Syntheses of Two Pairs of Enantiomeric C18-Sphingosines and a Palmitoyl Analogue of Gaucher Spleen Glucocerebroside[1)]

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Sixteen kinds of chiral C4-epoxides [(−)-10a—d, (+)-10a—d, (−)-11a—d, (+)-11a—d], which are synthons in our synthetic strategy for complex lipids, have been prepared from (2*Z*)-2-butene-1,4-diol (6) by employing a Sharpless asymmetric epoxidation. By using the chiral C4-epoxides [(+)-10a, (−)-10a, (−)-11a, (+)-11a] as starting compounds, two pairs of enantiomeric (D-*erythro*, L-*erythro*, D-*threo*, and L-*threo*)-C18-sphingosines (1, 2, 3, 4) have been synthesized *via* a regioselective ring-opening of the epoxide ring with azide anion followed by reduction of the azide group to an amino group and a Wittig reaction. Furthermore, D-*erythro*-C18-sphingosine (1) has been converted to a palmitoyl analogue (5a) of Gaucher spleen glucocerebroside (5) through a reaction pathway including successive condensations with palmitic acid and D-glucose.

Keywords complex lipid; sphingoglycolipid; sphingosine; D-*erythro*-C18-sphingosine; L-*erythro*-C18-sphingosine; D-*threo*-C18-sphingosine; L-*threo*-C18-sphingosine; Gaucher spleen glucocerebroside

Sphingoglycolipids have been considered to be present at the outer layer of biological cell membranes and to take part in antigen–antibody reaction and in communication between cells.[2)] Recently, Merrill *et al.*[3)] reported that C18-sphingosine, a common aminoalcohol of sphingoglycolipids, showed a potent inhibitory activity for protein kinase C (PKC). However, sphingoglycolipids are usually available from natural sources in only limited quantities and as hardly separable mixtures in terms of their fatty acid compositions, so that their versatile synthesis seems to be of importance, especially for their biochemical investigation.

For the synthesis of sphingoglycolipid, stereoselective introductions of the amino group (at C-2) and the hydroxyl group (at C-3) are most important. We conjectured that D- and L-*erythro*-C18-sphingosines (**1** and **2**) might be synthesized through a stereoselective reaction of an azide anion with the *E*-type C4-epoxide (**a**), followed by reduction of the azide group to an amino group and by elongation of the carbon chain (R^2 in **a**) up to C18 by means of a Wittig reaction. On the other hand, we anticipated that D- and L-*threo*-C18-sphingosines (**3** and **4**) might be constructed from the *Z*-type C4-epoxide (**b**) through a reaction sequence similar to that proposed for the synthesis of **1** and **2**.

In this paper, we report a new synthetic method for two pairs of enantiomeric (D-*erythro*, L-*erythro*, D-*threo*, L-*threo*)-C18-sphingosines (**1**, **2**, **3**, **4**) *via* chiral C4-epoxides [(+)-**10a**, (−)-**10a**, (−)-**11a**, (+)-**11a**],[4)] which are common synthons in our synthetic strategy. As a development of the synthetic method, we also report a total synthesis of a palmitoyl analogue (**5a**) of Gaucher spleen glucocerebroside (**5**)[5)] from D-*erythro*-C18-sphingosine (**1**).

Synthesis of Chiral C4-Epoxides The *E*-diol monopropionate (*E*-**7**) and the *Z*-diol monopropionate (*Z*-**7**) were prepared from (2*Z*)-2-butene-1,4-diol (**6**) according to North's procedure.[6)] The free hydroxyl functions of the *Z*- and *E*-diol monopropionates (*E*-**7** and *Z*-**7**) were respectively protected with a monomethoxytrityl (MMTr), a methoxymethyl (MOM), a benzyl (Bn), or a *tert*-butyldimethylsilyl (TBDMS) group. These protected derivatives were then hydrolyzed with 1% KOH–MeOH to provide the *E*-allyl alcohols (**8a—d**) and *Z*-allyl alcohols (**9a—d**) in good yields.

