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SYNTHESIS OF CEREBROSIDE B_{1b} WITH ANTIULCEROGENIC ACTIVITY II[1]. TOTAL SYNTHESIS AND DETERMINATION OF ABSOLUTE CONFIGURATION OF CEREBROSIDE B_{1b} AND ITS STEREOISOMERS

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Abstract: First total synthesis of optically active cerebroside B_{1b} (**1b**) is described. The absolute configuration of **1b** was determined to be (2S,3R,4E,8Z,2'R)-1-O-(ß-D-glucopyranosyl)-N-(2'-hydroxyhexadecanoyl)-4,8-sphingadienine.

Several total syntheses of the cerebrosides have been developed[2a),4)] since Shapiro and Flowers reported the first total synthesis of a cerebroside in 1961[3)]. In the preceding paper[1)], we reported the synthesis of the ceramide **5**, the aglycone of **1b**, and three other diastereomeric ceramides **6**, **7**, and **8** from **2** with **3** or **4**, respectively (Chart 1). We report here a full detail of the total synthesis of optically active cerebroside B_{1b} (**1b**)[5)] and its diastereomers. For the determination of the absolute configuration of **1b**, we planned to identify the derivatives **32**, **33** from a synthetic intermediate with that derived from the natural sphingosine, which is commercially available and the absolute configuration has been known.

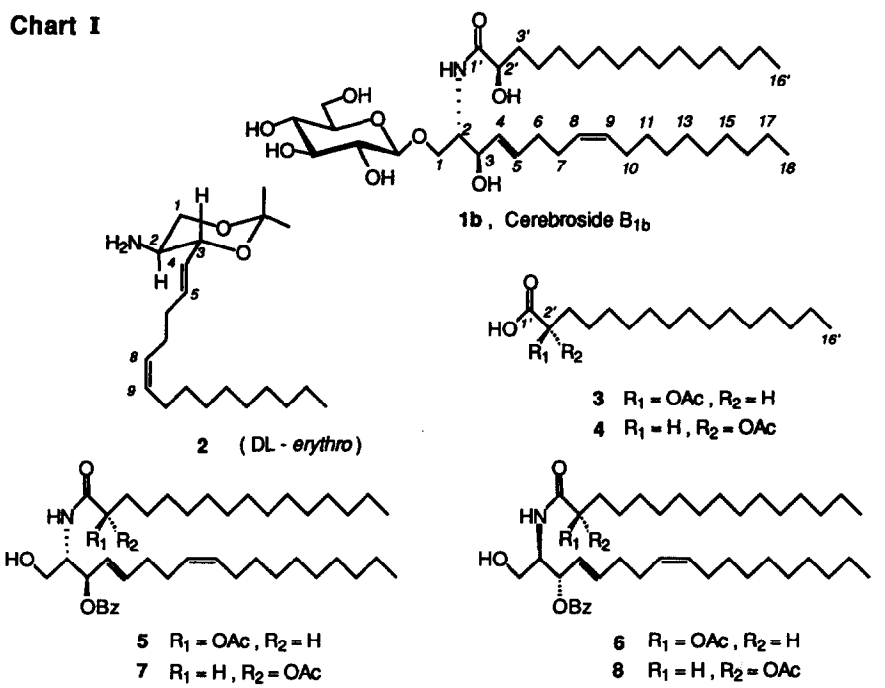
In preference to the total synthesis of **1b**, the glycosylation of the N-palmitoyl derivative **13**, which was prepared in a similar manner described in the preceding paper[1)], was investigated (Scheme I). Thus, the racemic-amine **2** was condensed with palmitoyl chloride **9** (1.0 equiv) in the presence of triethylamine in CH_2Cl_2 to give the ceramide **10** in 98% yield. Deacetonization of **10** in the presence of pyridinium p-toluenesulfonate (PPTS) in MeOH gave **11** in 90% yield. Subsequent tritylation of **11** with trityl chloride (1.2 equiv) in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine in CH_2Cl_2 gave **12** in 74% yield accompanied with a 17% yield of the recovered **11**. Benzoylation of **12** with benzoyl chloride in pyridine followed by detritylation with p-toluenesulfonic acid (TsOH) in MeOH-CH_2Cl_2 (1 : 1) afforded the 1-O-unprotected ceramide **13** in 92% yield.

ß-Glycosylation of **13** with O-(2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl)-trichloacetimidate **14** (2.5 equiv) in CH_2Cl_2 in the presence

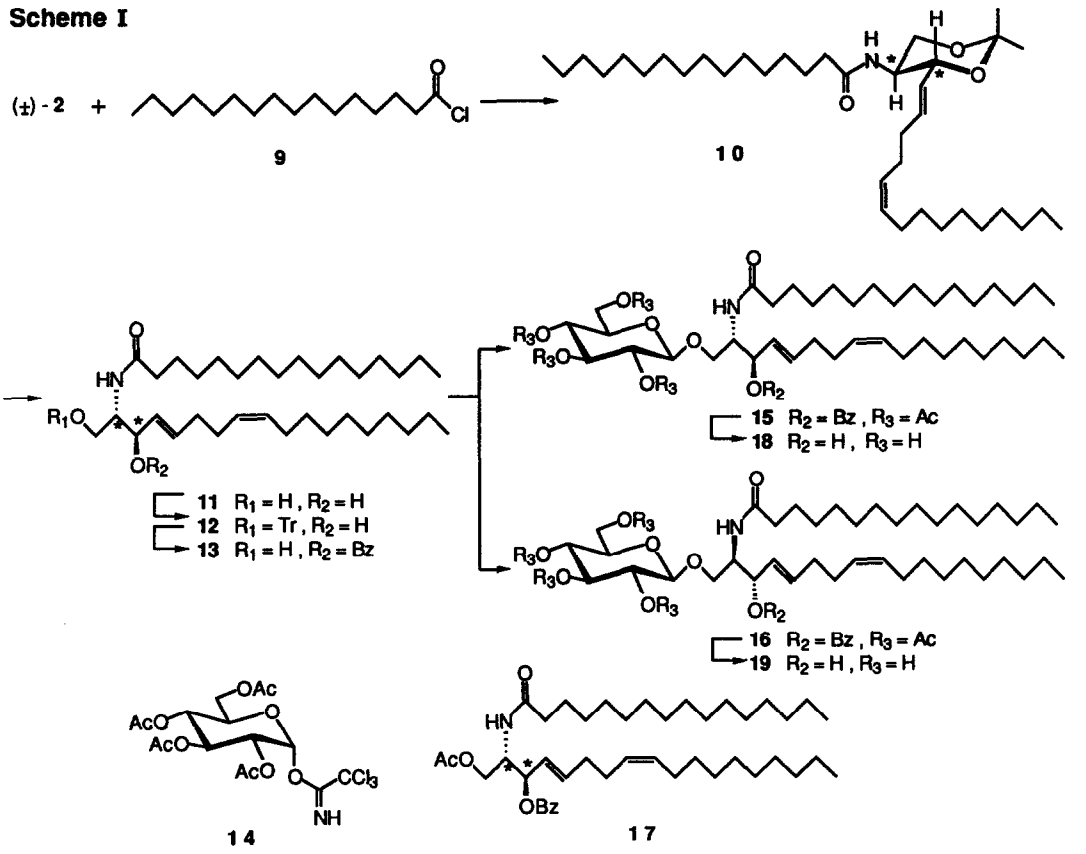
of BF_3-etherate (2.0 equiv) and molecular sieves 4A according to the method of Schmidt[6] gave the protected cerebrosides 15 and 16 (~78%) accompanied with some impurities derived from the imidate and a 22% yield of the acetylated byproduct 17. Despite only small differences in the R_f values, the separation of the diastereomers 15 and 16 could be realized by silica gel flash column chromatography. Stereochemistry of 15 and 16 was deduced to be D-erythro (2S, 3R) and L-erythro (2R, 3S), respectively, according to the report (tlc behavior) of Schmidt[4b]. Subsequent deprotection of 15 and 16 was performed with a catalytic amount of NaOMe in MeOH at room temperature but surprisingly, secondary benzoate resisted methanolysis. Complete deprotection of 15 and 16 was accomplished with excess NaOMe to afford the cerebrosides 18 and 19 in 84% and 60% yields, respectively.

Encouraged by these preliminary result, we carried out similar glycosylation and deprotection of four diastereomeric ceramides 5, 6, 7, and 8, which were prepared in the preceding paper[1] (Scheme II). Similar treatment of 5 with the imidate 14 (2.2 equiv) in CH_2Cl_2 in the presence of BF_3-etherate (2.2 equiv) and molecular sieves 4A gave 20 as the main product accompanied with a small amount of the acetylated compound 21. Complete deprotection of 20 with NaOMe (excess) in MeOH gave the cerebroside **1b** (mp 183°C, $[\alpha]_D$ +4.6°) in 57% yield from 5.

Chart I



Scheme I



Likewise, ceramides 6, 7, and 8 were converted to the corresponding cerebrosides 24 (55%, mp 149°C, $[\alpha]_D$ +1.7°), 27 (57%, mp 151°C, $[\alpha]_D$ -14.7°), and 30 (57%, mp 178°C, $[\alpha]_D$ -18.7°) via the protected cerebrosides 22, 25, and 28, respectively. During the glycosylation of 6, 7, and 8, the corresponding acetates 23, 26, and 29 were obtained as the minor product.

