Synthesis of (2*R*)- and (2*S*)-β-D-Glucopyranos-1-yl-2-*O*-palmitoyl-3-O-phosphatidylcholinylglycerol: A New Antifungal Phosphocholine

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The discovery of a new of antifungal agent, a glycosylated phosphatidylcholine, is reported, and the syntheses of the first two members of this series, (2*S*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol and (2*R*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol, are described. Their activities against the pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, and *Aspergillus fumigatus* are also reported.

Introduction

As part of an ethnobotanically directed screening program designed to detect antifungal agents from plants, an antifungal lead was isolated from the plant species *Irlbachia alata* (Aubl.) Maas.[1,2] This plant belongs to the family Gentianaceae and is commonly found throughout the Amazon basin. Although limited reports on *Irlbachia alata* exist,[3] ethnobotanical field research indicated that this plant species had a number of ethnomedical uses including the treatment of dermatological fungal infections and vaginal yeast infections.[4] The bioactive compound had structural features common to known inositol glycerol **1**, a novel phospholipid isolated from a fermentation broth of *Aspergillus fumigatus* which displays broad spectrum antifungal activity while reportedly having low mammalian toxicity.[5] Recognizing the need for new therapeutic agents against pathogenic fungi, we undertook a program to design a new class of glycerol phosphocholine derivatives with antifungal activity.[2c,d]

Previously, phosphatidylcholines have been the subject of intense study for their use as phospholipase inhibitors,[6] platelet-activating factors,[7] CNS agents,[8] cardiac agents,[8] and antitumor agents;[9] however, few reports exist which describe phosphatidylcholine derivatives as antifungal agents.[10] All of these phosphatidylcholines fall into the classes of acyl, diacyl, ether, or carbamate glycerol phosphocholines. A few glycosylated glycerol phosphates have been isolated[11] or synthesized,[12] and an inositol phosphate related to **1** has been synthesized;[13] none of these have been evaluated for use as antifungal agents.

Herewith we report the discovery of a new antifungal agent, a glycosylated phosphatidylcholine, and the synthesis of the first two members of this series: (2*S*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol and (2*R*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-

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(1) Aublet, F. *Histoire des plantes de la Guiane Françoise* **1775**, *1*, 204–205.

(2) (a) Tempesta, M. S.; Jolad, S. D.; King, S.; Mao, G.; Bruening, R. C.; Kuo, J. E.; Truong, T. V.; Bierer, D. E.; Dener, J. M. WO 9408563, April 28, 1994. (b) The isolation, structure elucidation, and synthesis of Irlbacholine, the antifungal lead isolated from *Irlbachia alata*, has been published in a separate account. See: Bierer, D. E.; Gerber, R. E.; Jolad, S. D.; Ubillas, R. P.; Randle, J.; Nauka, E.; LaTour, J.; Dener, J. M.; Fort, D. M.; Kuo, J. E.; Inman, W. D.; Dubenko, L. G.; Ayala, F.; Ozioko, A.; Obialor, C.; Elisabetsky, E.; Carlson, T.; Truong, T. V.; Bruening, R. C. *J. Org. Chem.* **1995**, *60*, 7022. (c) The design of **2a** and **2b** was based on the screening results of a series of natural lysolecithins, the references cited in ref 5, and on a partial structure determination. While **2a** and **2b** resemble the naturally occurring lysolecithins, they are synthetic compounds. The antifungal activity of naturally occurring lysolecithins was unreported prior to our recent patent disclosure cited in ref 2a. (d) The abstract citations (Derwent, CAS) for ref 2a contain errors and are ambiguous. The identification of the natural product isolated from *Irlbachia alata* is cited incorrectly or ambiguously. The natural product is Irlbacholine, and compounds **2a** and **2b** are synthetic compounds. In addition, one of the inventors names, Bierer, D. E., is incorrectly cited as Bierer, D. J. This paper, and our paper cited in ref 2b, shall serve to correct these mistakes and clarify this ambiguity.

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(4) (a) Ethnomedical information on the plant *Irlbachia alata* was obtained as part of Shaman Pharmaceutical's ethnobotanical field research. (b) For a reference on the role of ethnobotany in the drug discovery process, see Tempesta, M. S.; King, S. R. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A, Sr. Ed.; Venuti, M. C., Ed.; Academic Press: San Diego, 1994; Vol. 29, pp 325–330.

(5) (a) VanMiddlesworth, F.; Wilson, K. E.; Hensens, O. D.; Zink, D.; Lopez, M. B. U.S. Patent 5,164,375, Nov 17, 1992. (b) VanMiddlesworth, F.; Lopez, M.; Zweerink, M.; Edison, A. M.; Wilson, K. *J. Org. Chem.* **1992**, *57*, 4753–4754.

(6) Some representative examples are the following: (a) Cox, J. W.; Snyder, W. R.; Horrocks, L. A. *Chem. Phys. Lipids* **1979**, *25*, 369–380. (b) Chandrakumar, N. S.; Hajdu, J. *J. Org. Chem.* **1982**, *47*, 2144–2147. (c) Baba, N.; Yoneda, K.; Tahara, S.; Mikami, Y.; Iwasa, J.; Kaneko, T.; Matsuo, M. *Int. Congr. Ser.–Excerpta Med.* **1992**, *998* (Oxygen Radicals), 261–264. (d) Yuan, W.; Berman, R. J.; Gelb, M. H. *J. Am. Chem. Soc.* **1987**, *109*, 8071–8081. (e) Magolda, R. L.; Johnson, P. R. *Tetrahedron Lett.* **1985**, *26*, 1167–1170.

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(12) (a) Ogawa, T.; Katano, K.; Matsui, M. *Carbohydr. Res.* **1979**, *70*, 37–46. (b) van Boeckel, C. A. A.; Visser, G. M.; Hermans, J. P. G.; van Boom, J. H. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 526–537. (c) van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **1979**, 3561–3564.

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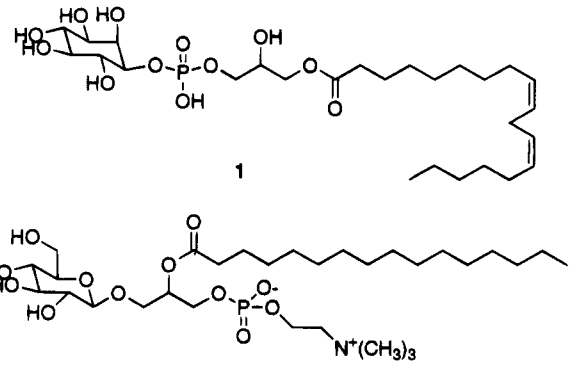
3-*O*-phosphatidylcholinylglycerol, **2a** and **2b**, respectively. We also report their *in vitro* activities against the pathogenic fungi *Candida albicans*, *Cryptococcus neoformans*, and *A. fumigatus*.



1

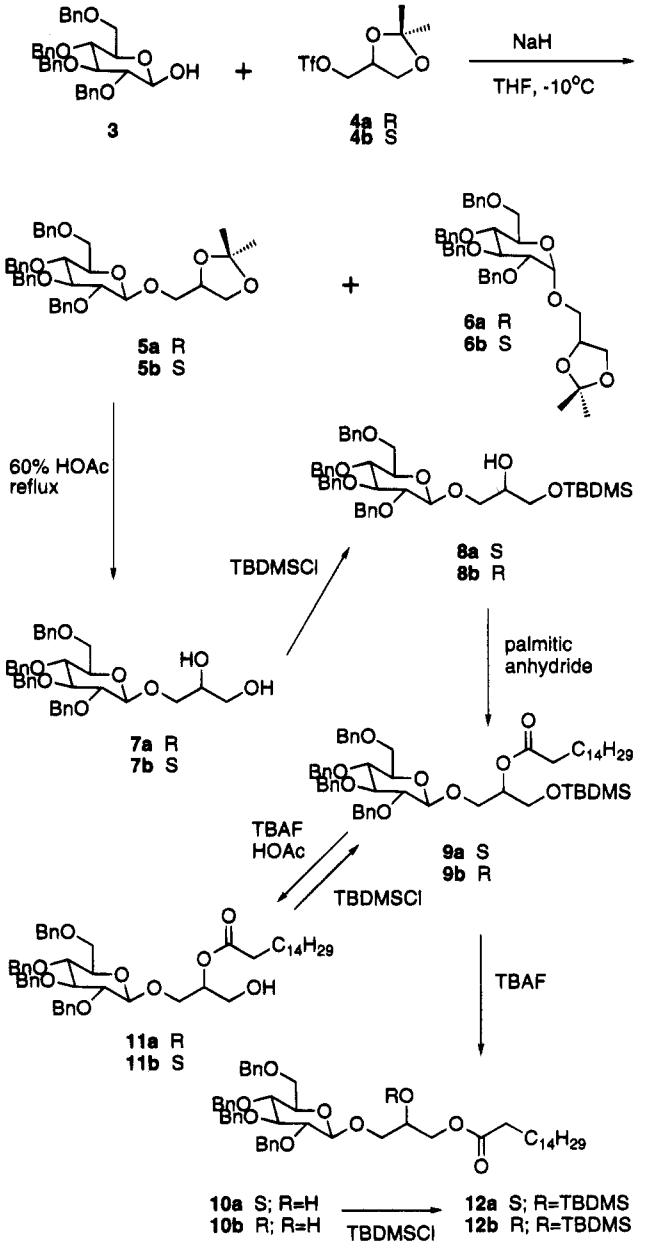
2a 2-(S) configuration (S) SP-19501
2b 2-(R) configuration (R) SP-19501

Results and Discussion

Our synthetic strategy to glycosylated phosphocholine antifungal agents was designed to allow for the synthesis of a variety of modifications of the acyl, sugar, and phosphocholine moieties, employing an optically active glycerol component as the chiral educt. Two synthetic approches were explored. The first approach involved initial glycosylation of the optically active glycerol component, followed by acylation and phosphorylation. The second approach involved initial phosphorylation of the chiral glycerol component, to be followed by acylation and then glycosylation. In both routes the synthesis of the parent glycosylated phosphocholines **2** began with (*R*)- and (*S*)-1,2-isopropylideneglycerol as the chiral educts.