Each of the eight kinds of allyl alcohols (**8a—d** and **9a—d**) was subjected to a Sharpless asymmetric epoxidation[7,8)] using (+)- and (−)-diethyl tartrate (DET) (1.0 mol eq) or (+)- and (−)-diisobutyl tartrate (DIPT) (0.06 mol eq, with molecular sieves 4A) as chiral sources, and sixteen kinds of chiral C4-epoxides [(−)-**10a—d**, (+)-**10a—d**, (−)-**11a—d**, (+)-**11a—d**] were prepared in favorable yields. The optical yield for each C4-epoxide (given in Table I) was determined by the proton nuclear magnetic resonance (^{1}H-NMR)

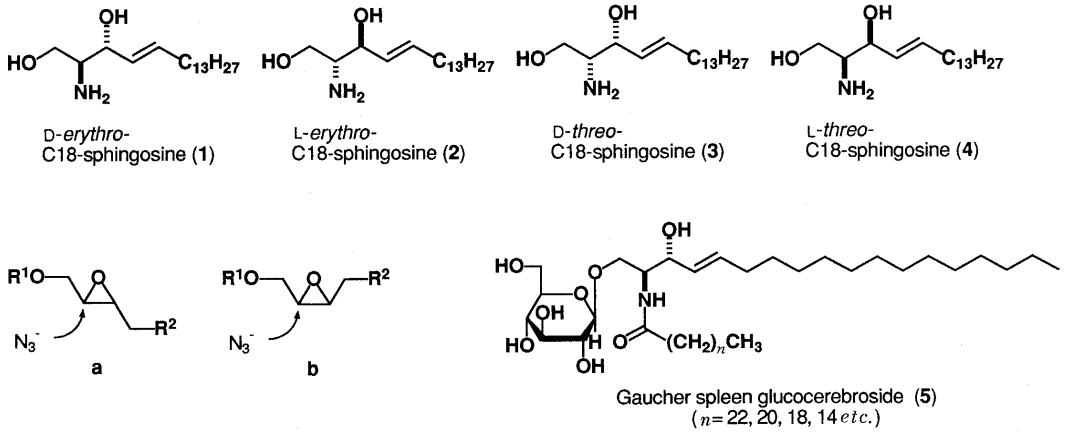

Fig. 1

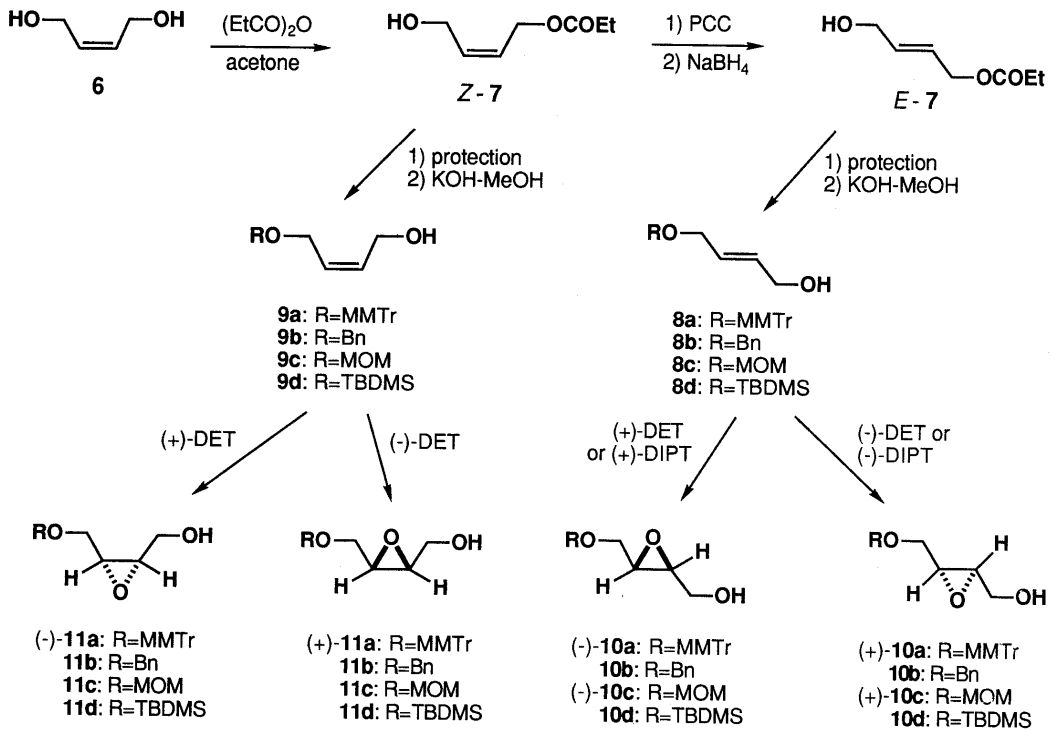

Chart I

TABLE I. Chemical and Optical Yields of C4-Epoxides from Various Monoprotected Allyl Alcohols

