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SYNTHESIS OF CEREBROSIDE B_{1b} WITH ANTIULCEROGENIC ACTIVITY I. SYNTHESIS OF CERAMIDES WITH OPTICALLY ACTIVE α-HYDROXYPALMITIC ACIDS.

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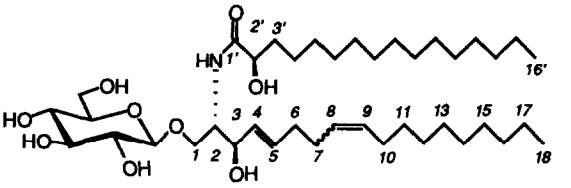
Abstract: Synthesis of four diastereomeric ceramides including the aglycone of cerebroside B_{1b}(**1b**) was described. The crucial step in the synthesis of cerebroside B_{1b} consists in a regio- and stereoselective formation of the erythro-sphingosine moiety by the reaction of dienal 4 with 2-nitroethanol followed by resolution with optically active α-hydroxypalmitic acids.

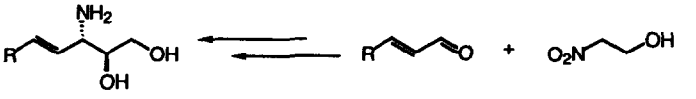
Cerebrosides are important constituents of biological membranes and contain various sugars, fatty acids, and sphingosines as the components.[2] Due to their biological importance, a number of syntheses of sphingosine and ceramides, a hydrophobic part of cerebrosides, have been reported.[3,4] Recently, cerebroside B_{1b}(1b) was isolated from Tetragonia tetragonides together with its (6*E*)-isomer B_{1a}(1a) as a principal constituent, showing antiulcerogenic activity and the structure was determined to be 1-*O*-ß-D-glucopyranosyl-*N*-2'-hydroxypalmitoyl-sphinga-4,6-dienine by Okuyama and Yamazaki in 1983.[5] However, due to a limited amount of the material, the final proof of the absolute configuration of C-2, C-3, and C-2' in 1 remained to be determined. We, therefore, have decided to solve this problem by the total synthesis of 1a and 1b. And the structurally homogeneous material of 1 and its isomers will be useful for the evaluation of the biological and pharmacological studies.

We have recently communicated the first total synthesis of cerebroside B_{1b}[6]. More recently, Schmidt[7] and Mori[8] achieved the total synthesis of cerebroside B_{1a} and B_{1b} by different approaches. We now report the full account of our synthesis of 1b in this and succeeding paper.



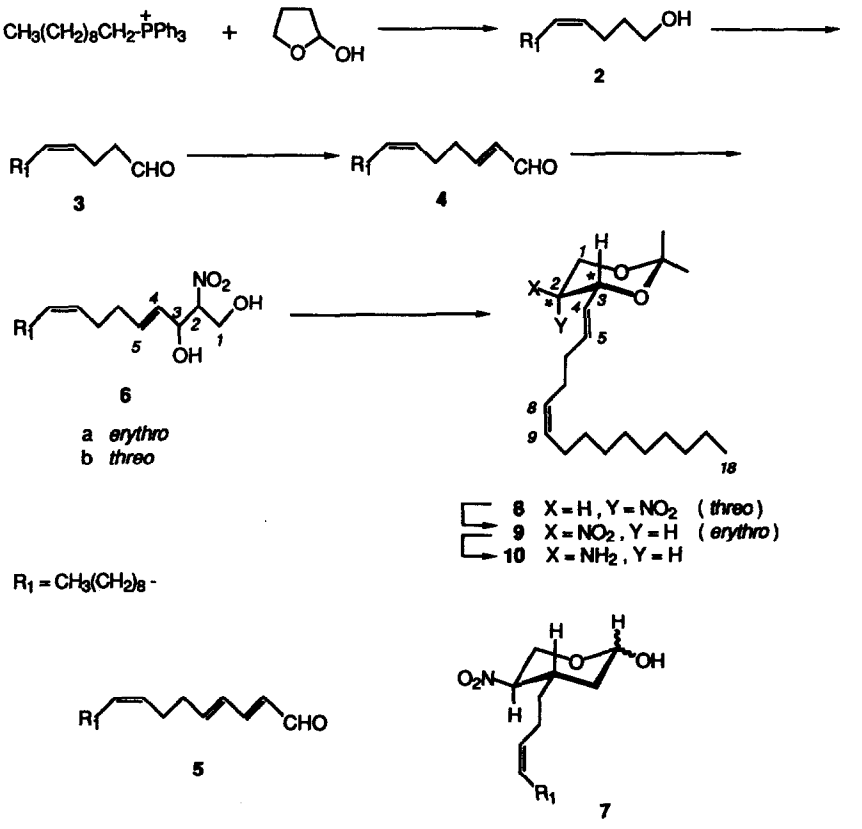
1a , 8E : Cerebroside B_{1a}
1 b , 8Z : Cerebroside B_{1b}

Scheme I



I R = $CH_3(CH_2)_{12}$ -

Scheme II



6

a *erythro*
b *threo*

8 X = H , Y = NO_2 (*threo*)
9 X = NO_2 , Y = H (*erythro*)
10 X = NH_2 , Y = H

R_1 = $CH_3(CH_2)_8$ -

5

7

Results and Discussion

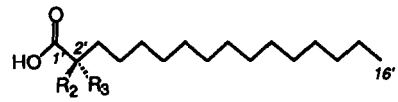
D-Erythro-unsaturated aminodiol moiety of type I is the common structural feature found in sphingolipids. A regio- and stereoselective formation of the unsaturated aminodiol moiety of I is one of the crucial steps in the synthesis of sphingolipids. We have developed an efficient means of construction of the type I moiety by 1,2-addition reaction of 2-nitroethanol to α,ß-unsaturated aldehydes followed by conversion of threo- to erythro-isomer by ancillary stereocontrol[9] (Scheme I) and synthesized sphingosines and ceramides[10].

