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Novel, Short, Stereospecific Synthesis of *lyxo*-(2*R*,3*R*,4*R*)-Phytosphingosine and *erythro*-(2*R*,3*S*)-Sphingosine†

Sadagopan Raghavan* and A. Rajender

Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India

purush101@yahoo.com

Received February 5, 2003

Abstract: *lyxo*-Phytosphingosine and *erythro*-sphingosine have been elaborated from a common intermediate. The key step in the reaction sequence involves stereo- and regiospecific functionalization of an olefin by intramolecular nucleophilic sulfinyl group participation.

Sphingolipids are widely distributed in eukaryotic cell membranes[1] and have been demonstrated to regulate biological processes. The sphingolipids have long-chain bases as the backbone, i.e., sphingosines, dihydrosphingosines, and phytosphingosines, which are also bioactive. The finding that diastereomers of sphingosines and phytosphingosines (Figure 1) exhibit different activities suggests subtle biostereoselectivities.[2−5] A great deal of effort has therefore been devoted toward the synthesis of sphingolipids for use in biological studies.

Synthetic efforts have primarily focused on the preparation of *arabino*- and *ribo*-phytoshingosines starting from compounds of the chiral pool[6] or by asymmetric induction.[7] In contrast, the *xylo*- and *lyxo*-phytosphingosines have attracted less attention from the synthetic community.[8] In continuation of our efforts aimed at the utilization of the pendant sulfoxide as an intramolecular nucleophile for regio- and stereoselective functionalization of olefins,[9,10] we disclose herein, the enantiospecific synthesis of *lyxo*-(2*R*,3*R*,4*R*)-C_{18}-phytosphingosine and *erythro*-(2*R*,3*S*)-C_{18}-sphingosine.

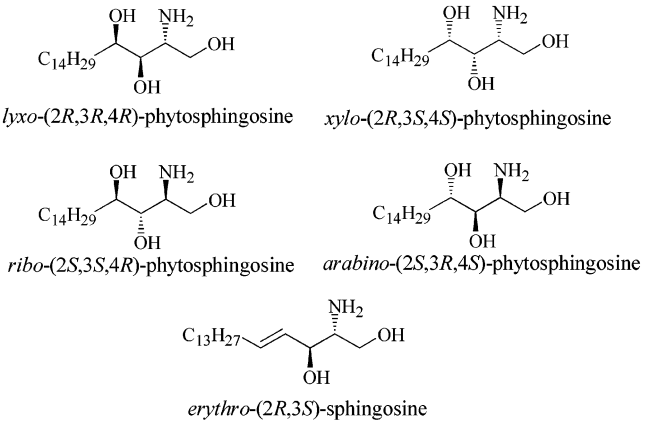

FIGURE 1. Representative phytosphingosines.

The synthesis began with the β-hydroxy-γ,δ-unsaturated sulfoxide (**2**), which was obtained by DIBAL-H reduction[11] of the ketosulfoxide (**1**), a compound previously reported by Solladie and co-workers.[12] Treatment of the unsaturated sulfoxide (**2**), with NBS in toluene in the presence of water, afforded the bromohydrin (**4**) as the sole product. The regio- and stereoselectivity of the reaction can be explained by the intermediacy of the sulfoxonium salt (**3**), (Scheme 1). The relative stereochemistry at C_2 and C_3 in **4** was unambiguously proven as *syn* by conversion to acetonide (**5**), the ^{13}C spectrum of which revealed signals at δ 27.2 and 27.5 for the methyl groups.[13] The *anti* disposition of the hydroxyl and bromine at C_3 and C_4, respectively, is expected from an overall *trans* addition of electrophile and nucleophile across the double bond.[14] It was required to introduce the amino functionality onto bromodiol (**4**) with retention of relative stereochemistry. This was achieved by a two-step transformation.