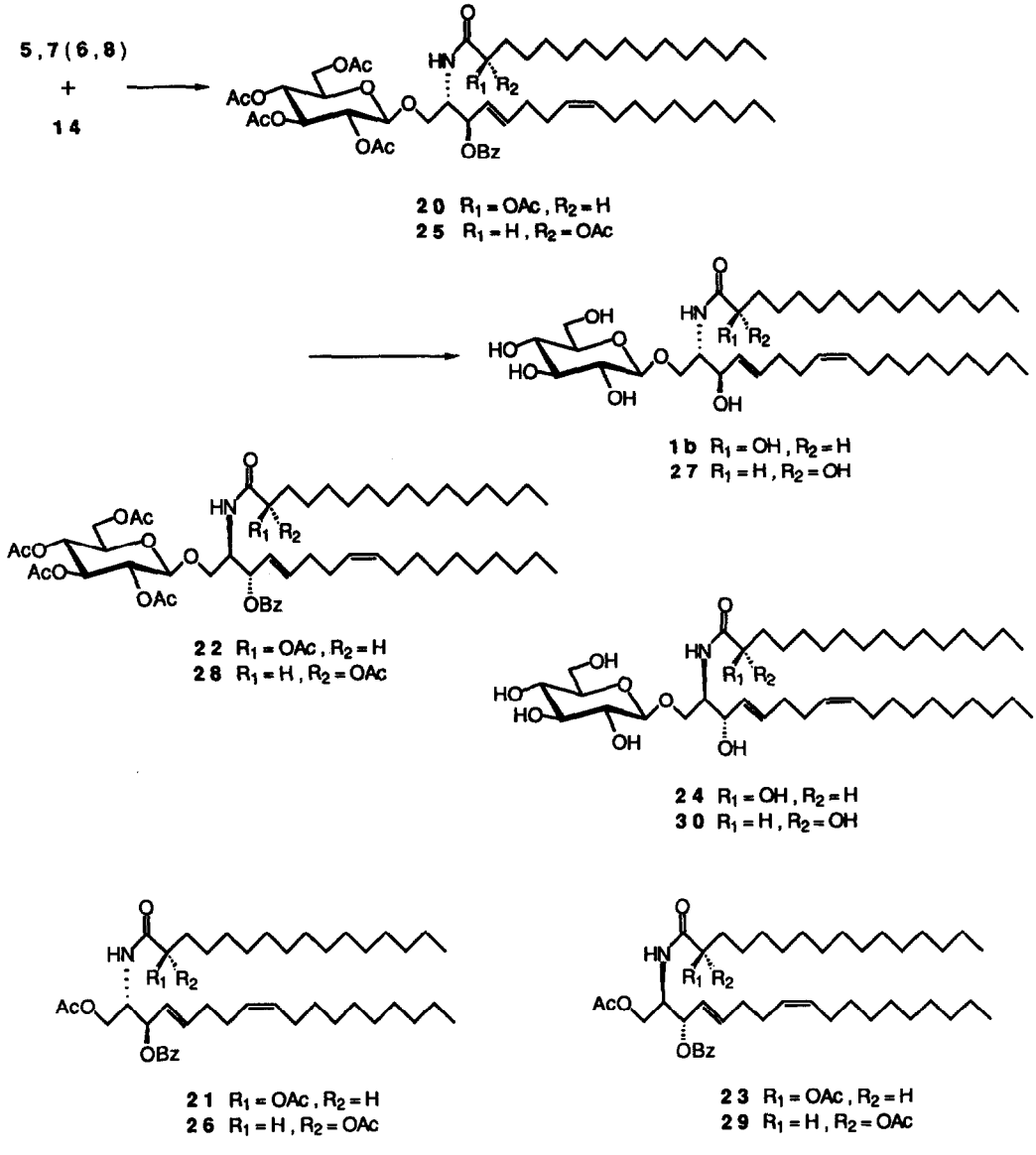
The cerebroside **1b** among four diastereomers was completely identical with the natural cerebroside B_{1b}[5] in all respects (mp, IR, Mass, and ^{1}H-NMR spectra, chromatographic mobility) (see Experimental). The purity of **1b** was assessed by the HPLC[7], which showed two peaks in the ratio of 92 : 8. The major and minor peaks were corresponded to those of the natural cereabroside B_{1b} (**1b**) and B_{1a} (**1a**)(8E isomer)[1], respectively. The contamination of **1a** was derived from Wittig reaction for preparation of tetradec-4(Z)-enol, which was described in detail in the preceding paper[1].

In order to elucidate the absolute configuration of **1b**, the synthetic intermediate 31 was hydrogenated over PtO_2 in MeOH followed by detritylation in the presence of p-toluenesulfonic acid in MeOH-CH_2Cl_2 (1 : 1) to give the

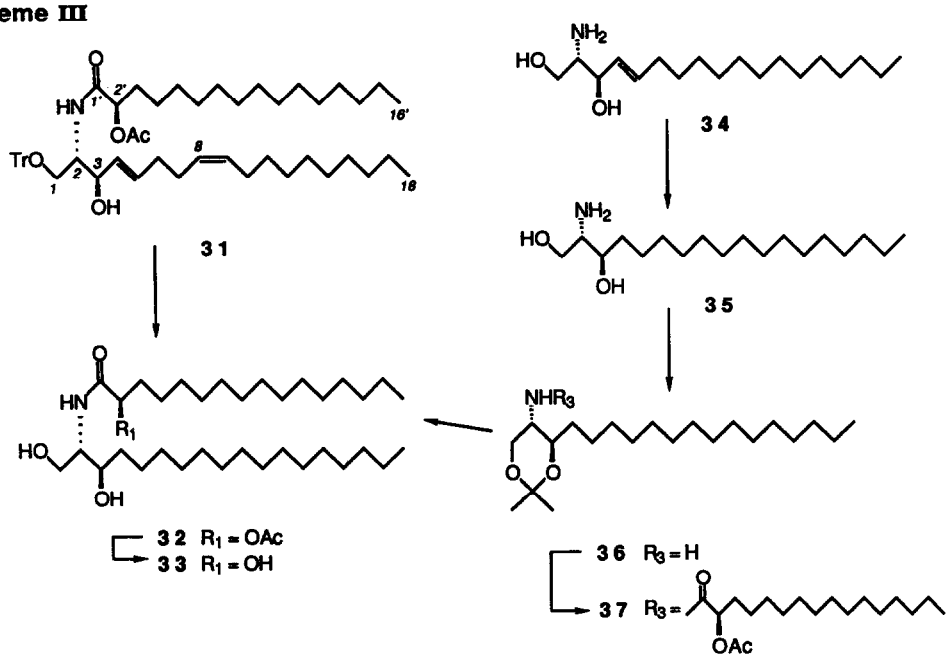
tetrahydro derivative 32 ($[\alpha]_D$ +11.3°) in 82% yield. Deacetylation of 32 with K_2CO_3 in MeOH afforded the ceramide 33 (mp 121.5-124°C, $[\alpha]_D$ +19.6°) in 86% yield (Scheme III).

On the other hand, hydrogenation of the natural sphingosine[8] 34 with PtO_2 in MeOH gave 35 in 98% yield. Acetonization of 35 with 2, 2-dimethoxypropane in the presence of (±)-10-camphorsulfonic acid gave 36 in 68% yield. Condensation of 36 with D(R)-α-acetoxypalmitic acid 3[9] in the presence of DCC and 1-hydroxybenzotriazole in CH_2Cl_2 gave the protected

Scheme II



Scheme III



ceramide 37 in 96% yield. Deacetonization of 37 in the presence of p-toluenesulfonic acid in MeOH-CH_2Cl_2 (1 : 1) gave 32 ($[\alpha]_D$ +11.9°) in 81% yield. Direct condensation of 35 with D(R)-3 in a similar manner also gave 32 in good yield, but the purification of the product 32 was difficult due to the contamination of dicyclohexylurea. Deacetylation of 32 with K_2CO_3 in MeOH afforded 33 (mp 121.5-124°C, $[\alpha]_D$ +19.6°) in 92% yield. Ceramides 32 and 33 thus obtained were completely identified with the synthetic specimens obtained as above, demonstrating that cerebroside B_{1b} (1b) has the same absolute configuration with natural sphingosine. In conclusion, the total synthesis of optically active cerebroside B_{1b} (1b) was achieved and the absolute configuration of which was determined to be (2S,3R,4E,8Z,2'R)-1-O-(ß-D-glucopyranosyl)-N-(2'-hydroxyhexadecanoyl)-4,8-shingadienine [(2S,3R)-1-O-ß-D-glucopyranosyl-N-2'-hydroxypalmitoyl-sphinga-4E,8Z-dienine)]. Further extension of the present method to the synthesis of cerebroside B_{1a} (1a) is in progress.