Our approach to cerebroside B_{1b} (1b) was based on synthesis of racemic erythro-sphingadienine by further application of the above method and conversion of which to optically active ceramides including the aglycone of 1b by acylation with optically active α-hydroxypalmitic acids. Our synthesis of 1b thus began with the preparation of (2E, 6Z)-hexadeca-dienal 4 as follows. The Wittig reaction of γ-butyrolactol with n-decyl triphenylphosphonium bromide in DMSO[11] gave (4Z)-tetradecenol 2 in 76% yield, which was oxidized to the aldehyde 3 in 76% yield with PDC (1.5 equiv) in refluxing CH_2Cl_2. Thus obtained 3 contained the (E)-isomer as the minor product. The ratio of the (Z)-and (E)- isomers in 3 was determined by 400 MHz ^{1}H-NMR spectrum to be approximately 7: 1 by comparing the ratio of C-6 allyl protons as well as the aldehyde proton with those of (4E)-tetradecenal which was prepared by Claisen rearrangement of 3-hydroxy-tetradec-1-ene[12] (4Z : δ 2.04 and δ 9.77 ; 4E : δ 1.97 and δ 9.76). The comparison of the ratio of vinyl carbons (C-4 and C-5) of 2 and 3 by ^{13}C-NMR spectrum indicated the similar ratios, respectively (chemical shifts were shown in Experimental part). The desired (Z)-isomer was produced as the major product, although the selectivity was moderate. Treatment of the crude 3 with formylmethylenetriphenylphosphorane[13] in refluxing toluene afforded the dienoaldehyde 4 in 62% yield accompanied with a 9% yield of the overreacted by-product 5 (Scheme II).

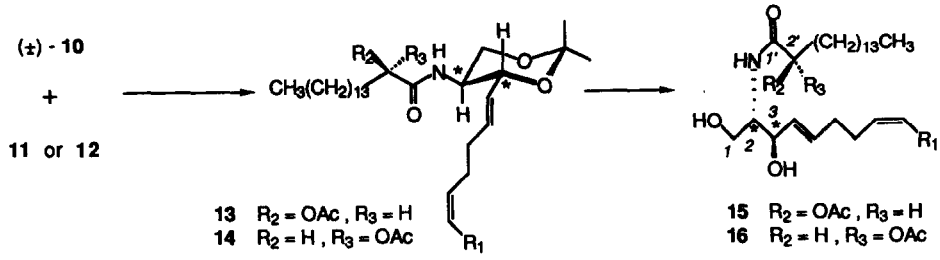
The reaction of 4 with 2-nitroethanol (2.6 equiv) in triethylamine at 0 °C for 5 days proceeded regioselectively to give the desired 1,2-adduct 6 in 72% yield. The 1,4-adduct 7 was accompanied with 6 in 12% yield and a 15% of the starting material was recovered. In order to improve the yield of 6, the reaction of an α,ß-unsaturated aldehyde such as hexadec-2-enal with $THPOCH_2CH_2NO_2$ using BuLi in THF-HMPA at -78 °C was carried out. However, only a low yield of nitrodiols (erythro, 9.7%; threo, 14.7%) was isolated and using other bases (K_2CO_3, KF, pyridine, NaH, LDA, etc.) under several conditions was less satisfactory. The addition of 2-nitroethanol to 4 was

regioselective but not stereoselective, providing a mixture of two diastereoisomers 6 (threo- and erythro-isomers). However, the threo-isomer was readily converted to the erythro-isomer via the acetonides. The diastereomeric mixture 6 was treated with 2, 2-dimethoxypropane in the presence of pyridinium p-toluenesulfonate (PPTS) in acetone to give the acetonides which were readily separated by silica gel column chromatography to the erythro- 9 and threo- 8 isomers in 28% and 34% yields, respectively.

Scheme III

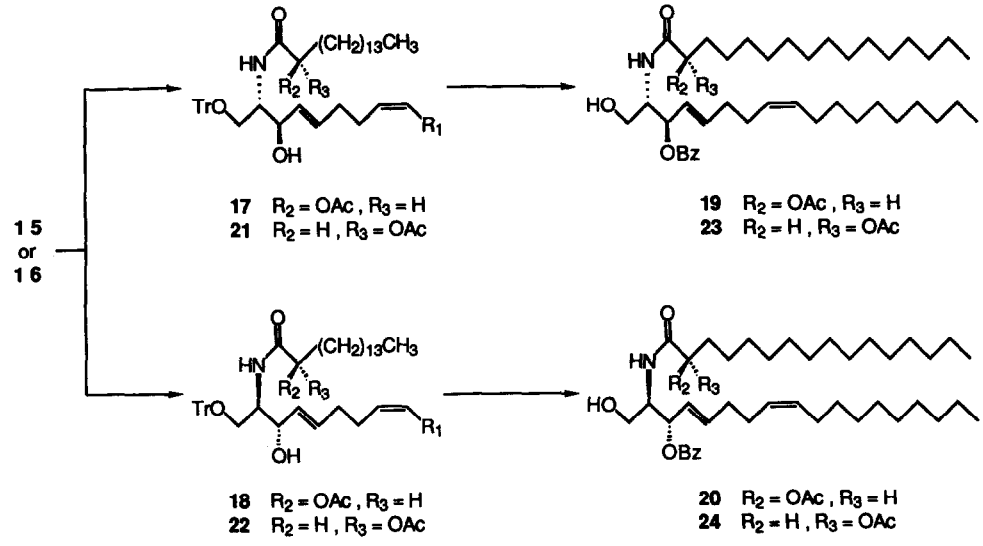


11 $R_2 = OAc, R_3 = H$
12 $R_2 = H, R_3 = OAc$



13 $R_2 = OAc, R_3 = H$
14 $R_2 = H, R_3 = OAc$

15 $R_2 = OAc, R_3 = H$
16 $R_2 = H, R_3 = OAc$



17 $R_2 = OAc, R_3 = H$
21 $R_2 = H, R_3 = OAc$

19 $R_2 = OAc, R_3 = H$
23 $R_2 = H, R_3 = OAc$

18 $R_2 = OAc, R_3 = H$
22 $R_2 = H, R_3 = OAc$

20 $R_2 = OAc, R_3 = H$
24 $R_2 = H, R_3 = OAc$

Refluxing the threo- isomer 8 in triethylamine resulted in the thermodynamically stable erythro-isomer 9 in excellent yield (93%). Acetonization of the crude 6 followed by epimerization with Et_3N, without separating the acetonides, afforded the erythro-acetonide 9 in 51% yield.