Thus, the bromohydrin (**4**) was converted into the epoxide (**6**) by treatment with K_2CO_3 in methanol. The epoxyalcohol (**6**) was regio- and stereoselectively transformed into the azidodiol (**7**) using the Sharpless protocol.[15] The crude ^1H NMR spectrum of (**7**) did not reveal the presence of any regiomer. The regioselectivity of the transformation was proven once again by conversion of the diol (**7**) into the acetonide (**8**). The ^{13}C NMR spectrum of **8** revealed signals at δ 26.7 and 26.9 for the methyl groups and at δ 110.3 for the ketal carbon, proving beyond doubt the *syn* disposition of the hydroxy groups on adjacent carbons.[13] The acetonide (**8**) was elaborated to *lyxo*-phytosphingosine as depicted in Scheme 2. Having

† IICT Communication no. 030107.

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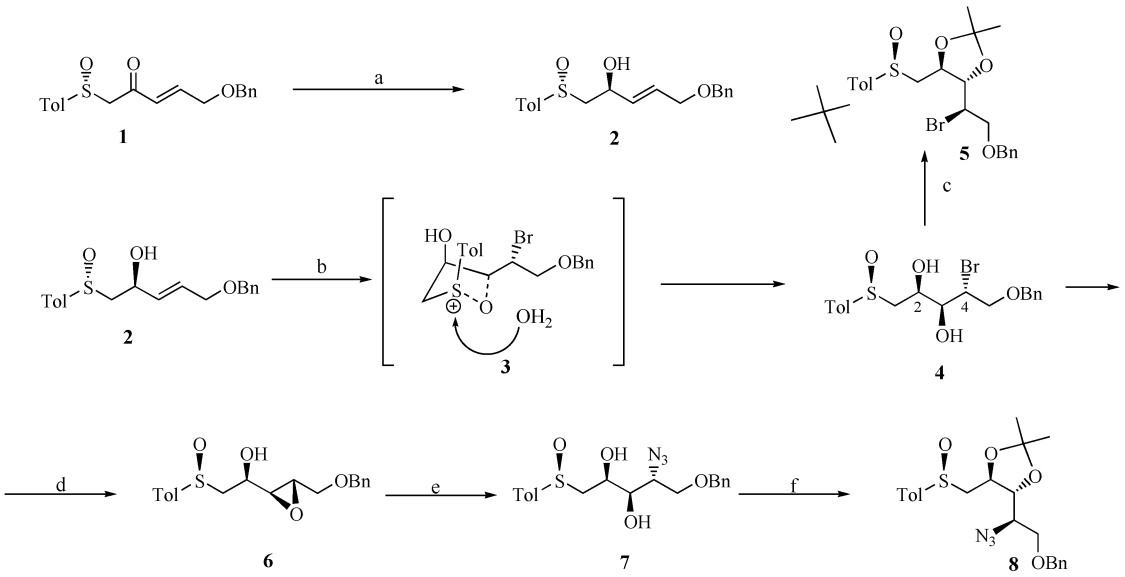
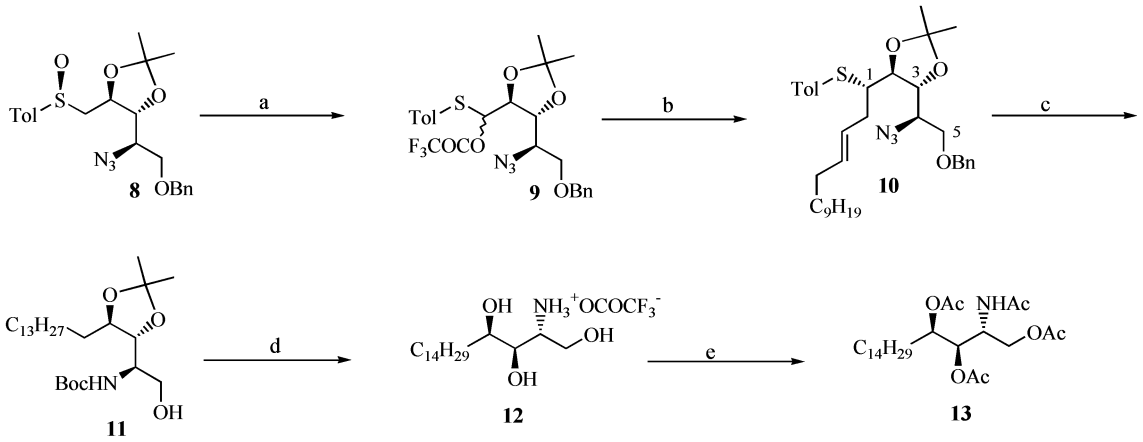
10.1021/jo034157w CCC: $25.00
Published on Web 08/14/2003

