Enantioselective Synthesis of 3-Deoxy-(*R*)-sphingomyelin from (*S*)-1-(4′-Methoxyphenyl)glycerol

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(*R*)-3-Deoxysphingomyelin (**2**) was prepared from (*S*)-1-(4′-methoxyphenyl)-glycerol (**3**). The latter was converted into either *p*-methoxyphenyl (PMP) (*S*)-oxiranylmethyl ether (**5**) or (*R*)-1-(4′-methoxyphenyl)glycerol 2,3-cyclic sulfate (**6**). Opening of **5** with lithium pentadecyne in the presence of $BF_3{\cdot}Et_2O$ gave PMP (*S*)-2-hydroxy-4-octadecynyl ether (**7**) in 65% yield. Alternatively, opening of cyclic sulfate **6** with excess lithium pentadecyne in the presence of catalytic cuprous iodide, followed by acidic workup, gave **7** in 90% yield. After introduction of the amide group via azide displacement, reduction, and *N*-acylation, simultaneous reduction of the triple bond and deprotection of the PMP group by Birch reduction (Li, $EtNH_2$) provided 3-deoxy-*N*-palmitoyl-(*R*)-ceramide (**9**). Finally, phosphitylation of **9**, oxidation of the cyclic phosphite with bromine, followed by in situ ring opening gave a (2-bromoethyl)phosphate ester, which on quaternization with aqueous trimethylamine afforded 3-deoxy-*N*-palmitoyl-(*R*)-sphingomyelin (**2**) in 49% overall yield from PMP (*S*)-2-hydroxy-4-octadecynyl ether (**7**).

Introduction

Sphingomyelin (**1**) is a major constituent of mammalian cell membranes, plasma lipoproteins, and the myelin sheath. Sphingolipids formed intracellularly as intermediates in the biosynthesis and catabolism of **1** evoke a wide range of stereospecific responses in cells.[1]

Many chiral syntheses of sphingolipids have been reported,[2] whereas methods for preparation of chiral analogues have not yet received appreciable attention. We reported previously the preparation of 3-deoxy-DL-*N*-stearoylsphingomyelin[3] and its use as an inhibitor of neutral sphingomyelinase[4] and as a probe of the role of the 3-hydroxy group of sphingomyelin in the interaction with cholesterol.[3,5] Here, we report an enantioselective synthesis of 3-deoxy-(*R*)-sphingomyelin (**2**) starting with (*S*)-1-(4′-methoxyphenyl)glycerol (**3**), which can be prepared conveniently on a large scale by asymmetric dihydroxylation[6] of allyl 4-methoxyphenyl ether using AD-mix β supplemented with potassium persulfate.[7] The synthesis involves the following sequence of reactions: (1) activation of the primary hydroxy group of glycerol **3** either by conversion to glycidol **5** (Scheme 1) or to cyclic sulfate **6** (Scheme 2); (2) preparation of PMP (*S*)-2-hydroxy-4-octadecynyl ether (**7**) by opening of glycidol **5** with lithium pentadecyne in the presence of $BF_3{\cdot}Et_2O$ (Scheme 1) or by nucleophilic substitution of cyclic sulfate **6** with lithium pentadecyne in the presence of CuI (Scheme 1); (3) conversion of the homopropargylic hydroxy group of **7** into an amide group by the sequence of mesylation, azide substitution, reduction, and acylation; (4) simultaneous reduction of the triple bond of amide **8** to an (*E*) double bond and deprotection of the PMP group by Birch reduction; and (5) insertion of the phosphocholine moiety into 3-deoxyceramide **9** by phosphitylation, followed by oxidation and opening of the cyclic phosphite with bromine and quaternization with aqueous Me_3N solution.

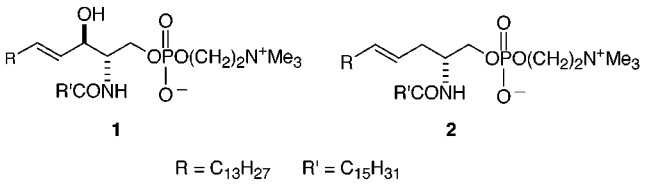

Figure 1.