Reduction of the nitro group of 9 with aluminium amalgam or $LiAlH_4$ in THF gave the erythro-amine 10 in 79% or 81% yield, respectively (Scheme II). Condensation of 10 with D(R)-α-acetoxypalmitic acid 11, which was prepared by optical resolution of α-hydroxy palmitic acid according to Karlsson's method[14), 15)] followed by acetylation, in the presence of DCC and 1-hydroxybenzotriazole in CH_2Cl_2 gave the corresponding ceramide 13 as a mixture of two diastereoisomers in 98% yield. Deacetonization of 13 in the presence of PPTS in MeOH gave the diol 15 as a mixture of two diastereomers in 92% yield. Separation of both 13 and 15 into their diastereoisomers by column chromatography was rather difficult[16)], but the 1-O-tritylated products were readily separated. Thus, tritylation of 15 with trityl chloride (2 equiv) in the presence of 4-dimethylaminopyridine (DMAP) and triethylamine in CH_2Cl_2 followed by silica gel column chromatography gave 17 (34%, $[\alpha]_D$ +3.5°), 18 (29%, $[\alpha]_D$ +5.7°), and 15 was recovered in 30% yield. Benzoylation of 17 with benzoyl chloride in pyridine followed by detritylation in the presence of p-toluene sulfonic acid in MeOH-CH_2CH_2 (1 : 1) gave the 1-O-unprotected ceramide 19 ($[\alpha]_D$ +36.4°) in 80% yield. Likewise, benzoylation and detritylation of 18 gave 20 ($[\alpha]_D$ -16.1°) in 80% yield (Scheme III).

An identical sequence using the antipode of 11, 12, gave 23 and 24 (in overall yield of 21% and 26%, respectively.) Thus, the condensation of the erythro-amine 10 with L(S)-12[14),15)] gave the diastereomeric mixture 14 in 99% yield. Deacetonization to 16 (89%) followed by tritylation gave 21 (29%, $[\alpha]_D$ -5.4°), 22 (35%, $[\alpha]_D$ -3.8°), and 26% yield of 16 was recovered. Finally, benzoylation and detritylation of 21 and 22 gave 23 ($[\alpha]_D$ +16.2°) and 24 ($[\alpha]_D$ -35.9°) in 81% and 84% yields, respectively.

In conclusion, four diastereomeric ceramides (19, 20, 23, and 24) were prepared by application of our method which involved the regioselective aldol reaction followed by ancillary stereocontrol. One of four diastereomeric cerebrosides derived from them is expected to be identical with natural cerebroside B_{1b} (1b). The absolute configuration of the synthetic ceramides were not determined in this paper but will be elucidated in the following paper. The total synthesis of cerebroside B_{1b} (1b) and unnatural cerebroside B_{1b} including the determination of the absolute configuration of 1b is reported in detail in the following paper.

Experimental

Melting points were determined with Yanagimoto micro melting point apparatus and is uncorrected. IR spectra were obtained with an Analect FX-6200 FT-IR spectrophotometer. Mass spectra (MS) were recorded on a JEOL JMS-HX 100 and DX-300 mass spectrometers. ^{1}H-NMR spectra were recorded at 200MHz with a JEOL JNM-FX 200 or at 400 MHz with a JEOL JNM-GSX 400 spectrometer. ^{13}C-NMR spectra were recorded at 67.5MHz with a JEOL JNM-FX 270 or a JEOL JNM-GX 270 spectrtometer. 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. Unless otherwise noted, IR spectra (ν in cm^{-1})refer to be neat and NMR spectra to solutions in $CDCl_3$.

γ-Butyrolactol (2-Hydroxytetrahydrofuran). 2,3- Dihydrofuran (97% purity) (50.0 g, 692 mmol) was added dropwise over a 20 min period to a mixture of concentrated HCl (10 ml) and water (100 ml) under ice-cooling. The reaction mixture was stirred for 30 min at the same temperature and then adjusted to pH 8 with 20% aqueous NaOH solution. Excess NaCl was added to this solution. The mixture was extracted with CH_2Cl_2 and the combined extracts were dried over anhydrous $MgSO_4$. Evaporation and distillation gave γ-butyrolactol (37.3 g, 61%) as a colorless liquid: bp 65-68°C/20 mm Hg.

n-Decyl triphenylphosphonium bromide. A solution of n-decyl bromide (44.3 g, 200 mmol) and triphenylphosphine (52.4 g, 200 mmol) in CH_3CN (100 ml) was refluxed for 4 days. Evaporation of the solvent gave a caramel residue, which was suspended with toluene (150 ml) and refluxed for 15 min. After cooling, toluene was decanted. This operation was repeated twice. Subsequently, the residue was suspended with hexane (200 ml) and triturated under heating. Hexane was decanted and the residue was treated similarly with hexane. The obtained residue was evaporated to dryness to give a phosphonium salt (94.5 g, 98%) as a slightly yellow caramel.

2(R)-Acetoxypalmitic acid(11). A solution of 2(R)-hydroxypalmitic acid[14] (mp 93-94°C; $[\alpha]_D^{20}$ -3.9°(1.21, $CHCl_3$) (650 mg, 2.39 mmol) in acetic anhydride (2 ml) and pyridine (10 ml) was stirred for 1 h at room temperature. To this solution was added water (10 ml) and the mixture was stirred for 15 min at room temperature. Then, the mixture was acidified with 10% aqueous HCl solution and extracted with $CHCl_3$. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave

colorless crystals, which were recrystallized from petr.ether to give colorless needles of **11** (735 mg, 98%); mp 59-61°C; $[\alpha]_D^{20}$ +11.8°C(c 1.60, $CHCl_3$); IR (KBr) 3440br, 2920, 2850, 1740, 1725, 1630, 1465, 1435, 1370, 1240, 1130, 1080, 1045, 930, 720.

