Notes

Stereospecific Total Syntheses of Sphingosine and Its Analogues from L-Serine

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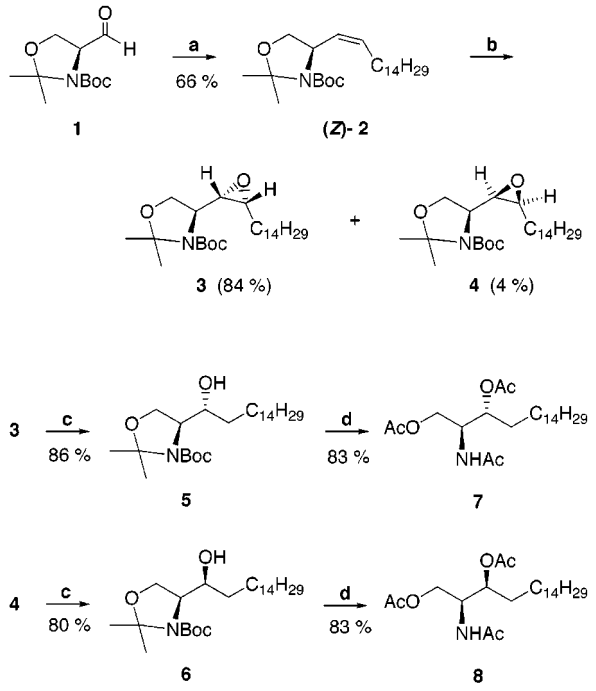
Introduction

Glycosphingolipids and sphingomyelins that are biomembrane components serve physiologically important roles in bioorganisms.[1] The lipophilic ceramide tail, a long chain acid amide derivative of the sphingosine amino alcohol moiety, acts as a membrane anchor, while the hydrophilic headgroup such as saccharide or phosphate, which is predominantly located on the external surface of the membrane, is associated with the molecular recognition process. Physiologically, sphingosines have been reported to function as a positive regulator of cell growth in Swiss 3T3 fibroblast[2] and a potent inhibitor of protein kinase C in vitro.[3] Recently, it has been suggested that sphingosines or their related lipids were used as a potent precursor for the biosynthesis of a sleep-inducing substance.[4] Until now, however, sphingosines,[5] dihydrosphingosines,[6] and phytosphingosines[7] have been independently synthesized by many workers from L-serine or various sugars by different methods. We present here a sophisticated method for synthesizing three different types of sphingosines with 18 carbon atoms passing through the (*Z*)-olefin **2** as the common intermediate.

Results and Discussion

(i) Dihydrosphingosines. The synthetic approach to dihydrosphingosines is outlined in Scheme 1. Garner's protected serine aldehyde **1** is the starting material of the present synthesis.[8] First, we have attempted to prepare geometrically pure (*Z*)-**2** olefin from this aldehyde under the Wittig reaction conditions. However, the ordinary Wittig olefination of **1** employing *n*-BuLi as a base with pentadecyltriphenylphosphonium bromide ($C_{15}H_{31}PPh_3Br$) resulted in only a low yield of the desired olefin. Previously, Dondoni and co-workers reported the Wittig olefination of a sterically hindered serine-derived aldehyde with tetradecyltriphenylphosphonium bromide (3.2 equiv);[5a] the use of 2.8 equiv of lithium hexamethyldisilazide (LHMDS freshly prepared from *n*-BuLi and $NH(SiMe_3)_2$) as the base produced a mixture of (*Z*)- and (*E*)-isomers in 80−84% isolated yield. Similarly, by using the $C_{15}H_{31}PPh_3Br$/LHMDS/**1** (mole ratio = 2.3:2.1:1) combination system, we have obtained a 90:10 mixture of (*Z*)- and (*E*)-isomers in 83% total yield based on ^1H NMR analysis after purification by column chromatography. Use of sodium hexamethyldisilazide (NaHMDS) as a base did not increase the population of the *Z* form;[13]

Scheme 1



[a] $C_{15}H_{31}PPh_3Br$, LHMDS, −78 °C. [b] *m*-CPBA, room temperature. [c] Excess $LiAlH_4$, 0 °C. [d] CF_3CO_2H, room temperature, then Ac_2O, DMAP, room temperature.

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Table 1. Solvent Effect for the Oxidation[a] of (*Z*)-2 with *m*-CPBA

solvent	reaction time	total yield[b] (%)	A:B ratio[c]
benzene	4 hours	87.2	82:18
CH_2Cl_2	1 day	91.5	70:30
tert-BuOH	2 days	86.7	89:11
THF	2 days	89.3	92:8

[a] Method: *m*-CPBA (2.5 equiv), Na_2HPO_4 (2.5 equiv), room temperature. [b] Obtained by column chromatography. [c] Analyzed by ^1H NMR.