Results and Discussion

Preparation of Glycidol 5 from (*S*)-Glycerol 3. It is well known that 1,2-diols can be converted to epoxides by the Mitsunobu reaction[8] and by monotosylation of a diol followed by base-induced cyclization.[9] Scheme 1 shows the application of these two routes for the conversion of protected diol **3** into glycidol **5**. Mitsunobu reaction of (*S*)-glycerol **3** in refluxing benzene gave only

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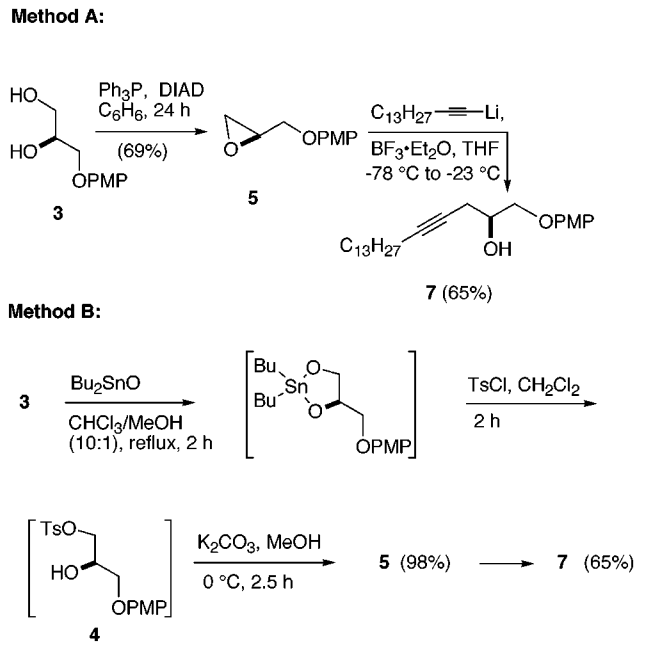
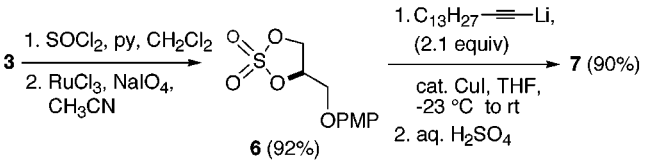
Scheme 1. Two Routes to PMP (*S*)-2-Hydroxy-4-octadecynyl Ether (7) from 3 via (*S*)-*O*-PMP-glycidol (5)



Scheme 2. Synthesis of 7 from 3 via Cyclic Sulfate 6

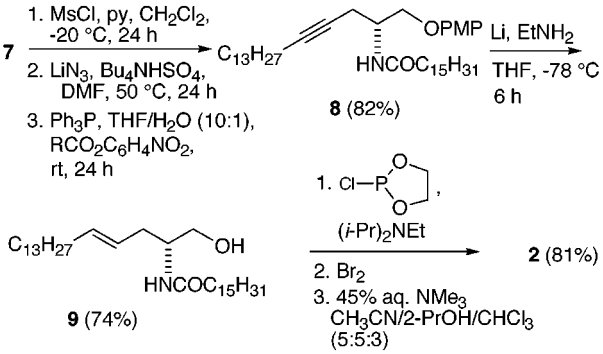


a moderate yield (69%) of glycidol **5**. The yield of **5** was improved markedly by using a route that involves the formation of a cyclic stannylene intermediate in $CHCl_3$–MeOH (10:1); the latter was converted into the monotosylate **4** by reaction with TsCl at room temperature in CH_2Cl_2. After the byproduct (probably Ts_2O) was removed by filtration through a silica gel pad, treatment of the monotosylate with K_2CO_3 in methanol at 0 °C resulted in the formation of glycidol **5** in 98% yield. The yield of the epoxide-forming step was reduced markedly when the reaction was carried at room temperature rather than at 0 °C, apparently because of opening of **5** by methanol.

Synthesis of Ether 7. Scheme 1 shows the regioselective opening reaction of glycidol **5** with lithium pentadecyne in the presence of BF_3•Et_2O to give ether **7** in 65% yield. Scheme 2 shows an alternative route to PMP (*S*)-2-hydroxy-4-octadecynyl ether (**7**). Previous work has shown that 1,2-cyclic sulfates are opened under nucleophilic substitution conditions.[10] (*S*)-Glycerol **3** was converted to cyclic sulfate **6** with $SOCl_2$ followed by oxidation of the resulting sulfite with catalytic RuO_4, giving **6** in 92% yield. Nucleophilic opening of **6** with 2.1 equiv of lithium pentadecyne in the presence of catalytic CuI at −23 °C and then overnight at room temperature, followed by acidic workup, provided ether **7** in 90% yield.