Glycosylation[14a] of 2,3,4,6-tetra-*O*-benzylglucopyranose (**3**) with (*S*)-1,2-isopropylideneglycerol was accomplished by activating the remaining free hydroxyl of the protected glycerol moiety as the triflate and coupling it with the sodium salt of **3** (Scheme 1). The reaction was carried out at −10 °C in THF and proceeded in 68% yield, providing **5a** as a white solid, along with a 19% yield of α-anomer **6a** as an oil. Control of the reaction temperature was critical: allowing the temperature to rise above −10 °C led to increased α-anomer formation, while lower temperatures required longer reaction times and gave reduced yields of **5a**. Hydrolysis of the isopropylidene protecting group was accomplished using 60% aqueous HOAc at reflux for 90 min, affording an 85% yield of **7a**. Protection of the primary hydroxyl group as the TBDMS ether gave **8a** in 88% yield. Acylation of the remaining hydroxyl group was best accomplished using palmitic anhydride in the presence of triethylamine and a catalytic amount of DMAP, providing a 97% yield of **9a**. Removal of the TBDMS moiety using tetrabutylammonium fluoride (TBAF) in THF led to secondary alcohol **10a** in 46% yield. Deprotection of **9a** with minimal acyl migration was accomplished by carrying out the desilylation reaction in the presence of excess acetic acid or by using a buffered TBAF/HOAc (pH 6.5) system. Both procedures afforded reproducible 90% yields of the desired primary alcohol **11a**.[15] The identities of primary alcohol **11a** and

Scheme 1



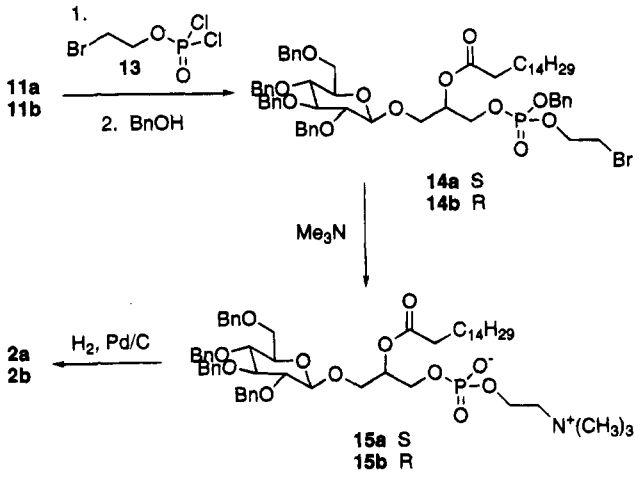
secondary alcohol **10a** were established by resubjecting each to silylation conditions and then comparing the products to the protected glycerol **9a**. The ^1H and ^{13}C NMR spectra obtained for the resilylation product of **11a** matched those of **9a** completely, while the NMR data obtained for the resilylation product of **10a** were different, corresponding to fully protected glycerol **12a**.[16]

The synthesis of epi-glycerol derivative **11b** required for the synthesis of **2a** was achieved in an analogous manner (Scheme 1). As before, the identities of **11b** as

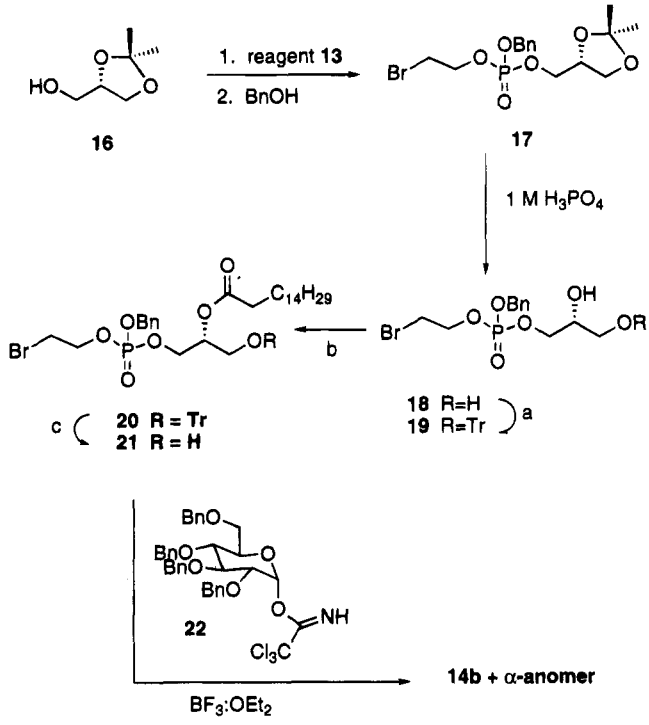
(14) (a) Schmidt, R. R.; Reichrath, M.; Moering, U. *J. Carbohydr. Chem.* **1984**, *3*, 67–84. (b) Reference 14a uses racemic 2,3-*O*-isopropylideneglycerol. Thus, the literature melting points cited for compounds **5a** and **7a** found in ref 14a are for diastereomeric mixtures about the C-2 glycerol carbon.

(15) (a) The purity of primary alcohols **11a,b** was conveniently established by HPLC. Primary alcohols **11a,b** and secondary alcohols **10a,b** are separable by HPLC, with t_R diferences of 2 min. The t_R for **10a**, **10b**, **11a**, and **11b** are 10.5 ± 0.2, 10.4 ± 0.2, 12.5 ± 0.2, and 12.5 ± 0.2 min, respectively under the following conditions: 8 μm SiO_2 column; photodiode array and Sedex 55 light scattering detectors; 1% 2-propanol–99% hexane, 0–20 min. Under these conditions, the purity of **11a** and **11b** following LPLC over Whatman silica gel ranged from 92 to 99% and was routinely 94–96%. A sample of **11a** stored at −20 °C for 2 years was reanalyzed and found to be 98% pure. (b) Small amounts of the **10a,b** impurity were removable at the subsequent phosphorylation step if necessary; phosphorylation occurred at a faster rate for **11a,b** than for **10a,b**.

Scheme 2



Scheme 3[a]



[a] Reagents: (a) trityl chloride, DIPEA, rt; (b) palmitic anhydride, Et_3N, DMAP, THF, rt; (c) HCOOH, THF, rt.

the primary alcohol and **10b** as the secondary alcohol were unambiguously established by resubjecting each to silylation conditions and comparing each to known **9b**.[15]

With the structure of all four isomeric glycerols established, our attention focused on completion of the synthesis of (*S*)- and (*R*)-SP-19501 (Scheme 2). Phosphorylation of glycerol **11a** was best accomplished through addition of alcohol **11a** to a mixture of 2-bromoethyl phosphorodichloridate[17] (**13**) (600 mol %) and triethylamine (5000 mol %) at 0 °C for 1.5–2 h (until **11a** disappeared by TLC) followed by quenching of the reaction with benzyl alcohol (1000 mol %). This procedure provided reproducible 40–43% yields of phosphotriester **14a**. Displacement of the bromine substituent was accomplished by treating a solution of triester **14a** in toluene with anhydrous trimethylamine in a Parr bomb at 55 °C for 24 h. This event was accompanied by loss of the benzyl group[18] on the phosphate moiety, providing choline **15a** in a 45.5% yield after purification by preparative TLC.[19] The benzyltrimethylammonium bromide byproduct was conveniently removed from the reaction mixture by trituration of the crude oil with ether. Hydrogenation of **15a** over 10% Pd/C in methanol at 60 psi afforded a 72% yield of **2a**. Using a similar sequence of steps, the (*R*)-diastereomer **2b** was obtained from glycerol **11b**.

