Stereospecific Synthesis of Thioether Glycerophospholipids. Catalytic Asymmetric Epoxidation Followed by in Situ Borohydride-Mediated Opening of Glycidol with Hexadecylmercaptan

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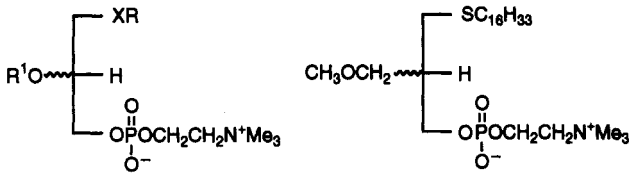
Alkyl lysophospholipids (ALPs) that contain a 16- or 18-carbon ether group at the *sn*-1 position, an *O*-methyl group at the *sn*-2 position, and a phosphate-containing group at the *sn*-3 position of a glycerol moiety are unnatural analogues of the naturally occurring platelet-activating factor found in many mammalian tissues.[1] 1-*O*-Octadecyl-2-*O*-methyl-*rac*-glycero-3-phosphocholine, ET-18-OMe (1),



1 X = O, R = $C_{18}H_{37}$, R^1 = Me (*rac*-ET-18-OMe) **2**

3 X = S, R = $C_{16}H_{33}$, R^1 = Me or Et

is one of the best known ALPs and is in clinical trials as an experimental anticancer drug.[2] Many analogues of 1 have been synthesized that have biological activity against neoplastic cells. Some of these analogues have a 1-(alkylthio) group in place of the 1-(alkoxy) group.[3] One such analogue is 1-*S*-hexadecyl-2-(deoxymethoxymethyl)-*rac*-thioglycerol-3-phosphocholine (2), which is also currently in clinical trials.[4] 1-(Alkylthio) analogues of 1, such as *rac*-3, have also been shown to possess antineoplastic activity similar to that of *rac*-1.[3]

The development of methods to prepare optically pure alkylthio lysophospholipid analogues would accelerate efforts to advance the understanding of the mechanisms of action of synthetic tumoricidal ether lipids. Unfortunately, relatively few methods are available for the introduction of a long-chain 1-(alkylthio) group into the glycerol moiety. For example, the alkylation of 3-thio-*rac*-glycerol (3-mercapto-1,2-propanediol) with a long-chain alkyl bromide and alcoholic potassium hydroxide proceeds in good yield, leading to racemic lipid **3**.[3,5] Another example is the preparation of *rac*-**2** by alkylation of 3-bromo-2-(methoxymethyl)propyl benzoate with hexadecylmercaptan.[6] However, long-chain thiolates have been reported to react sluggishly in S_N2 reactions with protected glycerol moieties bearing good leaving groups, giving dialkyl disulfide as the major product.[7] Therefore, a thioether substituent was introduced at the *sn*-1 position of glycerol via reduction of a glyceryl thioacetate, followed by alkylation of the resulting glyceryl mercaptan.[7] Since catalytic asymmetric epoxidation of water-soluble allylic alcohols, followed by in situ derivatization of the epoxide formed,[8] offers a convenient synthetic route to optically pure 1-(alkyloxy)glycerolipids,[9] we sought to synthesize optically active alkylthioglycerol derivatives using glycidol-based chemistry. It was reported recently that the ring opening of the triphenylmethyl (trityl) ether of glycidol (tritylglycidol) with alkylmercaptan in the presence of *n*-butyllithium gives a 1-alkylthioglycerol derivative.[10] Tritylglycidol, which is not available commercially, was synthesized by the catalytic asymmetric epoxidation of allyl alcohol and in situ tritylation of glycidol or by tritylation of commercially available chiral glycidol with trityl chloride in 53%[10a] and 36%[10b] yield, respectively. Although epoxides can be opened by thiols using basic conditions,[11] racemization of underivatized glycidol via Payne rearrangement[12] makes it necessary to avoid base-catalyzed nucleophilic ring opening of glycidol. We initially tried the opening reaction of glycidol or its tosylate derivative with hexadecylmercaptan in the presence of Lewis acids, but failed to obtain good yields. Here we report an efficient stereoselective synthesis of 1-alkylthioglycerophospholipid 4 by the in situ sodium borohydride mediated opening reaction of (*S*)-glycidol (prepared by asymmetric epoxidation of allyl alcohol) with hexadecylmercaptan. The enantiomeric phospholipid was prepared from (*R*)-glycidol using the same synthetic route.

