A New Synthetic Route to Chiral Glycerolipid Precursors Using a Cyclic Sulfate Synthon: Preparation of 1-*O*-Hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol and Its 1-Thio and 1-Aza Analogues

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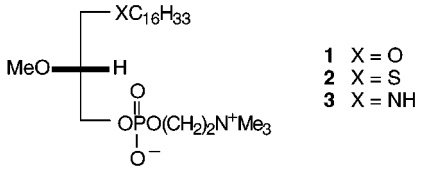
Phosphatidylcholines (PCs) are major components of cell membranes and play important physiological roles in many biological processes.[1] Structurally modified PCs have been widely used for drug delivery in liposomes[2] and for physical studies of membrane structure and function.[3] Unnatural ether-linked phospholipids such as alkyl lysophospholipids (ALPs, **1**), which contain a 1-*O*-16- or 18-carbon aliphatic chain at the *sn*-1 position and an *O*-methyl group at the *sn*-2 position of glycerophosphocholine, have potent cytotoxic activity toward various tumor cells, and are potential anticancer drugs in clinical trials.[4] Analogues of ALPs bearing an alkylthio or an alkylamino group at the *sn*-1 position of the glycerol backbone, for instance, 1-*S*-hexadecyl-2-*O*-methyl/ethyl-*rac*-thioglycerol-3-phosphocholine (**2**) and 1-*N*-hexadecyl-2-*O*-methyl-*sn*-aminoglycerol-3-phosphocholine (**3**), possess antineoplastic activity.[5] Single-chain ether lipids that bear an *ω*-carboxyl group at the *sn*-1 position[6a] represent another unnatural analogue of platelet-activating factor. Coupling of ether phospholipids to mechanically stable solid surfaces (e.g., silica propylamine) produces immobilized artificial membranes (IAMs), which have found wide applications in affinity chromatography.[6b]

The most widely used chiral synthons in the synthesis of PCs are various glycerol and glycidol derivatives in which a hydroxy group is masked as a trityl, benzyl, *tert*-butyldiphenylsilyl, or 4-methoxyphenyl ether.[7] A wide variety of cyclic sulfates have been shown to undergo regioselective ring opening with nucleophiles, providing precursors of natural products.[8] Here we report the application of the cyclic sulfate derived from (*R*)-1-PMP-glycerol **4**, (*S*)-1-(4′-methoxyphenyl)glycerol 2,3-cyclic sulfate (**5**),[9] to the preparation of the following four important glycerolipid precursors: 1-*O*-hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (**8**), 1-*S*-hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-thioglycerol (**9**), 1-*N*-hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-aminoglycerol (**10**), and 1-*N*-hexadecylamido-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (**12**). We also demonstrate in this paper that (*R*)-1-PMP-glycerol **4** is readily converted to (*R*)-PMP-glycidol **7** in high yield.



1 X = O
2 X = S
3 X = NH

Synthesis of Glycidol 7 via Cyclic Sulfate 5. Glycidol derivatives such as **7** are potential C-3 chiral synthons for the synthesis of many natural/unnatural products.[10] For example, **7** has recently been used in the synthesis of a chiral deoxysphingomyelin.[11a] There are several existing methods for preparing PMP-glycidol **7**.[11] However, a one-pot synthesis using the reaction of PMP-glycerol **4** with diisopropyl azodicarboxylate (DIAD) and triphenylphosphine gave **7** in a yield of only 69%,[11a] and other multistep synthetic routes presented also gave yields of ≤73%.[11b] An improved method gave a very high yield of **7**, but special care was required to thoroughly dry the cyclic stannylene intermediate, and a nonpolar impurity (presumably *p*-toluenesulfonic anhydride) must be removed before base-induced cyclization.[11a] We report here a new and highly convenient method (Scheme 1) that provides **7** in an overall yield of 94% from (*R*)-1-PMP-glycerol **4**. The diol **4** was prepared from *p*-methoxyphenyl allyl ether in large scale and high ee by using a modified asymmetric dihydroxylation reaction.[12] Diol **4** was treated with $SOCl_2$ in the presence of pyridine followed by oxidation of the cyclic sulfite with $NaIO_4$ in the presence of a catalytic amount of $RuCl_3 \cdot H_2O$ to give cyclic sulfate **5** in almost quantitative yield. The cyclic sulfate **5** was opened by LiBr in THF to provide bromohydrin **6**. Cyclization of bromohydrin **6** in methanolic

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(9) Compound **5** was prepared from (*R*)-1-PMP-glycerol **4** in almost quantitative yield using a published procedure (ref 13).