2(S)-Acetoxypalmitic acid (12). 2(S)-hydroxy palmitic acid[14] (mp 92.5-94°C; $[\alpha]_D^{20}$ +3.6°(c1.20, $CHCl_3$) (730 mg, 2.68 mmol) was acetylated in a similar manner mentioned above. Similar work-up and recrystallization gave colorless needles of **12** (816 mg, 97%); mp 59-61°C. $[\alpha]_D^{20}$ -12.3°C(c 1.52, $CHCl_3$); IR (KBr) 3440br, 2920, 2850, 1740, 1725, 1630, 1465, 1435, 1370, 1240, 1135, 1080, 1045, 930, 720.

Tetradec-4(Z)-enol(2) To a stirred solution of n-decyl triphenylphosphonium bromide (81.5 g, 169 mmol) in DMSO (130 ml) was added dropwise a solution of dimsyl anion, which was prepared from sodium hydride (60% dispersion)(7.08 g, 177 mmol) and DMSO (90 ml), under argon stream and the mixture was stirred for 15 min at room temperature. To this was added dropwise a solution of γ-butyrolactol (6.00 g, 68.1 mmol) in DMSO (10 ml) and the mixture was stirred for 60 mim at room temperature. The reaction mixture was diluted with hexane (500 ml) and quenched with brine (200 ml). The hexane layer was separated and the aqueous layer was extracted with hexane (300 ml). The combined hexane layer was washed with water (100 ml x3) and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (500 g, $CHCl_3$) to give a pale yellow oil (23.0 g). The crude oil was distilled to give **2** (10.9 g, 76%) as a colorless oil: bp 127-128°C/4 mmHg; IR 3325, 3000, 2950, 2920, 2850, 1460, 1430, 1170, 1115, 1060, 755, 715, 690; CIMS 213 (MH^+, 100%), 194; ^{1}H-NMR (400 MHz) 0.88 (3H, t, J=7.0 Hz, C_{14}-H), 1.26 (14H, s-like m, C_7-H ~ C_{13}-H), 1.63 (2H, quintet, J=7.0 Hz, C_2-H), 2.03 (2H, q, J=7.0 Hz, C_3-H or C_6-H), 2.12 (2H, q, J=7.2 Hz, C_3-H or C_6-H), 3.66 (2H, t, J=6.6 Hz, C_1-H), 5.39 (2H, m, C_4-H and C_5-H); ^{13}C-NMR 128.85 and 130.84 (Z: C_4-and C_5-vinyl carbons), 129.40 and 131.30 (E: C_4-and C_5-vinyl carbons).

Tetradec-4(Z)-enal(3). To a solution of **2** (24.7 g, 116 mmol) in CH_2Cl_2 (230 ml) was added PDC (67.0 g, 175 mmol) and the mixture was refluxed for 4 h under argon atmosphere. The reaction mixture was cooled to room temperature, filtered through Celite, and washed successively with CH_2Cl_2. The filtrate and washings were evaporated to give a dark brown residue, which was suspended with hexane and filtered through Celite. Evaporation of the filtrate gave a pale brown oil (22.8 g), which was purified by silica gel

column chromatography (300 g, $CHCl_3$: hexane = 1 : 1) to give 3 (18.7 g, 76%) as a colorless oil: IR 3000, 2950, 2920, 2850, 2710, 1725, 1460, 1405, 1385, 720; EIMS 210 (M^+), 84 (base peak); ^{1}H-NMR (400 MHz) 0.88 (3H, t, J=7.0 Hz, C_{14}-H), 1.27 (14H, s-like m, C_7-H ~ C_{13}-H), 2.04 (2H, q, J=7.0 Hz, C_6-H), 2.37 (2H, q, J=7.0 Hz, C_3-H), 2.48 (2H, m, C_2-H), 5.37 (1H, m, C_4-H or C_5-H), 5.42 (1H, m, C_4-H or C_5-H), 9.77 (1H, t, J=1.7 Hz, CHO); ^{13}C-NMR 127.07 and 131.76 (Z: C_4-and C_5-vinyl carbons), 127.67 and 132.16 (E: C_4-and C_5-vinyl carbons).

Hexadeca-2(E),4(Z)-dienal(4). To a solution of 3 (790 mg, 3.76 mmol) in toluene (40 ml) was added formylmethylenetriphenylphosphorane[10] (1.20 g, 3.94 mmol) and the mixture was refluxed for 15 h. The reaction mixture was evaporated to give a red brown wet solid, which was column chromatographed on silica gel (50 g; $CHCl_3$: hexane = 1 : 1). The first eluate gave 4 (547 mg, 62%) as a slightly yellow oil. The second eluate gave 5 (85 mg, 9%) as a pale yellow oil. 4 : IR 3000, 2920, 2850, 2725, 1690, 1630, 1460, 1130, 970, 720; EIMS 236 (M^+), 70 (base peak); ^{1}H-NMR(200 MHz) 0.88 (3H, t, J=6.8 Hz, C_{16}-H), 1.27 (14H, s-like m, C_9-H C_{15}-H), 2.01 (2H, m) and 2.19-2.42 (4H, m)(C_4-H, C_5-H, and C_8-H), 5.39 (2H, m, C_6-H and C_7-H), 6.13 (1H, ddt, J=15.6, 7.8, 1.5Hz, C_2-H), 6.85 (1H, dt, J=15.6, J=6.8 Hz, C_3-H), 9.50 (1H, d, J=7.8 Hz, CHO). 5 : IR 3000, 2920, 2845, 1680, 1635, 1610, 1460, 1150, 1110, 1010, 980, 720; EIMS 262 (M^+), 55 (base peak); ^{1}H-NMR (200 MHz) 0.88 (3H, t, J=6.6 Hz, C_{18}-H), 1.27 (14H, s-like m, C_{11}-H ~ C_{17}-H), 2.02 (2H, m) and 2.19-2.45 (4H, m) (C_6-H, C_7-H, and C_{10}-H), 5.38 (2H, m, C_8-H and C_9-H), 6.08 (1H, dd, J=15.1 ,7.8 Hz, C_2-H), 6.29 (2H, m, C_4-H and C_5-H), 7.07 (1H, dd, J=15.1, 10.3 Hz, C_3-H), 9.54 (1H, d, J=7.8 Hz, CHO).