Opening of Glycidol with Hexadecylmercaptan. In order to synthesize alkylthioglycerol derivatives we tried to open glycidyl tosylate with hexadecylmercaptan in the presence of boron trifluoride etherate, but the product was obtained in only 5–10% yield. Since glycidol was opened at the C-3 position with benzenethiol in the presence of 1 equiv of $Ti(O\text{-}i\text{-}Pr)_4$, providing the phenylthio diol in 88% yield and ca. 90% ee even under in situ

(1) (a) Berdel, W. E.; Munder, P. G. In *Platelet-activating Factor and Related Lipid Mediators*; Snyder, F., Ed.; Plenum: New York, 1987; pp 449–467. (b) Berdel, W. E. *Onkologie* **1990**, *13*, 245–250. (c) Berdel, W. E. *Br. J. Cancer* **1991**, *64*, 208–211.

(2) (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. (c) Khanavkar, B.; Ulbrich, F.; Gatzemeier, U.; Meyer-Schwickerath, E.; Lorenz, J.; Schreml, W.; Brugger, R.; Schick, H. D.; von Pawel, J.; Nordström, R.; Drings, P. *Contrib. Oncol.* **1989**, *37*, 224–235.

(3) (a) Morris-Natschke, S.; Surles, J. R.; Daniel, L. W.; Berens, M. E.; Modest, E. J.; Piantadosi, C. *J. Med. Chem.* **1986**, *29*, 2114–2117. (b) Morris-Natschke, S. L.; Gumus, F.; Marasco, C. J., Jr.; Meyer, K. L.; Marx, M.; Piantadosi, C.; Layne, M. D.; Modest, E. J. *J. Med. Chem.* **1993**, *36*, 2018–2025.

(4) (a) Berdel, W. E.; Fromm, M.; Fink, U.; Pahlke, W.; Bicker, U.; Reichert, A.; Rastetter, J. *Cancer Res.* **1983**, *43*, 5538–5543. (b) Hermann, D. B. J.; Neumann, H. A.; Heim, M. E.; Berdel, W. E.; Fromm, M.; Andreesen, R.; Queisser, W.; Boerner, D.; Sterz, R.; Besenfelder, E.; Bicker, U. *Contrib. Oncol.* **1989**, *37*, 236–247.

(5) (a) Lawson, D. D.; Getz, H. R.; Miller, D. A. *J. Org. Chem.* **1961**, *26*, 615–616. (b) Muramatsu, T. In *Platelet-activating Factor and Structurally Related Ether Lipids*; Benveniste, J., Arnoux, B., Eds.; INSERM Symposium No. 23; Elsevier Science: New York, 1983; pp 37–40.

(6) Bosies, E.; Herrmann, D. B. J.; Bicker, U.; Gall, R.; Pahlke, W. *Lipids* **1987**, *22*, 947–951.

(7) Bhatia, S. K.; Hajdu, J. *J. Org. Chem.* **1988**, *53*, 5034–5039.

(8) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

(9) For a recent review, see: Bittman, R. In *Phospholipids Handbook*; Cevc, G., Ed.; Marcel Dekker: New York, 1993; pp 141–232.