Experimental

Melting points were determined with a Yamato MP-21 or a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were obtained with an Analect FX-6200 FT-IR spectrophotometer. Mass spectra (MS) were recorded on a JEOL JMS-HX 100 mass spectrometer. ^{1}H-NMR spectra were recorded at 100 MHz

with a JEOL FX-100S, at 200 MHz with a JEOL JNM-FX 200, at 270 MHz with a JEOL JNM FX-270 or a JEOL GX-270, and at 400 MHz with a JEOL JNM-GSX 400 spectrometer. All chemical shifts are reported downfield from an internal Me_4Si standard and given as δ values (ppm). Optical rotations were recorded with an Union PM-201 automatic digital polarimeter. Elemental analyses were performed on a Perkin-Elmer 240 C, H, and N analyzer. Unless otherwise noted, IR spectra (ν in cm^{-1}) refer to KBr disks and NMR spectra to solutions in $CDCl_3$.

Condensation of 2 with palmitoyl chloride (9) to 10. To a stirred solution of **2** (1.44g, 4.27 mmol) and triethylamine (0.60 g, 5.93 mmol) in CH_2Cl_2 (20 ml) was added palmitoyl chloride **9** (1.17g, 4.26 mmol) under ice-cooling and the mixture was stirred for 30 min at the same temperature. The reaction mixture was diluted with AcOEt, washed with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless oily residue (2.64 g), which was purified by silica gel column chromatography (80 g; toluene : AcOEt = 4 : 1) to give **10** (2.40 g, 98%) as colorless waxy crystals, mp 37-9°C. IR 3280, 2990, 2920, 2850, 1640, 1550, 1460, 1375, 1260, 1220, 1200, 1160, 1120, 1085, 1025, 960, 870, 720; EIMS 575 (M^+), 560, 518, 281, 44 (bace peak), 43; ^{1}H-NMR (100 MHz), 0.88 (6H, t, C_{18}-H and C'_{16}-H), 1.0-1.7 (40H, m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 1.42 (3H, s, CH_3), 1.49 (3H, s, CH_3), 1.8-2.2 (8H, m, C_6-H, C_7-H, C_{10}-H, and C'_2-H), 3.5-4.2 (4H, m, C_1-H, C_2-H, and C_3-H), 5.22 (1H, d, J=7.0 Hz, NH, exch), 5.3-5.6 (3H, m, C_4-H, C_8-H, and C_9-H), 5.78 (1H, m, C_5-H).

Deacetonization of 10 to 11. A solution of **10** (2.40 g, 4.17 mmol) and pyridinium p-toluenesulfonate (PPTS) (0.50 g, 1.95 mmol) in MeOH (50 ml) was stirred for 3 days at room temperature under argon atmosphere. Evaporation of the solvent gave a residue, which was dissolved in $CHCl_3$. The solution was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless waxy solid (2.34 g), which was purified by silica gel column chromatography (70g; toluene : AcOEt = 1 : 1) to give **11** (2.01 g, 90%) as colorless waxy crystals. Recrystallization from ether-hexane afforded colorless waxy crystals **11**, mp 73-74°C. IR 3370br, 3280, 2940, 2900, 2830, 1630, 1540, 1460, 1370, 1250, 1040, 950, 710; EIMS 535(M^+), 517, 298, 281, 60(base peak), 43; ^{1}H-NMR (100 MHz) 0.88 (6H, t, C_{18}-H and C'_{16}-H), 1.26 (38H, m of s-like) and 1.63 (2H, m)(C_{11}-H ~ C_{17} and C'_3-H ~ C'_{15}-H), 1.8-2.3 (8H, m, C_6-H, C_7-H, C_{10}-H, and C'_2-H), 2.9-3.1 (2H, m, OH, exch), 3.6-4.0 (3H, m, C_1-H and C_2-H), 4.31 (1H, m, C_3-H; t-like after D_2O addition), 5.3-5.5 (2H, m, C_8-H and C_9-H), 5.53 (1H, dd, J=15.4, 5.6 Hz, C_4-

H), 5.81 (1H, m, C_5-H), 6.29 (1H, d, J=7.0 Hz, NH, exch). Anal. Calcd for $C_{34}H_{65}NO_3$: C, 76.20; H, 12.23; N, 2.61. Found : C, 76.46; H, 12.51; N, 2.57.

Tritylation of 11 to 12. A solution of 11 (1.14 g, 2.13 mmol), trityl chloride (0.72 g, 2.58 mmol), 4-dimethylaminopyridine (DMAP)(0.06 g, 0.491 mmol), and triethylamine (1.5 ml, 10.8 mmol) in CH_2Cl_2 (15 ml) was stirred for 16.5 h at room temperature under argon atmosphere. The reaction mixture was diluted with $CHCl_3$, washed succesively with water, saturated NH_4Cl soution, water, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale yellow caramel (2.39 g), which was column chromatographed on silica gel (90 g). The first eluate, with toluene-AcOEt (10 : 1), gave 12 (1.23 g, 74%) as colorless waxy crystals. The second eluate, with toluene-AcOEt (1 : 2), gave the recovered 11 (0.19 g, 17%) as colorless waxy crystals.

1-O-unprotected ceramide (13). To a stirred solution of 12 (753 mg, 0.968 mmol) in pyridine (10 ml) was added benzoyl chloride (280 mg, 1.99 mmol) and the mixture was stirred for 2.5 days at room temperature. The reaction mixture was evaporated to give a residue, which was dissolved in AcOEt. The solution was washed with water (x2) and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a slightly yellow caramel (1.11 g), which was purified by silica gel column chromatography (30 g; toluene : AcOEt = 20 : 1). The obtained colorless caramel (973 mg) was dissolved in MeOH-CH_2Cl_2 (20 ml, 1 : 1 by vol). To this solution was added p-toluenesulfonic acid (monohydrate) (190 mg, 1.00 mmol) and the resulting mixture was stirred for 100 min at room temperature. The reaction mixture was diluted with CH_2Cl_2, washed successively with saturated $NaHCO_3$ solution, water, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless residue, which was purified by silica gel column chromatography (35 g; toluene : AcOEt = 3 : 2) to give 13 (567 mg, 92%) as colorless waxy crystals. Recrystallization from hexane afforded colorless fine needles 13, mp 59-61°C. IR 3420br, 3320, 2925, 2860, 1710, 1640, 1550, 1465, 1450, 1375, 1310, 1270, 1170, 1110, 1065, 980, 705; EIMS 639 (M^+), 517, 280, 250, 122, 105, 69, 60, 43 (base peak); ^{1}H-MNR (100 MHz) 0.88 (6H, t, C_{18}-H and C'_{16}-H), 1.25 (40H, s-like m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 1.8-2.3 (8H, m, C_6-H, C_7-H, C_{10}-H, and C'_2-H), 2.98 (1H, m, OH, exch), 3.72 (2H, m, C_1-H; d after D_2O addition), 4.28 (1H, m, C_2-H; quintet-like after D_2O addition), 5.21-5.81 (5H, m, C_3-H, C_4-H, C_5-H, C_8-H, and C_9-H), 6.09 (1H, d, J=9.0 Hz, NH, exch), 7.35-7.68 (3H, m, arom H), 7.99-8.10 (2H, m, arom H). Anal. Calcd. for $C_{41}H_{69}NO_4$: C, 76.94; H, 10.87; N, 2.19. Found : c, 77.07; H, 10.99; N, 2.21.