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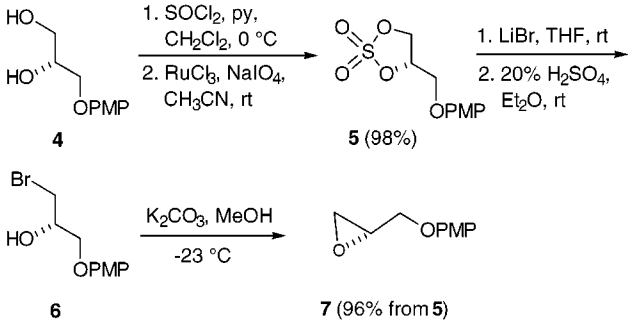
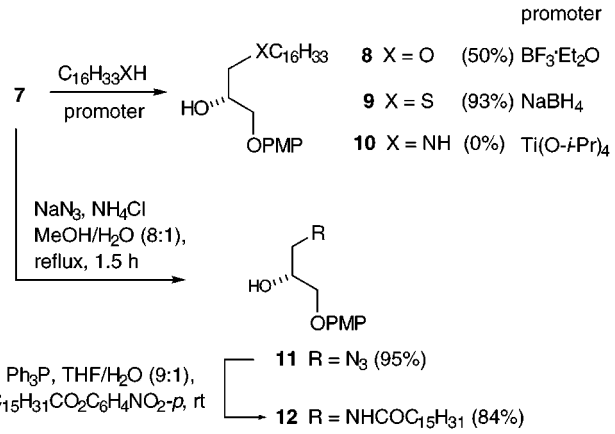
Scheme 1. Synthesis of (*R*)-*O*-PMP-glycidol 7 via Cyclic Sulfate 5



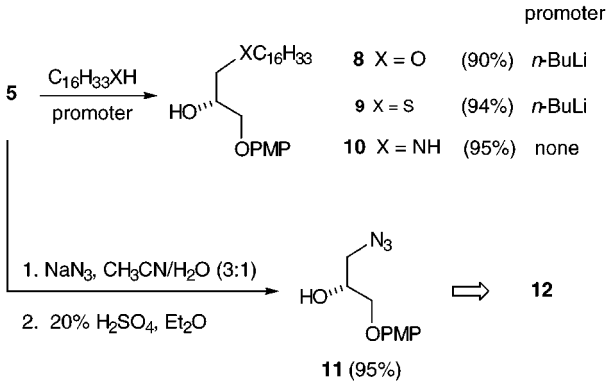
Scheme 2. Opening of Epoxide 7 with Nucleophiles



K_2CO_3 solution led to PMP-glycidol **7**. This synthetic route is stereospecific.[13,14]

Opening Reaction of Glycidol 7 with Nucleophiles. With (*R*)-1-PMP-glycidol **7** on hand, we next tested its ring-opening reactions with 1-hexadecanol, hexadecylmercaptan, and 1-hexadecylamine as shown in Scheme 2. The opening of glycidol derivatives with 1-hexadecanol in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ at room temperature in $CHCl_3$ is a well-known method for preparing glycerides bearing a 1-*O*-alkyl linkage.[7,15] Therefore, we used catalytic $BF_3{\cdot}Et_2O$ to open **7** with 1-hexadecanol and isolated the desired product **8**, but obtained a yield of only 50%. The yield of the reaction could not be improved by varying the reaction temperature. Although the reaction still proceeded rapidly at 0 °C, according to TLC several byproducts were formed. In contrast, the opening reaction with hexadecylmercaptan in the presence of $NaBH_4$[16] in THF at room temperature proceeded smoothly and gave the desired thioglycerol **9** in 93% yield; no regioisomer was detected by either TLC or ^1H NMR. Based on the rationale that primary amines are stronger ligating reagents toward Lewis acids than PMP-glycidol **7**, direct reaction (without any Lewis acid) of 1-hexadecylamine and PMP-glycidol in THF was initially attempted. No reaction was observed by TLC after 24 h of stirring under nitrogen. The same reaction was also unsuccessful when Ti(O-*i*-Pr)$_4$ (2 equiv) was tried. Not surprisingly, still no reaction occurred after 24 h of stirring since a strong chelating group (e.g. hydroxyl or carbonyl) next to the oxirane is required for Ti(O-*i*-Pr)$_4$ to mediate the ring opening.[17] Both starting materials were recovered in more than 90% yield. When 1-hexadecylamine was refluxed with PMP-glycidol **7** in EtOH, a complex mixture was obtained.[18] This was presumably due to polyalkylation of the amine.

