of THF was added 29.6 g (70 mmol) of 1-*O*-hexadecyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**7a**) at 0 °C. After the evolution of hydrogen had stopped, 13.3 mL (213 mmol) of methyl iodide and 0.78 g (2.42 mmol) of tetrabutylammonium iodide were added. After 24 h the solvent was removed under reduced pressure, and the residue was diluted with ether and washed with water. The organic layer was concentrated under reduced pressure to give 30.1 g (99%) of **8a**[12] as a white low-melting solid: IR (KBr) 2966, 2919, 2849, 1226, 1125, 1043 cm^{-1}; ^{1}H NMR δ 7.30–6.80 (m, 4H), 4.08–3.97 (m, 3H), 3.77 (s, 3H), 3.69–3.42 (m, 4H), 3.52 (s, 3H), 1.54–1.58 (m, 2H), 1.26 (br s, 26H), 0.88 (t, 3H, J = 5.96 Hz). Anal. Calcd for $C_{27}H_{48}O_4$: C, 74.27; H, 11.08. Found: C, 74.34; H, 11.25.

3-*O*-Hexadecyl-2-*O*-methyl-1-*O*-(4-methoxyphenyl)-*sn*-glycerol (8b). This compound was prepared in 98% yield by the procedure described above.

1-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol [(−)-4a]. Ceric ammonium nitrate (110.7 g, 202 mmol) was slowly added at 0 °C to a vigorously stirring solution of 29.4 g (67.3 mmol) of 1-*O*-hexadecyl-2-*O*-methyl-3-*O*-(4-methoxyphenyl)-*sn*-glycerol (**8a**) in a mixture of acetonitrile and water (200 mL, 2:1). After the mixture had stirred for 4 h at rt, the reaction was quenched by the addition of sodium sulfite (25 g), giving a pale yellow solution. (Workup using sodium bicarbonate instead of sodium sulfite gave a dark brown solution.) The product was extracted with ether, washed with brine, and dried over anhydrous sodium sulfate. Removal of solvent gave crude product **4a**, which was purified by flash chromatography on silica gel (elution with hexane–ethyl acetate 4:1) to give 21.1 g (95%) of **4a** as a white solid: mp 30–31

(12) Surprisingly, compounds **7** and **8** gave observed optical rotation values of zero for both isomers in chloroform or benzene at a concentration of 0.9 g/100 mL. However, the final product **4a,b** gave satisfactory specific rotations.

°C [lit.[13a] mp 30–31 °C; lit.[13b] mp 29–30 °C]; $[\alpha]^{25}_D$ −10.13° (*c* 1.5, $CHCl_3$) [lit.[13a] $[\alpha]^{25}_D$ −9.95° (*c* 1.64, $CHCl_3$); lit.[13b] $[\alpha]^{25}_D$ −9.96° (*c* 1.64, $CHCl_3$)]; IR (KBr) 3401, 2920, 2837, 1120, 1060 cm^{-1}; ^1H NMR δ 3.80 and 3.74 (AB q, 1H, J = 4.14 and 10.6 Hz), 3.67 and 3.62 (AB q, 1H, J = 5.04 and 10.6 Hz), 3.56–3.41 (m, 3H), 3.47 (s, 3H), 1.96 (br s, 1H), 1.54–1.58 (m, 2H), 1.26 (s, 26H), 0.88 (t, 3H, J = 5.96 Hz). Anal. Calcd for $C_{20}H_{42}O_3$: C, 72.67; H, 12.81. Found: C, 72.36; H, 12.87.

3-*O*-Hexadecyl-2-*O*-methyl-*sn*-glycerol [(+)-4b]. This compound was prepared in 93% yield by the procedure described above; $[\alpha]^{25}_D$ +9.82° (*c* 1.65, $CHCl_3$).

(13) (a) Ohno, M.; Fujita, K.; Nakai, H.; Kobayashi, S.; Inoue, K.; Nojima, S. *Chem. Pharm. Bull.* **1985**, *33*, 572–582. (b) Guivisdalsky, P. N.; Bittman, R. *J. Org. Chem.* **1989**, *54*, 4637–4642.

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Registry No. Ammonium cerium(IV) nitrate, 16774-21-3; benzyl chloride, 100-44-7; 1-*O*-benzyl-*sn*-glycerol 17325-85-8; 3-*O*-benzyl-*sn*-glycerol 56552-80-8; cesium fluoride, 13400-13-0; dibutyltin oxide, 818-08-6; 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol, 120964-49-0; iodomethane, 74-88-4; potassium osmate(VI) dihydrate, 19718-36-6; potassium persulfate, 7727-21-1.