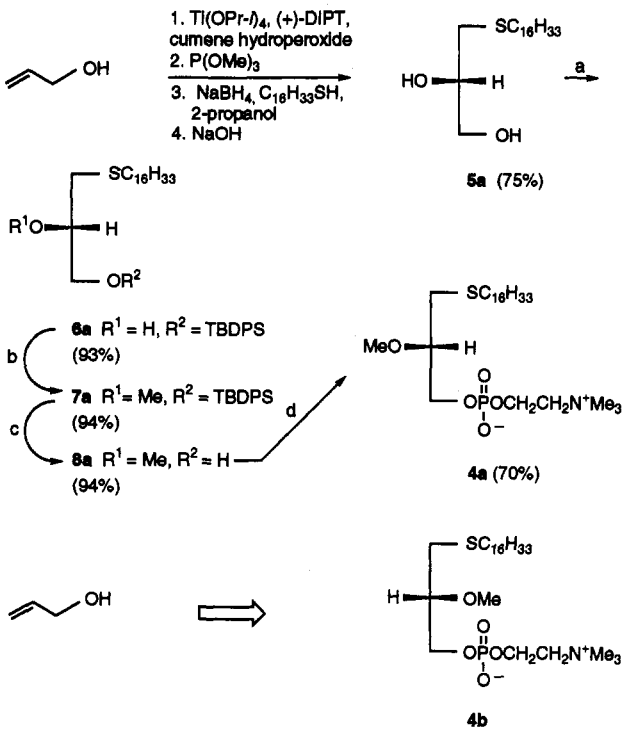
(10) (a) Hendrickson, H. S.; Hendrickson, E. K. *Chem. Phys. Lipids* **1990**, *53*, 115–120. (b) Lin, H.-K.; Gelb, M. H. *J. Am. Chem. Soc.* **1993**, *115*, 3932–3942.

(11) Chini, M.; Crotti, P.; Giovani, E.; Macchia, F.; Pineschi, M. *Synlett* **1992**, 303–305.

(12) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1378–1380.

0022-3263/94/1959-0668$04.50/0

Scheme 1[a]



[a] Reagents: (a) TBDPSCl, imidazole, CH_2Cl_2; (b) NaH, CH_3I, C_6H_6, 24 h; (c) n-Bu_4NF, THF; (d) (i) $POCl_3$, Et_3N, $CHCl_3$, −20 °C; (ii) choline tosylate, py, rt.

conditions,[13] we attempted the Ti(O-*i*-Pr)$_4$-mediated opening reaction with hexadecylmercaptan. This procedure also failed to give reproducibly good yields. Moreover, aqueous workup of the reaction mixture containing the titanium alkoxides and DIPT leads to inefficient extraction of the lipid product. We found that sodium borohydride assisted the ring-opening reaction of in situ generated glycidol with the long-chain mercaptan, affording ring-opened product **5** stereoselectively. Diol **5** is easily isolated and recrystallized and then converted into phospholipid **4** by using established methods.

Synthesis. Scheme 1 shows the conversion of allyl alcohol into the desired enantiomers of 1(3)-*S*-hexadecyl-2-*O*-methyl-*sn*-thioglycero-3(1)-phosphocholine (**4**). Catalytic asymmetric epoxidation of allyl alcohol with cumene hydroperoxide in the presence of Ti(O-*i*-Pr)$_4$ and diisopropyl tartrate (DIPT)[8] followed by reduction of the excess hydroperoxide with trimethyl phosphite and reaction of the resulting crude glycidol with hexadecylmercaptan in the presence of 1.1 equiv of sodium borohydride in 2-propanol gave 1-*S*-hexadecyl-*sn*-thioglycerol (**5a**) in 75–78% overall yield. The configuration of the alkylthioglycerol formed in this reaction depends on the choice of (+)-DIPT or (−)-DIPT in the asymmetric epoxidation reaction. Alkylthio diol **5** was isolated by crystallization and purified by two recrystallizations from methanol. The primary hydroxy group of **5a** was protected as a *tert*-butyldiphenylsilyl (TBDPS) ether (**6a**) in 93–95% yield. Reaction of **6** with a large excess of methyl iodide and sodium hydride in benzene gave methyl ether **7** in 94–96% yield. (However, reaction of the C-2 hydroxy group of **6** with methyl iodide in THF gave a low yield of **7**.) Removal of the *tert*-butyldiphenylsilyl group with tetra-*n*-butylammonium fluoride in THF gave alcohol **8a**. Phosphorylation of alcohol **8a** with phosphorus oxychloride in chloroform at −20 °C followed by reaction with choline tosylate provided the desired *S*-hexadecylthio phospholipid **4a** in 70–72% yield.