An alternative strategy to phosphotriester **14b** involving an initial phosphorylation step was simultaneously explored (Scheme 3). Condensation of 2-bromoethyl phosphorodichloridate (**13**) with (*S*)-2,3-*O*-isopropylideneglycerol (**16**) in the presence of *N*-methylmorpholine gave, after quenching of the reaction with benzyl alcohol, phosphotriester **17** in 45% yield. Unlike the previous route, removal of the isopropylidine protecting group was not successful using aqueous acetic acid, as significant decomposition of **17** was observed. However, this transformation was realized by simple treatment of **17** with 1 M H_3PO_4 at room temperature overnight, affording diol **18** in 80% yields. Diol **18** is unstable, and best results were obtained using freshly prepared material. Protection of the primary hydroxyl function with the TBDMS moiety was unsuccessful. Use of the trityl protecting group to accomplish this selective blocking step was successful [TrCl (105 mol %), DIPEA (105 mol %), rt, 40 h], providing secondary alcohol **19** in 52% yield. Treatment of **19** with palmitic anhydride (110 mol %) in the presence of triethylamine (110 mol %) and DMAP (20 mol %) gave fully functionalized glycerol **20** in 92% yield. Removal of the trityl protecting group was accomplished by treatment of **20** with a 1:1 mixture of formic acid/THF at room temperature providing **21** in 56–72% yields.[20] Glycosylation of **21** was carried out using the trichloroacetimidate method of Schmidt.[21] Treatment of **21** with α-D-glucopyranosyl trichloroacetimidate (**22**) in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at −10 to −20 °C or room temperature gave the (*R*)-phosphotriester in 43% and 22% yields, respectively, as a mixture of **14b** and its α-anomer.[22]

(*R*)- and (*S*)-SP-19501 were tested in an antifungal susceptibility test using a 96 well microplate broth

(16) ^{1}H NMR for **12a** ($CDCl_3$): δ 7.42–7.3 (m, 18H), 7.23–7.2 (m, 2H), 4.99 and 4.97 (overlapping doublets, 2H, J = 11.2, J = 11.2), 4.85 (t, 2H, J = 12), 4.76 (d, 1H, J = 11.2), 4.67 and 4.60 and 4.59 (3 overlapping doublets, 3H, J = 11.2, J = 10.8, J = 10.8), 4.47 (d, 1H, J = 7.6), 4.36 (d, 1H, J = 8.0), 4.13 (m, 2H), 3.87 (dd, 1H, J = 12, J = 4.2), 3.8–3.6 (m, 5H), 3.50 (m, 2H) 2.35 (t, 2H, J = 7.2), 1.68 (t, 2H, J = 7.2), 1.31 (br s, 24H), 1.0–0.9 (m, with s at δ 0.93, 12H), 0.15 (s, 3H), 0.14 (s, 3H). A diagnostic difference between **9a** and **12a** in the ^{1}H NMR spectrum: **9a** has a 1H multiplet at δ 5.06 which is absent in **12a**.

(17) (a) Hansen, W. J.; Murari, R.; Wedmid, Y.; Baumann, W. J. *Lipids* **1982**, *17*, 453–459. (b) Renshaw, R. R.; Hopkins, C. Y. *J. Am. Chem. Soc.* **1929**, *51*, 953–954.

(18) Removal of a benzyl group from a phosphate triester with iodide ion has precedent, see: (a) Inoue, K.; Suhara, Y.; Nojima, S. *Chem. Pharm. Bull.* **1963**, *11*, 1150–1156. (b) Molotkovski, Y. G.; Lazurkina, T. Y.; Bergel'son, L. D. *Izv. Akad. Nauk, SSSR Ser. Khim.* **1969**, 1784–1789.

(19) Alternatively, **15a,b** could be purified by reversed-phase HPLC on a C-18 column using water–methanol (1:99).

(20) Also isolated was the corresponding secondary alcohol in 11 to 18% yields.

(21) (a) Schmidt, R. R.; Michel, J. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 731–732. (b) Schmidt, R. R.; Michel, J. *Tetrahedron Lett.* **1984**, *25*, 821–824. (c) Schmidt, R. R.; Michel, J. *J. Carbohydr. Chem.* **1985**, *4*, 141–169.

(22) **14b** and its α-anomer (3:2 ratio at −10 to −20 °C; 1:1 ratio at rt; detemined from a gated ^{13}C NMR experiment) were not separable by HPLC. Since this route was deemed inferior to the other route, possible separation at a subsequent step was not attempted.

assay[23] against three pathogenic fungi: *C. albicans*, *C. neoformans*, and *A. fumigatus*. (*R*)-SP-19501 (**2b**) displayed activities of 16, 8, and 8 μg/mL against *C. albicans*, *C. neoformans*, and *A. fumigatus*, respectively. The diastereomer (*S*)-SP-19501 (**2a**) was inactive against all three fungi (>1000 μg/mL). By comparison, inositol **1**, isolated from an *A. fumigatus* fermentation broth, has reported activities of 32-64 and 16 μg/mL against various strains of *C. albicans* and *C. neoformans*.[5a,24]

Conclusion

We have synthesized both (2*S*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol (**2a**) and (2*R*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol (**2b**) and demonstrated the discovery of a new class of glycerol phosphocholines which have antifungal activity. The described synthetic routes to **2a** and **2b** will allow for variation of the sugar, acyl, and phosphocholine moieties. The observed antifungal activity of **2b** is comparable with respect to *C. albicans* and *C. neoformans* to that reported for known inositol glycerol **1**.[5] The stereochemistry of the 2-glycerol substituent is critical to the observed activity against all three test fungi.

Experimental Section