Glycosylation of 13 to 15 and 16. To a mixture of the ceramide **13** (100 mg, 0.156 mmol), the imidate **14**[6] (190 mg, 0.386 mmol), and molecular sieves 4A (0.50 g) was added CH_2Cl_2 (4 ml) via syringe under argon atmosphere and the mixture was cooled in an ice bath. To this mixture was added dropwise a solution of BF_3-etherate (0.04 ml, 0.317 mmol) in CH_2Cl_2 (1 ml) via syringe and the mixture was stirred for 1 h at the same temperature and for 4 h at room temperature. To the mixture was added saturated $NaHCO_3$ solution (1 ml) and the resulting mixture was filtered and washed with $CHCl_3$. The filtrate and washings were washed successively with saturated $NaHCO_3$ solution, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (280 mg), which was column chromatographed on silica gel (25 g, toluene : acetone = 10 : 1). The first eluate gave **17** (23 mg, 22%) as colorless waxy crystals. The second eluate gave the mixture of **15** and **16** (143 mg) as a colorless waxy solid, which was rechromatographed on silica gel with flash column (30 g; toluene : acetone = 10 :1). The first eluate gave **15** (40 mg) as a colorless waxy solid. The second eluate gave the mixture of **15** and **16** (27 mg). The third eluate gave **16** (56 mg) as a colorless waxy solid with some impurities derived from the imidate (a total yield of **15** and **16** was 123 mg; ~78%). **17** : mp 49°C. IR (neat) 3320, 3070, 3010, 2920, 2850, 1730, 1720, 1640, 1600, 1580, 1535, 1460, 1415, 1360, 1340, 1315, 1260, 1220, 1180, 1110, 1070, 1030, 970, 940, 850, 830, 800, 710, 680, 610; EIMS 681 (M^+), 621, 559, 280, 122, 105, (base peak), 57, 43; ^{1}H-NMR (100 MHz) 0.88 (6H, t, C_{18}-H and C'_{16}-H), 1.25 (40H, s-like m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 2.04 (3H, s, CH_3CO), 1.8-2.3 (8H, m, C_6-H, C_7-H, C_{10}-H, and C'_2-H), 4.1-4.4 (2H, m, C_1-H), 4.60 (1H, m, C_2-H), 5.3-5.9 (5H, m, C_3-H, C_4-H, C_5-H, C_8-H, and C_9-H), 5.75 (1H, d, J=9.0 Hz, NH, exch), 7.38-7.67 (3H, m, arom H), 7.98-8.08 (2H, m, arom H). **15** : IR (neat) 3350, 2920, 2850, 1745, 1710, 1650, 1595, 1525, 1460, 1450, 1430, 1370, 1310, 1255, 1220, 1170, 1110, 1040, 960, 905, 840, 800, 710, 685, 600; EIMS 847 (M^+-$PhCO_2H$), 788, 728, 331, 262, 169 (base peak), 122, 109, 105, 43; ^{1}H-NMR (270 MHz) 0.88 (6H, t, J=6.9 Hz, C_{18}-H and C'_{16}-H), 1.26 (40H, s-like m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 1.60 (2H, m, C_6-H, C_7-H, or C_{16}-H), 1.9-2.2 (18H, m, C_6-H, C_7-H, or C_{10}-H, C'_2-H, and CH_3CO x4), 3.64 (1H, m, H-5), 3.71 (1H, dd, J=10.0, 2.7 Hz, C_1-H), 3.91 (1H, dd, J=10.0, 3.6 Hz, C_1-H), 4.07 (1H, dd, J=12.5, 2.4 Hz, H-6), 4.25 (1H, dd, J=12.5, 4.9 Hz, H-6), 4.42 (1H, d, J=7.6 Hz, H-1), 4.49 (1H, m, C_2-H), 5.0-5.2 (3H, m, H-2, H-3, and H-4), 5.25-5.40 (2H, m, C_8-H and C_9-H), 5.40-5.55 (2H, m, C_3-H and C_4-H), 5.80 (1H, d, J=9.2 Hz, NH, exch), 5.79-5.89 (1H, m, C_5-H), 7.46 (2H, m, arom H), 7.59 (1H, m, arom H), 8.02 (2H, m, arom H). **16** : IR (neat) 3370, 3325, 3250, 3190, 2920, 2850, 1740, 1710, 1690, 1650, 1610, 1600, 1530, 1460, 1450, 1430, 1370, 1310, 1250, 1220, 1170, 1105, 1065, 1040, 960, 905, 830, 745, 710, 645, 615, 600; EIMS 847 (M^+-$PhCO_2H$),

788, 728, 331, 262, 169 (base peak), 122, 109, 105, 43; ^{1}H-NMR (270 MHz) 0.88 (6H, t, J=6.9 Hz, C_{18}-H and C'_{16}-H), 1.25 (40H, s-like m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 1.60 (2H, m, C_6-H, C_7-H, or C_{10}-H), 1.9-2.2 (18H, m, C_6-H, C_7-H, or C_{10}-H, C'_2-H, and CH_3CO x4), 3.66 (2H, m, C_1-H and H-5), 3.99 (1H, dd, J=12.2, 2.1 Hz, H-6), 4.03 (1H, dd, J=9.9, 4.0 Hz, C_1-H), 4.13 (1H, dd, J=12.2, 4.9 Hz, H-6), 4.48 (1H, d, J=7.9 Hz, H-1), 4.49 (1H, m, C_2-H), 4.97 (1H, dd, J=9.8, 7.9 Hz, H-2), 5.07 (1H, dd, J= 9.8, 9.8 Hz, H-3 or H-4), 5.17 (1H, dd, J=9.5, 9.5 Hz, H-3, or H-4), 5.2-5.4 (2H, m, C_8-H and C_9-HO, 5.4-5.6 (2H, m, C_3-H and C_4-H), 5.78 (1H, d, J=8.9 Hz, NH, exch), 5.88 (1H, m, C_5-H), 7.45 (2H, m, arom H), 7.57 (1H, m, arom H), 8.02 (2H, m, arom H).

Deprotection of 15 to 18. A solution of **15** (43 mg, 0.0443 mmol) and NaOMe (excess) in MeOH (2 ml) was stirred for 3 h at room temperature and evaporated to give a residue, which was purified by silica gel column chromatography (10g; $CHCl_3$: MeOH = 10 : 1) to afford **18** (26 mg, 84%) as a colorless waxy solid. Recrystallization from MeOH-H_2O gave a colorless solid **18**, mp 158°C. IR 3360br, 2920, 2850, 1645, 1535, 1460, 1430, 1370, 1260, 1160, 1070, 1040, 890, 715, 630; FABMS 698 (MH^+), 680, 519, 280, 262; ^{1}H-NMR (270 MHz) 0.88 (6H, t, J=6.6 Hz, C_{18}-H and C'_{16}-H), 1.25 (40H, s-like m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 1.56 (2H, m, C_6-H, C_7-H, or C_{10}-H), 1.9-2.2 (6H, m, C_6-H, C_7-H, or C_{10}-H and C'_2-H), 3.3-3.6 (5H, m, H-2 H-6), 3.8-4.0 (4H, m, C_1-H, C_2-H, and H-6), 4.07 (1H, m, C_3-H), 4.2-4.5 (3H, m, OH, exch), 4.35 (1H, d, J=7.0 Hz, H-1), 5.11 (1H, br, OH, exch), 5.29-5.42 (3H, m, C_8-H, C_9-H, and OH; ZH after D_2O addition), 5.48 (1H, dd, J=15.2, 6.6 Hz, C_4-H), 5.75 (1H, m, C_5-H), 6.64 (1H, d-like, NH, exch). Anal. Calcd for $C_{40}H_{75}NO_8$: C, 68.83; H, 10.83; N, 2.01. Found : C, 68.69, H, 11.12; N, 1.97.

Deprotection of 16 to 19. A solution of **16** (53 mg, 0.0546 mmol) and NaOMe (excess) in MeOH (2 ml) was stirred for 9 h at room temperature and then evaporated to give a residue, which was purified by silica gel column chromatography (10 g; $CHCl_3$: MeOH = 10 : 1) to afford **19** (23 mg, 60%) as a colorless waxy solid. Recrystallization from MeOH-H_2O gave a colorless solid **19**, mp 159°C. IR 3400br, 2910, 2845, 1640, 1535, 1460, 1370, 1160, 1070, 1040, 715; FABMS 698 (MH^+), 680, 518, 280, 262; ^{1}H-NMR (270 MHz) 0.88 (6H, t, J=6.7 Hz, C_{18}-H and C'_{16}-H), 1.26 (40H, s-like m, C_{11}-H ~ C_{17}-H and C'_3-H ~ C'_{15}-H), 1.60 (2H, m, C_6-H, C_7-H, or C_{10}-H), 1.9-2.2 (6H, m, C_6-H, C_7-H, or C_{10}-H and C'_2-H), 3.25 (1H, br, OH, exch), 3.37 (3H, m, methine-H x2 and exch OH), 3.55 (2H, m, methine-H), 3.72 (1H, dd-like, methine-H or C_1-H), 3.8-4.3 (7H, m, methine-H, C_1-H, and exch OH x2), 4.33 (1H, d, J=7.6 Hz, H-1), 4.47 (1H, br, OH, exch), 5.29-5.43 (2H, m, C_8-H and C_9-H), 5.50 (1H, dd, J=15.5,

6.3 Hz, C_4-H), 5.76 (1H, m, C_5-H), 6.31 (1H, d, J=8.2 Hz, NH, exch). Anal. Calcd for $C_{40}H_{75}NO_8 \cdot 2/3H_2O$: C, 67.66; H, 10.84; N, 1.97. Found : C, 67.66; H, 10.88; N, 1.98.