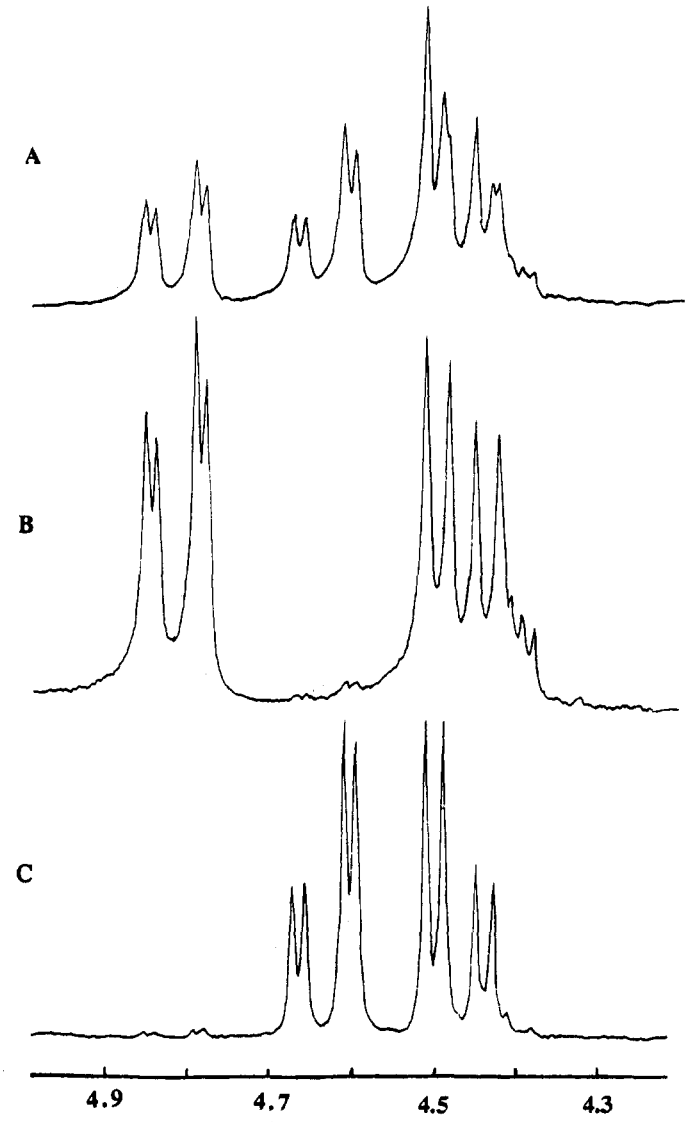


Figure 1. Partial ^{1}H NMR spectra of bis-(*R*)-(+)-MTPA ester of **5**: (A) *rac*-**5**; (B) **5a**; (C) **5b**.

Evaluation of Optical Purity. To determine the enantiomeric excess (ee) of the twice-recrystallized *S*-hexadecylthioglycerol **5**, we prepared its (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ((*R*)-(+)-MTPA) esters. The diastereomeric ratio of the resulting mixture was analyzed by 200-MHz ^{1}H NMR. Figure 1A shows the ^{1}H NMR spectrum (δ 4.2–5.0) of a racemic mixture of the bis-MTPA ester prepared from *rac*-glycidol. Integration of the two AB quartets on an expanded scale indicated a 1:1 ratio of the areas of the signals at δ 4.58–4.70 compared with those at δ 4.76–4.89. The individual diastereotopic protons of CH_2OMTPA in each enantiomer show near-base-line separation. The lower field AB quartet at δ 4.85 and 4.79 is assigned to the protons of CH_2OMTPA of the 1-*S*-hexadecyl-*sn*-thioglycerol bis-MTPA ester (see Figure 1B), and the higher field AB quartet at δ 4.67 and 4.60 corresponds to the protons of CH_2OMTPA of the 3-*S*-hexadecyl-*sn*-thioglycerol bis-MTPA ester (see Figure 1C). The virtual absence in Figure 1B of the signals at δ 4.67 and 4.60 and in Figure 1C of the signals at δ 4.85 and

(13) Kao, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 5413–5415.