SCHEME 1. Preparation of Azidoacetonide 8[a]



[a] (a) DIBAL, THF, −78 °C, 92%; (b) NBS, H_2O, toluene, rt, 88%; (c) 2,2-DMP, acetone, CSA (cat.), rt, 86%; (d) K_2CO_3, MeOH, 0 °C, 83%; (e) NaN_3, NH_4Cl, MeOH/H_2O, reflux, 85%; (f) 2,2-DMP, acetone, CSA (cat.), rt, 87%.

SCHEME 2. Preparation of *lyxo*-Phytosphingosine[a]



[a] (a)TFAA, CH_2Cl_2, 0 °C; (b) $C_{13}H_{26}$, $SnCl_4$, 0 °C, 76% for the two steps; (c) Ra-Ni, H_2, $(Boc)_2O$, methanol, rt−reflux, 75%; (d) TFA/H_2O; (e) Ac_2O, DMAP (cat.), pyridine, rt, 70% for the two steps.

introduced the functional groups on the C_5 chain, the next step called for chain elongation. The C_{13} hydrocarbon chain was introduced by the Pummerer ene reaction.[16] Thus, treatment of the sulfoxide (**8**) with TFAA in DCM afforded the intermediate (**9**), which without isolation was reacted in the same pot with 1-tridecene and $SnCl_4$ to yield the sulfide (**10**) as the only product. The configuration at the newly created one in sulfide (**10**) was not rigorously established, although it is expected to have the structure depicted, since it was of no consequence for the synthesis of the target molecules. Treatment of the sulfide (**10**) with Raney Ni in ethanol in the presence of di-*tert*-butyl dicarbonate under an atmosphere of hydrogen afforded the urethane (**11**) in a one-pot five-step transformation. The double bond and the azide are reduced, the resulting amine is transformed into an urethane, and the toluene thio group and the benzyl ether is hydrogenolysed under the reaction conditions. Deprotection of the acetonide afforded the triol (**12**), which was subsequently converted into the tetraacetate (**13**), which was found to be identical (except for sign of $[\alpha]_D$) to that reported in the literature.[8c]

The *erythro*-(2*R*,3*S*)-sphingosine[17] was synthesized following the reaction sequence depicted in Scheme 3. The sulfide (**10**) was oxidized to the sulfone (**14**) by treatment with oxone.[18] The sulfone (**14**) was subsequently transformed in a one-pot four-step operation into the urethane (**15**) by reaction with $Pd(OH)_2/C$ in the presence of $(Boc)_2O$ under an atmosphere of H_2. Reduction of **15** with Na−Hg[19] led to the concomitant loss of acetone to afford

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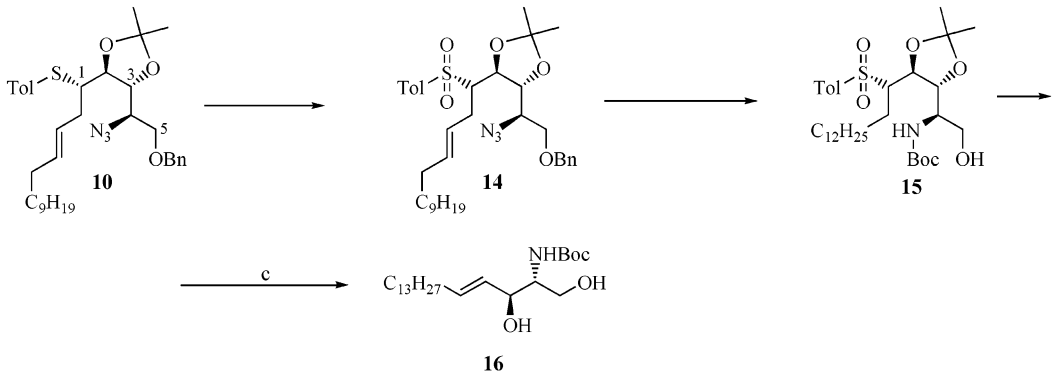
SCHEME 3. Preparation of *erythro*-Sphingosine[a]