Glycosylation and deprotection of 5 to 1b. To a mixture of the ceramide 5 (300 mg, 0.430 mmol), the imidate 14[6] (460 mg, 0.934 mmol), and molecular sieves 4A (1.5 g) was added CH_2Cl_2 (9 ml) via syringe under argon atmosphere and the mixture was cooled in an ice bath. To this mixture was added dropwise a solution of BF_3-etherate (0.12 ml, 0.951 mmol) in CH_2Cl_2 (1 ml) via syringe at the same temperature. The cooling bath was removed and the reaction mixture was stirred for 1 h at room temperature. To the mixture was added a saturated $NaHCO_3$ solution (2 ml) and the resulting mixture was filtered and washed with $CHCl_3$. The filtrate and washings were washed successively with saturated $NaHCO_3$ solution, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave an almost colorless caramel (770 mg), which was column chromatographed on silica gel (80 g; toluene : acetone = 10 : 1). The first eluate gave **21** (38 mg, 12%) as a colorless waxy solid. The second eluate gave **20** (452 mg) as a colorless caramel with some impurities derived from the imidate. **21**: $[\alpha]_D^{20}$ +19.5°(c 0.38, $CHCl_3$); IR(Neat) 3340, 3070, 3005, 2960, 2920, 2850, 1740, 1715, 1665, 1660, 1580, 1540, 1490, 1470, 1450, 1430sh, 1375, 1315, 1260, 1235, 1180, 1145, 1115, 1100sh, 1070, 1045, 1030, 970, 940, 890, 850, 810, 715, 690, 645, 605, 560; EIMS 739 (M^+), 680, 618, 105, 43 (base peak); ^{1}H-NMR (200 MHz) 0.88 (6H, t, J=6.4 Hz, C_{18}-H and C_{16}'-H), 1.25 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.79 (2H, m) and 1.9-2.2 (6H, m, C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.02 (3H, s, CH_3CO), 2.12(3H, s, CH_3CO), 4.13 (1H, m, C_1-H), 4.3-4.6 (2H, m, C_1-H and C_2-H), 5.13 (1H, dd, J=7.3, 4.9 Hz, C_2'-H), 5.22-5.63 (4H, m, C_3-H, C_4-H, C_8-H, and C_9-H), 5.91 (1H, m, C_5-H), 6.49 (1H, d, J=8.8 Hz, NH), 7.46 (2H, t-like, J=7.3 Hz), 7.56 (1H, m), and 8.04 (2H, d-like, J=7.3 Hz)(arom H). **20**: FABMS 1028 (MH^+), 906, 443, 331. The protected cerebroside **20** (452 mg) was dissolved in MeOH (6 ml). To this solution was added NaOMe (53 mg) and the mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated to give a residue, which was purified by silica gel column chromatography (35 g; $CHCl_3$: MeOH = 10 : 1) to give **1b** (176 mg, 57%) as a colorless solid; $[\alpha]_D^{20}$ +4.6° (c 1.76, $CHCl_3$: MeOH = 1 : 1 by vol). Recrystallization from MeOH-H_2O gave a clolrless solid **1b** (155 mg); mp 183°C. IR 3400br, 3000, 2960sh, 2920, 2850, 1645, 1530, 1460, 1430, 1375, 1310br, 1260sh, 1160, 1075, 1040sh, 890, 720; FABMS 714 (MH^+), 696, 534, 280, 262; ^{1}H-NMR (400 MHz)($CDCl_3$-CD_3OD, 30 : 25 by vol) 0.89 (6H, t, J=6.9 Hz, C_{18}-H and C_{16}'-H), 1.27 (36H, s-like m) and 1.42 (2H, m)(C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.57 (1H, m), 1.75 (1H, m), 2.02 (2H, q, J=6.6 Hz), and 2.11 (4H, m)(C_6-H, C_7-H, C_{10}-H, and C_3'-H), 3.24 (1H, t, J=8.5 Hz, H-2, H-3, or H-4), 3.31 (1H, m, H-5), 3.41 (2H, t, J=8.5 Hz, H-

2, H-3, or H-4), 3.72 (1H, dd, J=12.0, 5.4 Hz, H-6), 3.75 (1H, dd, J= 10.1, 3.2 Hz, C_1-H), 3.87 (1H, dd, J=12.1, 2.4 Hz, H-6), 4.02 (2H, dd-like m, C_2-H and C_2'-H), 4.08 (1H, dd, J=10.1, 5.7 Hz, C_1-H), 4.14 (1H, t, J=7.3 Hz, C_3-H), 4.28 (1H, d, J=7.8 Hz, H-1), 5.36 (2H, m, C_8H and C_9-H), 5.49 (1H, dd, J=15.4, 7.2 Hz, C_4-H), 5.75 (1H, dt, J=15.4, 6.7 Hz, C_5-H); (400 MHz)(in Pyridine-d_5) 0.87 (6H, t, J=6.8 Hz, C_{18}-H and C_{16}'-H), 1.27 (36H, s-like m) and 1.67-1.85 (2H, m)(C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.98-2.25 (8H, m, C_6-H, C_7-H, C_{10}-H, and C_3'-H), 3.91 (1H, m, H-5; ddd-like after D_2O addition), 4.03 (1H, m, H-2, H-3, or H-4; t, J=8.2 Hz after D_2O addition), 4.22 (2H, m, H-2, H-3, or H-4; t-like after D_2O addition), 4.26 (1H, dd, J=10.4, 3.4 Hz, C_1-H), 4.36 (1H, dt, J=11.5, 5.8 Hz, H-6; dd, J=11.9, 5.5 Hz after D_2O addition), 4.52 (1H, m, H-6; dd, J=11.9, 2.4 Hz after D_2O addition), 4.58 (1H, dt, J=8.0, 4.0 Hz, C_2'-H; dd, J= 8.0, 3.8 Hz after D_2O addition), 4.71 (1H, dd, J=10.5, 5.7 Hz, C_1-H), 4.78 (2H, m, C_2-H and C_3-H), after D_2O addition : 4.77 (1H, t, J=6.1 Hz, C_3-H) and 4.81 (1H, ddd-like, C_2-H) , 4.91 (1H, d, J=7.8 Hz, H-1), 5.49 (2H, t-like m, J=4.7 Hz, C_8-H and C_9-H), 5.93 (1H, dt, J=15.4, 5.6 Hz, C_5-H), 6.01 (1H, dd, J=15.6, 6.0 Hz, C_4-H), 6.35 (1H, br.t, OH, exch), 6.87 (1H, d, J=4.9 Hz, OH, exch), 7.14 (1H, br.s, OH, exch), 7.20 (2H, br.s, OH, exch), 7.63 (1H, d, J=5.0 Hz, OH, exch), 8.36 (1H, d, J=8.4 Hz, NH, exch); (400 MHz)(DMSO-d_6) 0.85 (6H, t, J=6.8 Hz, C_{18}-H and C'$_{16}$-H), 1.23 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C'$_{15}$-H), 1.42 (1H, m, C_3'-H), 1.56 (1H, m, C_3'-H), 1.99 (6H, m, C_6-H, C_7-H, and C_{10}-H), 2.95 (1H, td, J=8.5, 4.4 Hz, H-2; t, J=8.4 Hz after D_2O addition), 3.03 (1H, td, J=9.0, 5.0 Hz, H-4; t, J=9.1 Hz after D_2O addition), 3.07 (1H, dd-like m, J=5.6, 2.0 Hz, H-5), 3.14 (1H, td, J=8.7, 4.9 Hz, H-3; t, J=8.8 Hz after D_2O addition), 3.43 (1H, dt, J=11.9, 6.0 Hz, H-6; dd, J=11.8, 5.8 Hz after D_2O addition), 3.53 (1H, dd, J=10.3, 3.6 Hz, C_1-H), 3.67 (1H, ddd-like, J=11.8, 6.0, 2.0 Hz, H-6; dd, J=11.8, 2.0 Hz after D_2O addition), 3.81 (2H, m, C_2-H and C_2'-H), 3.92 (1H, dd, J=10.3, 5.8 Hz, C_1-H), 4.00 (1H, q, J=6.3 Hz, C_3-H; t, J=7.0 Hz after D_2O addition), 4.12 (1H, d, J=7.8 Hz, H-1), 4.49 (1H, t, J=5.9 Hz, OH, exch), 4.88 (1H, d, J=4.9 Hz, OH, exch), 4.89 (1H, d, J=4.7 Hz, OH, exch), 4.93 (1H, d, J=5.3 Hz, C_3-OH, exch), 4.94 (1H, d, J=4.0 Hz, OH, exch), 5.34 (2H, m, C_8-H and C_9-H), 5.41 (1H, dd, J=15.4, 6.7 Hz, C_4-H), 5.49 (1H, d, J=5.2 Hz, C_2'-OH, exch), 5.59 (1H, dt, J=15.2, 6.3 Hz, C_5-H), 7.38 (1H, d, J=9.2 Hz, NH, exch). Anal. Calcd for $C_{40}H_{75}NO_9 \cdot 3/4H_2O$: C, 66.04; H, 10.60; N, 1.93. Found : C, 66.03; H, 10.75; N, 1.88.

Glycosylation and deprotection of 6 to 24. The mixture of the ceramide **6** (264 mg, 0.378 mmol), the imidate **14** (390 mg, 0.792 m mol), and molecular sives 4A (1.5 g) in CH_2Cl_2 (9 ml) was treated with a solution of BF_3-etherate (0.10 ml, 0.793 mmol) in CH_2Cl_2 (1 ml) in a similar manner mentioned above.