Synthesis of Amide 8 from Ether 7. The amide group was introduced by a modification of our procedure for the preparation of diamido glycerolipids.[11] The following three-step sequence of reactions, without purification of the intermediates, was used (Scheme 3): (1) mesylation of secondary alcohol **7** by reaction with MsCl in the presence of pyridine in CH_2Cl_2, (2) S_N2 substitution of the mesylate group with lithium azide in the presence of catalytic Bu_4NHSO_4 in DMF at 50 °C, and (3) reduction of the azide with Ph_3P-H_2O and in-situ acylation of the resulting amine with the 4-nitrophenyl ester of palmitic acid. To minimize the possible elimination reaction, the mesylation was carried out at −20 °C. For azide displacement of the mesylate, lithium azide was used in the presence of Bu_4NHSO_4 in DMF. Azide displacement, followed by reduction of the azide with Ph_3P-H_2O in the presence of 4-nitrophenyl palmitate, provided amide **8** in 82% overall yield. In contrast, the three-step overall yield was only 35% when sodium azide was used at 90 °C in the absence of the phase-transfer catalyst, possibly because at high-temperature elimination competes with substitution.

Scheme 3. Synthesis of 3-Deoxy-(*R*)-sphingomyelin (2) from 7



Synthesis of Deoxysphingomyelin (2) from Amide 8. The *E* double bond was introduced into **8** by Birch reduction of the triple bond. Under the reduction conditions used, aryl ethers are also reduced to 1-alkoxy-1,4-cyclohexadienes, with the addition of hydrogen taking place at positions other than those occupied by the alkoxy group.[12] The resulting enol ether tends to undergo acid-catalyzed hydrolysis and liberate the alcohol. Thus, during the reduction of the triple bond, the PMP protecting group of amide **8** can be removed also. Addition of a solution of amide **8** in THF to a blue solution of lithium metal in $EtNH_2$ provided 3-deoxyceramide **9** in 74% yield. Finally, insertion of the phosphocholine moiety into 3-deoxyceramide **9** was performed by the reported phosphitylation procedure[13] to provide deoxysphingomyelin (**2**) in 81% yield.

Experimental Section

General Information. See refs 7 and 11 for general experimental protocols.

4′-Methoxyphenyl (*S*)-2-Oxiranylmethyl Ether ((+)-5). Method A (Scheme 1). To a solution of 1.99 g (10.0 mmol) of (*S*)-1-(4′-methoxyphenyl)glycerol (**3**) and 3.93 g (15.0 mmol) of Ph_3P in 100 mL of C_6H_6 was added 3.0 g (15.0 mmol) of diisopropyl azodicarboxylate (DIAD). After the mixture was refluxed for 24 h, the solvent was removed under reduced