General Procedures. THF was distilled from K/benzophenone. Et_2O was distilled from $LiAlH_4$. Benzene, Et_3N, CH_2Cl_2, *N*-methylmorpholine, and benzyl alcohol were distilled from CaH_2. 2-Bromoethyl phosphorodichloridate was prepared according to the procedure reported by Baumann[17a] and was freshly distilled prior to use. Trifluromethanesulfonic anhydride was freshly distilled under N_2. Anhyd DMF was obtained from Aldrich. (*S*)-(+)-1,2-*O*-Isopropylideneglycerol and (*R*)-(−)-1,2-*O*-isopropylideneglycerol were obtained from Lancaster. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose was obtained from Sigma. α-D-Glucopyranosyl trichloroacetimidate was prepared according to the method of Schmidt.[21] (*R*)- and (*S*)-2,3-*O*-isopropylidene-1-*O*-(trifluoromethanesulfonyl)glycerol were prepared by the method of Schmidt which used racemic 2,3-*O*-isopropylideneglycerol (solketal).[14a] All other reagents were used as received. All moisture sensitive reactions were done under a nitrogen atmosphere, using dry solvents, and all reactions were monitored by TLC. Reaction mixtures following workup were dried over Na_2SO_4 or $MgSO_4$ and then filtered prior to rotary evaporation. Evaporation of solvents was done at room temperature. TLC was performed on Whatman 250 μm F_{254} silica gel plates. Preparative TLC was performed on Whatman 2000 μm F_{254} silica gel plates. Low-pressure liquid chromatography (LPLC) was performed on Whatman 230−400 mesh silica gel using nitrogen pressure. Analytical samples of **9a**, **11a**, and **11b** were purified by preparative HPLC using an 8 μm SiO_2 column and a 0−1% 2-propanol−hexane gradient; analytical samples of **15a**, **15b**, **2a**, and **2b** were purified using a Hamilton PRP-1 (12−20 μm, 21.5 × 250 mm) reversed-phase column and an acetonitrile−water gradient. Preparative HPLC was performed using a UV detector, with detection at 220 nm. Analytical HPLC was performed using a photodiode array detector and a Sedex 55 light scattering detector, the latter allowing for detection of non-UV active components. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded on a 400 MHz spectrometer. ^{13}C NMR multiplicities as determined by DEPT experiments are reported in parentheses following the chemical shift value according to the following format: quaternary (0), methine (1), methylene (2), and methyl (3). ^{31}P NMR spectral data are reported using 85% H_3PO_4 as an external reference at 0.0 ppm. NMR coupling constants are reported in hertz. High-resolution mass spectra were obtained from the Analytical Services Department at the University of California, Berkeley, or at Shaman Pharmaceuticals. Elemental analyses were performed by the Analytical Services Department at the University of California, Berkeley. Melting points are uncorrected.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2,3-*O*-isopropylideneglycerol (5a) and (2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-2,3-*O*-isopropylideneglycerol (6a). To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (100 g, 0.182 mol) in THF (1.4 L) at −10 °C in a 3-L three-necked morton flask fitted with a thermometer and mechanical stirrer was added NaH (60% suspension in oil, 16.1 g, 0.403 mol) in four increments over 10 min. The solution was stirred for 30 min, and then a solution of freshly prepared (*R*)-2,3-*O*-isopropylidene-1-*O*-(trifluoromethanesulfonyl)glycerol (60.0 g, 0.227 mol) in THF (500 mL) was added dropwise via an addition funnel to the reaction mixture over a 30 min period. The solution was stirred at −10 °C for 7 h, and then the reaction was quenched by addition of methanol (200 mL) dropwise. The reaction mixture was concentrated, and the residue was dissolved in $CHCl_3$ (750 mL) and washed with water (2 × 750 mL). The combined aqueous layers were extracted with $CHCl_3$ (3 × 500 mL), and the organic layers were pooled and concentrated to give a white solid, which contained both the β- and α-epimers **5a** and **6a**. This solid was triturated with ether to give **5a** as a white solid and a mother liquor which contained α- and β-epimers. The mother liquor was concentrated and purified by LPLC (20% EtOAc/hexanes). The combined yield of **5a** was 81 g (68%): mp 91−91.7 °C (lit.[14] mp 83−84 °C); R_f 0.40 (25% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 7.4−7.29 (m, 18H), 7.20−7.16 (m, 2H), 4.96 (d, 2H, *J* = 10.8), 4.84 (t, 2H, *J* = 10.8), 4.75 (d, 1H, *J* = 10.8), 4.65 (d, 1H, *J* = 12.4), 4.57 and 4.56 (overlapping doublets, 2H, *J* = 12, *J* = 10.4), 4.46 (d, 1H, *J* = 7.2), 4.38 (m, 1H), 4.12−4.02 (m, 2H), 3.89 (t, 1H, *J* = 7.2), 3.79−3.6 (m, 5H), 3.50 (pseudo t, 2H), 1.46 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.53 (0), 138.37 (0), 138.07 (0), 138.01 (0), 128.43, 128.41, 128.13, 128.02, 127.90, 127.81, 127.73, 127.67, 109.40 (0), 103.82, 84.63, 82.12, 77.71, 75.75 (2), 75.06 (2), 74.89, 74.85, 74.31 (2), 73.50 (2), 70.32 (2), 68.76 (2), 66.90 (2), 26.88 (3), 25.39 (3); MS (LSIMS) 653.4 (M − 1). Anal. Calcd for $C_{40}H_{46}O_8$: C, 73.37; H, 7.08. Found: C, 73.28; H, 7.06. α-Epimer **6a** was isolated in 19% yield (23 g) as a colorless oil: R_f 0.34 (25% EtOAc/hexanes); ^1H NMR ($CDCl_3$) δ 7.4−7.24 (m, 18H), 7.14 (m, 2H), 4.98 (d, 1H, *J* = 10.8), 4.88−4.78 (m, 3H), 4.67 (d, 1H, *J* = 12), 4.62 (d, 1H, *J* = 11.6), 4.47 (d, 2H, *J* = 11.6), 4.37 (m, 1H), 4.07 (t, 1H, *J* = 8.4), 3.96 (t, 1H, *J* = 8.8), 3.8−3.54 (m, 9H), 1.43 (s, 3H), 1.37 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.76 (0), 138.20 (0), 138.16 (0), 137.82 (0), 128.44, 128.39, 128.36, 128.03, 127.95, 127.92, 127.89, 127.70, 127.59, 109.42 (0), 97.48, 81.88, 79.89, 77.51, 75.70 (2), 75.09 (2), 74.54, 73.46 (2), 73.11 (2), 70.28, 69.02 (2), 68.31 (2), 67.04 (2), 26.83 (3), 25.42 (3); MS (LSIMS) 653.4 (M − 1). Anal. Calcd for $C_{40}H_{46}O_8$: C, 73.37; H, 7.08. Found: C, 73.14; H, 7.09.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-glycerol (7a). A 5 L three-necked morton flask fitted with a mechanical stirrer, condenser, and stopper was charged with glycoside **5a** (50 g, 76.2 mmol) in 60% aqueous acetic acid (2.5 L). The acidic solution was refluxed for 1.5 h at 103 °C and then cooled to rt. Water (1.5 L) was added to the solution causing precipitation of a white solid. The acidic reaction mixture was extracted with CH_2Cl_2 (4 × 1 L), and the CH_2Cl_2 layers were pooled, washed with saturated $NaHCO_3$ solution, dried, and then concentrated. Trituration with ether gave diol **7a** as a white solid. The mother liquor was purified by LPLC (50% EtOAc/hexanes) to give additional **7a**. The combined