Scheme 3. Opening of Cyclic Sulfate 5 with Nucleophiles



Amido-linked glycerol derivative **12**, which is a precursor of several ALP analogues,[19] was also prepared via azide **11**. PMP-glycidol **7** was opened with azide anion in 8:1 MeOH−H_2O in the presence of 2.5 equiv of NH_4Cl.[17a] The reaction was complete after 1.5 h of reflux. After separation by column chromatography, azide **11** was isolated in 95% yield; in addition, (2*S*)-2-azido-1-*O*-(4′-methoxyphenyl)-1,3-propanediol, the regioisomer of **11**, was obtained in 1.8% yield and characterized by NMR. An alternative route to azide **11** was achieved by reaction of cyclic sulfate **5** with NaN_3 in 3:1 Me_2CO-H_2O followed by hydrolysis (20% H_2SO_4/Et_2O). This reaction gave a similar chemical yield (94%), but a lower regioselectivity (ratio of **11** to isomer = 19:1). The reduction of azide **11** with Ph_3P-H_2O in THF followed by in situ acylation with *p*-nitrophenyl palmitate provided amide **12** in 80% overall yield from PMP-glycidol **7** or 79% overall yield from cyclic sulfate **5**, demonstrating that this is an efficient synthesis of the important intermediate **12**.[20]

Substitution Reaction of Cyclic Sulfate 5 with Nucleophiles. Although the above problems might have been solved through further experimentation by either changing the reaction conditions or using other activating agents, we chose instead to try nucleophilic substitution of the cyclic sulfate **5** with the corresponding alcohol, thiol, and amine to synthesize **8**, **9**, and **10**. It is well known that cyclic sulfates are more reactive than epoxides in many reactions.[8a] As illustrated in Scheme 3, excellent yields were obtained for all three reactions with different nucleophiles. Slightly different procedures were

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(20) Attempts to convert amidoglycerol **12** to aminoglycerol **10** with $BH_3{\cdot}THF$ complex using published procedures[23] were unsuccessful.

employed for each reaction based on the nature of the nucleophiles. Direct reaction of cyclic sulfate **5** with hexadecylamine in THF followed by hydrolysis of the sulfate with dilute H_2SO_4/ether and neutralization with NaOH gave aminoglycerol **10** in 95% yield. The ring-opening reactions with $C_{16}H_{33}OH$ and $C_{16}H_{33}SH$ were carried out by first converting the alcohol and thiol into their anions. As our first choice, NaH in THF was tried. However, it seemed that even the conversion of the thiol was very sluggish at room temperature. The reaction between NaH and hexadecylmercaptan was not complete after 4 h of stirring, while at higher temperature (60−65 °C), hydrogen gas generated could be troublesome since it made the soaplike $NaSC_{16}H_{33}$ into a foam which pushed all the way up to the rim of the flask, making stirring impossible. For a quick and quantitative conversion, *n*-BuLi was used instead. Thus, 1 equiv of *n*-BuLi and ROH or RSH was allowed to react in THF at 0 °C for 10 min, followed by injection of cyclic sulfate **5** in THF at room temperature. Immediate precipitation was observed when the thiol was mixed with *n*-BuLi, whereas no clear change was observed in the alcohol reaction. Ring opening with RS^- proceeded rapidly and was complete within 2 h. However, in the reaction of the fatty alkoxide ion, 5−6 h was required for the full consumption of the cyclic sulfate **5**. Thioglyceride **9** was purified from excess $C_{16}H_{33}SH$ by flash chromatography. However, because the polarity of $C_{16}H_{33}OH$ and product **8** are very similar in all of the solvent systems we tried, at least two column separations by gravity were required to obtain pure **8** (elution with chloroform only).[21]