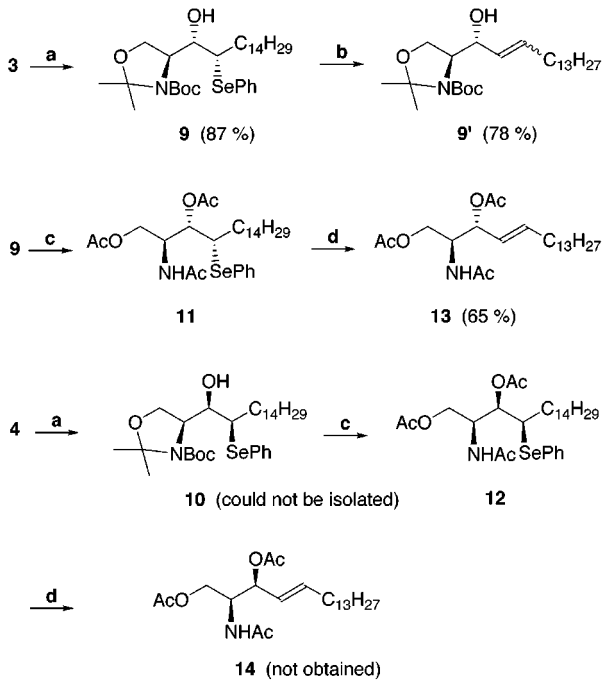
no significant improvement in selectivity was observed (*Z*/*E* = 91:9) with slightly decreased yield to 74%. Nevertheless, column chromatographic purification and isolation with *n*-hexane−EtOAc (20:1) as an eluent, gave pure (*Z*)-**2** in 66% yield. The (*Z*)-olefin **2** thus formed may be synthetically more valuable than the corresponding (*E*)-olefin, as will be substantiated below, because the former is more susceptible to steric hindrance toward attacking reagents due to its bulky *N*-Boc group than the latter.

Next, the epoxidation of each olefin using 2 equiv of *m*-CPBA was examined in various solvents in the presence of 2 equiv of Na_2HPO_4 as the base. Addition of the phosphate was effective in avoiding the unfavorable acid-catalyzed ring-opening of the epoxide once formed. Little or no diastereoselectivity was observed for (*E*)-**2** in a wide range of solvents tested, while remarkably high diastereoselectivity was observed for (*Z*)-**2**. Table 1 indicates that THF is the best of choice among the solvents, in which **3** and **4** were formed with a 92:8 ratio. The epoxide **3** and **4** were readily separated by column chromatography with *n*-hexane−diethyl ether (4:1) and obtained in 84% and 4% yields, respectively. Incidentally, the epoxidation of (*Z*)-**2** employing the $Mo(CO)_6$−TBHP system failed due probably to the bulkiness of the oxidant.[9]

The epoxide **3** thus formed was reduced with $LiAlH_4$ in diethyl ether at 0 °C to give rise to the desired 3-hydroxy compound **5** with an excellent regioselectivity, demonstrating that the less hindered carbon atom of the epoxide is vulnerable to the preferred attack of the relatively small hydride anion.[10] The removal of the protective *N*-Boc group of **5** with trifluoroacetic acid, followed by acetylation, a technique for easy purification and characterization of the product, afforded *N*,*O*,*O*-triacetyl-D-*erythro*-dihydrosphingosine **7** in 83% yield. The overall yield based on **1** was 39%. The free form of the triacetyl compound **7** is an amino component of symbioramide, an activator of a sarcoplasmic reticulum Ca^{2+}-ATPase.[11] The *threo*-isomer **8** could also be prepared from **4** in the same manner (see the Experimental Section for the detail).