Substrate	Tartrate	Amount of tartrate (eq)	Product	Chemical yield (%)	ee (%)
MMTrO—OH **8a**	(+)-DET	1.0	(−)-**10a**	84	97
	(−)-DET	1.0	(+)-**10a**	79	94
BnO—OH **8b**	(+)-DET	1.0	(−)-**10b**	86	83
	(−)-DET	1.0	(+)-**10b**	89	87
MOMO—OH **8c**	(+)-DET	1.0	(−)-**10c**	62	91
	(+)-DIPT	0.06		83	93
	(−)-DET	1.0	(+)-**10c**	64	89
	(−)-DIPT	0.06		82	93
TBDMSO—OH **8d**	(+)-DET	1.0	(−)-**10d**	75	87
	(−)-DET	1.0	(+)-**10d**	76	81
MMTrO—OH **9a**	(+)-DET	1.0	(−)-**11a**	81	97
	(−)-DET	1.0	(+)-**11a**	78	93
BnO—OH **9b**	(+)-DET	1.0	(−)-**11b**	84	83
	(−)-DET	1.0	(+)-**11b**	89	87
MOMO—OH **9c**	(+)-DET	1.0	(−)-**11c**	65	92
	(−)-DET	1.0	(+)-**11c**	60	94
TBDMSO—OH **9d**	(+)-DET	1.0	(−)-**11d**	74	85
	(−)-DET	1.0	(+)-**11d**	77	84

MMTr: monomethoxytrityl, Bn: benzyl, MOM: methoxymethyl, TBDMS: *tert*-butyldimethylsilyl, DET: diethyltartrate, DIPT: diisopropyl tartrate.

analysis of the corresponding acetates in the presence of tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium (III)[8] or by that of the corresponding (+)-α-methoxy-α-(trifluoromethyl)phenylacetates (MTPA).[9] It has been found that, among these, four C4-epoxides having an MMTr group [(−)-**10a**, (+)-**10a**, (−)-**11a**, (+)-**11a**], which were prepared by using (+)- and (−)-DET, were obtained in high optical yields. In addition, two C4-epoxides having a MOM group [(−)-**10c**, (+)-**10c**], prepared by using (+)- and (−)-DIPT, were also considered useful for the synthesis of chiral complex lipids.

Syntheses of D-*erythro*- and L-*erythro*-C18-Sphingosines On treatment with a reagent[10] prepared from titanium tetraisopropoxide and trimethylsilyl azide, the *E*-type C4-epoxide having an MMTr group [(+)-**10a**] was transformed in a good yield into a 1,2-diol (**12**) and a 1,3-diol (**13**) in a ratio of 14:1. The structures of **12** and **13** were substantiated by ^{1}H-NMR spin-decoupling experiments on their dibenzoate derivatives (**12a** and **13a**). The major product **12** was then converted to a hydroxyamide (**15**) in a satisfactory overall yield *via* an azide-monobenzoate (**14**) through successive reactions, *i.e.*, i) selective benzoylation of the primary hydroxyl group, ii) methoxymethylation of the secondary hydroxyl group, iii) reduction of the azide group, and finally iv) acetylation of the amino group.

The hydroxy-amide (**15**) thus prepared was converted to a mixture of *N*-acetyl-D-*erythro*-C18-sphingosine (**16**) and its 4*Z*-isomer (**17**) in a ratio of 1:2, by Swern oxidation [$(COCl)_2$, dimethyl sulfoxide (DMSO), Et_3N], and a Wittig reaction (triphenylphosphine tetradecyl bromide, *n*-BuLi) and subsequent acidic hydrolysis (9% HCl–MeOH). The content ratio (1:2) of **16** to **17** could be increased to 5:1 by photoisomerization, *i.e.*, irradiation with a 500 W high-pressure mercury lamp through a Pyrex filter for 6 h in the presence of 1 eq of diphenyldisulfide.[11] The photolysis product, after acetylation, was separated by high performance liquid chromatography (HPLC) with a normal phase adsorbent to afford *N*,*O*,*O*-triacetyl-D-*erythro*-C18-sphingosine (**18**)[12] and its 4*Z*-isomer (**19**). The structures of **19** and **20** were confirmed by the chemical shifts (**18**: δ_C 32.3, **19**: δ_C 28.1) of the respective allylic methylene carbons at C-6 in their carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra.