In summary, a novel and efficient synthetic route toward the preparation of three important intermediates, **8**, **9**, and **10**, from cyclic sulfate **5** using the same strategy has been developed. Substitution of cyclic sulfate **5** with nucleophiles has the following advantages over the corresponding opening reactions of PMP-glycidol **7**: (i) all three direct approaches begin with a common substrate; (ii) the synthetic route is shorter; (iii) the reactions are easier to handle; (iv) the yields are higher. The three reactions of cyclic sulfate **5** with a long-chain alcohol, thiol, and amine described here are, to the best of our knowledge, the first examples of such reactions. Furthermore, we also present a new and efficient method to prepare PMP-glycidol **7**, an important synthon in natural/unnatural product synthesis, and an efficient synthesis of amidoglycerol **12**, an important intermediate in the preparation of amidoglycerolipids.

Experimental Section

General Information. See refs 7b and 12 for experimental protocols. ^1H and ^{13}C NMR spectra were recorded on a 400-MHz Bruker spectrometer.

(*S*)-1-(4′-Methoxyphenyl)glycerol 2,3-Cyclic Sulfate ((−)-5). To an ice-cooled solution of 6.9 g (34.8 mmol) of (*R*)-1-(4′-methoxyphenyl)glycerol [**4**, 90% ee, $[\alpha]^{25}_D$ −7.35° (*c* 1.5, MeOH)][12] and 7.7 g (97.0 mmol) of pyridine in 100 mL of CH_2Cl_2 was injected 3.5 mL (48.7 mmol) of $SOCl_2$. The reaction mixture was stirred at 0 °C for 30 min and then filtered through a pad of silica gel, which was washed with 400 mL of hexanes−EtOAc (2:1). The filtrate was concentrated in a rotary evaporator and further dried using a vacuum pump (1 h, 0.5 Torr). The cyclic sulfite (8.5 g, 100%) was obtained as a colorless oil. To a solution of the cyclic sulfite in 100 mL of CH_3CN were added 10.4 g (48.7 mmol) of $NaIO_4$ and 80 mg (0.35 mmol) of $RuCl_3 \cdot H_2O$ in 20 mL of H_2O. After the purplish suspension was stirred at room temperature for 20 min, 80 mL of H_2O and 100 mL of Et_2O were added. The layers were separated, and the aqueous layer was extracted with two portions of Et_2O (100 mL each). The combined ether layer was dried over Na_2SO_4, and the solvents were removed by rotary evaporation (*i*-PrOH was used to remove the residual H_2O) and further dried under vacuum. Pure cyclic sulfate **5** (8.9 g, 98%) was obtained as a white solid; mp 90.0−91.0 °C; R_f 0.46 (hexane/EtOAc 2/1); $[\alpha]^{25}_D$ −2.84° (*c* 4.3, $CHCl_3$). The other physical data (mp, R_f, IR, ^1H and ^{13}C NMR, and HR-MS) were identical to data reported for the enantiomer.[11a]