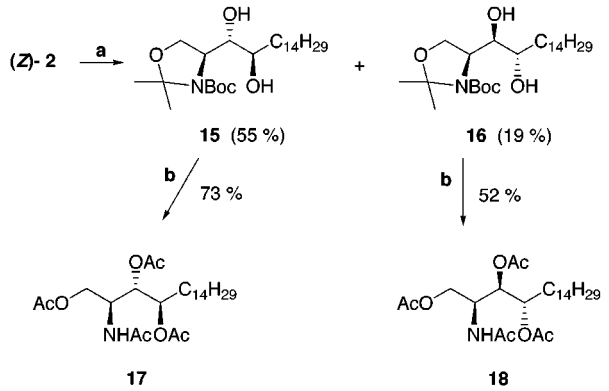
(ii) Sphingosines. The epoxide **3** was converted to the allylic alcohol **9′** according to the method described by Sharpless[12] (Scheme 2); treatment of **3** with diphenyl diselenide (PhSeSePh) and sodium tetrahydroborate gave the hydroxy selenide **9**, which was the sole product detected by ^1H NMR spectroscopy after purification of the reaction mixture by column chromatography. The subsequent oxidation of the crude hydroxyselenide **9** with 30% hydrogen peroxide resulted in a comparatively low selectivity of a 9:1 mixture of (*E*)- and (*Z*)-allylic alcohols, irrespective of Sharpless' rule that the alkyl selenoxide will exclusively decompose to the (*E*)-allylic alcohol.[12] Probably, such a low observed selectivity appears to be attributed to too large a steric hindrance by the large

Scheme 2



[a] PhSeSePh, $NaBH_4$, reflux. [b] 30% H_2O_2, room temperature. [c] CF_3CO_2H, room temperature, then Ac_2O, DMAP, room temperature. [d] 30% H_2O_2, $NaHCO_3$, room temperature.

Scheme 3



[a] *N*-methylmorpholine *N*-oxide hydrate, OsO_4, room temperature. [b] CF_3CO_2H, room temperature, then Ac_2O, DMAP, room temperature.

N-Boc group around the selenoxide moiety. Therefore, the smaller *N*-Ac derivative **11** was substituted for the *N*-Boc derivative **9** for the sake of selective elimination of the selenoxide group; actually, when the *N*-Ac derivative **11** was oxidized with 30% hydrogen peroxide, followed by facile PhSeOH-elimination, *N*,*O*,*O*-triacetyl-D-*erythro*-sphingosine **13** was obtained in 31% isolated yield, as expected. Attempts to prepare the *threo*-isomer **14** from **4** entirely failed because no target molecule **10** could be detected in the reaction mixture.

(iii) Phytosphingosines. To obtain the 3,4-diol **15**, we have examined the osmylation of the olefin (*Z*)-**2** (Scheme 3); OsO_4/*N*-methylmorpholine *N*-oxide[7c] converted (*Z*)-**2** into a mixture of diols **15** and **16**, which were readily separated by column chromatography using *n*-hexane−EtOAc (3:1) in 55% and 19% yields, respectively. The isolated **15** and **16** were deprotected and then acetylated to provide *N*,*O*,*O*,*O*-tetraacetyl-D-*ribo*-phyto-

sphingosine **17** and *arabino*-isomer **18**, respectively. The overall yield of **17** from **1** was 27%.

Conclusions

Three different types of sphingosine derivatives, **7**, **13**, and **17**, were prepared from L-serine through the common intermediate (*Z*)-**2**. It is found for the first time that both the oxidation of (*Z*)-**2** with *m*-CPBA or OsO_4/*N*-methylmorpholine *N*-oxide and the epoxy-ring opening reaction with $LiAlH_4$ or $PhSe^-$ take place stereoselectively; these high selectivities appear to arise from the presence of a sterically encumbered *N*-Boc group near the reacting centers.

Experimental Section

All the materials were obtained commercially (guaranteed reagent grade) and used without further purification. All solvents were freshly distilled under nitrogen before use; THF and diethyl ether were distilled from $LiAlH_4$; CH_2Cl_2 was distilled from P_2O_5; EtOH was distilled from CaO. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$, C_6D_6 or DMSO-d_6 solution with TMS as an internal standard. Column chromatography was performed on silica gel (Wakogel C-200).

(*R*,*Z*)-2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylideneoctadec-3-en-1-ol ((*Z*)-2). To a solution of 1,1,1,3,3,3-hexamethyldisilazane (8.13 g, 50.4 mmol) in dry THF (100 mL) was added *n*-BuLi (1.6 M in *n*-hexane, 31.5 mL) at room temperature (LHMDS solution). The LHMDS solution was treated dropwise with pentadecyltriphenylphosphonium bromide (30.6 g, 55.3 mmol) in dry THF (100 mL). The resulting dark red solution was added dropwise to a solution of Garner's aldehyde[8] **1** (5.52 g, 24 mmol) in dry THF (50 mL) at −78 °C. After stirring overnight at room temperature, the mixture was poured into an ice-cooled 1 M HCl solution and extracted with EtOAc. After drying with Na_2SO_4, the solvent was concentrated and the residue was purified by column chromatography with chloroform to give a mixture of (*Z*)- and (*E*)-isomers in a 9:1 ratio (by ^1H NMR analysis). Further purification by column chromatography with *n*-hexane−EtOAc (20:1) gave the major isomer (*Z*)-**2** as a colorless oil (6.78 g, 66.4%).