4.79 indicates that the ee of the *S*-hexadecylthioglycerol is >99% (the limits of detection). Although asymmetric epoxidation of allyl alcohol gives glycidol of only ca. 90% ee,[8] the optical purity of **5** is enriched because it was recrystallized twice prior to derivatization.

Experimental Section

General Procedures. Melting points were taken on a capillary melting point apparatus (Thomas Hoover) and are uncorrected. ^{1}H NMR spectra were recorded on an IBM-Bruker WP 200-MHz spectrometer; 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) 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: dichloromethane was distilled from calcium hydride; 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, dried over calcium chloride, and then distilled over sodium metal. Choline tosylate was prepared from (*N*,*N*-dimethylamino)ethanol and methyl tosylate in dry THF and dried thoroughly over P_2O_5 in a vacuum oven. Hexadecylmercaptan, cumene hydroperoxide (80% technical grade), titanium(IV) isopropoxide, diisopropyl tartrate, trimethyl phosphite, *tert*-butylchlorodiphenylsilane, *rac*-glycidol, (*R*)-MTPA, methyl iodide, and sodium borohydride were from Aldrich.

1-*S*-Hexadecyl-*sn*-thioglycerol [(+)-5a]. To a stirred mixture of powdered molecular sieves (3.5 g, 3A, activated at 150 °C under 0.1 mmHg), L-(+)-diisopropyl tartrate (1.39 g, 1.25 mL, 5.95 mmol), and allyl alcohol (5.81 g, 6.8 mL, 0.10 mol) in 190 mL of methylene chloride was added titanium(IV) isopropoxide (1.4 g, 1.5 mL, 5.0 mmol) at −5 °C. After 30 min cumene hydroperoxide (36 mL, technical grade, ca. 0.2 mol) was added slowly over a period of 30 min. The mixture was stirred for 6 h at −5 °C and then cooled to −20 °C and quenched by the careful addition of trimethyl phosphite (14.9 g, 14.1 mL, 0.2 mol). To a solution of freshly opened hexadecylmercaptan (33.5 mL, technical grade, 92%, ca. 0.1 mol) in 190 mL of 2-propanol was slowly added sodium borohydride (4.2 g, 0.11 mol). After the sodium borohydride mixture was stirred for 2 h at room temperature, the unpurified glycidol prepared above was filtered, and the filtrate was added directly to the mercaptan–sodium borohydride mixture. The reaction mixture was stirred overnight at room temperature and diluted with 500 mL of ether, and then 200 mL of 0.5 N sodium hydroxide solution was added. The reaction mixture was stirred for 24 h at room temperature, the organic phase was separated, and the product was extracted with ether. The combined organic layer was washed with water, 5% hydrochloric acid, and brine and then dried over sodium sulfate and concentrated to afford a solid. The solid was recrystallized twice with methanol to give 25.1 g (75%) of the product as a white solid: mp 65–68 °C; R_f 0.44 (hexane/ethyl acetate (1:1)); $[\alpha]^{25}_D$ + 18.6° (*c* 5.0, chloroform); IR (KBr) 3330, 3013, 2919, 2849, 1461, 1214, 1108, 1061, 1020, 926, 873, 761 cm^{-1}; ^{1}H NMR δ 3.81–3.70 (m, 2H), 3.62–3.53 (m, 1H), 2.6–2.8 (m, 2H), 2.54 (t, 2H, J = 7.4 Hz), 2.04 (br t, 1H, J = 6.0 Hz), 1.76–1.51 (m, 3H), 1.2–1.4 (m, 26H), 0.88 (t, 3H, J = 6.7 Hz). Anal. Calcd for $C_{19}H_{40}SO_2$: C, 68.62; H, 12.12; S, 9.64. Found: C, 68.60; H, 12.43; S, 9.63.