4′-Methoxyphenyl (*R*)-2-Oxiranylmethyl Ether ((−)-7). To a solution of 7.0 g (26.9 mmol) of cyclic sulfate **5** in 140 mL of dry THF was added 9.4 g (108.2 mmol) of LiBr. The suspension was stirred at room temperature until the disappearance of **5** was noted by TLC. After the solvent was removed under vacuum to give a slurry, 100 mL of ether and 100 mL of 20% aqueous H_2SO_4 were added. The heterogeneous solution was stirred vigorously at room temperature overnight. The layers were separated, and the aqueous layer was extracted with two more portions of ether (100 mL each). The combined ether layer was dried over Na_2SO_4 and concentrated to give 7.0 g of 1-*O*-(4′-methoxyphenyl)-3-bromo-1,2-propanediol (**6**) as a slightly yellow oil. To a solution of crude **6** in 100 mL of MeOH at −23 °C was added 14.0 g (107.0 mmol) of ground K_2CO_3. The heterogeneous solution was stirred at this temperature under nitrogen until the disappearance of starting material (2 h), and then 50 mL of saturated NH_4Cl aqueous solution was added slowly, followed by extraction with CH_2Cl_2 (3 × 100 mL). The extracts were dried over Na_2SO_4 and concentrated to give 4.65 g (96% from **5**) of pure glycidol **7** as a white solid; mp 41.0−41.8 °C; R_f 0.64 (hexane/EtOAc 2/1); $[\alpha]^{25}_D$ −10.2° (*c* 1.29, MeOH) [lit.[11b] $[\alpha]^{30}_D$ −11.72° (*c* 1.06, MeOH)]; IR (NaCl) 1031, 1232 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73 and 2.75 (ABq, 1H, J = 2.6 Hz, $\Delta\nu$ = 4.2 Hz), 2.89 (t, 1H, J = 4.6 Hz), 3.31−3.35 (m, 1H), 3. 77 (s, 3H), 3.90 and 3.94 (ABq, 1H, J = 5.6 Hz, $\Delta\nu$ = 9.24 Hz), 4.15−4.19 (ABq, 1H, J = 3.2 Hz, $\Delta\nu$ = 10.6 Hz), 6.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 44.72, 50.27, 55.69, 69.51, 114.64, 115.71, 152.64, 154.17.

1-*O*-Hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (8). Method A (Scheme 2): To a stirred solution of 364 mg (1.5 mmol) of 1-hexadecanol and 181 mg (1.0 mmol) of PMP-glycidol **7** in 25 mL of dry THF was injected 12 μL (0.1 mmol) of $BF_3 \cdot Et_2O$. The reaction mixture was stirred at room temperature under nitrogen until the full consumption of **7**. The solvent was removed and the solid residue was purified by column chromatography (elution with $CHCl_3$) to give 211 mg (50%) of glycerol **8**[22] as a white solid; mp 63.0−64.2 °C. **Method B (Scheme 3)**: To an ice-cooled solution of 727 mg (3.0 mmol) of 1-hexadecanol in 60 mL of THF was injected 1.2 mL (3.0 mmol) of 2.5 M *n*-BuLi in hexane. The solution was stirred at this temperature for 10 min, and then the ice-bath was removed. A solution of cyclic sulfate **5** (521 mg, 2.0 mmol) in 10 mL of THF was injected. The solution was stirred at room temperature under nitrogen until the disappearance of **5**. Ether (40 mL) and 20% H_2SO_4 (40 mL) were added, and the reaction mixture was stirred vigorously for 24 h at room temperature. The two layers were separated, and the aqueous layer was extracted with two more portions of ether (80 mL each). The combined ether layer was dried over Na_2SO_4 and concentrated to give a solid residue that was purified by column chromatography (elution with $CHCl_3$). Glycerol **8** (761 mg, 90%) was obtained as a white solid; mp 63.4−64.5 °C [lit.[12] mp 64−65 °C]; R_f 0.64 (hexane/EtOAc 2/1); IR (NaCl) 1043, 1109, 1465, 1523 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.6 Hz), 1.24 (m, 26H), 1.56 (m, 2H), 2.37 (br s, 1H), 3.47 (dt, 2H, J = 6.7 Hz,), 3.53 (dd, 1H, J = 9.7, 6.0 Hz), 3.58 (dd, 1H, J = 9.8, 4.5 Hz), 3.75 (s, 3H), 3.95 (m, 2H), 4.12 (m, 1H), 6.78−6.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.67, 26.08, 29.34, 29.45, 29.58, 29.68, 31.91, 55.68, 69.14, 69.72, 71.45, 71.74, 114.60, 115.51, 152.75, 154.03; HRMS [M^+] Calcd for m/z $C_{26}H_{46}O_4$ 422.3396, found 422.3397.

1-*S*-Hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-thioglycerol ((−)-9). Method A (Scheme 2): To a solution of 517 mg (2.0

(21) When compound **8** was prepared on a large scale (e.g. ≥10 g), purification by crystallization from hexane/EtOAc instead of column chromatography provided chirally enriched, pure **8** (see ref 7d).

(22) The observed optical rotation value of compound **8** is zero (see ref 7d).