Similar work-up and chromatography gave 22 (344 mg) as a colorless caramel and 23 (49 mg, 18%) as a colorless waxy solid. 23: $[\alpha]_D^{20}$ -1.3° (c 0.49, $CHCl_3$); IR (Neat) 3340, 3330, 3090, 3070, 3010, 2920, 2850, 1740, 1715, 1665, 1600, 1580, 1535, 1490, 1465, 1450, 1430sh, 1370, 1340, 1315, 1260, 1230, 1180, 1110, 1100sh, 1070, 1040, 1030, 970, 935, 920, 890, 850, 800, 770, 710, 685, 670, 650, 600; EIMS 739 (M^+), 617, 105, 43 (base peak); ^{1}H-NMR (200 MHz) 0.88 (6H, t, J=6.6 Hz, C_{18}-H and C_{16}'-H), 1.25 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.79 (2H, m) and 1.9-2.2 (6H, m)(C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.02 (3H, s, CH_3CO), 2.06 (3H, s, CH_3CO), 4.23 (1H, dd, J=11.4, 4.6 Hz, C_1-H), 4.34 (1H, dd, J=11.4, 6.6 Hz, C_1-H), 4.55 (1H, m, C_2-H), 5.11 (1H, t-like, J=6.1 Hz, C_2'-H), 5.2-5.6 (4H, m, C_3-H, C_4-H, C_8-H, and C_9-H), 5.89 (1H, m, C_5-H), 6.50 (1H, d, J=9.3 Hz, NH), 7.46 (2H, t-like, J=7.3 Hz), 7.56 (1H, m), and 8.02 (2H, d-like, J=7.3 Hz)(arom H). 22: FABMS 1028 (MH^+), 906, 331, 262. Similar deprotection of 22 (344 mg) with NaOMe (57 mg) in MeOH (7 ml) and purification gave 24 (149 mg, 55%) as a colorless solid; $[\alpha]_D^{20}$ +1.7° (c 1.49, $CHCl_3$: MeOH = 1 : 1 by vol). Recrystallization from MeOH-H_2O gave a colorless solid 24 (140 mg); mp 149°C. IR 3400br, 3000, 2960sh, 2920, 2850, 1650, 1525, 1460, 1430, 1405, 1370, 1310, 1270br, 1160, 1070, 1030sh, 890, 720; FABMS 714 (MH^+), 696, 535, 280, 262; ^{1}H-NMR (400 MHz)($CDCl_3$-CD_3OD, 30 : 25 by vol) 0.89 (6H, t, J=6.9 Hz, C_{18}-H and C_{16}'-H), 1.27 (37H, m of s-like) and 1.43 (1H, m)(C_{11}-H C_{17}-H and C_4'-H C_{15}'-H), 1.53 (1H, m), 1.81 (1H, m), 2.02 (2H, q, J=6.7 Hz), and 2.10 (4H, m)(C_6-H, C_7-H, C_{10}-H, and C_3'-H), 3.25 (1H, t, J=8.5 Hz, H-2, H-3, or H-4), 3.29 (1H, m, H-5), 3.40 (2H, t-like m, H-2, H-3, or H-4), 3.72 (1H, dd, J=12.3, 5.0 Hz, H-6), 3.83 (1H, dd, J=10.7, 3.2 Hz, C_1-H), 3.87 (1H, dd, J=12.3, 2.5 Hz, H-6), 3.94 (1H, dt, J=7.0, 3.5 Hz, C_2-H), 3.99 (1H, dd, J=8.7, 3.6 Hz, C_2'-H), 4.09 (1H, dd, J=10.8, 3.9 Hz, C_1-H), 4.19 (1H, t, J=6.7 Hz, C_3-H), 4.28 (1H, d, J=7.8 Hz, H-1), 5.37 (2H, m, C_8-H and C_9-H), 5.53 (1H, dd, J=15.4, 7.0 Hz, C_4-H), 5.75 (1H, dt, J=15.4, 6.5 Hz, C_5-H); (400 MHz)(Pyridine-d_5) 0.87 (6H, t, J=6.8 Hz, C_{18}-H and C_{16}'-H), 1.25 (36H, s-like m) and 1.83 (1H, m)(C_{11}-H~ C_{17}-H and C_4'-H ~ C_{15}'-H), 2.03-2.15 (7H, m) and 2.27 (1H, m)(C_6-H, C_7-H, C_{10}-H, and C_3'-H), 3.93 (1H, m, H-5), 4.03 (1H, m, H-2, H-3, or H-4; t, J=8.3 Hz after D_2O addition), 4.20 (2H, m, H-2, H-3, or H-4), after D_2O addition : 4.18 (1H, t, J=8.6 Hz) and 4.22 (1H, t, J=8.4 Hz) , 4.37 (1H, dt, J=11.9, 6.0 Hz, H-6; dd, J=12.1, 5.5 Hz after D_2O addition), 4.43 (1H, dd, J=10.8, 3.4 Hz, C_1-H), 4.57 (2H, m, C_2'-H and H-6), after D_2O addition : 4.54 (1H, dd, J=11.9, 2.0 Hz, H-6) and 4.58 (1H, dd, J=8.4, 3.7 Hz, C_2'-H), 4.63 (1H, dd, J=10.8, 4.6 Hz, C_1-H), 4.82 (2H, m, C_2-H and C_3-H), after D_2O addition : 4.81 (1H, m, C_2-H) and 4.83 (1H, t, J=6.4 Hz, C_3-H) , 4.95 (1H, d, J=7.8 Hz, H-1), 5.46 (2H, t-like m, J=4.7 Hz, C_8-H and C_9-H), 5.93 (1H, dt, J=15.3, 5.8

Hz, C_5-H), 6.04 (1H, dd, J=15.3, 6.0 Hz, C_4-H), 6.26 (1H, t, OH, exch), 6.69 (1H, d, J=5.2 Hz, OH, exch), 7.15 (1H, d, J=4.0 Hz, OH, exch), 7.17 (1H, br.s, OH, exch), 7.28 (1H, d, J=3.8 Hz, OH, exch), 7.56 (1H, d, J=5.8 Hz, OH, exch), 8.44 (1H, d, J=8.4 Hz, NH, exch); (400 MHz)(DMSO-d_6) 0.85 (6H, t, J=6.9 Hz, C_{18}-H and C_{16}'-H), 1.23 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H~~ C_{15}'-H), 1.39 (1H, m, C_3'-H), 1.60 (1H, m, C_3'-H), 1.99 (6H, m, C_6-H, C_7-H, and C_{10}-H), 2.96 (1H, td, J=8.9, 4.4 Hz, H-2, H-3, or H-4 ; t, J=8.3 Hz after D_2O addition), 3.02 (1H, td, J=8.6, 5.1 Hz, H-2, H-3, or H-4; t, J=9.1 Hz after D_2O addition), 3.07 (1H, dd-like m, J=5.8, 1.8 Hz, H-5), 3.13 (1H, td, J=8.7, 4.7 Hz, H-2, H-3, or H-4; t, J=8.8 Hz after D_2O addition), 3.42 (1H, dt, J=11.6, 5.8 Hz, H-6; dd, J=11.8, 6.0 Hz after D_2O addition), 3.66 (1H, ddd, J=11.8, 6.3, 2.0 Hz, H-6; dd, J=11.9, 2.0 Hz after D_2O addition), 3.71 (1H, dd, J=10.5, 4.1 Hz, C_1-H), 3.79 (3H, m, C_1-H, C_2-H, and C_2'-H), 4.02 (1H, q, J=6.4 Hz, C_3-H; t, J=6.4 Hz after D_2O addition), 4.14 (1H, d, J=7.8 Hz, H-1), 4.51 (1H, t, J=6.1 Hz, OH, exch), 4.87 (1H, d, J=5.7 Hz, OH, exch), 4.88 (1H, d, J=5.0 Hz, OH, exch), 4.91 (2H, d, J=4.6 Hz, OH, exch), 5.33 (2H, m, C_8-H and C_9-H), 5.34 (1H, d, J=6.0 Hz, C_2-OH, exch), 5.42 (1H, dd, J=15.6, 6.6 Hz, C_4-H), 5.58 (1H, dt, J=15.3, 6.4 Hz, C_5-H), 7.37 (1H, d, J=8.9 Hz, NH, exch). Anal. Calcd for $C_{40}H_{75}NO_9$: C, 67.28; H, 10.59; N, 1.96. Found : C, 67.31; H, 10.63; N, 1.95.

Glycosylation and deprotection of 7 to 27. The mixture of the ceramide 7 (320mg, 0.458 mmol), the imidate 14 (490 mg, 0.995 mmol), and molecular sieves 4A (1.5 g) in CH_2Cl_2 (9 ml) was treated with a solution of BF_3-etherate (0.13 ml, 1.03 mmol) in CH_2Cl_2 (1 ml) in a similar manner mentioned above. Similar work-up and chromatography gave 25 (447 mg) as a colorless caramel and 26 (59 mg, 17%), $[\alpha]_D^{20}$ +1.3°(c 0.59, $CHCl_3$) as a colorless waxy solid, which was confirmed with 23 by TLC and IR spectrum. 25 : FABMS 1028 (MH^+), 906, 331, 262. Similar deprotection of 25 (447 mg) with NaOMe (65 mg) in MeOH (8 ml) and purification gave 27 (187 mg, 57%) as a colorless solid; $[\alpha]_D^{20}$ -14.7°(c 1.87, $CHCl_3$: MeOH = 1 : 1 by vol). Recrystallization from MeOH-H_2O gave a colorless solid 27 (147 mg); mp 151°C. IR 3360br, 3005, 2960, 2920, 2850, 1650, 1550sh, 1535, 1465, 1430, 1410, 1375, 1310sh, 1270br, 1160, 1075, 1040, 970sh, 910sh, 895, 720, 630-580br; FABMS 714 (MH^+), 696, 534, 280, 262 ; ^{1}H-NMR (400 MHz)($CDCl_3$-CD_3OD, 30 : 25 by vol) 0.89 (6H, t, J=6.9 Hz, C_{18}-H and C_{16}'-H), 1.27 (36H, s-like m) and 1.44 (2H, m)(C_{11}-H ~ C_{17}-H and C_4'-H~ C_{15}'-H), 1.57 (1H, m), 1.78 (1H, m), 2.02 (2H, q, J=6.6 Hz), and 2.11 (4H, m)(C_6-H, C_7 -H, C_{10}-H, and C_3'-H), 3.23 (1H, t, J=7.6 Hz, H-2, H-3, or H-4), 3.30 (1H, m, H-5), 3.39 (2H, m, H-2, H-3, or H-4), 3.73 (2H, m, C_1-H and H-6), 3.88 (1H, dd, J=10.0, 1.5 Hz, H-6), 4.02 (3H, m, C_1-H, C_2-H, and C_2'-H), 4.22 (1H, t, J=5.5 Hz, C_3-H), 4.27 (1H, d, J=7.6 Hz, H-1), 5.37 (2H,