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pressure, and Et_2O was added to the residue to precipitate Ph_3PO formed during the reaction. The precipitate was removed by filtration, and the remaining light brown filtrate was concentrated in a rotary evaporator. The residue was purified by chromatography on silica gel (elution with 9:1 hexane/EtOAc) to give 1.25 g (69%) of glycidol **5** as a white solid: mp 40.6−41.3 °C (lit.[7] mp 42−43 °C); R_f 0.53 (3:1 hexane/EtOAc); $[\alpha]^{25}_D$ +9.13° (*c* 5.0, MeOH) [lit.[7] $[\alpha]^{28}_D$ +11.04° (*c* 1.08, MeOH) (lit.[14] $[\alpha]^{30}_D$ +11.3° (*c* 0.98, MeOH))]. **Method B (Scheme 1).** A suspension of 1.99 g (10.0 mmol) of (*S*)-1-(4′-methoxyphenyl)glycerol (**3**) and 2.49 g (10.0 mmol) of dibutyltin oxide in 100 mL of 10:1 $CHCl_3$/MeOH was refluxed for 2 h (after 1 h it became a clear solution). After the solvents were removed under reduced pressure, the residue was dissolved in 50 mL of $CHCl_3$. The solvent was evaporated under reduced pressure, and the residue was dried under high vacuum for 5 h. To a solution of the residue in 25 mL of CH_2Cl_2 was added 2.48 g (13.0 mmol) of *p*-toluenesulfonyl chloride. After the reaction mixture was stirred overnight, the reaction was quenched with 0.2 mL (11.1 mmol) of H_2O. After 2 h, the mixture was diluted with 100 mL of hexane and filtered through a pad of silica gel. The pad was washed with 200 mL of 10:1 hexane/EtOAc in order to remove a nonpolar impurity (probably *p*-toluenesulfonic anhydride). Monotosylate **4** was eluted with 200 mL of 1:1 hexane/EtOAc. The filtrate was concentrated to give 3.70 g (105%) of crude **4**: R_f 0.19 (3:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 7.78 (d, 2H, J = 8.2 Hz), 7.31 (d, 2H, J = 8.2 Hz), 6.74−6.84 (m, 4H), 4.12−4.23 (m, 3H), 3.93 (d, 2H, J = 4.8 Hz), 3.76 (s, 3H), 2.61 (br s, 1H), 2.42 (s, 3H). To a suspension of the crude **4** in 25 mL of MeOH was added 6.82 g (49.3 mmol) of powdered K_2CO_3 at 0 °C. After the reaction mixture was stirred for 2.5 h at 0 °C, it was diluted with 100 mL of Et_2O. The mixture was filtered through a pad of silica gel, which was washed with 200 mL of Et_2O. The filtrate was concentrated to give 1.77 g (98%) of glycidol **5** as a white solid: mp 40.0−40.8 °C; R_f 0.53 (3:1 hexane/EtOAc); $[\alpha]^{25}_D$ +10.5° (*c* 5.0, MeOH); IR (NaCl) 1232, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.81−6.91 (m, 4H), 4.15 and 4.19 (ABq, 1H, J = 3.2 Hz, $\Delta\nu$ = 10.6 Hz), 3.90 and 3.94 (ABq, 1H, J = 5.6 Hz, $\Delta\nu$ = 9.24 Hz), 3.77 (s, 3H), 3.31−3.35 (m, 1H), 2.89 (t, 1H, J = 4.6 Hz), 2.73 and 2.75 (ABq, 1H, J = 2.6 Hz, $\Delta\nu$ = 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ 154.17, 152.64, 115.71, 114.64, 69.51, 55.69, 50.26, 44.72; HRMS [FAB, MH^+] calcd for $C_{10}H_{13}O_3$ *m*/*z* 180.0786, found 180.0780.

(*R*)-1-(4′-Methoxyphenyl)glycerol 2,3-Cyclic Sulfate ((+)-6). To a solution of 3.0 g (15.1 mmol) of (*S*)-1-(4′-methoxyphenyl)glycerol (**3**) and 2.40 g (30.3 mmol) of pyridine in 25 mL of CH_2Cl_2 was added 1.4 mL (19.2 mmol) of $SOCl_2$. After the mixture was stirred for 2 h at 0 °C, 50 mL of EtOAc was added. The mixture was filtered through a pad of silica gel, which was washed with 100 mL of EtOAc. After the filtrate was concentrated, the residue was dissolved in 25 mL of CH_3CN. To the solution of the cyclic sulfite (diastereomeric ratio 1:1, R_f 0.50 and 0.60, developed with hexane/EtOAc 2:1) were added 4.90 g (22.9 mmol) of $NaIO_4$ and 8 mg (0.03 mmol) of $RuCl_3 \cdot 3H_2O$, followed by 25 mL of water at room temperature. After 2 h, the mixture was diluted with EtOAc, the two phases were separated, and the organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine. The solution was dried ($MgSO_4$) and then filtered through a pad of silica gel to remove the brown color. The filtrate was concentrated to give 3.53 g (92%) of cyclic sulfate **6** as a white solid: mp 90.1−90.8 °C; R_f 0.46 (2:1 hexane/EtOAc); $[\alpha]^{25}_D$ +2.88° (*c* 5.6, $CHCl_3$); IR (NaCl) 1237, 1202, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.84 (m, 4H), 5.18−5.24 (m, 1H), 4.81 and 4.83 (ABq, 1H, J = 6.6 Hz, $\Delta\nu$ = 6.0 Hz), 4.70 and 4.72 (ABq, 1H, J = 8.9 Hz, $\Delta\nu$ = 6.0 Hz), 4.18−4.26 (m, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 154.88, 151.60, 115.87, 115.64, 115.04, 114.84, 78.93, 69.71, 66.60, 55.70; HRMS [FAB, M^+] calcd for $C_{10}H_{12}O_6S$ *m*/*z* 260.0355, found 260.0348.