(23) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912−916.

mmol) of hexadecylmercaptan in 30 mL of THF was added 79 mg (2.1 mmol) of $NaBH_4$. The heterogeneous solution was stirred for 4 h at room temperature under nitrogen, 270 mg (1.5 mmol) of PMP-glycidol **7** was added, and the solution was stirred at room temperature until the full consumption of **7**. MeOH (2 mL) was added, and the solution was stirred for an additional 1 h. The reaction mixture was filtered through a pad of silica gel in a sintered funnel, which was rinsed with hexane/EtOAc 4/1. After the removal of solvents, the residue was purified by flash chromatography (elution with hexanes−EtOAc 6/1). There was obtained 612 mg (93%) of the desired product **9** as a white solid; mp 71.0−72.0 °C; $[\alpha]^{25}_D$ −2.7° (*c* 2.2, $CHCl_3$). **Method B (Scheme 3)**: To an ice-cooled solution of 776 mg (3.0 mmol) of hexadecylmercaptan in 60 mL of THF was injected 1.2 mL (3.0 mmol) of a solution of *n*-BuLi (2.5 M in hexane). The milklike suspension was stirred at this temperature for 10 min, and then the ice-bath was removed. A solution of cyclic sulfate **5** (520 mg, 2.0 mmol) in 10 mL of THF was injected, and the solution was stirred at room temperature under nitrogen until the disappearance of **5**. Diethyl ether (40 mL) and 20% aqueous H_2SO_4 (40 mL) were added to the above reaction mixture, and the reaction mixture was stirred vigorously for 24 h at room temperature. The two layers were separated, and the aqueous layer was extracted with two more portions of ether (80 mL each). The combined ether layer was dried over Na_2SO_4 and concentrated to give a solid residue that was purified by flash chromatography (elution with hexanes−EtOAc 6/1), affording 825 mg (94%) of the desired product **9** as a white solid; mp 71.5−72.4 °C; R_f 0.6 (hexane/EtOAc 4/1); $[\alpha]^{25}_D$ −2.9° (*c* 2.45, $CHCl_3$); IR (NaCl) 1040, 1466, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.6 Hz), 1.24 (m, 24H), 1.35 (m, 2H), 1.57 (m, 2H), 2.19 (br s, 1H), 2.54 (t, 2H, J = 7.4 Hz), 2.70 (dd, 1H, J = 13.7, 5.2 Hz), 2.83 (dd, 1H, J = 13.6, 7.2 Hz), 3.75 (s, 3H), 3.94−4.06 (m, 3H), 6.80−6.85 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.11, 22.68, 28.83, 29.21, 29.36, 29.51, 29.59, 29.65, 29.69, 31.92, 32.61, 35.88, 55.70, 68.64, 71.16, 114.65, 115.55, 152.61, 154.13; HRMS [M^+] Calcd for *m*/*z* $C_{26}H_{46}O_3S$ 438.3168, found 438.3171.

1-*N*-Hexadecyl-3-*O*-(4′-methoxyphenyl)-*sn*-aminoglycerol ((+)-10). A solution of 362 mg (1.5 mmol) of 1-hexadecylamine and 261 mg (1.0 mmol) of cyclic sulfate **5** in 25 mL of THF was stirred under nitrogen until the disappearance of **5**. Ether (40 mL) and 20% H_2SO_4 (20 mL) were added, and the white suspension was stirred vigorously at room temperature for 24 h. Sodium hydroxide pellets were added to the ice-cooled reaction mixture slowly until the pH reached >12. The layers were separated, and the aqueous layer was extracted with three more portions of ether (40 mL each). The combined ether layer was dried over Na_2SO_4. After the removal of solvents, the residue was purified by flash chromatography (elution with $CHCl_3$/MeOH 9/1). The aminoglycerol **10** was dissolved in $CHCl_3$ and passed through a Cameo filter (Fisher Scientific) to remove the dissolved silica gel. After lyophilization from benzene, 401 mg (95%) of the desired aminoglycerol **10** was obtained as a white solid; mp 255.0−258.5 °C (dec); R_f 0.64 ($CHCl_3$/MeOH 9/1); $[\alpha]^{25}_D$ +25.8° (*c* 3.15, $CHCl_3$); IR (NaCl) 1037, 1463, 1508 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.5 Hz), 1.14−1.28 (m, 28H), 1.69 (br s, 1H), 3.07 (m, 2H), 3.30 (m, 1H), 3.70 (s, 3H), 3.71 (m, 1H), 4.08−4.16 (m, 2H), 5.06 (m, 1H), 6.72−6.79 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.69, 25.64, 26.63, 29.22, 29.38, 29.59, 29.62, 29.69, 29.75, 31.94, 48.79, 49.19, 55.55, 68.13, 71.80, 114.64, 115.41, 151.91, 154.40; HRMS [MH^+] Calcd for *m*/*z* $C_{26}H_{48}NO_3$ 422.3634, found 422.3635.