[a] (a)2KHSO$_5$·KHSO$_4$·K$_2$SO$_4$, MeOH/H$_2$O/THF, 0 °C−rt, 82%; (b) Pd(OH)$_2$/C, (Boc)$_2$O, H$_2$, EtOH, rt, 71%; (c) Na−Hg, Na$_2$HPO$_4$, MeOH, 20 °C, rt, 60%.

the sphingosine derivative (**16**) as the sole product. The ^{1}H NMR spectrum of **16** revealed the absence of the isomeric *cis* olefin. The sphingosine (**16**) was found to possess identical physical characteristics (except for the sign of rotation of plane polarized light) to those reported in the literature.[8a] In conclusion, we have reported a efficient, flexible, atom-economical, and stereospecific synthesis of *lyxo*-phytosphingosine and *erythro*-sphingosine. The key steps include stereoselective bromohydrin formation using the sulfinyl moiety as an intramolecular nucleophile, chain extension by Pummerer ene reaction, and one-pot atom-economical five-/four-step transformations. It is worthwhile to note that starting from the C_2 diastereomer of the alcohol (**2**), the *lyxo*-(2*S*,3*S*,4*S*)-phytosphingosine and *erythro*-(2*S*,3*R*)-sphingosine can be synthesized following an identical reaction sequence as detailed above. Also the strategy is flexible and would permit the synthesis of sphingolipids with different chain lengths by using olefins of different chain lengths.

Experimental Section

All air- or moisture-sensitive reactions were carried out under nitrogen atmosphere. Solvents were distilled freshly over Na/benzophenone ketyl for THF, over P_2O_5 followed by CaH_2 for DCM, and over P_2O_5 for toluene. Commercially available reagents were used without further purification except for NBS, which was freshly recrystallized from hot water before use. Thin-layer chromatography was performed with precoated silica gel plates. Column chromatography was carried out using silica gel (60−120 mesh). NMR spectra were recorded on a 200-, 300-, or 400-MHz spectrometer. ^{1}H NMR and ^{13}C NMR samples were internally referenced to TMS (0.00 ppm).

5-Benzyloxy-4-bromo-1-(4-methylphenylsulfinyl)-(2*S*,3*S*,4*R*)-pentane-2,3-diol (4). To the solution of the sulfoxide **2** (1.56 g, 4.75 mmol) in dry toluene (19 mL) was added water (171 mg, 9.5 mmol) followed by *N*-bromosuccinimide (1.01 g, 5.7 mmol), and the reaction mixture was stirred at room temperature for 15 min. The reaction was quenched by the addition of saturated $NaHCO_3$ solution. The layers were separated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were successively washed with water and brine and dried over Na_2SO_4. Evaporation of the solvent afforded crude product, which was purified by column chromatography using AcOEt/hexane (2:3) as the eluent to yield bromohydrin **4** (1.95 g, 4.18 mmol) in 88% yield as white solid. Mp 137−139 °C. $[\alpha]^{25}_D$ −120.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.52 (d, J = 8.2 Hz, 2H), 7.4−7.25 (m, 7H), 4.68 (m, 1H), 4.59 (s, 2H), 4.2 (m, 1H), 4.01−3.81 (m, 3H), 3.1 (dd, J = 13.4, 8.2 Hz, 1H), 2.84 (dd, J = 13.4, 3.7 Hz, 1H), 2.8−2.5 (bs, 2-OH), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 51.0, 61.1, 67.9, 71.4, 73.3, 74.7, 124.1, 127.7, 127.8, 128.4, 130.1, 137.4, 139.7, 142.0. HRMS−FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{19}H_{22}BrO_4S$ 427.0578, found 427.0573.