(23) (a) McGinnis, M. R. *Laboratory Handbook of Medical Mycology*; Academic Press: New York, 1980; p 661. (b) NCCLS Document M27-P, Proposed Standard; National Committee for Clinical Laboratory Standards: Villanova, PA, 1980; Vol. 12, No. 25. (c) The following fungal strains were used for antifungal testing: *Candida albicans* (ATCC 10259), *Cryptococcus neoformans* (ATCC 36556), and *Aspergillus fumigatus* (ATCC 13073).

(24) The use of molar concentrations is more meaningful. Activity of **2b**: 24 nM, 12 nM, and 12 nM against *C. albicans*, *C. neoformans*, and *A. fumigatus* respectively. Activity of **2a**: >1520 nM against all three fungi. Activity of 1: 54−102 nM against *C. albicans*, 27 nM against *C. neoformans*.

yield of **7a** was 61.9 g (83%): mp 101.5–102.4 °C (lit.[14] mp 76–78 °C); R_f 0.21 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.40–7.26 (m, 18H), 7.22–7.17 (m, 2H), 5.0–4.7 (m, 5H), 4.64–4.5 (m, 3H), 4.46 (d, 1H, J = 8.0), 4.0–3.5 (m, 11H), 2.55 (s, 2H, OH's); ^{13}C NMR ($CDCl_3$) δ 138.53 (0), 138.33 (0), 137.95 (0), 137.74 (0), 128.53, 128.50, 128.48, 128.19, 128.11, 128.09, 127.93, 127.87, 127.75, 104.28, 84.65, 82.16, 77.82, 75.78 (2), 75.08 (2), 75.03 (2), 74.53, 73.57 (2), 73.21 (2), 71.20, 68.88, (2), 63.35 (2); MS (LSIMS) 615.4 (MH^+). Anal. Calcd for $C_{37}H_{42}O_8$: C, 72.29; H, 6.89. Found: C, 72.10; H, 6.90.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)glycerol (8a). A solution of diol **7a** (9.0 g, 14.7 mmol), imidazole (2.05 g, 30.2 mmol), and *tert*-butyldimethylsilyl chloride (2.28 g, 15.1 mmol) in anhyd DMF (45 mL) was stirred for 2.5 days at rt, transferred to a 1 L separatory funnel, and then diluted with CH_2Cl_2 (250 mL) and water (250 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 250 mL), and then the combined organic layer was washed with water (2 × 100 mL). After drying and concentration, purification by LPLC (33% EtOAc/hexanes) gave 9.2 g (88%) of **8a** as a colorless oil: R_f 0.44 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.48–7.32 (m, 18H), 7.25–7.21 (m, 2H), 5.00 (d, 2H, J = 11.2), 4.89 and 4.88 (overlapping doublets, 2H, J = 10.8, J = 10.4), 4.83 (d, 1H, J = 11.2), 4.67 (d, 1H, J = 12.4), 4.60 and 4.59 (overlapping doublets, 2H, J = 12.4, J = 10.8), 4.50 (d, 1H, J = 7.6), 4.06–3.92 (m, 2H), 3.9–3.62 (m, 7H), 3.6–3.52 (m, 2H), 3.04 (s, 1H, OH), 0.98 (s, 9H), 0.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.55 (0), 138.38 (0), 138.01 (0), 137.96 (0), 128.46, 128.44, 128.12, 128.06, 127.93, 127.86, 127.77, 127.73, 127.70, 104.38, 84.69, 82.22, 77.80, 75.77 (2), 75.07 (2), 74.96 (2), 74.72, 73.54 (2), 73.08 (2), 71.06, 68.79 (2), 64.00 (2), 25.97 (3), 18.37 (0), −5.30 (3); MS (LSIMS) 729.89 (MH^+), 728.98 (M^+), 727.9 (M − 1). Anal. Calcd for $C_{43}H_{56}O_8Si$: C, 70.85; H, 7.74. Found: C, 71.15; H, 7.72.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoyl-3-*O*-(*tert*-butyldimethylsilyl)glycerol (9a). To a solution of **8a** (9.3 g, 12.8 mmol) and palmitic anhydride (6.94 g, 14.0 mmol) in dry THF (200 mL) were added DMAP (316 mg, 2.6 mmol) and triethylamine (2.04 mL, 14.7 mmol). After being stirred for 12 h at rt, the mixture was transferred to a 2 L separatory funnel and diluted with ether (500 mL) and water (500 mL). The layers were separated, the aqueous layer was filtered through Whatman No. 1 paper, and the solid was washed with ether. The filtered aqueous layer was extracted with ether (2 × 500 mL), and then the ethereal extracts were combined, dried, and concentrated. Purification by LPLC (14% EtOAc/hexanes) gave 12.1 g (97%) of **9a** as a light-yellow oil: R_f 0.60 (16.7% EtOAc/hexanes); R_f 0.25 (12.5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.41–7.29 (m, 18H), 7.21–7.19 (m, 2H), 5.16 (m, 1H), 4.99 (t, 2H, J = 11.2), 4.85 (t, 2H, J = 11.6), 4.76 (d, 1H, J = 11.2), 4.67 (d, 1H, J = 12), 4.59 (dd, 2H, J = 12, J = 11.6), 4.44 (d, 1H, J = 7.2), 4.12 (dd, 1H, J = 5.2, J = 10.8), 3.9–3.6 (m, 7H), 3.49 (m, 2H), 2.32 (t, 2H, J = 7.2), 1.61 (m, 2H), 1.25 (br s, 24H), 0.98–0.91 (m containing 9H s at 0.93 ppm, 12H), 0.10 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.28, 138.60, 138.44, 138.13, 138.10, 128.38, 128.36, 128.33, 128.09, 127.98, 127.86, 127.78, 127.75, 127.61, 127.58, 103.83, 84.56, 81.98, 77.72, 75.69, 75.02, 74.88, 74.60, 73.49, 72.90, 68.75, 67.82, 61.66, 34.43, 33.95, 31.94, 29.72, 29.69, 29.65, 29.62, 29.50, 29.46, 29.38, 29.30, 29.15, 25.83, 24.95, 22.72, 18.27, 14.16, −5.38. Anal. Calcd for $C_{59}H_{86}O_9Si$: C, 73.25; H, 8.96. Found: C, 72.88; H, 8.77.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoylglycerol (11a). Procedure A. A 3 L three-necked morton flask fitted with a mechanical stirrer, thermometer, and 500-mL addition funnel was charged with a solution of glycerol **9a** (34.0 g, 35.1 mmol) in THF (1.4 L). The solution was chilled to 0 °C; then a solution of TBAF (520 mL of 1.0 M in THF) which was buffered to pH = 6.5 with acetic acid was added dropwise. The reaction mixture was stirred for 11 h at 0 °C, left at −15 °C for 12 h, and then stirred again at rt for 4 h. Water (100 mL) was added, and the solution was concentrated to about 200 mL of solution. The concentrate was redissolved in CH_2Cl_2 (750 mL) and washed with water (750 mL, 2 × 500 mL), the aqueous layer was back-extracted with ether (500 mL), and then the combined organic layers were dried and concentrated to give a red oil. Purification by LPLC (33–40% gradient of EtOAc/hexanes) gave 28.0 g (93%) of **11a** as a white solid: mp 44.3–45.4 °C; R_f 0.36 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.39–7.26 (m, 18H), 7.19–7.15 (m, 2H), 5.06 (m, 1H), 4.95 and 4.93 (dd, 2H, J = 10.8, J = 10.8), 4.82 and 4.80 (dd, 2H, J = 10.8, J = 11.2), 4.74 (d, 1H, J = 11.2), 4.61–4.5 (m, 3H), 4.43 (d, 1H, J = 7.2), 4.10 (dd, 1H, J = 3.2, J = 10.8), 3.96–3.84 (m, 2H), 3.79–3.44 (m, 8H), 2.32 (t, 2H, J = 7.6), 1.62 (m, 2H), 1.27 (br s, 24H), 0.90 (t, 3H, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 173.47, 138.48, 138.27, 137.89, 137.76, 128.41, 128.38, 128.10, 128.01, 127.94, 127.83, 127.76, 127.73, 127.63, 103.86, 84.50, 81.84, 77.70, 75.68, 75.02, 74.72, 74.57, 73.48, 72.92, 68.73, 68.03, 60.96, 34.35, 31.93, 29.70, 29.66, 29.62, 29.48, 29.37, 29.27, 29.12, 24.96, 22.70, 14.15; MS (LSIMS) 851.9 (M − 1). Also isolated was 1.7 g (5.6%) of secondary alcohol **10a**: R_f 0.45 (25% EtOAc/hexanes). **Procedure B.** A solution of glycerol **9a** (500 mg, 0.52 mmol) in THF (20 mL) was treated with glacial acetic acid (9.5 mL), and the solution was chilled to 0 °C. TBAF (5.16 mL, 1.0 M in THF) was added, and stirring was continued at 0 °C for 8 h and then at rt for 25 h. The reaction mixture was extracted with CH_2Cl_2 (50 mL), and the CH_2Cl_2 layer was was neutralized with a 1 M Na_2HPO_4 solution (2 × 75 mL), separated, dried, and then concentrated. Purification by LPLC (25–40% gradient of EtOAc/hexanes) gave 424 mg (95%) of glycerol **11a** as a colorless oil which solidified upon standing. HRMS (FAB, M^+) calcd for $C_{53}H_{72}O_9$ 852.5176, found 852.5182. Anal. Calcd for $C_{53}H_{72}O_9$: C, 74.62; H, 8.51. Found: C, 74.53, H; 8.49.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-3-*O*-palmitoylglycerol (10a). To a solution of glycerol **9a** (3.0 g, 3.1 mmol) in THF (120 mL) was added TBAF (54 mL, 1.0 M in THF) via an addition funnel over a 15 min period. Glacial acetic acid (18 mL) was added, and then the solution was stirred for 45 min. The solution was concentrated under reduced pressure to approximately 30 mL of liquid and then redissolved in CH_2Cl_2 (150 mL). The organic layer was washed with water (3 × 120 mL) and neutralized with $NaHCO_3$ solution (2 × 150 mL), and then the combined aqueous layer was back-extracted with CH_2Cl_2 (100 mL). The combined organic layer was dried, filtered, concentrated, and then purified by LPLC (25% EtOAc/hexanes) to give 1.3 g (46%) of **10a** as a colorless oil: R_f 0.45 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.4–7.3 (m, 18H), 7.12–7.16 (m, 2H), 4.96 (d, 1H, J = 11.2), 4.93 (d, 1H, J = 11.2), 4.84 (d, 2H, J = 11.2), 4.79 (d, 1H, J = 11.2), 4.63 (d, 1H, J = 11.2), 4.56 (d, 1H, J = 11.2), 4.54 (d, 1H, J = 11.0), 4.46 (d, 1H, J = 8.0), 4.2–4.14 (m, 2H), 4.10–4.05 (m, 1H), 3.96 (dd, 1H, J = 11.6, J = 4.0), 3.82–3.49 (m, 8H), 2.38 (t, 2H, J = 7.2), 1.64 (m, 2H), 1.27 (br s, 24H), 0.90 (t, 3H, J = 7.2); ^{13}C NMR ($CDCl_3$) δ 173.61, 138.56, 138.36, 138.13, 138.08, 128.38, 128.35, 128.08, 127.97, 127.84, 127.73, 127.60, 127.58, 103.85, 84.66, 82.16, 77.80, 75.70, 75.01, 74.91, 74.84, 73.50, 70.74, 69.61, 68.80, 65.96, 34.27, 31.92, 29.70, 29.66, 29.62, 29.47, 29.37, 29.30, 29.18, 25.73, 24.94, 22.70, 14.14, −4.72, −4.78. Anal. Calcd for $C_{53}H_{72}O_9$: C, 74.62; H, 8.51. Found: C, 74.68; H, 8.45. Further elution gave primary alcohol **11a** as a white solid (400 mg, 0.469 mmol) in 15% yield, which was identical with that isolated above.

Resilylation of (2*R*)-[1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoylglycerol (11a). *tert*-Butyldimethylsilyl chloride (281 mg, 1.86 mmol) and imidazole (254 mg, 3.73 mmol) were added to a solution of primary alcohol **11a** (318 mg, 0.373 mmol) in DMF (8 mL), and the solution was stirred for 22 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL), the organic layer was washed with water (50 mL), and then the aqueous layer was back-extracted with CH_2Cl_2 (2 × 50 mL). The pooled CH_2Cl_2 layers were washed with water (2 × 75 mL), dried, filtered, and then concentrated. Purification by LPLC (14% EtOAc/hexanes) gave 239 mg (66%) of **9a** as a yellow oil, which was identical with **9a** isolated previously.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoyl-3-*O*-[(2-bromoethoxy)benzoxyphosphoryl]-glycerol (14a). Procedure A. A solution of freshly distilled 2-bromoethyl phosphorodichloridate (**13**) (1.72 g, 7.11 mmol)