Compound (*Z*)-2: $[\alpha]^{25}_D = +55.9°$ (*c* 1.72, $CHCl_3$); IR ($CHCl_3$) 2975, 2855, 1701, 1460, 1385, 1366, 1252, 1176, 1096, 1037, 851 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 0.91 (t, 3 H, J = 6.8 Hz), 1.34 (s, 24 H), 1.44 (s, 9 H), 1.60 (s, 3 H), 1.70 (s, 3 H), 2.12 (brs, 2 H), 3.55 (dd, 1 H, J = 3.4, 8.8 Hz), 3. 85 (dd, 1 H, J = 6.3, 8.8 Hz), 4.61 (brs, 1 H), 5.37−5.52 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 14.0, 22.9, 24.8, 27.1, 27.7, 28.5, 29.6, 29.8, 29.9, 30.0, 30.1, 32.2, 55.0, 69.1, 77.5, 79.2, 130.9, 152.0. HRMS (FAB, direct) Calcd for $C_{26}H_{49}NO_3$: $[M + H]^+$ 424.3791. Found: 424.3779 (13%). Anal. Calcd: C, 73.71; H, 11.66; N, 3.31. Found: C, 73.71; H, 11.68; N, 3.27.

Compound (*E*)-2: $[\alpha]^{25}_D = -4.63°$ (*c* 2.1, $CHCl_3$); IR ($CHCl_3$) 2926, 2855, 1701, 1460, 1385, 1366, 1254, 1178, 1099, 1057, 964, 851 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 0.91 (t, 3 H, J = 6.8 Hz), 1.33 (s, 24 H), 1.46 (s, 9 H), 1.57 (s, 3 H), 1.72 (s, 3 H), 2.0 (dt, 2 H, J = 6.8, 6.3 Hz), 3.56 (dd, 1 H, J = 3.4, 8.8 Hz), 3.78 (dd, 1 H, J = 6.0, 8.8 Hz), 4.20 (brs, 1 H), 5.49 (dd, 1 H, J = 7.2, 15.4 Hz), 5.62 (dt, 1 H, J = 15.4, 6.3 Hz). HRMS (FAB, direct) Calcd: $[M + H]^+$ 424.3791. Found: 424.3787 (11%). Anal. Calcd for $C_{26}H_{49}NO_3$: C, 73.71; H, 11.66; N, 3.31. Found: C, 73.64; H, 11.7; N, 3.25.

(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylidene-3,4-epoxyoctadecan-1-ol (3). To a solution of (*Z*)-**2** (4.24 g, 10 mmol) and Na_2HPO_4 (3.55 g, 25 mmol) in dry THF (100 mL) was added *m*-CPBA (4.31 g, 25 mmol) at 0 °C. The mixture was stirred for 1 h and then 2 days at room temperature. The solution was treated with saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and concentrated to give a residue containing the epoxide **3** and the (2*S*,3*R*,4*S*)-isomer **4** in a 92:8 ratio (by ^1H NMR analysis), which was purified by column chromatography with *n*-hexane−diethyl ether (4:1), affording **3** (3.67 g, 83.5%) and **4** (170 mg, 3.9%) as solids, respectively.

Compound 3: mp 43 °C; $[\alpha]^{25}_D = +33.4°$ (*c* 2.0, $CHCl_3$); IR (KBr) 2920, 2851, 1699, 1472, 1387, 1366, 1167, 1103, 1059, 868 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 0.91 (t, 3 H, J = 6.8 Hz), 1.33 (s, 24 H), 1.41 (s, 9 H), 1.49 (s, 3 H), 1.50−1.60 (m, 2 H), 1.65 (s, 3 H), 2.89−2.93 (m, 1 H), 3.0 (dd, 1 H, J = 3.9, 7.8 Hz), 3.72−3.77 (m, 1 H), 3.76 (t, 1 H, J = 6.3 Hz), 4.13 (dd, 1 H, J = 8.3, 2.0 Hz). HRMS (FAB, direct) Calcd for $C_{26}H_{49}NO_4$: $[M + H]^+$ 440.3740. Found: 440.3736 (9%). Anal. Calcd: C, 71.03; H, 11.23; N, 3.19. Found: C, 70.9; H, 11.25; N, 3.16.