The reaction of 4 with 2-nitroethanol --- the mixture of (±)-threo-and erythro-2-nitro-octadeca-4(E),8(Z)-diene-1,3-diol(6). Triethylamine (12 ml) was added to a mixture of 4 (1.20 g, 5.08 mmol) and 2-nitroethanol (1.20 g, 13.2 mmol). The reaction mixture was stirred for 8 h with ice-cooling under argon atmosphere and then stored for 5 days in a refrigerator. The reaction mixture poured into an ice-cooled mixtuer of ether (30 ml) and 5% aqueous HCl solution (30 ml). The ether layer was separated and the aqueous layer was extracted with ether (30 ml). The combined ether layer was washed successively with water, saturated $NaHCO_3$ solution, water, and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale brown oily residue (1.92 g), which was column chromatographed on silica gel (60 g; toluene : AcOEt = 3 : 1). The first eluate gave the recovered aldehyde 4 (0.18 g, 15%) as a pale yellow oil. The second eluate gave the Michael adduct

7 (0.20 g, 12%) as a pale yellow viscous oil. The third eluate gave the mixture of (±)-threo-and erythro-nitro diols 6 (1.20 g, 72%) as a pale yellow oil. 6 :IR 3400br, 3000, 2920, 2850, 1550, 1460, 1360, 1050, 970; FABMS 350 $(M+Na)^+$, 109; ^{1}H-NMR (200 MHz) 0.88 (3H, t, J=6.6 Hz, C_{18}-H), 1.27 (14H, m, C_{11}-H ~ C_{17}-H), 1.60 (1H, br.s, OH, exch), 2.01 (2H, m) and 2.13 (4H, m)(C_6-H, C_7-H, and C_{10}-H), 2.30 (1H, m, OH, exch), 4.0-4.1 (2H, m, C_1-H), 4.5-4.6 (2H, m, C_2-H and C_3-H), 5.3-5.6 (3H, m, C_4-H, C_8-H, and C_9-H), 5.86 (1H, m, C_5-H). 7: IR 3420br, 3005, 2955, 2920, 2850, 1550, 1460, 1390, 1350, 1250, 1120, 1075, 1020, 980, 920, 890, 860, 820, 780, 755, 720; EIMS 327 (M^+), 41 (base peak); ^{1}H-NMR (200 MHz) 0.88 (3H, t , J=6.4 Hz, C_{18}-H), 1.27 (16H, s-like m, C_{11}-H ~ C_{17}-H and C_6-H), 1.9-2.4 (6H, m, C_2-H, C_7-H and C_{10}-H), 2.6-2.8 (1.5H, m, C_3-H and OH, 1H after D_2O addition), 3.02 (0.5H, d, J=5.4 Hz, OH, exch), 3.84 (m) and 3.92 (dd, J=10.0, 4.2 Hz)(total 1H, C_5-H), 4.24-4.47 (2H, m, C_4-H and C_5-H), 4.92 (0.5H ,m, C_1-H), 5.1-5.4 (2.5H, m, C_1-H, C_8-H, and C_9-H).

(±)-threo- and erythro-2,2-Dimethyl-5-nitro-4-pentadeca-1'(E),5'(Z)-dienyl-1,3-dioxane(8) and (9). A mixture of the nitro diol 6 (1.20 g, 3.67 mmol) and pyridinium p-toluenesulfonate (PPTS) (95 mg, 0.371 mmol) in a mixed solvent of 2, 2-dimethoxypropane (18 ml) and acetone (6 ml) was refluxed for 2.5 h. The reaction mixture was diluted with AcOEt (100 ml), washed with brine (20 ml), and dried over anhydrous $NaSO_4$. Evaporation of the solvent gave a yellow brown oil (1.30 g), which was column chromatographed on silica gel (30 g, toluene). The first eluate gave the acetonide 9 (187 mg ,28%) as a slightly yellow viscous oil. The second eluate gave the threo-acetonide 8 (231 mg, 34%) as a slightly yellow viscous oil.
8: IR 2990, 2920, 2850, 1550, 1450, 1370, 1350, 1330, 1270, 1195, 1160, 1130, 1080, 1030, 965, 895, 870, 860, 845, 720; FABMS 368 (MH^+), 109; ^{1}H-NMR (400 MHz) 0.88 (3H, t, J=7.0 Hz, C_{18}-H), 1.27 (14H, s-like m, C_{11}-H ~ C_{17}-H), 1.48 (3H, s, CH_3), 1.51 (3H, s , CH_3), 2.00 (2H, m) and 2.11 (4H, m)(C_6-H, C_7-H, and C_{10}-H), 4.24 (1H, dd, J=13.1, 4.1 Hz, C_1-H), 4.37 (1H, dd, J=13.1, 2.9 Hz, C_1-H), 4.48 (1H, td, J=4.1, 3.1 Hz, C_2-H), 4.61 (1H, dd, J=6.0, 3.2 Hz, C_3-H), 5.32 (1H, m, C_8-H or C_9-H), 5.39 (1H, m, C_8-H or C_9-H), 5.55 (1H, dd, J=15.4, 6.4 Hz, C_4-H), 5.86 (1H, dt, J=15.4, 6.3 Hz, C_5-H). 9: IR 2990, 2920, 2845, 1545, 1460, 1370, 1350, 1265, 1220, 1200, 1090, 1025, 965, 870, 780; FABMS 368 (MH^+), 109; ^{1}H-NMR (400 MHz) 0.88 (3H, t, J=7.0 Hz, C_{18}-H), 1.27 (14H, s-like m, C_{11}-H ~ C_{17}-H), 1.43 (3H, s, CH_3), 1.56 (3H, s, CH_3), 1.99 (2H, m) and 2.10 (4H, m)(C_6-H, C_7-H, and C_{10}-H), 4.18 (1H, dd, J=11.6, 5.5 Hz, C_1-H), 4.26 (1H, dd, J=11.6, 8.9 Hz, C_1-H), 4.49 (1H, td, J=8.9, 5.5 Hz, C_2-H), 4.68 (1H, dd, J=9.3, 7.3 Hz, C_3-H), 5.29 (1H, m, C_8-H or C_9-H), 5.38

(1H, m, C_8-H or C_9-H), 5.45 (1H, dd, J=15.4, 7.3 Hz, C_4-H), 5.84 (1H, dt, J=15.4, 6.4 Hz, C_5-H). (The numbering for the protons of the compounds 8 10: see Scheme 11).