4′-Methoxyphenyl (*S*)-2-Hydroxy-4-octadecynyl Ether ((+)-7). Method A (Scheme 1). To a solution of 2.70 g (13.0 mmol) of 1-pentadecyne in 250 mL of dry THF was added 5.0 mL (12.5 mmol) of *n*-butyllithium (a 2.5 M solution in hexane) at −23 °C. After the mixture had stirred for 2 h at −23 °C and 2 h at room temperature, 0.75 g (4.2 mmol) of glycidol **5** was added. The mixture was cooled to −78 °C, and 1.9 mL (15 mmol) of $BF_3 \cdot Et_2O$ was added. The reaction mixture was stirred for 6 h and allowed to warm to −23 °C. After 24 h, the reaction mixture was diluted with Et_2O. The mixture was washed with 1 N HCl solution and then with H_2O. The organic layer was dried over Na_2SO_4 and concentrated. The product was purified by silica gel chromatography (elution with 6:1 hexane/EtOAc) to give 1.17 g (65%) of ether **7** as a white solid: mp 55.0−55.1 °C; R_f 0.37 (5:1 hexane/EtOAc); $[\alpha]^{25}_D$ +12.0° (*c* 5.0, $CHCl_3$). **Method B (Scheme 2).** To a solution of 4.40 g (21.1 mmol) of 1-pentadecyne in 250 mL of dry THF was added 8.0 mL (20.0 mmol) of *n*-butyllithium (a 2.5 M solution in hexane) at −23 °C. After the mixture was stirred for 2 h at −23 °C and 2 h at room temperature, 2.60 g (10.0 mmol) of cyclic sulfate **6** and 95 mg (0.50 mmol) of CuI were added at −23 °C. After 4 h, the mixture was warmed to room temperature and stirred overnight. To the mixture were added 100 mL of 20% aqueous H_2SO_4 and 100 mL of ether. After the biphasic mixture was stirred overnight, the product was extracted with ether. The organic layer was washed with 10% aqueous ammonium hydroxide solution, water, and brine and dried ($MgSO_4$). After concentration, the crude product was purified by column chromatography on silica gel, eluting with 6:1 hexane−EtOAc, to give 3.50 g (90%) of ether **7** as a white solid: mp 55.1−55.5 °C; R_f 0.37 (5:1 hexane/EtOAc); $[\alpha]^{25}_D$ +11.8° (*c* 5.0, $CHCl_3$); IR (NaCl) 3355, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.82−6.88 (m, 4H), 4.08−4.10 (m, 1H), 4.02 and 4.05 (ABq, 1H, J = 4.1 Hz, $\Delta\nu$ = 8.3 Hz), 3.92 and 3.96 (ABq, 1H, J = 6.5 Hz, $\Delta\nu$ = 6.6 Hz), 3.77 (s, 3H), 2.52−2.54 (m, 2H), 2.13−2.18 (m, 2H), 1.93 (br s, 1H), 1.44−1.49 (m, 2H), 1.30−1.37 (m, 2H), 1.25 (s, 18H), 0.88 (t, 3H, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 154.53, 153.10, 115.98, 115.07, 71.79, 56.15, 32.36, 30.12, 30.10, 30.00, 29.78, 29.60, 29.36, 24.36, 23.13, 19.18; HRMS [FAB, M^+] calcd for $C_{25}H_{40}O_3$ *m*/*z* 388.2977, found 388.2976.