in anhyd ether (20 mL) was cooled to 0 °C, and triethylamine (8.15 mL, 58.5 mmol) was injected into the solution, causing precipitation of a white solid. A solution of **11a** (1.0 g, 1.17 mmol) in anhyd ether (55 mL) was added, and then the ice bath was removed. After 30 min, benzyl alcohol (1.21 mL, 11.7 mmol) was injected, and then the reaction mixture was stirred at rt for 5 days. The precipitated triethylamine hydrochloride was filtered off, and then the filtrate was concentrated and purified by LPLC (0–33% EtOAc/hexanes), affording 566 mg (43%) of **14a** as a light-yellow oil: R_f 0.36 (33% EtOAc/hexanes); R_f 0.08 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.38–7.25 (m, 23H), 7.18–7.14 (m, 2H), 5.25 (m, 1H), 5.10 (m, 2H), 4.92 (dd, 2H, J = 10.8, J = 11.2), 4.80 (t, 2H, J = 11.2), 4.69 (d, 1H, J = 11.2), 4.61 (d, 1H, J = 12.4), 4.53 (d, 2H, J = 11.6), 4.37 (d, 1H, J = 7.2), 4.31–4.18 (m, 4H), 4.06 (dd, 1H, J = 11.2, J = 4.4), 3.76–3.58 (m, 5H), 3.46–3.36 (m, 4H), 2.27 (m, 2H), 1.57 (br m, 2H), 1.26 and 1.25 (br d, 24H), 0.89 (t, 3H, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 172.98, 138.56, 138.36, 138.10, 138.07, 128.67, 128.63, 128.33, 128.32, 128.30, 127.96, 127.88, 127.76, 127.73, 127.70, 127.61, 127.52, 103.86, 84.54, 81.97, 77.65, 75.59 (2), 74.94 (2), 74.91 (2), 74.69 (2), 73.48 (2), 70.43 (d, 1, J = 8.5), 69.64 (d, 2, J = 6.1), 68.78 (2), 67.28 (2), 66.90 (2), 66.07 (d, 2, J = 3.0), 34.17, 31.89, 29.66, 29.62, 29.60, 29.45, 29.32, 29.24, 29.08, 24.80, 22.65, 14.05; ^{31}P NMR ($CDCl_3$) δ −1.24; MS (LSIMS) 1130.18 (M + 2$^+$), 1128.14 (M$^+$), 836.1 (loss of $C_9H_{11}O_4PBr$, 313.4 (loss of $C_{34}H_{35}O_5$ and loss of $C_9H_{11}O_4PBr$). **Procedure B.** A solution of freshly distilled 2-bromoethyl phosphorodichloridate (**13**) (1.42 g, 5.85 mmol) in CH_2Cl_2 (15 mL) was cooled to 0 °C, and a solution of **11a** (1.0 g, 1.17 mmol) and *N*-methylmorphiline (1.28 mL, 11.7 mmol) dissolved in CH_2Cl_2 (35 mL) was injected into the solution over a 10 min period. The reaction mixture was stirred at 0 °C for 5.5 h at which point a new TLC spot which coeluted with secondary alcohol **10a** appeared. Stirring was continued for another 30 min, and benzyl alcohol (1.21 mL, 11.7 mmol) was injected into the reaction. After 6 days, the reaction mixture was transferred to a 500 mL separatory funnel, and CH_2Cl_2 (150 mL) and water (200 mL) were added. The layers were separated, and the organic layer was dried, concentrated, and then purified by LPLC (33% EtOAc/hexanes), affording a 19% yield of **14a** (250 mg) as a yellow oil. Anal. Calcd for $C_{62}H_{82}O_{12}BrP$: C, 65.89; H, 7.31. Found: C, 66.15, H, 7.30.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol (15a). A 45 mL Parr bomb equipped with a magnetic stirring bar was charged with a solution of phosphate **14a** (880 mg, 0.778 mmol) in toluene (10 mL). Condensed anhyd trimethylamine (12 mL) was added quickly in one portion, and then the vessel was sealed and heated in an oil bath at 55 °C for 24 h. The reaction mixture was concentrated to a viscous oil and triturated with ethyl ether, upon which a white precipitate formed. The precipitate was filtered off and washed with ether, and then the combined ethereal solutions were concentrated. Purification of this residue by preparative TLC (2000 μm, double elution with 75%:12.5%:12.5% CH_2Cl_2/methanol/hexanes) gave 361 mg (45.5%) of **15a** as an oily wax: R_f 0.15 CH_2Cl_2/methanol/hexanes 1:1:1); ^{1}H NMR ($CDCl_3$) δ 7.38–7.24 (m, 18H), 7.18–7.14 (m, 2H), 5.20 (br m, 1H), 4.96 (d, 1H, J = 11.2), 4.91 (d, 1H, J = 11.2), 4.83 (d, 1H, J = 11.2), 4.76 (d, 1H, J = 11.2), 4.67 (d, 1H, J = 10.8), 4.59–4.44 (three overlapping doublets, 3H, J = 11.6, J = 10.8, J = 12.0), 4.37 (d, 1H, J = 8.0), 4.27–4.14 (m, 3H), 4.00 (br m, 2H), 3.73 (br s, 2H), 3.7–3.38 (m, 7H), 3.13 (s, 9H), 2.2 (t, 2H, J = 7.2), 1.53 (m, 2H), 1.25 and 1.21 (br d, 24H), 0.88 (t, 3H, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 173.36, 138.48, 138.45, 138.06, 137.96, 128.46, 128.34, 128.21, 128.12, 129.02, 127.86, 127.70, 127.59, 127.56, 104.05, 84.47, 81.89, 77.52, 75.66, 74.94, 74.57, 74.47, 73.32, 71.57 (d, J = 7.5), 68.63, 68.47, 66.18 (br m), 63.43 (br m), 59.18 (d, J = 4.6), 54.22, 34.30, 31.90, 29.71, 29.58, 29.35, 29.15, 24.91, 22.67, 14.12; ^{31}P NMR ($CDCl_3$) δ −0.81; MS (LSIMS) 1019 (MH$^+$); HRMS (FAB, MH$^+$) calcd for $C_{58}H_{84}O_{12}$-NP 1018.5809, found 1018.5420.

(2*S*)-β-D-Glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol (2a). A solution of phosphatidylcholine **15a** (200.4 mg, 0.197 mmol) in reagent grade methanol (25 mL) was hydrogenated at 60 psi over 10% Pd/C (40 mg, 20 wt %). After 30 h, the catalyst was filtered off through Celite and the methanol washings were combined and concentrated. The residue was dissolved in fresh methanol (25 mL) and resubjected to hydrogenation at 60 psi over 80 mg (40 wt %) of 10% Pd/C. After 48 h, the reaction was still incomplete. After filtration, washing of the catalyst, and then concentration, the residue was subjected to hydrogenation using 400 mg (200 wt %) of Pd/C at 60 psi in methanol (25 mL). After 22 h, the catalyst was filtered off through Celite and the methanol filtrate and washings were combined and concentrated to afford 92.8 mg (71.6%) of **2a** as a white amorphous solid: ^{1}H NMR (CD_3OD) δ 5.20 (br m, 1H), 4.32 (br m, 3H), 4.14–3.65 [m containing d at 3.88 (J = 12) and dd at 3.80 (J = 5.1, J = 10.5), 8H], 3.4–3.1 (m containing 9H s at 3.18, 13H), 2.4–2.3 (m, 2H), 1.62 (bm, 2H), 1.31 (br s, 24H), 0.92 (t, 3H, J = 6.8); ^{13}C NMR (CD_3OD) δ 174.93, 104.80, 78.08, 77.93, 75.19, 71.53, 71.49, 70.76 (d, J = 7.6), 67.76 (d, J = 5.3), 67.50 (br s), 62.52, 60.54 (d, J = 4.5), 54.79 (t, J = 3.8), 34.88, 33.15, 30.85, 30.77, 30.66, 30.56, 30.46, 30.26, 26.10, 23.82, 14.56; ^{31}P NMR (CD_3OD) δ 1.65; MS (LSIMS) 658.4 (MH$^+$); HRMS (FAB, MH$^+$) calcd for $C_{30}H_{60}NO_{12}P$ 658.3931, found 658.3919.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2,3-*O*-isopropylideneglycerol (5b). To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (65 g, 0.12 mol) in THF (800 mL) at −10 °C in a 3 L three-necked morton flask fitted with a thermometer and mechanical stirrer was added NaH (60% suspension in oil, 33 g, 0.825 mol) in four increments over 10 min. The solution was stirred for 1 h, and then a solution of (*S*)-2,3-*O*-isopropylidene-1-*O*-(trifluoromethanesulfonyl)glycerol (**4b**) (0.15 mol) in THF (200 mL) was added dropwise via an addition funnel over a 20 min period, maintaining the internal temperature between −10 and −15 °C. The solution was stirred at −10 to −15 °C for 6 h, filtered through a short plug of silica gel, and concentrated to give 114 g of an orange brown oil. Purification by LPLC (50% ether/hexanes) gave 39.8 g (67.6%) of β-epimer **5b** as a white solid, along with 4 g (5.1%) of a mixture of the α- and β-epimers. Characterization of **5b**: mp 85.7–87.2 °C; R_f 0.40 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 18H), 7.19–7.14 (m, 2H), 4.97 (d, 1H, J = 10.8), 4.94 (d, 1H, J = 10.8), 4.82 (t, 2H, J = 10.8), 4.72 (d, 1H, J = 10.4), 4.63 (d, 1H, J = 12.4), 4.55 (d, 1H, J = 12.4) and 4.53 (d, 1H, J = 10.8), 4.45 (d, 1H, J = 7.2), 4.36 (m, 1H), 4.08 (t, 1H, J = 8.4), 3.92 (d, 1H, J = 10.0), 3.91 (d, 1H, J = 9.6), 3.82–3.57 (m, 6H), 3.47 (pseudo t, 2H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 138.56 (0), 138.38 (0), 138.07 (0), 138.02 (0), 128.36, 128.34, 128.26, 127.96, 127.86, 127.77, 127.70, 127.62, 127.61, 109.47 (0), 103.87, 84.59, 82.08, 77.71, 75.68 (2), 75.01 (2), 74.82 (2 carbons), 74.51 (2), 73.46 (2), 71.15 (2), 68.79 (2), 67.02 (2), 26.90 (3), 25.39 (3); MS (LSIMS) 653.4 (M − 1). Anal. Calcd for $C_{40}H_{46}O_8$: C, 73.37; H, 7.08. Found: C, 72.92; H, 6.99.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-glycerol (7b). A suspension of **5b** (20 g, 30.5 mmol) in 60% acetic acid (800 mL) was heated to reflux for 1 h. Workup was similar to that described for diol **7a**, providing 18 g (96% yield) of **7b** as a white solid, which was of sufficient purity after trituration with ether for the subsequent step. Diol **7b** could be recrystallized from ether/hexane: mp 89.6–90.9 °C; R_f 0.21 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.38–7.27 (m, 18H), 7.19–7.14 (m, 2H), 4.98–4.74 (m, 5H), 4.61–4.5 (m, 3H), 4.42 (d, 1H, J = 8.0), 3.89–3.80 (m, 3H), 3.72–3.63 (m, 4H), 3.62–3.44 (m, 4H), 2.59 (s, 2H, OH's); ^{13}C NMR ($CDCl_3$) δ 138.37 (0), 138.12 (0), 137.78 (0), 137.69 (0), 128.46, 128.45, 128.43, 128.06, 128.04, 127.96, 127.89, 127.85, 127.81, 127.70, 104.19, 84.62, 82.04, 77.74, 75.73 (2), 75.04 (2, 2 carbons), 74.47, 73.48 (2), 72.31 (2), 70.77, 68.73, (2), 63.35 (2); MS (LSIMS) 615.4 (MH$^+$). Anal. Calcd for $C_{37}H_{42}O_8$: C, 72.29; H, 6.89. Found: C, 72.31; H, 6.90.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-3-*O*-(*tert*-butyldimethylsilyl)glycerol (8b). A solution of diol **7b** (28.0 g, 45 mmol), imidazole (5.71 g, 90 mmol), and *tert*-butyldimethylsilyl chloride (6.92 g, 45.3 mmol) in anhyd DMF (75 mL) was stirred overnight at rt, transferred to a 1 L separatory funnel, and diluted with $CHCl_3$ (300 mL) and water