3-*S*-Hexadecyl-*sn*-thioglycerol [(−)-5b]. This compound was prepared in 78% yield by the procedure above in the presence of D-(−)-diisopropyl tartrate: $[\alpha]^{25}_D$ −18.7° (*c* 5.0, chloroform).

Procedure for Preparation of the Bis-MTPA Ester of 1(3)-*S*-Hexadecylthioglycerol. To a solution of the hexadecylthio diol **5** (50 mg, 0.15 mmol) and (*N*,*N*-dimethylamino)-pyridine (40 mg, 0.33 mmol) in dichloromethane (1 mL) was added (*R*)-(−)-MTPA chloride (0.060 mL, 0.32 mmol). After the mixture had stirred overnight at room temperature, the solvent was removed under reduced pressure, and the residue was suspended in ether. The suspended mixture was filtered through a pad of silica gel, and the filtrate was concentrated to give a colorless oil (115 mg, 100%). **Bis-MTPA ester of 1-*S*-hexadecyl-*sn*-thioglycerol (5a):** ^{1}H NMR δ 7.55–7.25 (m, 10H), 5.39–5.31 (m, 1H), 4.85 and 4.79 (ABq, 1H, J = 2.5, 13.3 Hz), 4.50 and 4.44 (ABq, 1H, J = 4.3, 12.3 Hz), 3.48 (s, 3H), 3.42 (s, 3H), 2.80–2.67 (m, 2H), 2.50 (t, 2H, J = 7.3 Hz), 1.46–1.57 (m, 2H), 1.26 (s, 26H), 0.88 (t, 3H, J = 6.8 Hz). **Bis-MTPA ester of 3-*S*-hexadecyl-*sn*-thioglycerol (5b):** ^{1}H NMR δ 7.55–7.25 (m, 10H), 5.39–5.31 (m, 1H), 4.67 and 4.60 (ABq, 1H, J = 2.9, 12.3 Hz), 4.50 and 4.44 (ABq, 1H, J = 4.3, 12.3 Hz), 3.48 (s, 3H), 3.42 (s, 3H), 2.80–2.67 (m, 2H), 2.50 (t, 2H, J = 7.3 Hz), 1.46–1.57 (m, 2H), 1.26 (s, 26H), 0.88 (t, 3H, J = 6.8 Hz).

1-*S*-Hexadecyl-3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-thioglycerol [(+)-6a]. To a solution of *tert*-butylchlorodiphenylsilane (3.02 g, 11 mmol) in 25 mL of methylene chloride was added imidazole (1.50 g, 22 mmol). After the reaction mixture was stirred for 1 h at room temperature, 1-*S*-hexadecyl-*sn*-thioglycerol (**5a**) (3.33 g, 10 mmol) was added. After 1 h the mixture was diluted with 50 mL of ether, washed with water and brine, and then dried over sodium sulfate and concentrated under vacuum to give a pale yellow liquid, which was purified by flash chromatography (elution with 10:1 hexane/ethyl acetate) to give 5.31 g (93%) of **6a** as a white solid: mp 36–37 °C; R_f 0.51 (hexane/ethyl acetate (9:1)); $[\alpha]^{25}_D$ +5.48° (*c* 5.0, benzene); IR (KBr) 3460, 3060, 3048, 2919, 2849, 1467, 1420, 1108, 820, 970 cm^{-1}; ^{1}H NMR δ 7.63–7.69 (m, 2H), 7.48–7.33 (m, 3H), 3.84–3.75 (m, 1H), 3.71 (d, 2H, J = 4.6 Hz), 2.76 and 2.70 (ABq, 1H, J = 5.4, 13.5 Hz), 2.63 and 2.57 (ABq, 1H, J = 6.9, 13.5 Hz), 2.50 (t, 2H, J = 7.5 Hz), 1.63–1.44 (m, 2H), 1.26 (s, 26H), 1.07 (s, 9H), 0.88 (t, 3H, J = 6.7 Hz). Anal. Calcd for $C_{35}H_{58}SO_2Si$: C, 73.62; H, 10.24; S, 5.62. Found: C, 73.96; H, 10.00; S, 5.35.