4′-Methoxyphenyl (*R*)-2-(Hexadecanamido)-4-octadecynyl Ether ((+)-8). To a solution of 1.00 g (2.57 mmol) of **7** in 20 mL of CH_2Cl_2 and 0.60 mL (7.4 mmol) of pyridine was added 0.25 mL (3.2 mmol) of methanesulfonyl chloride at −20 °C, and the mixture was allowed to stand for 24 h. The reaction mixture was diluted with Et_2O and washed with a 10% aqueous $CuSO_4$ solution, a saturated aqueous $NaHCO_3$ solution, and finally with H_2O. The Et_2O layer was dried (Na_2SO_4), filtered, and concentrated to give 1.30 g (108%) of the crude mesylate: R_f 0.66 ($CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 6.84−6.89 (s, 4H), 4.93−4.99 (m, 1H), 4.22 and 4.25 (ABq, 1H, J = 3.5 Hz, $\Delta\nu$ = 10.1 Hz), 4.13 and 4.17 (ABq, 1H, J = 6.8 Hz, $\Delta\nu$ = 8.2 Hz), 3.77 (s, 3H), 3.07 (s, 3H), 2.73−2.78 (m, 2H), 2.12−2.16 (m, 2H), 1.43−1.50 (m, 2H), 1.30−1.37 (m, 2H), 1.25 (s, 18H), 0.88 (t, 3H, J = 6.9 Hz). After the crude mesylate was dissolved in 10 mL of DMF, 0.63 g (12.9 mmol) of LiN_3 and 340 mg (1.0 mmol) of Bu_4NHSO_4 were added. The mixture was heated at 50 °C for 24 h. The resulting viscous, caramel-colored reaction mixture was diluted with Et_2O and washed with H_2O. The Et_2O layer was dried (Na_2SO_4), filtered, and concentrated. To remove the color, the residue was dissolved in hexane/EtOAc 10:1 and filtered through a pad of silica gel, which was washed with 100 mL of hexane/EtOAc 10:1. The filtrate was concentrated to give 0.95 g (88%) of crude azide as a colorless liquid: R_f 0.81 (4:1 hexane/EtOAc); ^{1}H NMR ($CDCl_3$) δ 6.80−6.87 (m, 4H), 3.92−3.95 (m, 1H), 3.79−3.84 (m, 2H), 3.60 (s, 3H), 2.74−2.87 (m, 2H), 2.12−2.16 (m, 2H), 1.53−1.67 (m, 2H), 1.30−1.37 (m, 2H), 1.26 (s, 18H), 0.88 (t, 3H, J = 6.9 Hz). To a solution of the azide in 25 mL of THF−H_2O (10:1) were added 0.67 g (2.55 mmol) of Ph_3P and 0.96 g (2.55 mmol) of *p*-nitrophenyl hexadecanoate. After 24 h, the reaction mixture was diluted with 100 mL of CH_2Cl_2 and washed with 1 N NaOH solution and H_2O. The organic layer was dried (Na_2SO_4) and concentrated in a rotary evaporator. The residue was purified by column chromatography (elution with 8:1 hexane/EtOAc) to give 1.33 g (82% overall yield from

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7) of amide **8** as a white solid: mp 81.0−82.2 °C; R_f 0.47 (4:1 hexane/EtOAc); $[\alpha]^{25}_D$ +6.35° (*c* 5.0, $CHCl_3$); IR (NaCl) 3295, 1637, 1043 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.81−6.88 (m, 4H), 5.81 (d, 1H, J = 8.4 Hz), 4.35 (s, 1H), 4.08 and 4.12 (ABq, 1H, J = 3.8 Hz, $\Delta\nu$ = 8.5 Hz), 3.91 and 3.94 (ABq, 1H, J = 5.7 Hz, $\Delta\nu$ = 7.4 Hz), 3.77 (s, 3H), 2.58−2.63 (m, 1H), 2.49 and 2.54 (ABq, 1H, J = 7.8 Hz, $\Delta\nu$ = 14.9 Hz), 2.20 (t, 2H, J = 7.6 Hz), 2.14 (t, 2H, J = 6.9 Hz), 1.63 (t, 2H, J = 6.9 Hz), 1.43−1.50 (m, 2H), 1.25 (s, 44H), 0.88 (t, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 173.18, 154.53, 153.10, 115.96, 115.04, 68.60, 56.09, 47.65, 37.23, 32.31, 30.05, 29.89, 29.75, 29.64, 29.56, 29.34, 26.11, 23.08, 21.75, 19.10, 14.51; HRMS [FAB, MH^+] calcd for $C_{41}H_{72}O_3N$ *m*/*z* 626.5512, found 626.5515.