(300 mL). The layers were separated, the aqueous layer was extracted with $CHCl_3$ (2 × 100 mL), and then the combined organic layer was washed with water (3 × 100 mL). After drying and concentration, purification by LPLC (50% ethyl ether/hexanes) gave 29.5 g (90%) of **8b** as a colorless oil: R_f 0.43 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.40–7.28 (m, 18H), 7.21–7.17 (m, 2H), 4.97 and 4.96 (overlapping doublets, 2H, J = 11.2, J = 11.2), 4.85 and 4.84 (overlapping doublets, 2H, J = 10.8, J = 10.4), 4.78 (d, 1H, J = 11.2), 4.64 (d, 1H, J = 12.4), 4.57 and 4.56 (overlapping doublets, 2H, J = 12.4, J = 10.4), 4.46 (d, 1H, J = 7.6), 3.96–3.81 (m, 3H), 3.78–3.60 (m, 6H), 3.56–3.49 (m, 2H), 2.80 (br s, 1H, OH), 0.92 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 138.53, 138.38, 137.95 (2 carbons), 128.41, 128.11, 127.99, 127.85, 127.81, 127.75, 127.66, 127.64, 104.25, 84.62, 82.14, 77.73, 75.71 (2), 75.03 (2), 74.94 (2), 74.68 (1), 73.49 (2), 72.09 (2), 70.80 (1), 68.73 (2), 63.76 (2), 25.89 (3), 18.30 (0), −5.35, −5.40; MS (LSIMS) 729.89 (MH^+), 728.98 (M^+), 727.9 (M − 1). Anal Calcd for $C_{43}H_{56}O_8Si$: C, 70.85; H, 7.74. Found: C, 70.69; H, 7.66.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoyl-3-*O*-(*tert*-butyldimethylsilyl)glycerol (9b). A mixture of **8b** (22.2 g, 30.4 mmol), palmitic anhydride (16.5 g, 33.4 mmol), DMAP (741 mg, 6.08 mmol), triethylamine (3.78 g, 5.2 mL, 37.3 mmol), and anhyd THF (250 mL) was stirred at rt overnight. Workup followed the procedure used for glycerol **9a** and gave, following LPLC (33% ethyl ether/hexanes), 28.2 g (96%) of glycerol **9b** as a light-yellow oil: R_f 0.25 (12.5% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.36–7.24 (m, 18H), 7.18–7.16 (m, 2H), 5.11 (m, 1H), 4.92 and 4.91 (overlapping doublets, 2H, J = 10.4, J = 10.8), 4.81 and 4.77 (overlapping doublets, 2H, J = 11.2, J = 11.2), 4.68 (d, 1H, J = 11.2), 4.62 (d, 1H, J = 12.4), 4.54 and 4.52 (overlapping doublets, 2H, J = 12.4, J = 10.4), 4.42 (d, 1H, J = 8.0), 4.18 (dd, 1H, J = 10.3, J = 4.2), 3.8–3.68 (m, 5H), 3.68–3.58 (m, 2H), 3.42 (m, 2H), 2.23 (m, 2H), 1.54 (m, 2H), 1.26 and 1.22 (br d, 24H), 0.90–0.87 (m containing singlet at 0.88, 12H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 173.32, 138.54, 138.37, 138.06, 128.36, 128.33, 128.32, 128.01, 127.95, 127.84, 127.76, 127.73, 127.58, 127.55, 103.87, 84.54, 81.95, 77.68, 75.67 (2), 75.00 (2), 74.85 (2), 74.58, 73.49 (2), 73.18, 68.75 (2), 68.20 (2), 61.81 (2), 34.35, 31.91, 29.69, 29.65, 29.61, 29.45, 29.35, 29.27, 29.11, 25.78 (3), 24.86, 22.68, 18.2 (0), 14.2 (3), −5.45. Anal. Calcd for $C_{59}H_{86}O_9Si$: C, 73.25; H, 8.96. Found: C, 72.80; H, 8.87. Compound **9b** could be carried on to the next transformation without chromatographic purification as well.

(2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoylglycerol (11b). A solution of crude **9b** (30.4 mmol based on **8b**) in THF (100 mL) was chilled to 0 °C; then a premixed solution of TBAF (520 mL, 1.0 M in THF) which was buffered to pH = 6.37 with acetic acid was added dropwise via an addition funnel. The reaction mixture was stirred at 0 °C for 1 h and then at −15 °C overnight. The reaction mixture was concentrated to about 100 mL of solution, water (100 mL) was added, and then the resulting mixture was extracted with $CHCl_3$ (3 × 300 mL). The combined $CHCl_3$ layer was washed with water (4 × 500 mL), the combined aqueous layer was back-extracted with ether (500 mL), and then the combined organic layer was dried, filtered, and concentrated. Purification of the crude red oil by LPLC (50% ethyl ether/hexanes) afforded 24.6 g (94.6% yield for two steps) of primary alcohol **11b** as a white solid: mp 57.7–59.2 °C; R_f 0.36 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.36–7.24 (m, 18H), 7.17–7.14 (m, 2H), 5.05 (m, 1H), 4.90 (pseudo t, 2H, J = 11.2, J = 12.4), 4.79 and 4.78 (overlapping doublets, 2H, J = 11.2, J = 11.2), 4.71 (d, 1H, J = 11.2), 4.56 (AB_q, 2H, J = 12), 4.49 (d, 1H, J = 10.8), 4.43 (d, 1H, J = 8.0), 4.02 (dd, 1H, J = 10.0, J = 6.8), 3.91–3.7 (m, 3H), 3.7–3.4 (m, 6H), 2.30 (m, 2H), 1.59 (m, 2H), 1.25 (br s, 24H), 0.88 (t, 3H, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 173.59, 138.41, 138.17, 137.80, 137.67, 128.41, 128.07, 128.05, 127.85, 127.78, 127.74, 127.65, 103.88, 84.51, 81.85, 77.69, 75.70 (2), 75.01 (2), 74.78 (2), 74.49, 73.44 (2), 72.83, 68.66 (2), 67.17 (2), 61.37 (2), 34.29, 31.92, 29.68, 29.65, 29.61, 29.46, 29.36, 29.26, 29.10, 24.89, 22.70, 14.10 (3); MS (LSIMS) 851.9 (M − 1). Anal. Calcd for $C_{53}H_{72}O_9$: C, 74.62; H, 8.51. Found: C, 74.31; H, 8.52.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-3-*O*-palmitoylglycerol (10b). To a solution of glycerol **9b** (2.33 g, 2.41 mmol) in THF (150 mL) at 0 °C was added TBAF (24.1 mL, 1.0 M in THF) over a 5 min period. Glacial acetic acid (13.8 mL, 241 mmol) was added and the resulting solution stirred for 30 min. The reaction mixture was poured into a separatory funnel containing ice water (500 mL) and CH_2Cl_2 (200 mL), the layers were separated, and then the aqueous layer was back-extracted with CH_2Cl_2 (2 × 100 mL). The organic layers were combined, washed with brine (400 mL), dried, filtered, and then concentrated. Purification by LPLC (20% EtOAc/hexanes) gave 0.96 g (46.8%) of secondary alcohol **10b** as a colorless oil, which turned to a wax upon standing under high vacuum: mp 34.8–35.8 °C; R_f 0.45 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.40–7.29 (m, 18H), 7.19–7.16 (m, 2H), 5.0–4.76 (m, 5H), 4.7–4.5 (m, 3H), 4.43 (d, 1H, J = 8.0), 4.26–4.12 (m, 2H), 4.06–3.86 (m containing br s at 3.99 for OH, 3H), 3.78–3.48 (m, 6H), 3.32 (d, 1H, J = 6.4), 2.36 (t, 2H, J = 8.0), 1.65 (m, 2H), 1.29 (br s, 24H), 0.92 (t, 3H, J = 6.4); ^{13}C NMR ($CDCl_3$) δ 173.80, 138.44, 138.19, 137.88, 137.83, 128.44, 128.41, 128.40, 128.07, 128.02, 127.88, 127.85, 127.83, 127.80, 127.72, 127.66, 104.26, 84.62, 82.05, 77.72, 75.70, 75.04 (2 carbons), 74.68, 73.50, 72.76, 68.89, 68.6, 65.02, 34.19, 31.93, 29.70, 29.66, 29.63, 29.48, 29.37, 29.29, 29.16, 24.94, 22.71, 14.16. Anal. Calcd for $C_{53}H_{72}O_9$: C, 74.62; H, 8.51. Found: C, 74.64; H, 8.46. Further elution gave 238 mg (11.6%) of primary alcohol **11b**, whose spectral data matched the data reported above. Also isolated was a mixture of the two alcohols in 5.3% yield.