3-*S*-Hexadecyl-1-*O*-(*tert*-butyldiphenylsilyl)-*sn*-thioglycerol [(−)-6b]. This compound was prepared in 95% yield from thioglycerol **5b** by the procedure described above: $[\alpha]^{25}_D$ −5.57° (*c* 5.0, benzene).

1-*S*-Hexadecyl-2-*O*-methyl-3-*O*-(*tert*-butyldiphenylsilyl)-*sn*-thioglycerol [(+)-7a]. Sodium hydride (0.3 g, 10 mmol, 80% in white oil) was washed with dry hexane twice. To the suspension of sodium hydride in 50 mL of dry benzene was added a solution of 2.86 g (5.0 mmol) of **6a** under nitrogen at room temperature. After the evolution of hydrogen had stopped, 4 mL (64 mmol) of methyl iodide was added, and the reaction mixture was stirred for 12 h at room temperature. Hexane (50 mL), ethanol (1 mL), and water (0.5 mL) were added successively, and the product was extracted with hexane. The combined organic layer was washed with brine and then dried over sodium sulfate. After the solvents were evaporated under vacuum, the residue was purified by flash chromatography (elution with 97:3 hexane/ethyl acetate) to give 2.74 g (94%) of a colorless oil: R_f 0.76 (hexane/ethyl acetate (9:1)); $[\alpha]^{25}_D$ +4.32° (*c* 5.0, chloroform); IR (film) 3072, 3048, 2919, 2450, 1461, 1425, 1108, 820, 738, 697 cm^{-1}; ^{1}H NMR δ 7.70–7.63 (m, 4H), 7.47–7.33 (m, 6H), 3.81 and 3.75 (ABq, 1H, J = 2.0, 13.5 Hz), 3.73 and 3.67 (ABq, 1H, J = 1.9, 13.5 Hz), 3.41–3.32 (m, 1H, J = 4.6 Hz), 3.36 (s, 3H), 2.82 and 2.76 (ABq, 1H, J = 5.3, 13.5 Hz), 2.67 and 2.51 (ABq, 1H, J = 6.5, 13.5 Hz), 2.53 (t, 2H, J = 7.5 Hz), 1.60–1.50 (m, 2H), 1.26 (s, 26H), 1.06 (s, 9H), 0.88 (t, 3H, J = 6.7 Hz). Anal. Calcd for $C_{36}H_{60}SO_2Si$: C, 73.91; H, 10.34; S, 5.48. Found: C, 73.72; H, 10.30; S, 5.71.

3-*S*-Hexadecyl-2-*O*-methyl-1-*O*-(*tert*-butyldiphenylsilyl)-*sn*-thioglycerol [(−)-7b]. This compound was prepared in 96% yield from **6b** by the procedure above: $[\alpha]^{25}_D$ −4.34° (*c* 5.0, chloroform).

1-*S*-Hexadecyl-2-*O*-methyl-*sn*-thioglycerol [(−)-8a]. To a solution of 2.35 g (4.0 mmol) of **7a** in 10 mL of THF was added a solution of tetra-*n*-butylammonium fluoride (8 mL of a 1.0 M solution in THF, 8.0 mmol). After the mixture was stirred at room temperature overnight, water was added, and the product was extracted with ether. The combined organic layer was dried over sodium sulfate, and the solvents were evaporated under vacuum. The residue was purified by flash chromatography (elution with 4:1 hexane/ethyl acetate) to give 1.29 g (92%) of a white solid: mp 36–37 °C; R_f 0.30 (hexane/ethyl acetate (4:1));