(*R*)-*N*-(Hexadecanamido)-4-octadecen-1-ol ((+)-9). To a blue solution of 102 mg (147 mmol) of lithium metal in 75 mL of $EtNH_2$ was added dropwise a solution of 1.01 g (1.61 mmol) of amide **8** in 40 mL of THF at −78 °C. During the addition of the amide solution, the blue color of the reaction mixture was maintained by adjusting the speed of the addition. After all of the amide solution had been added, the reaction mixture was stirred for 6 h at −78 °C. The reaction was quenched by adding 7.86 g (147 mmol) of NH_4Cl, and the mixture was warmed to room temperature overnight, during which time the $EtNH_2$ evaporated. The mixture was then diluted with water and neutralized by the addition of 1 N HCl. The product was extracted with CH_2Cl_2, and the organic layer was dried (Na_2SO_4). Concentration of the organic layer gave a brown residue, which was purified by column chromatography on silica gel (elution with 1:1 hexane/EtOAc) followed by recrystallization from hexane to give 630 mg (75%) of (*R*)-3-deoxyceramide **9** as a white solid: mp 76.8−79.0 °C; R_f 0.37 (1:1 hexane/EtOAc); $[\alpha]^{25}_D$ +3.06° (*c* 5.0, $CHCl_3$); IR (NaCl) 3355, 3296, 1637 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.92 (br s, 1H), 5.50−5.57 (m, 1H), 5.31−5.38 (m, 1H), 3.93 (br s, 1H), 3.66 and 3.70 (ABq, 1H, J = 3.1 Hz, $\Delta\nu$ = 10.7 Hz), 3.58 and 3.62 (ABq, 1H, J = 6.2 Hz, $\Delta\nu$ = 9.1 Hz), 3.00 (s, 1H), 2.14−2.31 (m, 6H), 1.97−2.02 (m, 2H), 1.60−1.64 (m, 2H), 1.25 (s, 44 H), 0.88 (t, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 174.67, 134.95, 125.00, 65.74, 52.02, 36.68, 34.37, 32.59, 31.94, 29.72, 29.68, 29.55, 29.47, 29.38, 29.26, 25.86, 22.70, 14.13; HRMS [FAB, MH^+] calcd for $C_{34}H_{68}O_2N$ *m*/*z* 522.5250, found 522.5251.

(*R*)-*N*-Hexadecanoyl-3-deoxysphingomyelin ((−)-2). To a solution of 100 mg (0.19 mmol) of **9** in 20 mL of THF were added 96 mg (130 μL, 0.74 mmol) of *N*,*N*-diisopropylethylamine and 51 μL (0.57 mmol) of ethylene chlorophosphite at −23 °C. After the reaction mixture was stirred for 2 h at −23 °C, 29 μL (0.57 mmol) of Br_2 was added. After 5 min, the P−Br bond was hydrolyzed by the addition of 10 mL of H_2O. After the reaction mixture was warmed to room temperature, the solvents were removed in a rotary evaporator. The residue was dissolved in 10 mL of CH_3CN-2-PrOH−$CHCl_3$ (5:5:3), and 10 mL of 45% aqueous Me_3N was added. The mixture was stirred overnight at room temperature. The solvents were removed in a rotary evaporator, and the residue was dissolved in a minimal amount of 9:1 THF−H_2O. The solution was passed through a column of TMD-8 exchange resin (elution with 9:1 THF/H_2O), and the product was concentrated in a rotary evaporator. The resulting residue was lyophilized from C_6H_6 to give crude deoxysphingomyelin (**2**) as a white solid. Final purification by column chromatography on silica gel (elution with 9:1 $CHCl_3$/MeOH and then with 65:25:4 $CHCl_3$/MeOH/H_2O) gave 106 mg (81%) of 3-deoxysphingomyelin **2** as a white solid: R_f 0.28 (65:25:4 $CHCl_3$/MeOH/H_2O); $[\alpha]^{25}_D$ −7.46° (*c* 1.0, 1:1 $CHCl_3$/MeOH); IR (NaCl) 3293, 1637, 1237, 1084, 1055 cm^{-1}; ^1H NMR ($CDCl_3$−CD_3OD) δ 5.47−5.53 (m, 1H), 5.31−5.36 (m, 1H), 3.23−4.26 (m, 7H), 3.18 (s, 9H), 2.14−2.31 (m, 4H), 1.97−2.02 (m, 2H), 1.60−1.64 (m, 2H), 1.25 (s, 46 H), 0.88 (t, 6H, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 174.30, 133.94, 124.68, 66.71, 66.02, 59.01, 53.91, 36.31, 33.91, 32.40, 31.64, 29.43, 29.38, 29.31, 29.26, 29.19, 29.08, 29.05, 25.81, 22.39, 13.71; HRMS [FAB, MH^+] calcd for $C_{39}H_{80}O_5N_2P$ *m*/*z* 687.5805, found 687.5774.

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Supporting Information Available: Copies of ^1H and ^{13}C NMR spectra for compounds **2** and **5**−**9** (12 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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