Resilylation of (2*S*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoylglycerol (11b). The identity of **11b** was established by resilylation according to the procedure described above for corresponding (*R*)-isomer **11a**. The spectral data for the product matched the spectral data reported above for **9b**.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoyl-3-*O*-[(2-bromoethoxy)benzoxyphosphoryl]-glycerol (14b). A solution of freshly distilled 2-bromoethyl phosphorodichloridate (17.2 g, 71.1 mmol) in anhyd ether (500 mL) was chilled to 0 °C, and triethylamine (81.5 mL, 0.585 mol) was added, causing precipitation of a white solid. A solution of **11b** (10.0 g, 11.7 mmol) in ether (250 mL) was cannulated into the morton flask, and the solution was stirred for 1.5 h, after which TLC showed disappearance of **11b**. Benzyl alcohol (12.1 mL, 0.117 mol) was injected, and then the mixture was stirred at rt for 16 h. The reaction mixture was filtered, the filtrate was concentrated, and then the residue was purified twice by LPLC (first using 33% EtOAc/hexanes, then using 25% EtOAc/hexanes), providing 5.5 g (42%) of phosphate **14b** as an oil: R_f 0.36 (33% EtOAc/hexanes); R_f 0.08 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.4–7.2 (m, 23 H), 7.17–7.12 (m, 2H), 5.23 (br m, 1H), 5.12 (dd, 1H, J = 8.8, J = 4.0), 4.94–4.75 (m, 4H), 4.70 (d, 1H, J = 11.6), 4.61 (d, 1H, J = 11.6), 4.52 (d, 1H, J = 11.2), 4.41 (d, 1H, J = 8.0), 4.30–4.10 (br m, 4H), 4.05 (dd, 1H, J = 12, J = 4.4), 3.78–3.55 (m, 5H), 3.50–3.37 (m, 4H), 2.23 (m, 2H), 1.54 (br m, 2H), 1.26 and 1.22 (br d, 24H), 0.89 (t, 3H, J = 6.4); ^{13}C NMR ($CDCl_3$) δ 173.03, 138.40, 138.17, 137.92, 137.90, 128.68, 128.61, 128.33, 128.30, 127.99, 127.98, 127.89, 127.75, 127.72, 127.62, 127.55, 103.63, 84.46, 81.84, 77.49, 75.64, 74.96, 74.76, 74.69, 73.41, 70.4 (d, J = 8.0), 69.63 (d, J = 6.2), 68.57, 67.18, 66.69 (d, J = 5.4), 66.05 (d, J = 5.4), 34.15, 31.93, 29.71, 29.67, 29.64, 29.48, 29.38, 29.29, 29.10, 24.75, 22.71, 14.17; ^{31}P NMR ($CDCl_3$) δ −1.18; MS (LSIMS) 1130.18 (M + 2), 1128.14 (M^+), 836.1 (loss of $C_9H_{11}O_4PBr$, 313.4 (loss of $C_{34}H_{35}O_5$ and loss of $C_9H_{11}O_4PBr$). Anal. Calcd for $C_{62}H_{82}O_{12}BrP$: C, 65.89; H, 7.31. Found: C, 65.75; H, 7.26.

(2*R*)-1-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol (15b). A 45 mL Parr bomb equipped with a magnetic stirring bar was charged with a solution of **14b** (1.17 g, 1.04 mmol) in benzene (15 mL). Condensed anhyd trimethylamine (15 mL, 0.145 mmol) was added quickly, and then the vessel was sealed and heated in an oil bath at 55 °C for 24 h. The bomb vessel was cooled to −78 °C, opened, and left in a hood to evaporate the trimethylamine. The remaining solution was concentrated,

dissolved in a small amount of CH_2Cl_2, and purified by preparative TLC (2000 μm). Double elution with 75%:12.5%:12.5% CH_2Cl_2/methanol/hexanes gave 223 mg (21%) of **15b** as an oily wax: R_f 0.15 CH_2Cl_2/methanol/hexanes 1:1:1); ^{1}H NMR ($CDCl_3$) δ 7.36–7.21 (m, 18H), 7.15–7.12 (m, 2H), 5.20 (m, 1H), 4.84 and 4.83 (overlapping doublets, 2H, J = 11.2, J = 11.2), 4.80 (d, 1H, J = 11.2), 4.74 (d, 1H, J = 11.2), 4.63 (d, 1H, J = 11.2), 4.59 (d, 1H, J = 11.2), 4.48 (pseudo t, 2H, J = 12.6), 4.40 (d, 1H, J = 8.0), 4.26–4.14 (m, 3H), 3.94 (br m, 2H), 3.85–3.50 (m, 7H), 3.44–3.38 (m, 2H), 3.12 (s, 9H), 2.19 (m, 2H), 1.45 (br m, 2H), 1.33–1.11 (m, 24H), 0.87 (t, 3H, J = 6.8); ^{13}C NMR ($CDCl_3$) δ 173.38, 138.48, 138.37, 138.07, 137.99, 129.74, 128.44, 128.34, 128.30, 128.06, 127.85, 127.81, 127.73, 127.70, 127.62, 127.54, 103.88, 84.46, 81.95, 77.52, 75.63 (2), 74.92 (2), 74.54 (2 carbons, 2), 73.31, 71.88 (d, 1, J = 7.6), 68.63 (2), 68.42 (2), 66.25 (m, 2), 63.53 (d, 2, J = 5.3), 59.20 (d, 2, J = 4.5), 54.27 (3), 34.24, 31.90, 29.71, 29.66, 29.54, 29.35, 29.33, 29.14, 24.77, 22.67, 14.11; ^{31}P NMR ($CDCl_3$) δ −0.91; MS (LSIMS) 1019 (MH^+); HRMS (FAB, MH^+) calcd for $C_{58}H_{84}O_{12}NP$ 1018.5809, found 1018.5434.

(2*R*)-β-D-glucopyranos-1-yl-2-*O*-palmitoyl-3-*O*-phosphatidylcholinylglycerol (2b). A solution of phosphatidylcholine **15b** (130 mg, 0.127 mmol) in reagent grade methanol (25 mL) was hydrogenated at 60 psi over 10% Pd/C (52 mg, 40 wt %). After 23 h, TLC showed an incomplete reaction. The catalyst was filtered off through Celite, and the methanol washings were combined and concentrated. The residue was dissolved in fresh methanol (25 mL) and resubjected to hydrogenation at 60 psi over 240 mg (185 wt %) of 10% Pd/C. After 20 h, the catalyst was filtered off through Celite and the methanol filtrate and washings were combined and concentrated to afford 64.0 mg (76.6%) of **2b** as a white amorphous solid: ^{1}H NMR (CD_3OD) δ 5.20 (m, 1H), 4.31 (m, 3H), 4.16–3.96 (m, 3H), 3.91–3.60 [m containing d at 3.87 (J = 12) and dd at 3.77 (J = 5.1, J = 10.5), 5H], 3.45–3.10 [m containing 9H s at 3.24, 13H], 2.37 (t, 2H, J = 6.8), 1.63 (m, 2H), 1.31 (br s, 24H), 0.92 (t, 3H, J = 6.8); ^{13}C NMR (CD_3OD) δ 174.99, 104.89, 78.09, 78.05, 75.05, 72.90 (d, 1, J = 8.5), 71.53, 68.56 (2), 67.50 (t, 2, J = 3.7), 64.96 (d, 2, J = 5.4), 62.66 (2), 60.52 (d, 2, J = 5.3), 54.74 (t, 3, J = 3.8), 35.15, 33.12, 30.86, 30.69, 30.54, 30.29, 26.01, 23.79, 14.52 (3); ^{31}P NMR (CD_3OD) δ 1.35; MS (LSIMS) 658.4; HRMS (FAB, MH^+) calcd for $C_{30}H_{60}NO_{12}P$ 658.3931, found 658.3926.

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Supporting Information Available: Experimental procedure for **12a** and ^{1}H NMR spectra and HPLC chromatograms of **15a**, **15b**, **2a**, and **2b** (16 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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