$[\alpha]^{25}_D$ −20.4° (c 2.5, chloroform); IR (KBr) 3427, 2908, 3837, 1642, 1461, 1096, 1043, 756, 714 cm^{-1}; ^1H NMR δ 3.87–3.76 (m, 1H), 3.68–3.56 (m, 1H), 3.45–3.35 (m, 1H), 2.78 and 2.71 (ABq, 1H, J = 5.1, 13.4 Hz), 2.64 and 2.57 (ABq, 1H, J = 7.4, 13.4 Hz), 2.55 (t, 2H, J = 7.3 Hz), 2.09 (br t, 1H, J = 6.0 Hz), 1.62–1.51 (m, 2H), 1.26 (s, 26H), 0.88 (t, 3H, J = 6.7 Hz). Anal. Calcd for $C_{20}H_{42}SO_2$: C, 69.30; H, 12.21; S, 9.25. Found: C, 69.34; H, 12.14; S, 9.30.

3-*S*-Hexadecyl-2-*O*-methyl-*sn*-thioglycerol [(−)-8b]. This compound was prepared in 95% yield from **7b** by the procedure described above: $[\alpha]^{25}_D$ +20.8° (c 2.5, chloroform).

1-*S*-Hexadecyl-2-*O*-methyl-*sn*-thioglycero-3-phosphocholine [(−)-4a]. To a solution of 0.134 g (0.90 mmol) of phosphorus oxychloride and 163 μL (0.90 mmol) of triethylamine in 5 mL of alcohol-free chloroform at −20 °C under nitrogen was added a solution of 0.25 g (0.72 mmol) of **8a** in 5 mL of chloroform over a 30-min period. The mixture was allowed to warm to room temperature and was stirred for an additional 30 min. Choline tosylate (0.30 g, 1.08 mmol) and pyridine (0.5 mL) were added, and the mixture was stirred for 16 h. After addition of 0.2 mL of water the mixture was stirred for 30 min. The solvents were removed, and the residue was dissolved in dichloromethane–toluene (1:1). The mixture was filtered, and the filtrate was concentrated under vacuum to give a residue that was dissolved in a minimum volume of THF–water (9:1) and passed through an Amberlite MB-3 column two times (elution with THF–water (9:1)). After removal of the solvents, the residue was purified by flash chromatography (elution with chloroform–methanol–water (65:25:4)) to give 258 mg (70%) of a very hygroscopic white solid: R_f 0.41 (chloroform–methanol–water (65:25:4)); $[\alpha]^{25}_D$ −5.42° (c 2.1, $CHCl_3$/MeOH (1:1)); IR (KBr) 3413, 2919, 2849, 1643, 1461, 1226, 1085, 1049, 967, 756, 714 cm^{-1}; ^1H NMR δ: 4.2–4.4 (m, 22H), 3.8–4.1 (m, 2H), 3.7–3.5 (m, 2H), 3.55–3.45 (m, 1H), 3.41 (s, 3H), 3.28 (s, 9H), 2.67 (d, 2H, J = 5.5 Hz), 2.53 (t, 2H, J = 7.4 Hz), 1.53–1.38 (m, 2H), 1.26 (s, 26H), 0.8 (t, 3H, J = 6.6 Hz); HRMS (FAB, MH^+) m/e calcd for $C_{25}H_{55}SPNO_5$ 512.3545, found 512.3552. Anal. Calcd for $C_{25}H_{54}SPNO_5 \cdot 2.5H_2O$: C, 53.94; H, 10.68; S, 5.76; P, 5.56; N, 2.52. Found: C, 53.97; H, 10.00; S, 5.51; P, 5.77; N, 2.51.

3-*S*-Hexadecyl-2-*O*-methyl-*sn*-thioglycero-1-phosphocholine [(+)-4b]. This compound was prepared in 72% yield from **8b** by the procedure above: $[\alpha]^{25}_D$ + 5.11° (c 2.0, $CHCl_3$/MeOH (1:1)).

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Registry Nos. provided by the author: hexadecylmercaptan, 2917-26-2; (*R*)-glycidol, 57044-25-4; (*S*)-glycidol, 60456-23-7.