Compound 4: mp 39 °C; $[\alpha]^{25}_D = +10.5°$ (*c* 2.0, $CHCl_3$); IR (KBr) 2920, 2855, 1699, 1474, 1391, 1366, 1252, 1092, 1057, 845 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 0.89 (t, 3 H, J = 6.8 Hz), 1.29 (s, 26 H), 1.54 (s, 9 H), 1.58 (s, 3 H), 1.73 (s, 3 H), 2.54−2.58 (m, 1 H), 2.87 (dd, 1 H, J = 4.4, 7.6 Hz), 3.57 (dd, 1 H, J = 7.8, 1.6 Hz), 3.69−3.76 (m, 2 H). HRMS (FAB, direct) Calcd for $C_{26}H_{49}NO_4$: $[M + H]^+$ 440.3740. Found: 440.3725 (12%). Anal. Calcd: C, 71.03; H, 11.23; N, 3.19. Found: C, 71.04; H, 11.22; N, 3.07.

(2*S*,3*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylideneoctadecane-1,3-diol (5). To a solution of the epoxide **3** (400 mg, 0.9 mmol) in dry diethyl ether (50 mL) was added $LiAlH_4$ (140 mg, 3.6 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C under N_2. The reaction mixture was cooled at −78 °C, and EtOAc was added to quench. The resulting white emulsion was poured into an ice-cooled 1 M HCl solution and extracted with EtOAc; the organic layer was dried with Na_2SO_4 and concentrated. Purification by column chromatography with *n*-hexane−EtOAc (5:1) gave **5** (340 mg, 85.5%) as an oil: $[\alpha]^{25}_D = -12.6°$ (*c* 2.51, $CHCl_3$) {lit.[6d] $[\alpha]^{20}_D = -12.7°$ (*c* 1.09, $CHCl_3$)}; ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 0.90 (t, 3 H, J = 6.8 Hz), 1.33 (s, 28 H), 1.42 (s, 9 H), 1.46 (s, 3 H), 1.63 (s, 3 H), 3.67 (dd, 1 H, J = 6.8, 8.8 Hz), 3.79−3.90 (m, 3 H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 14.0, 22.9, 24.1, 26.4, 26.8, 28.4, 29.6, 29.9, 30.0, 32.2, 33.9, 62.7, 64.5, 72.6, 80.0, 94.3. MS (FAB, direct) Calcd for $C_{26}H_{51}NO_4$: $[M + H]^+$ 442.4. Found: 442.5 (11%).

(2*S*,3*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylideneoctadecane-1,3-diol (6). The reaction was carried out as described above starting from **4** (300 mg, 0.68 mmol), although the amount of adding $LiAlH_4$ was 2-fold equimolar. Purification by column chromatography with *n*-hexane−EtOAc (5:1) gave **6** (240 mg, 79.9%) as an oil: $[\alpha]^{25}_D = -36.9°$ (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3450, 2924, 2855, 1701, 1670, 1394, 1366, 1258, 1175, 1109, 1061 cm^{-1}; ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 0.91 (t, 3 H, J = 6.8 Hz), 1.33 (s, 28 H), 1.40 (s, 9 H), 1.47 (s, 3 H), 1.65 (s, 3 H), 3.65−3.73 (m, 2 H), 3.80−3.90 (m, 2 H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 14.0, 22.9, 24.2, 25.9, 27.1, 28.3, 29.6, 30.0, 30.1, 32.2, 34.3, 62.7, 65.0, 75.5, 80.3, 94.3. HRMS (FAB, direct) Calcd for $C_{26}H_{51}NO_4$: $[M + H]^+$ 441.3818. Found: 442.3896 (11%). Anal. Calcd: C, 70.70; H, 11.64; N, 3.17. Found: C, 70.39; H, 11.63; N, 3.17.

***N*,*O*,*O*-Triacetyl-D-*erythro*-dihydrosphingosine (7).** To the protected sphingosine **5** (200 mg, 0.45 mmol) was added a solution of trifluoroacetic acid (1 mL) and water (0.3 mL). After 1 h, the solvent was evaporated in vacuo and a saturated aqueous $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried with Na_2SO_4, and concentrated. To the residue dissolved in pyridine (10 mL) were added DMAP (170 mg, 1.35 mmol) and acetic anhydride (230 mg, 2.25 mmol). After 1 day of stirring, the solvent was removed in vacuo. Saturated aqueous $NaHCO_3$ was added to the residue, and the mixture was extracted with diethyl ether. The organic layer was dried with Na_2SO_4 and concentrated. Purification by column chromatography with *n*-hexane−EtOAc (5:1) gave **7** (160 mg, 83.1%) as a solid: mp 97−98 °C (lit.[6d] mp 90−93 °C and lit.[6c] mp 93−94 °C); $[\alpha]^{25}_D = +17.4°$ (*c* 1.0, $CHCl_3$) {lit.[6d] $[\alpha]^{19}_D = +16.0°$ (*c* 0.5, $CHCl_3$) and lit.[6c] $[\alpha]^{23}_D = +17.5°$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 7.0 Hz), 1.24 (s, 26 H), 1.59 (brs, 2 H), 2.00 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 4.05 (dd, 1 H, J = 3.9, 11.2 Hz), 4.35−4.41 (m, 1H), 4.90 (dt, 1 H, J = 7.3, 5.4 Hz), 5.96 (d, 1 H, J = 9.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.8, 21.0, 22.6, 23.3, 25.3, 29.3, 29.4, 29.5, 29.6, 31.4, 31.9, 50.4, 62.6, 73.9, 169.7, 170.9, 171.1. MS (FAB, direct) Calcd for $C_{24}H_{45}NO_5$: $[M + H]^+$ 428.3. Found: 428.4 (83%).