m, C_8-H and C_9-H), 5.51 (1H, dd, J= 15.3, 6.9 Hz, C_4-H), 5.76 (1H, dt, J=15.5, 7.0 Hz, C_5-H); (400 MHz)(Pyridine-d_5) 0.87 (6H, t, J=6.7 Hz, C_{18}-H and C_{16}'-H), 1.25 (36H, s-like m) and 1.68-1.84 (2H, m)(C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 2.03-2.27 (8H, m, C_6-H, C_7-H, C_{10}-H, and C_3'-H), 3.92 (1H, m, H-5; ddd-like after D_2O addition), 4.06 (1H, m, H-2, H-3, or H-4; t, J=8.4 Hz after D_2O addition), 4.24 (2H, m, H-2, H-3, or H-4), after D_2O addition: 4.22 (1H, t, J=6.7 Hz) and 4.24 (1H, t, J=8.4 Hz), 4.31 (1H, dd, J=10.8, 4.1 Hz, C_1-H), 4.37 (1H, dt, J=11.9, 5.7 Hz, H-6; dd, J=11.9, 5.3 Hz after D_2O addition), 4.49 (1H, ddd, H-6; dd, J=11.6, 2.0 Hz, after D_2O addition), 4.59 (1H, dt-like, C_2'-H; dd, J=8.0, 3.8 Hz after D_2O addition), 4.67 (1H, dd, J=10.6, 6.0 Hz, C_1-H), 4.85 (2H, m, C_2-H and C_3-H), 4.96 (1H, d, J=7.6 Hz, H-1), 5.46 (2H, t-like m, J=4.6 Hz, C_8-H and C_9-H), 6.00 (2H, d-like m, J=4.1 Hz, C_4-H and C_5-H), 6.27 (1H, t, J=6.5 Hz, OH, exch), 6.85 (1H, d, J=4.4 Hz, OH, exch), 7.15 (1H, d, J=4.8 Hz, OH, exch), 7.18 (1H, d, J=4.0 Hz, OH, exch), 7.50 (1H, d, J=5.6 Hz, OH, exch), 8.37 (1H, d, J=8.2 Hz, NH, exch); (400 MHz)(DMSO-d_6) 0.85 (6H, t, J=6.9 Hz, C_{18}-H and C_{16}'-H), 1.23 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.41 (1H, m, C_3'-H), 1.57 (1H, m, C_3'-H), 2.01 (6H, m, C_6-H, C_7-H, and C_{10}-H), 2.95 (1H, td, J=8.3, 4.1 Hz, H-2, H-3, or H-4; t, J= 8.4 Hz, after D_2O addition), 3.06 (2H, m, H-2, H-3, or H-4 and H-5), after D_2O addition : 3.04 (1H, t, J=8.9 Hz, H-2, H-3, or H-4) and 3.07 (1H, m, H-5), 3.12 (1H, td, J=8.7, 4.9 Hz, H-2, H-3, or H-4; t, J=9.1 Hz after D_2O addition), 3.44 (1H, dt, J=11.8, 6.0 Hz, H-6), 3.49 (1H, dd, J=10.2, 4.4 Hz, C_1-H), 3.66 (1H, dd, J= 12.2, 6.3 Hz, H-6; dd, J=11.9, 2.0 Hz after D_2O addition), 3.81 (2H, m, C_2-H and C_2'-H), after D_2O addition : 3.80 (1H, dd, J=7.6, 4.2 Hz, C_2'-H) and 3.81 (1H, partially overlapped with C_2'-H peak, C_2-H), 3.88 (1H, dd, J=10.1, 6.0 Hz, C_1-H), 4.05 (1H, q, J= 6.0 Hz, C_3-H; t, J=6.5 Hz after D_2O addition), 4.10 (1H, d, J=7.8 Hz, H-1), 4.47 (1H, t, J=6.0 Hz, OH, exch), 4.88 (1H, d, J=4.7 Hz, OH, exch), 4.90 (1H, d, J=4.7 Hz, OH, exch), 4.93 (1H, d, J=5.5 Hz, OH, exch), 4.95 (1H, d, J=4.7 Hz, OH, exch), 5.29 (1H, d, J=5.8 Hz, C_2'-OH, exch), 5.34 (2H, m, C_8-H and C_9-H), 5.44 (1H, dd, J=15.3, 6.3 Hz, C_4-H), 5.61 (1H, dt, J=15.4, 6.6 Hz, C_5-H), 7.38 (1H, d, J=8.9 Hz, NH, exch). Anal. Calcd for $C_{40}H_{75}NO_9$ 1/2 H_2O : C, 66.45; H, 10.60; N, 1.94. Found : C, 66.58; H, 10.82; N, 1.90.

Glycosylation and deprotction of 8 to 30. The mixture of the ceramide **8** (430 mg, 0.616 mmol), the imidate **14** (660 mg, 1.34 mmol), and molecular sieves 4A (2.0 g) in CH_2Cl_2 (12 ml) was treated with a solution of BF_3-etherate (0.17 ml, 1.35 mmol) in CH_2Cl_2 (1 ml) in a similar manner mentioned above. Similar work-up and chromatography gave **28** (660 mg) as a colorless caramel and **29** (66 mg, 15%), $[\alpha]_D^{20}$ -19.4°(c 0.66, $CHCl_3$) as a colorless waxy solid, which was confirmed with **21** by TLC and IR spectrum. **28**: FABMS 1028 (MH^+), 906, 331,

262. Similar deprotection of **28** (660 mg) with NaOMe (96 mg) in MeOH (8 ml) and purification gave **30** (249 mg, 57%) as a colorless solid; $[\alpha]_D^{20}$ -18.7°(c 2.49, $CHCl_3$: MeOH = 1 : 1 by vol). Recrystallization from MeOH-H_2O gave a colorless solid **30** (209 mg); mp 178°C. IR 3380br, 3005, 2960, 2850, 1645, 1530, 1465, 1430, 1375, 1320, 1285, 1160, 1075, 1040, 970sh, 895, 720, 630br; FABMS 714 (MH^+), 696, 534, 262; ^{1}H-NMR (400 MHz)($CDCl_3$-CD_3OD, 30 : 25 by vol) 0.89 (6H, t, J=6.7 Hz, C_{18}-H and C_{16}'-H), 1.27 (36H, s-like m) and 1.43 (2H, m)(C_{11}-H ~ C_{17} and C_4'-H ~ C_{15}'-H), 1.54 (1H, m), 1.75 (1H, m), 2.02(2H, q, J=6.6 Hz), and 2.10 (4H, m)(C_6-H, C_7-H, C_{10}-H and C_3'-H), 3.25 (1H, t, J=8.2 Hz, H-2, H-3 or H-4), 3.29 (1H, m, H-5), 3.41 (2H, t, J=8.8 Hz, H-2, H-3, H-4), 3.72 (1H, dd, J=12.2, 5.3 Hz, H-6), 3.87 (2H, dd-like, C_1-H and H-6), 3.96 (1H, m, C_2-H), 4.00 (1H, dd, J=8.1, 3.7 Hz, C_2'-H), 4.06 (1H, dd, J=10.4, 4.0 Hz, C_3-H), 4.12 (1H, t, J= 6.4 Hz, C_3-H), 4.27 (1H, d, J=7.8 Hz, H-1), 5.37 (2H, m, C_8-H and C_9-H), 5.51 (1H, dd, J=15.4, 7.3 Hz, C_4-H), 5.75 (1H, dt, J=15.4, 6.3 Hz, C_5-H); (400 MHz)(pyridine-d_5) 0.88 (6H, t, J=6.8 Hz, C_{18}-H and C_{16}'-H), 1.27 (36H, s-like m), 1.74 (1H, m), and 1.81 (1H, m)(C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 2.01-2.26 (8H, m, C_6-H, C_7-H, C_{10}-H, and C_3'-H), 3.92 (1H, m, H-5; ddd after D_2O addition), 4.02 (1H, dt, H-2, H-3 or H-4; t, J=8.3 Hz after D_2O addition), 4.19 (2H, m, H-2, H-3, or H-4), after D_2O addition: 4.16 (1H, t, J=9.1 Hz) and 4.22 (1H, t, J=8.7 Hz) , 4.35 (1H, dt, J=11.6, 5.8 Hz, H-6; dd, J=12.0, 5.6 Hz after D_2O addition), 4.47 (1H, dd, J=10.0, 2.0 Hz, C_1-H), 4.57 (3H, m, C_1-H, C_2'-H, and H-6), after D_2O addition: 4.52 (1H, dd, J=11.7, 2.1 Hz, H-6), 4.57 (1H, dd, J=10.0, 3.0 Hz, C_1-H) , and 4.59 (1H, dd, J=8.1, 3.8 Hz, C_2'-H), 4.79 (2H, m, C_2-H and C_3-H; d-like, J=3.4 Hz after D_2O addition), 4.95 (1H, d, J=7.6 Hz, H-1), 5.49 (2H, t-like m, J=5.7 Hz, C_8-H and C_9-H), 5.92 (1H, dt, J=15.4, 5.8 Hz, C_5-H), 6.03 (1H, dd, J=15.4, 5.6 Hz, C_4-H), 6.45 (1H, t, J=6.4 Hz, OH, exch), 6.73 (1H, d, J=5.2 Hz, OH, exch), 7.14 (1H, d, J=4.1 Hz, OH, exch), 7.18 (1H, d, J=4.0 Hz, OH, exch), 7.32 (1H, d, J= 4.2 Hz, OH, exch), 7.60 (1H, d, J=5.3 Hz, OH, exch), 8.36 (1H, d, J= 8.4 Hz, NH, exch); (400 MHz)(DMSO-d_6) 0.85 (6H, t, J=6.9 Hz, C_{18}-H and C_{16}'-H), 1.23 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.40 (1H, m, C_3'-H), 1.55 (1H, m, C_3'-H), 1.98 (4H, m) and 2.03 (2H, m)(C_6-H, C_7-H, and C_{10}-H), 2.96 (1H, td, J=8.5, 4.3 Hz, H-2, H-3, or H-4; t, J=8.4 Hz after D_2O addition), 3.03 (1H, td, J=8.7, 5.2 Hz, H-2, H-3, or H-4; t, J=9.0 Hz after D_2O addition), 3.08 (1H, dd-like, J=5.7, 2.0 Hz, H-5), 3.13 (1H, td, J=8.8, 4.9 Hz, H-2, H-3, or H-4; t, J=8.7 Hz after D_2O addition), 3.42 (1H, dt, J=11.6, 5.8 Hz, H-6; dd, J=11.9, 6.0 Hz after D_2O addition), 3.66 (1H, ddd, J=12.1, 6.3, 2.0 Hz, H-6; dd, J=12.0, 2.0 Hz after D_2O addition), 3.72-3.81 (4H, m, C_1-H, C_2-H, and C_2'-H), 4.00 (1H, q, J=6.9 Hz, C_3-H; t, J=6.9 Hz after D_2O addition), 4.15 (1H, d, J=7.8 Hz, H-1), 4.54 (1H, t, J=6.0 Hz, OH, exch), 4.87 (1H, d, J=5.6 Hz, OH, exch), 4.88 (1H, d, J=5.0