Epimerization of threo-isomer(8) to erythro-isomer(9). A solution of the threo-isomer 8 (100 mg, 0.272 mmol) in triethylamine (3 ml) was refluxed for 3 h. Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography (10 g; toluene) to give the erythro-isomer 9 (93 mg, 93%) as an almost colorless viscous oil.

Acetonization followed by epimerization of 6 to 9. A mixture of the nitro diol 6 (600 mg, 1.83 mmol) and PPTS (47 mg, 0.183 mmol) in a mixed solvent of 2, 2-dimethoxypropane (9 ml) and acetone (3 ml) was refluxed for 2.5 h. The reaction mixture was diluted with AcOEt (50 ml), washed with brine (10 ml), and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a yellow brown oil (0.65 g), which was dissolved in triethylamine (10 ml). The solution was refluxed for 3 h and then evaporated to give a yellow brown viscous oil, which was purified by column chromatography on silica gel (30 g; toluene) to afford the erythro-acetonide 9 (342 mg, 51%) as a slightly yellow viscous oil.

(±)-erythro-5-Amino-2,2-dimethyl-4-pentadeca-1'(E),5'(Z)-dienyl-1,3-dioxane(10).---(i) By aluminium amalgam reduction. To a suspension of aluminium amalgam in THF (100 ml), which was prepared from aluminium (10 g), was added a solution of 9 (5.89 g, 16.0 mmol) in THF (100 ml)-H_2O (10 ml). The mixture was spontaneously refluxed for 30 min and then heated under reflux for 60 min. The reaction mixture was filtered through Celite and washed successively with THF. The filtrate and washings were evaporated to leave a residue, which was reduced once again with a similar operation. After similar filtration and evaporation, the residue was dissolved in $CHCl_3$, washed with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave an almost colorless viscous oil (6.09 g), which was purified by silica gel column chromatography (150 g; AcOEt : hexane = 4 : 1) to afford the amine 10 (4.26 g, 79%) as an almost colorless viscous oil. IR 3380, 3300, 2990, 2920, 2850, 1620br, 1460, 1380, 1370sh, 1265, 1200, 1160, 1080, 1025, 970, 875; EIMS 337 (M^+), 43 (base peak); ^{1}H-NMR (200 MHz) 0.88 (3H, t, J=6.8 Hz, C_{18}-H), 1.07 (2H, br.s, NH_2, exch), 1.27 (14H, s-like m, C_{11}-H ~ C_{17}-H), 1.42 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.00 (2H, m) and 2.15 (4H, m)(C_6-H, C_7-H, and C_{10}-H), 2.69 (1H, td, J=10.2, 5.4 Hz, C_2-H), 3.54 (1H, t, J=10.3 Hz, C_1-H), 3.79-3.92 (2H, m, C_1-H and C_3-H), 5.36 (2H, m, C_8-H and C_9-H), 5.40 (1H, dd, J=15.0, 8.0 Hz, C_4-H), 5.82 (1H, m, C_5-H).

(ii) By $LiAlH_4$ reduction. To a solution of **9** (554 mg, 1.51 mmol) in THF (10 ml) was added portionwise $LiAlH_4$ (240 mg, 6.32 mmol) at room temperature. The reaction mixture was stirred for 5 h at room temperature and then the excess of $LiAlH_4$ was quenched with water. The mixture was diluted with $CHCl_3$ and filtered to remove insoluble material. The organic layer was separated, washed with brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless oil (509 mg), which was purified by silica gel column chromatography (15 g; AcOEt : hexane = 2 : 1) to afford **10** (414 mg, 81%) as a colorless viscous oil.

Condensation of 10 with 2(R)-acetoxypalmitic acid (11) to 13. To a stirred suspension of **11** (650 mg, 2.07 mmol), DCC (470 mg, 2.28 mmol), and 1-hydroxybenzotriazole (310 mg, 2.29 mmol) in CH_2Cl_2 (20 ml) was added dropwise a solution of **10** (700 mg, 2.07 mmol) in CH_2Cl_2 (10 ml). The reaction mixture was stirred for 1.5 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 colorless caramel (2.17 g), which was purified by silica gel column chromatography (100 g; AcOEt : hexane = 1 : 3) to afford the diastereomeric mixture of ceramides **13** (1.28 g, 98%) as a colorless viscous oil. IR 3300, 3000, 2930, 2855, 1745, 1650, 1540, 1460, 1370, 1230, 1200, 1160, 1085, 1030, 970, 870, 720; EIMS 633 (M^+), 43(base peak) ; ^{1}H-NMR (200 MHz) 0.88 (6H, t, J=6.8 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), 1.43 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.78 (2H, m), 2.00 (2H, m), and 2.10 (4H, m), (C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.13 (s) and 2.14 (s)(total 3H, CH_3CO), 3.58-4.16 (4H, m, C_1-H, C_2-H, and C_3-H), 5.04 (t, J=6.3 Hz) and 5.09 (t, J=5.9 Hz)(total 1H, C_2'-H), 5.20-5.49 (3H, m, C_4-H, C_8-H, and C_9-H), 5.65-5.82 (2H, m, C_5-H and NH).

Condensation of 10 with 2(S)-acetoxypalmitic acid (12) to 14. The amine **10** (920 mg, 2.73 mmol) was treated with **12** (850 mg, 2.70 mmol) in the presence of DCC (620 mg, 3.01 mmol) and 1-hydroxybenzotriazole (410 mg, 3.03 mmol) in CH_2Cl_2 (40 ml) in a similar manner mentioned above. Similar work-up and chromatography of the crude mixture gave the diastereomeric mixture of ceramides **14** (1.69 g, 99%) as a colorless viscous oil, which was confirmed with **13** by TLC and IR spectrum.