1-[3-Benzyloxymethyl-3(*S*)-oxiran-2-yl]-2-(methylphenylsulfinyl)-1-(*S*)-ethan-1-ol (6). To the solution of **4** (1.8 g, 4.05 mmol) in methanol (16 mL) was added K_2CO_3 (615 mg, 4.45 mmol) at 0° C, and the mixture was allowed to attain room temperture in 45 min. After the reaction mixture stirred at room temperature for 1 h, TLC revealed the complete conversion of starting material. Ether (15 mL) was added to the reaction mixture, and after 10 min the mixture was filtered and evaporated to afford the epoxide **6** (1.16 g, 3.35 mmol) in 83% yield as a white solid. This was taken ahead to the next step without further purification. Mp 104−106 °C. $[\alpha]^{25}_D$ −104.3 (*c* 0.75, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (d, J = 8.2 Hz, 2H), 7.36−7.22 (m, 7H), 4.52 (s, 2H), 4.25 (m, 1H), 3.72 (dd, J = 11.2, 3.0 Hz, 1H), 3.48 (dd, J = 11.2, 5.2 Hz, 1H), 3.3 (d, J = 4.5 Hz, 1H), 3.21 (m, 1H), 3.08 (dd, J = 3.7, 2.2 Hz, 1H), 2.98 (m, 1H), 2.86 (dd, J = 13.4, 4.5 Hz, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 54.4, 57.3, 59.7, 66.7, 69.1, 73.3, 124.1, 127.1, 127.7, 128.4, 130.2, 137.7, 140.1, 142.1. HRMS−FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{19}H_{27}O_4S$ 347.1317, found 347.1312.

4-Azido-5-benzyloxy-1-(4-methylphenylsulfinyl)-(2*S*,3*R*,4*R*)-pentane-2,3-diol (7). To the epoxide **6** (1.04 g, 3.1 mmol) in a solvent mixture of MeOH/H_2O (8:1, 18 mL) was added NH_4Cl (498 mg, 9.3 mmol) followed by NaN_3 (1.21 g, 18.6 mmol), and the mixture refluxed for 6 h. The reaction mixture allowed to attain room temperature, and the solvent was evaporated. The residue was extracted with ethyl acetate (2 × 30 mL). The crude reaction mixture was purified by column chromatography using AcOEt/hexane (2:3) to afford the azidodiol **7** (1.03 g, 2.64 mmol) in 85% yield as a white solid. Mp 95−96 °C. $[\alpha]^{25}_D$ −103.4 (*c* 0.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.51 (d, J = 8.2 Hz, 2H), 7.38−7.24 (m, 7H), 4.57 (s, 2H), 4.44 (m, 1H), 3.9 (m, 1H), 3.76−3.64 (m, 2H), 3.5 (d, J = 8.2 Hz, 1H), 3.22 (bs, 2-OH), 3.1 (dd, J = 13.4, 6.7 Hz), 2.9 (dd, J = 13.4, 4.5 Hz,1H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 60.1, 62.0, 65.2, 70.5, 73.5, 124.4, 127.5, 127.7, 128.4, 130.1, 137.7, 139.2, 141.9. HRMS−FAB (*m*/*z*) [M + H]$^+$ calcd for $C_{19}H_{23}N_3O_4S$ 390.1487, found 390.1478.