(2*R*)-3-Azido-1-*O*-(4′-methoxyphenyl)-1,2-propanediol ((+)-11). Method A (Scheme 2): To a solution of 361 mg (2.0 mmol) of PMP-glycidol **7** in 27 mL of MeOH and H_2O 8/1 was added 235 mg (4.4 mmol) of NH_4Cl, followed by 650 mg (10.0 mmol) of NaN_3. The reaction mixture was heated under reflux until the full consumption of **7** was noted (1.5 h). Water (40 mL) was added, and the solution was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated to give a solid residue that was purified by column chromatography (elution with hexane/EtOAc 2/1), giving 436 mg (95%) of product **11** as an oil and 8 mg (1.8%) of the regioisomer. **Method B (Scheme 3)**: To a solution of 521 mg (2.0 mmol) of cyclic sulfate **5** in 30 mL of acetone and 10 mL of H_2O was added 260 mg (4.0 mmol) of NaN_3. The heterogeneous solution was stirred at room temperature until the disappearance of **5** (2 h). After most of the acetone was removed in a rotary evaporator, 50 mL of ether and 20 mL of 20% H_2SO_4 were added, and the heterogeneous solution was stirred vigorously at room temperature overnight. The two layers were separated, and the aqueous layer was extracted with two more portions of ether (50 mL each). The combined organic layer was dried over Na_2SO_4. Concentration gave a light yellow oil that was purified by column chromatography (elution with hexane/EtOAc 2/1) to give 431 mg (94%) of the desired product **11** and 21 mg (4.7%) of the regioisomer, both as oils; **11:** R_f 0.49 (hexane/EtOAc 2/1); $[\alpha]^{25}_D$ +15.76° (*c* 3.93, $CHCl_3$); IR (NaCl) 1042, 1059, 2106, 2253, 3580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.48 (br s, 1H), 3.49 (m, 2H), 3.75 (s, 3H), 3.95 (m, 2H), 4.12 (m, 1H), 6.82 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 53.36, 55.70, 69.38, 69.79, 114.71, 115.57, 152.32, 154.32.

1-*N*-Hexadecylamido-3-(4′-methoxyphenyl)-*sn*-glycerol ((+)-12). To a solution of 229 mg (1.0 mmol) of 1-(4′-methoxyphenyl)-3-azido-1,2-propanediol **11** in 18 mL of THF and 2 mL of H_2O was added 755 mg (2.0 mmol) of 4-nitrophenyl palmitate followed by 524 mg (2.0 mmol) of Ph_3P. The reaction mixture was stirred at room temperature for 48 h under nitrogen. Concentration gave a yellow solid that was purified by column chromatography (elution with EtOAc) to give 367 mg (84%) of amidoglycerol **12** as a white solid; mp 102.0−103.5 °C; R_f 0.6 (EtOAc); $[\alpha]^{25}_D$ +8.7° (*c* 2.7, $CHCl_3$); IR (NaCl) 1045, 1527, 1659, 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (t, 3H, J = 6.6 Hz), 1.23 (m, 26H), 1.62 (m, 2H), 2.21 (t, 2H, J = 7.5 Hz), 3.40 (m, 1H), 3.60 (m, 1H), 3.75 (s, 3H), 3.87 (m, 1H), 4.07 (m, 1H), 6.02 (br s, 1H), 6.81 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.12, 22.68, 25.78, 29.24, 29.32, 29.35, 29.47, 29.61, 29.65, 29.68, 31.92, 26.30, 43.09, 55.71, 69.58, 69.99, 114.70, 115.44, 152.41, 154.21, 175.34; HRMS [M^+] Calcd for *m*/*z* $C_{26}H_{46}NO_4$ 436.3427, found 436.3423.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **8**−**12** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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