***N*,*O*,*O*-Triacetyl-L-*threo*-dihydrosphingosine (8).** The reaction was carried out as described above for **7**, starting from **6** (160 mg, 0.32 mmol). Purification by column chromatography with *n*-hexane−EtOAc (5:1) gave **8** (160 mg, 83.1%) as a solid:

mp 43−44 °C; $[\alpha]^{25}_D = -6.86°$ (*c* 2.0, $CHCl_3$); IR (KBr) 3304, 2920, 2851, 1746, 1653, 1558, 1541, 1369, 1244, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3 H, $J = 6.8$ Hz), 1.22 (s, 26 H), 1.50−1.57 (m, 2 H), 2.00 (s, 3 H), 2.03 (s, 3 H), 2.05 (s, 3 H), 4.00 (d, 2 H, $J = 5.7$ Hz), 4.37 (ddt, 1 H, $J = 9.3$, 3.4, 6.4 Hz), 5.04 (ddd, 1 H, $J = 3.9$, 7.3, 5.9 Hz), 5.74 (d, 1 H, $J = 9.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.7, 20.9, 22.6, 23.1, 25.1, 29.2, 29.3, 29.3, 29.4, 29.6, 29.6, 31.2, 31.8, 49.9, 63.2, 72.3, 170.0, 170.3, 170.7. HRMS (FAB, direct) Calcd for $C_{24}H_{45}NO_5$: $[M + H]^+$ 428.3376. Found: 428.3369 (72%). Anal. Calcd: C, 67.41; H, 10.61; N, 3.28. Found: C, 67.38; H, 11.61; N, 3.24.

(2*S*,3*S*,4*S*)-2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylidene-4-phenylselenyloctadecane-1,3-diol (9). To a solution of diphenyl diselenide (160 mg, 0.51 mmol) in absolute ethanol (3 mL) was added sodium tetrahydroborate (42 mg, 1.11 mmol, evolution of H_2) at room temperature. The mixture was stirred under N_2; the yellow solution turned colorless. Then a solution of **3** (400 mg, 0.91 mmol) in absolute ethanol (3 mL) was added dropwise and the mixture was heated under reflux for 2 h. After cooling to room temperature, the mixture was poured into an ice-cooled 1 M HCl solution and extracted with diethyl ether. After drying with Na_2SO_4, the solvent was removed in vacuo. Purification by column chromatography with *n*-hexane−diethyl ether (3:1) gave **9** (470 mg, 86.5%) as an oil: $[\alpha]^{25}_D = -16.9$ ° (*c* 1.92, $CHCl_3$); IR ($CHCl_3$) 3470, 2926, 2855, 1699, 1477, 1366, 1258, 1173, 1094, 847 cm^{-1}; ^1H NMR (400 MHz, DMSO, 100 °C) δ 0.86 (t, 3 H, $J = 6.8$ Hz), 1.17−1.35 (m, 24 H), 1.43 (s, 9 H), 1.45 (s, 3 H), 1.50 (s, 3 H), 1.62−1.71 (m, 1 H), 1.78−1.87 (m, 1 H), 3.27−3.33 (m, 1 H), 3.82−3.87 (m, 1 H), 3.85 (dd, 2 H, $J = 6.3$, 8.8 Hz), 4.02−4.07 (m, 1 H), 4.22 (dd, 1 H, $J = 2.0$, 8.8 Hz), 5.03 (d, 1 H, $J = 5.4$ Hz, exchanged with D_2O), 7.2−7.24 (m, 3 H), 7.55−7.59 (m, 2 H). HRMS (FAB, direct) Calcd for $C_{32}H_{55}NO_4Se$: $[M]^+$ 597.3296. Found: 597.3317 (11%). Anal. Calcd: C, 64.41; H, 9.29; N, 2.35. Found: C, 64.46; H, 9.31; N, 2.31.