Deacetonization of 13 to 15. To a stirred solution of **13** (1.26 g, 1.99 mmol) in MeOH (30 ml) was added PPTS (510 mg, 1.99 mmol) and the mixture was stirred for 22.5 h at room temperature. The reaction mixture was evaporated to give 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 (1.23 g), which was purified by silica gel column chromatography (50 g; AcOEt : hexane = 2 : 1) to afford **15** (1.08 g, 92%) as a colorless waxy crystalline solid. IR (KBr) 3410, 3300, 2955, 2920, 2850, 1740, 1730, 1650, 1550, 1465, 1370, 1235, 1070, 1050, 1030, 960, 720; EIMS 593 (M^+), 43 (base peak); ^{1}H-NMR(200 MHz) 0.88 (6H, t, J=6.8 Hz, C_{18}-H and C_{16}'-H), 1.26 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.83 (2H, m), 2.01 (2H, m), and 2.14 (4H, m)(C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.15 (3H, s, CH_3CO), 2.56 (0.5H, overlapped with C_3-OH peak, C_1-OH, exch), 2.57 (0.5H, d, J=4.9 Hz, C_3-OH, exch), 2.65 (0.5H, dd, J=7.3, 3.9 Hz, C_1-OH, exch), 2.72 (0.5H, d, J=5.3 Hz, C_3-OH, exch), 3.69 (1H , m, C_2-H), 3.85 (1H, m, C_1-H), 3.88 (1H, m, C_1-H), 4.33 (1H, m, C_3-H), 5.07 (1H, m, C_2'-H), 5.24-5.40 (2H, m, C_8-H and C_9-H), 5.52 (1H, dd, J=15.4, 5.1 Hz, C_4-H), 5.78 (1H, m, C_5-H), 6.73 (0.5H, d, J=7.8 Hz, NH), 6.75 (0.5H, d, J=7.8 Hz, NH).

Deacetonization of 14 to 16. The acetonide **14** (1.66 g, 2.62 mmol) was treated with PPTS (670 mg, 2.61 mmol) in MeOH (30 ml) for 21.5 h at room temperature. Similar work-up and chromatography mentioned above gave **16** (1.38 g, 89%) as a colorless waxy crystalline solid, which was confirmed with **15** by TLC and IR spectrum.

Tritylation of 15 and resolution to 17 and 18. A solution of **15** (1.08 g, 1.82 mmol), trityl chloride (1.02 g, 3.66 mmol), 4-dimethylaminopyridine (DMAP) (0.23 g, 1.88 mmol), and triethylamine (1.5 ml) in CH_2Cl_2 (15 ml) was stirred for 3 days at room temperature under argon atmosphere. The reaction mixture was diluted with $CHCl_3$, washed successively with water, saturated NH_4Cl solution, water, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a pale yellow caramel (2.60 g), which was column chromatographed on silica gel (130 g). The first eluate, with toluene-AcOEt(10 : 1), gave **17** (512 mg, 34%) as a colorless caramel. The second eluate, with the same solvent, gave **18** (445 mg, 29%) as a colorless caramel. The third eluate, with toluene-AcOEt (1 : 2), gave the recovered **15** (320 mg, 30%) as a colorless waxy crystalline solid. **17**: $[\alpha]_D^{20}$ +3.5°(c 0.60, $CHCl_3$); IR 3440, 3080, 3060, 3020, 3000, 2920, 2850, 1745, 1665, 1590, 1520, 1490, 1460, 1445, 1370, 1310, 1220, 1180, 1150, 1070, 1030, 1000, 970, 925, 895, 760, 740, 700, 640, 630, 600; FABMS 858 $(M+Na)^+$, 576, 363; ^{1}H-NMR (200 MHz) 0.88 (6H, t, J=6.4 Hz, C_{18}-H and C_{16}'-H), 1.26 (38H, s-like m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.8 -2.1 (8H, m, C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.04 (3H, s, CH_3CO), 3.13 (1H, d, J=8.3 Hz, OH, exch), 3.26 (1H, dd, J=9.3, 3.4 Hz, C_1-H), 3.39 (1H, dd, J=9.3, 3.4 Hz, C_1-H), 4.04 (1H, dd, J=8.3, 3.9 Hz, C_2-H), 4.17 (1H, m, C_3-H), 5.20-5.38 (4H, m, C_4-H, C_8-H, C_9-H, and C_2'-

H), 5.65 (1H, m, C_5-H), 6.93 (1H, d, J=7.8 Hz, NH), 7.20 -7.38 (15H, m, arom H). **18**: $[\alpha]_D^{20}$ +5.7° (c 0.60, $CHCl_3$); IR 3440, 3080, 3060, 3020, 3000, 2920, 2850, 1745, 1665, 1590, 1520, 1490, 1460, 1445, 1370, 1310, 1220, 1180, 1150, 1070, 1030, 1000, 970, 925, 895, 760, 740, 700, 640, 630, 600; FABMS 858 $(M+Na)^+$, 576, 363; ^{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), 1.8-2.1 (8H, m, C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.12 (3H, s, CH_3CO), 2.99 (1H, d, J= 7.8 Hz, OH, exch), 3.31 (1H, dd, J=9.3, 3.9 Hz, C_1-H), 3.40 (1H, dd, J=9.7, 3.9 Hz, C_1-H), 4.02 (1H, dd, J=8.3, 3.9 Hz, C_2-H), 4.16 (1H, m, C_3-H), 5.15-5.38 (4H, m, C_4-H, C_8-H, C_9-H, and C_2'-H), 5.63 (1H, m, C_5-H), 6.85 (1H, d, J=8.3 Hz, NH), 7.20-7.43 (15H, m, arom H).

Tritylation of 16 and resolution to 21 and 22. A solution of **16** (1.34 g, 2.26 mmol), trityl chloride (1.26 g, 4.52 mmol), DMAP (0.28 g, 2.29 mmol), and triethylamine (2.0 ml) in CH_2Cl_2 (20 ml) was stirred for 4 days at room temperature under argon atmosphere. Similar work-up and chromatography mentioned above gave **21** (544 mg, 29%), $[\alpha]_D^{20}$ -5.4°(c 1.13, $CHCl_3$) as a slightly yellow caramel, **22** (664 mg, 35%), $[\alpha]_D^{20}$ -3.8°(c 1.05, $CHCl_3$) as a slightly yellow caramel, and the recovered **16** (349 mg, 26%) as a colorless waxy crystalline solid. **21** and **22** were confirmed with **18** and **17** by TLC and IR spectrum, respectively.