Hz, OH, exch), 4.90 (1H, d, J=4.9 Hz, OH, exch), 4.96 (1H, d, J= 4.3 Hz, OH, exch), 5.33 (2H, m, C_8-H and C_9-H), 5.39 (1H, dd, J= 15.4, 6.7 Hz, C_4-H), 5.58 (1H, dt, J=15.1, 5.8 Hz, C_5-H), 5.58 (1H, d, J=5.0 Hz, C_2'-OH, exch), 7.35 (1H, d, J=9.0 Hz, NH, exch). Anal Calcd for $C_{40}H_{75}NO_9$ 1/4 H_2O : C, 66.86; H, 10.59; N, 1.95. Found : C, 66.93; H, 10.95; N, 1.95.

Reduction and detritylation of 31 to 32. A solution of the ceramide 31 (130 mg, 0.156 mmol) in MeOH (16 ml) was hydrogenated with PtO_2 (50 mg) under H_2 gas for 110 min. To the reaction mixture was added $CHCl_3$ (10 ml) and then filtered. The filtrate was evaporated to give colorless crystals (130 mg), which were dissolved in CH_2Cl_2-MeOH (10 ml, 1 : 1 by vol). To this solution was added p-toluenesulfonic acid (monohydrate)(30 mg, 0.158 mmol) and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was diluted with $CHCl_3$ (50 ml), washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (130 mg), which was purified by silica gel column chromatography (20 g; $CHCl_3$: MeOH = 40 : 1) to afford 32 (76 mg, 82%) as a colorless solid. $[\alpha]_D^{20}$ +11.3° (c 0.76, $CHCl_3$: MeOH = 1 : 1 by vol).

Deacetylation of 32 to 33. To a solutuon of 32 (76 mg, 0.127 mmol) in MeOH (10 ml) was added K_2CO_3 (170 mg, 1.23 mmol) and the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with $CHCl_3$ (50 ml), washed with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was purified by silica gel column chromatography (20 g; $CHCl_3$: MeOH = 20 : 1) to afford 23 (61 mg, 86%) as a colorless crystalline solid. $[\alpha]_D^{20}$ +20.7° (c 0.61, $CHCl_3$: MeOH = 1 : 1 by vol). Recrystallization from MeOH gave a colorless crystalline powder; mp 121.5-124°C. $[\alpha]_D^{20}$ +19.6°(c 0.32, $CHCl_3$: MeOH = 1 : 1 by vol). IR 3380br, 2955, 2915, 2850, 1645, 1530, 1465, 1130, 1100, 1070, 1040sh, 720; EIMS 555 (M^+), 537, 297, 60 (base peak), 43; ^{1}H-NMR (200 MHz)($CDCl_3$-DMSO-d_6) 0.88 (6H, t, J=6.8 Hz, C_{18}-H and C_{16}'-H), 1.1-1.9 (54H, m, C_4-H ~ C_{17}-H and C_3'-H ~ C_{15}'-H), 3.6-4.1 (7H, m, C_1-H, C_2-H, C_3-H, C_2'-H, C_1-OH, and C_3'-OH), after D_2O addition : 3.60-3.94 (4H, m, C_1-H, C_2-H, and C_3-H) and 4.05 (1H, q, C_2'-H) , 4.33 (1H, d, J=4.9 Hz, C_2'-OH, exch), 7.35 (1H, d, J=7.8 Hz, NH, exch). Anal. Calcd for $C_{34}H_{69}NO_4$: C, 73.46; H, 12.51; N, 2.52. Found : C, 73.67; H, 12.68; N, 2.52.

Catalytic hydrogenation of D-sphingosine (34) to 35. A solution of commercial D-sphingosine[8] (80 mg, 0.267 mmol) in MeOH (15 ml) was hydrogenated with PtO_2 (30 mg) under H_2 gas for 130 min. The reaction mixture was filtered and evaporated to give 35 as a colorless solid (79 mg, 98%).

Acetonization of 35 to 36. A solution of 35 (79 mg, 0.262 mmol) and (+)-10-camphorsulfonic acid (90 mg, 0.387 mmol) in 2,2-dimethoxypropane (15 ml) was refluxed for 1 h and then evaporated to give a residue, which was dissolved

in AcOEt (50 ml). The solution was washed successively with saturated $NaHCO_3$ solution, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a yellow caramel, which was purified by silica gel column chromatography (20 g; $CHCl_3$: MeOH = 40 : 1) to afford **36** (62 mg, 69%) as a colorless caramel.

Condensation of 36 with 2(R)-acetoxypalmitic acid (3) to 37. To a stirred suspension of 2(R)-3[9] (60 mg, 0.191 mmol), DCC (42 mg, 0.204 mmol) and 1-hydroxybenzotriazole (27 mg, 0.200 mmol) in CH_2Cl_2 (6 ml) was added dropwise a solution of **36** (62 mg, 0.182 mmol) in CH_2Cl_2 (4 ml). The reaction mixture was stirred for 1 h at room temperature, passed through Celite, and washed with $CHCl_3$. The filtrate and washings were washed successively with saturated $NaHCO_3$ solution, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (20 g; toluene : AcOEt = 5 : 1) to afford **37** (111 mg, 96%) as a colorless waxy solid.

Deacetonization of 37 to 32. To a solution of **37** (111 mg, 0.174 mmol) in MeOH-CH_2Cl_2 (10 ml, 1 : 1 by vol) was added p-toluenesulfonic acid (monohydrate) (30 mg, 0.158 mmol) and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with $CHCl_3$ (50 ml), washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was purified by silica gel column chromatography (20 g; $CHCl_3$: MeOH = 40 : 1) to afford **32** (88 mg, 85%) as a colorless solid. $[\alpha]_D^{20}$ +11.9°(c 0.88, $CHCl_3$: MeOH = 1 : 1 by vol).

Deacetylation of 32 to 33 (from natural sphingosine). To a solution of **32** (88 mg, 0.147 mmol) in MeOH (10 ml) was added K_2CO_3 (200 mg, 1.45 mmol) and the mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with $CHCl_3$ (50 ml), washed with water and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless solid, which was purified by silica gel column chromatography (20 g; $CHCl_3$: MeOH = 20 : 1) to afford **33** (75 mg, 92%) as a colorless crystalline solid. $[\alpha]_D^{20}$ +20.8° (c 0.75, $CHCl_3$: MeOH = 1 : 1 by vol). Recrystallization from MeOH gave a colorless crystalline powder; mp 121.5-124°C. $[\alpha]_D^{20}$ +19.6°(c 0.36, $CHCl_3$: MeOH = 1 : 1 by vol). Anal. Calcd for $C_{34}H_{69}NO_4$: C, 73.46; H, 12.51; N, 2.52. Found : C, 73.43 ; H, 12.36 ; N, 2.47. This **33** was completely identical with the synthetic one obtained as above by TLC, IR, MS, and ^{1}H-NMR spectra.

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8. Natural sphingosine was purchased from Sigma Chemical Co..
9. See preceding paper and references cited therein.