***N*,*O*,*O*-Triacetyl-D-*erythro*-shingosine (13) via (2*S*,3*S*,4*S*)-*N*,*O*,*O*-Triacetyl-2-amino-4-phenylselenyloctadecane-1,3-diol (11).** The reaction was carried out as described above for **7** starting from **9** (400 mg, 0.67 mmol) without purification. The obtained crude product **11** was dissolved in a mixture of EtOAc−THF (2:1, 5 mL), and $NaHCO_3$ (160 mg, 1.9 mmol) was added to the mixture. To the solution was added slowly 30% hydrogen peroxide (0.3 mL) at 0 °C. The mixture was stirred for 30 min at 0 °C and then for 1 h at room temperature. The solution was treated with saturated aqueous $Na_2S_2O_3$ and was stirred for 30 min. The mixture was extracted with EtOAc. After drying with Na_2SO_4, the solvent was concentrated to give **13** (190 mg, 66.6%) as a colorless solid after recrystallization from *n*-hexane−EtOAc: mp 106 °C (lit.[5a] mp 105−106 °C); $[\alpha]^{25}_D = -13.0°$ (*c* 1.0, $CHCl_3$) {lit.[5a] $[\alpha]_D = -12.9°$ (*c* 1.0, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3 H, $J = 6.8$ Hz), 1.25 (brs, 22 H), 1.99 (s, 3 H), 2.07 (s, 3 H), 2.08 (s, 3 H), 2.01−2.07 (m, 2 H), 4.04 (dd, 1 H, $J = 11.7$, 3.9 Hz), 4.29 (dd, 1 H, $J = 11.7$, 6.1 Hz), 4.42 (m, 1 H), 5.28 (dd, 1 H, $J = 6.4$, 6.8 Hz), 5.39 (dd, 1 H, $J = 7.3$, 15.1 Hz), 5.64 (d, 1 H, $J = 8.8$ Hz), 5.79 (dt, 1 H, $J = 15.1$, 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.8, 21.1, 22.7, 23.3, 28.9, 29.2, 29.3, 29.4, 29.6, 29.6, 31.9, 32.3, 50.6, 62.6, 73.8, 124.1, 137.5, 169.7, 170.0, 171.0. MS (FAB, direct) Calcd for $C_{24}H_{43}NO_5$: $[M + H]^+$ 426.3. Found: 426.4 (38%).

(2*S*,3*S*,4*R*)-2-[(*tert*-Butoxycarbonyl)amino]-1,2-*O*,*N*-isopropylideneoctadecane-1,3,4-triol (15). A solution of *N*-methylmorpholine *N*-oxide hydrate (50% in water, 320 mg) and acetone (3 mL) was treated with osmium tetroxide (12.7 mg, 0.05 mmol) in *tert*-butyl alcohol (3 mL). After 15 min at room temperature, **2** (500 mg, 1.22 mmol) in acetone (2 mL) was added dropwise to the solution. After stirring the mixture for 1 day at room temperature, the solution was treated with saturated aqueous $Na_2S_2O_3$ and was stirred for 30 min. The mixture was extracted with EtOAc. After drying with Na_2SO_4, the solvent was concentrated and the residue was purified by column chromatography with *n*-hexane−EtOAc (3:1) to give **15** (300 mg, 55.4%) and the (2*S*,3*R*,4*S*)-isomer **16** (100 mg, 18.5%) as solids, respectively.

Compound 15: mp 55 °C; $[\alpha]^{25}_D = -5.36°$ (*c* 2.0, $CHCl_3$); IR (KBr) 3412, 2957, 2851, 1688, 1472, 1402, 1366, 1261, 1186, 1111, 1069, 1042, 853 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 130 °C) δ 0.88 (t, 3 H, $J = 6.8$ Hz), 1.28 (s, 24 H), 1.45 (s, 12 H), 1.51 (s, 3 H), 1.41−1.58 (m, 2 H), 3.34−3.38 (m, 1 H), 3.74 (m, 1 H), 3.80 (d, 1 H, $J = 5.9$ Hz, exchanged with D_2O), 3.84 (dd, 1 H, $J = 6.8$, 3.4, 8.8 Hz), 3.88 (d, 1 H, $J = 6.3$ Hz, exchanged with D_2O), 4.04 (dt, 1 H, $J = 6.8$, 3.4 Hz), 4.10 (dd, $J = 3.4$, 8.3 Hz). HRMS (FAB, direct) Calcd for $C_{26}H_{51}NO_5$: $[M + H]^+$ 458.3845. Found: 458.3841 (17%). Anal. Calcd: C, 68.23; H, 11.23; N, 3.06. Found: C, 67.94; H, 11.25; N, 3.02.