1-O-Unprotected ceramide (19). To a stirred solution of **17** (512 mg, 0.162 mmol) in pyridine (10 ml) was added benzoyl chloride (180 mg, 1.28 mmol) and the mixture was stirred for overnight at room temperature. The reaction mixture was evaporated to a residue, which was dissolved in AcOEt. The solution was washed with 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 (30 g; toluene : AcOEt = 20 : 1). The obtained colorless caramel (595 mg) was dissolved in MeOH-CH_2Cl_2 (20 ml, 1 : 1 by vol). To this solution was added p-toluenesulfonic acid (monohydrate)(120 mg, 0.631 mmol) and the resulting mixture was stirred for 2.5 h at room temperature. The reaction mixture was diluted with $CHCl_3$, washed successively with saturated $NaHCO_3$ solution, water, and brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a colorless caramel (660 mg), which was purified by silica gel column chromatography (30 g; toluene : AcOEt = 3 : 2) to afford **19** (341 mg, 80%) as colorless waxy crystals; mp 42°C. $[\alpha]_D^{20}$ +36.4°(c 1.10, $CHCl_3$); IR (KBr) 3430br, 3000, 2920, 2850, 1740sh, 1720, 1665, 1600, 1525, 1460,1450, 1370, 1310, 1265, 1240, 1170, 1110, 1070, 1025, 965, 710; EIMS 697(M^+), 575, 105, 43(base peak); ^{1}H-NMR (200 MHz) 0.88 (6H, t, J=6.8 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), 1.82 (2H, m), 1.98 (2H, m), and 2.10-2.19 (4H, m)(C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.14 (3H, s, CH_3CO), 2.72 (1H, dd-like, OH, exch), 3.71 (2H, m, C_1-H), 4.23 (1H, m, C_2-H), 5.17 (1H, dd, J=7.3, 4.9 Hz, C_2'-H), 5.36 (2H, m) and 5.58 (1H, m)(C_3-H, C_8-H, and C_9-H), 5.64 (1H, dd, J=16.0, 7.0 Hz, C_4-H), 5.90 (1H, m, C_5-H), 6.78 (1H, d, J=8.8 Hz, NH), 7.46 (2H, t-like, J=7.3 Hz), 7.60 (1H, m) and 8.04 (2H, d-like, J=7.3 Hz)(arom H); HRMS, m/z 698.5346 (698.5359 calcd for $C_{43}H_{72}O_6N$, M^+).

1-O-Unprotected ceramide (20). Tritylated ceramide **18** (445 mg, 0.532 mmol) was treated with benzoyl chloride (150 mg, 1.07 mmol) in pyridine (10 ml) followed by detritylation with p-toluenesulfonic acid (monohydrate)(100 mg, 0.526 mmol) in MeOH-CH_2Cl_2 (20 ml, 1 : 1 by vol) in a similar manner mentioned above. Similar work-up and chromatogtaphy gave **20** (298 mg, 80%) as a colorless waxy solid; mp 66°C. $[\alpha]_D^{20}$ -16.1°(c 0.67, $CHCl_3$) ;IR (KBr) 3570, 3310, 3065, 3000, 2920, 2850, 1720, 1655, 1600, 1550, 1465, 1450, 1370, 1310, 1270, 1245, 1175, 1115, 1070, 1025, 970, 710; EIMS 697(M^+), 575, 105, 43 (base peak); ^{1}H-NMR (200 MHz) 0.88(6H, t, J=6.8 Hz, C_{18}-H and C_{16}'-H), 1.25 (38H, m, C_{11}-H ~ C_{17}-H and C_4'-H ~ C_{15}'-H), 1.80 (2H, m), 1.99 (2H, m), and 2.09-2.13 (4H, m) (C_6-H, C_7-H, C_{10}-H, and C_3'-H), 2.13 (3H, s, CH_3CO), 2.78 (1H, br.t-like, OH, exch), 3.75 (2H, m, C_1-H), 4.26 (1H ,m, C_2-H), 5.11 (1H, t, J=6.8 Hz, C_2'-H), 5.35 (2H, m) and 5.56 (1H, m)(C_3-H, C_8-H, and C_9-H), 5.61 (1H, dd, J=15.0, 7.0 Hz, C_4-H), 5.86 (1H, m, C_5-H), 6.70 (1H, d, J=8.8 Hz, NH), 7.46 (2H, t-like, J=7.3 Hz), 7.60 (1H, m), and 8.04 (2H, d-like, J=6.8 Hz)(arom H); HRMS, m/z 698.5377 (698.5359 calcd for $C_{43}H_{72}O_6N$, M^+).

1-O-Unprotected ceramide(23). Tritylated ceramide **21** (530 mg, 0.634 mmol) was treated with benzoyl chloride (180 mg, 1.28 mmol) in pyridine (10 ml) followed by detritylation with p-toluene-sulfonic acid (monohydrate)(121 mg, 0.636 mmol) in MeOH-CH_2Cl_2 (20 ml, 1 : 1 by vol) in a similar manner mentioned above. Similar work-up and chromatography gave **23** (356 mg, 81%) as a colorless waxy solid, which was confirmed with **20** by TLC and IR and ^{1}H-NMR spectra; mp 67°C, $[\alpha]_D^{20}$ + 16.2°(c 1.01, $CHCl_3$); HRMS, m/z 698.5319 (698.5359 calcd for $C_{43}H_{72}O_6N$, M^+).

1-O-Unprotected ceramide(24). Tritylated ceramide **22** (664 mg, 0.794 mmol) was treated with benzoyl chloride (230 mg, 1.64 mmol) in pyridine (10 ml) followed by tritylation with p-toluenesulfonic acid (monohydrate)(151 mg, 0.794 mmol) in MeOH-CH_2Cl_2 (20 ml, 1 : 1 by vol) in a similar manner mentioned above. Similar work-up and chromatography gave **24** (465 mg, 84%) as

colorless waxy crystals, which was confirmed with 19 by TLC and IR and ^{1}H-NMR spectra; mp 41°C, $[\alpha]_D^{20}$ - 35.9°(c 1.12, $CHCl_3$); HRMS, m/z 698.5326 (698.5359 calcd for $C_{43}H_{72}O_6N$, M^+).

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