4-[1-Azido-2-benzyloxy-(1*R*)-ethyl]-2,2-dimethyl-5-(4-methylphenylsulfinylmethyl)-(4*R*,5*S*)-1,3-dioxolane (8). To the solution of the azidodiol **7** (973 mg, 2.5 mmol) in a mixture of 2,2-dimethoxypropane and acetone (1:3, 10 mL) was added CSA (24 mg, 0.1 mmol), and the reaction mixture was stirred at ambient temperature for 1 h. The organic layer was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography using AcOEt/hexane (1:4) as the eluent to yield acetonide **8** (925 mg, 2.15 mmol) as a visous liquid in 87% yield. $[\alpha]^{25}_D$ −47.5 (*c* 0.6, $CHCl_3$). LSIMS *m*/*z* 430 [M + H]$^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (d, J = 8.2 Hz, 2H), 7.38−7.25 (m, 7H), 4.52 (s, 2H), 4.02−3.9 (m, 2H), 3.7 (dd,

J = 9.4, 3.1 Hz, 1H), 3.62 (m, 1H), 3.54 (dd, J = 9.4, 7.3 Hz, 1H), 3.22 (dd, J = 13.4, 7.3 Hz, 1H), 3.07 (dd, J = 13.4, 3.1 Hz, 1H), 2.42 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 26.7, 26.9, 60.7, 62.7, 70.2, 73.4, 74.4, 78.2, 110.3, 124.4, 127.6, 127.8, 128.4, 129.9, 137.3, 140.0, 141.9. Anal. Calcd for $C_{22}H_{27}N_3O_4S$: C, 61.52; H, 6.34; N, 9.78; S, 7.46. Found: C, 61.39; H, 6.52; N, 9.97; S, 7.49.

2-Azido-2-[2,2-dimethyl-5-[1-(4-methylphenylsulfinyl)-(*E*)-3-tetradecenyl]-(4*R*,5*S*)-1,3-dioxolan-4-yl]-ethyl-benzyl ether (10). To the mixture of the acetonide **8** (885 mg, 2.05 mmol) and 1-tridecene (560 mg, 3.08 mmol) in dichloromethane (10 mL) cooled at 0 °C was added trifluoroacetic anhydride (1.3 g, 6.15 mmol) dropwise over 5 min, and the mixture was stirred for 1 h at the same temperature. $SnCl_4$ (550 mg, 2.05 mmol) was added, and after 10 min at 0 °C the reaction mixture was quenched by the addition of saturated Na_2CO_3 solution. Extraction into diethyl ether and usual workup followed by purification by column chromatography using AcOEt/hexane (1:49) afforded **10** (930 mg, 1.57 mmol) in 76% yield as pale yellow liquid. $[\alpha]^{25}_D$ +15.8 (*c* 1.0, $CHCl_3$). LSIMS *m*/*z* 593 (M^+). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34−7.25 (m, 7H), 7.02 (d, J = 7.2 Hz, 2H), 5.47 (dt, J = 15.3, 6.6 Hz, 1H), 5.32 (dt, J = 15.3, 6.8 Hz, 1H), 4.54 (s, 2H), 4.19−4.1 (m, 2H), 3.77 (dd, J = 9.7, 3.1 Hz, 1H), 3.66 (td, J = 7.5, 3.1 Hz, 1H), 3.54 (dd, J = 9.7, 7.5 Hz, 1H), 3.14 (m, 1H), 2.46−2.41 (m, 2H), 2.32 (s, 3H), 1.97−1.92 (m, 2H), 1.45 (s, 3H), 1.44−1.40 (m, 2H), 1.35 (s, 3H), 1.32−1.2 (m, 17H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C (75 MHz, $CDCl_3$) δ 14.1, 21.0, 22.6, 26.9, 27.0, 29.1, 29.3, 29.5, 29.6, 31.9, 32.5, 37.6, 52.1, 63.8, 70.8, 73.4, 76.6, 80.0, 109.8, 126.6, 127.5, 127.7, 128.4, 129.6, 132.0, 132.3, 134.0, 137.0, 137.6. Anal. Calcd for $C_{35}H_{51}N_3O_3S$: C, 70.79; H, 8.66; N, 7.08; S, 5.40. Found: C, 70.56; H, 8.91; N, 7.12; S, 5.44.