Compound 16: mp 38−39 °C; $[\alpha]^{25}_D = -30.3°$ (*c* 2.0, $CHCl_3$); IR (KBr) 3464, 2920, 2853, 1678, 1472, 1396, 1366, 1248, 1171, 1105, 1074, 1059, 1043, 890 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 130 °C) δ 0.88 (t, 3 H, $J = 6.8$ Hz), 1.28 (s, 24 H), 1.46 (s, 12 H), 1.53 (s, 3 H), 1.45−1.65 (m, 2 H), 3.33−3.37 (m, 2 H), 3.76 (d, 1 H, $J = 6.3$ Hz, exchanged with D_2O), 3.89−3.96 (m, 3 H, exchanged with D_2O), 4.04−4.07 (m, 1 H). HRMS (FAB, direct) Calcd for $C_{26}H_{51}NO_5$: $[M + H]^+$ 458.3845. Found: 458.3835 (11%). Anal. Calcd: C, 68.23; H, 11.23; N, 3.06. Found: C, 68.16; H, 11.23; N, 3.16.

***N*,*O*,*O*,*O*-Tetraacetyl-D-*ribo*-phytosphingosine (17).** The reaction was carried out as described above for **7**, starting from **15** (140 mg, 0.31 mmol). Purification by column chromatography with *n*-hexane−EtOAc (5:1) gave **17** (110 mg, 73.1%) as a solid; mp 46 °C (lit.[7c] mp 48 °C); $[\alpha]^{25}_D = +26.2°$ (*c* 2.0, $CHCl_3$) {lit.[7c] $[\alpha]^{20}_D = +26.3°$ (*c* 2.0, $CHCl_3$)}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, 3 H, $J = 7.2$ Hz), 1.23 (s, 24 H), 1.63 (brs, 2 H), 2.01 (s, 3 H), 2.03 (s, 6 H), 2.06 (s, 3 H), 3.98 (dd, 1 H, $J = 11.7$, 2.9 Hz), 4.26 (dd, 1 H, $J = 11.2$, 5.9 Hz), 4.42−4.48 (m, 1 H), 4.91 (dt, 1 H, $J = 9.6$, 2.9 Hz), 5.09 (dd, 1 H, $J = 8.3$, 2.9 Hz), 6.16 (d, 1 H, $J = 9.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.7, 21.0, 22.6, 23.2, 25.4, 28.0, 29.2, 29.3, 29.4, 29.5, 29.6, 31.9, 47.5, 62.8, 71.8, 72.9, 169.8, 170.1, 170.8, 171.1; MS (FAB, direct) Calcd for $C_{26}H_{47}NO_7$: $[M + H]^+$ 486.3. Found: 486.4 (75%).

***N*,*O*,*O*,*O*-Tetraacetyl-L-*arabino*-phytosphingosine (18).** The reaction was carried out as described above for **7**, starting from **16** (90 mg, 0.20 mmol). Purification by column chromatography with *n*-hexane−EtOAc (5:1) gave **18** (50 mg, 52.3%) as a solid; mp 47−48 °C; $[\alpha]^{25}_D = -25.1°$ (*c* 1.5, $CHCl_3$); IR (KBr) 3933, 2918, 2851, 1749, 1684, 1518, 1373, 1232, 1209, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, 3 H, $J = 6.83$ Hz), 1.24 (s, 24 H), 1.54 (brs, 2 H), 1.99 (s, 3 H), 2.05 (s, 3 H), 2.06 (s, 3 H), 2.11 (s, 3 H), 4.00 (d, 2 H, $J = 6.4$ Hz), 4.57−4.63 (m, 1 H), 5.00 (dt, 1 H, $J = 4.4$, 7.3 Hz), 5.19 (dd, 1 H, $J = 3.2$, 6.3 Hz), 5.63 (d, 1 H, $J = 9.8$ Hz); HRMS (FAB, direct) Calcd for $C_{26}H_{47}NO_7$: $[M + H]^+$ 486.3431. Found: 486.3449 (53%). Anal. Calcd: C, 64.3; H, 9.75; N, 2.88. Found: C, 64.21; H, 9.71; N, 2.8.

Supporting Information Available: Characterization data for all new compounds (*Z*)- or (*E*)-**2**, **3**, **4**, **6**, **8**, **9**, **15**, **16**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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