2-(*N*-*tert*-Butyloxycarbonyl)amino-2-[2,2-dimethyl-5-tetradecyl-(4*R*,5*S*)-1,3-dioxalan-4yl]-1-ethanol (11). To the mixture of **10** (297 mg, 0.5 mmol), $(Boc)_2O$ (218 mg, 1.0 mmol) in methanol (5 mL) was added Raney Ni (2.5 g). The reaction mixture was stirred under H_2 pressure for 2 h at room temperature and then refluxed for 6 h, when TLC examination revealed completion of the reaction. The reaction mixture was allowed to attain room temperature and was filtered through a small pad of Celite, which was repeatedly washed with methanol (25 mL × 5). Evaporation of the solvent under reduced pressure followed by purificaion of the crude product by column chromatography using AcOEt/hexane (1:4) afforded the amino alcohol **11** (169 mg, 0.37 mmol) as a white solid in 74% yield. Mp 47−49 °C. $[\alpha]^{25}_D$ +12.8 (*c* 2.5, $CHCl_3$). LSIMS *m*/*z* 458 $[M + H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.05 (bs, NH, 1H), 3.88−3.72 (m, 2H), 3.62−3.47 (m, 3H), 1.92 (bs, OH, 1H), 1.51−1.01 (m, 42H), 0.8 (t, J = 6.7 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 22.6, 26.2, 27.0, 27.2, 28.3, 29.3, 29.6, 31.9, 33.8, 52.9, 62.6, 79.3, 81.8, 108.7, 156.0. Anal. Calcd for $C_{26}H_{51}NO_5$: C, 68.23; H, 11.23; N, 3.06. Found: C, 68.62; H, 11.41; N, 3.09.

2-(*N*-*tert*-Butoxycarbonyl)amino-(2*R*,3*S*,4*E*)-4-octadecene-1,3-diol (16). Na−Hg (6%, 250 mg) was added to the solution of **15** (100 mg, 0.16 mmol) and Na_2HPO_4 (58 mg, 0.32 mmol) in methanol (3.2 mL) at −20 °C, and the mixture was allowed to attain room temperature in 30 min. After further stirring for 1 h, the reaction mixture was cooled to 0 °C, diluted with water (3.2 mL), and evaporated under pressure. The residue was extracted with ethyl acetate to afford the crude product. After evaporation of the solvent, purification by column chromatography using AcOEt/hexane (1:4) afforded the sphingosine **16** (38 mg, 0.097 mmol) in 60% yield as a low melting oily solid. $[\alpha]^{25}_D$ +1.4 (*c* 1, $CHCl_3$) [lit.[8a] $[\alpha]^{24}_D$ −1.4 (*c* 1.0 $CHCl_3$) for the enantiomer]. LSIMS *m*/*z* 400 $[M + H]^+$. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.77 (dt, J = 15.1, 6.7 Hz, 1H), 5.52 (dd, J = 15.1, 6.7 Hz, 1H), 4.31 (m, 1H), 3.88 (m, 1H), 3.64 (m, 1H), 3.53 (m, 1H), 2.6−2.24 (bs, OH), 2.05 (m, 2H), 1.44−1.11 (m, 31H), 0.88 (t, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 28.4, 29.1, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.3, 55.5, 62.7, 74.8, 79.9, 128.9, 134.2, 156.2. Anal. Calcd for $C_{23}H_{45}NO_4$: C, 69.13; H, 11.35; N, 3.51. Found: C, 69.45, H, 11.62, N, 3.59.

Acknowledgment. S.R. is thankful to Dr. J. S. Yadav, Head, Organic Div. I for constant support and encouragement and to Dr. A. C. Kunwar for NMR spectra. A.R, is thankful to CSIR (New Delhi) for the senior research fellowship. Financial assistance from DST is gratefully acknowledged.

Supporting Information Available: Experimental details for the preparation of compounds **2**, **5**, **14**, and **15** and copies of ^{1}H and ^{13}C NMR data of all reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034157W