Finally, D-*erythro*-C18-sphingosine (**1**)[13,14] was prepared

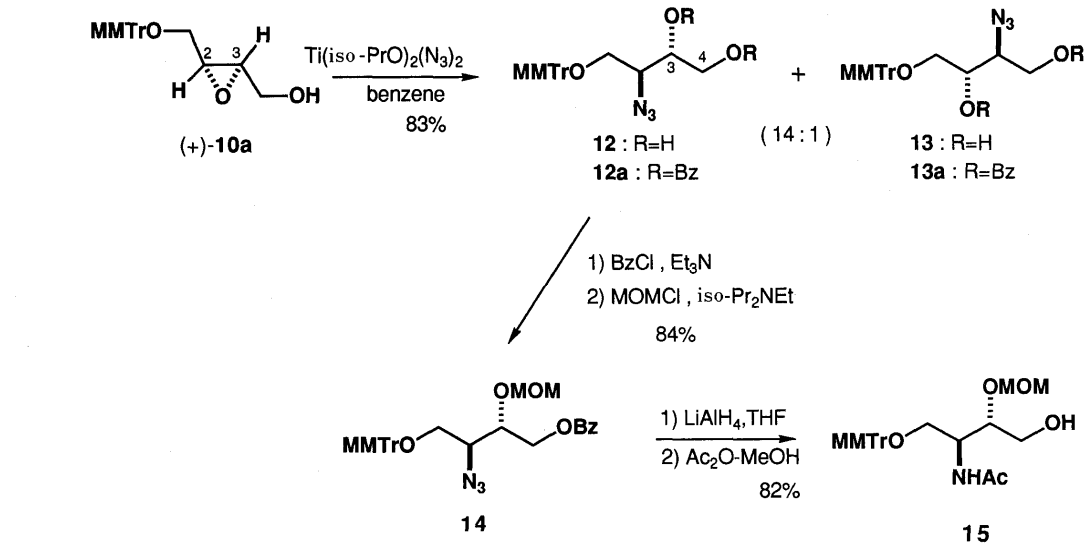

Chart 2

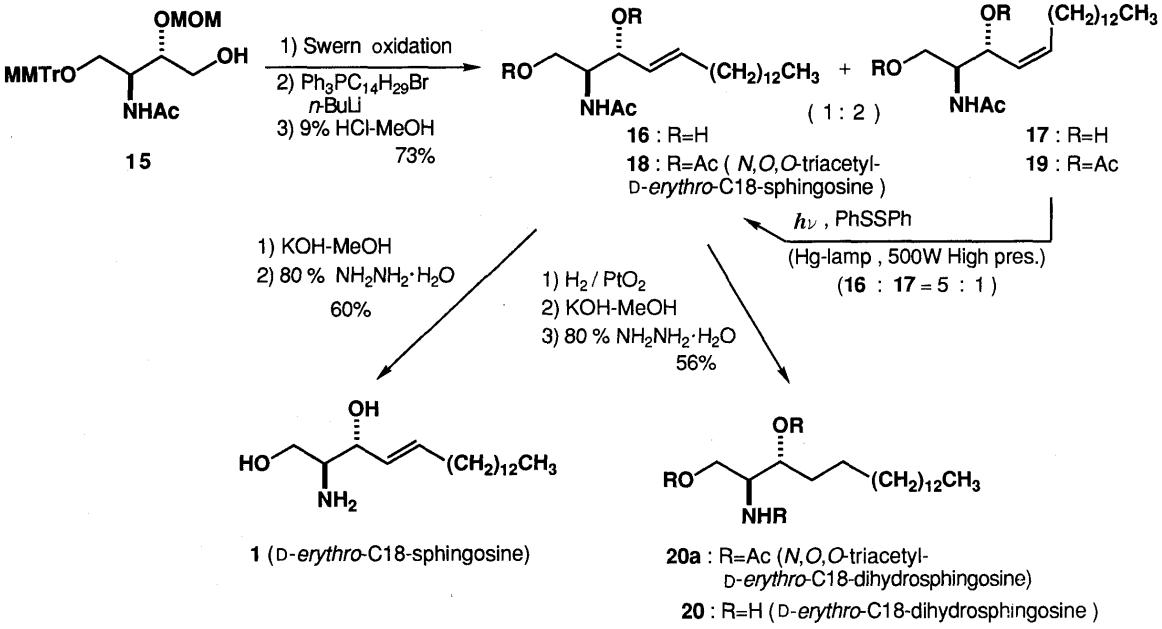

Chart 3

from **18** by alkaline hydrolysis and subsequent treatment with 80% hydrazine hydrate in 60% yield. Further, catalytic hydrogenation of **18** afforded *N,O,O*-triacetyl-D-*erythro*-C18-dihydrosphingosine (**20a**),[13] which was then transformed into D-*erythro*-C18-dihydrosphingosine (**20**)[15] through a procedure similar to that used for the synthesis of **1** from **18**. The physical data including optical rotations of **1**, **18**, **20** and **20a** were identical with those reported in the literature.

On the other hand, another chiral C4-epoxide [(−)-**10a**], which is an enantiomer of (+)-**10a**, was transformed into *N,O,O*-triacetyl-L-*erythro*-C18-sphingosine (**23**) and its 4*Z*-isomer (**24**) *via* a 1,2-diol (**21**) and a hydroxy-amide (**22**) as described above from (+)-**10a** to **18** and **19** *via* **12** and **15**. Then, L-*erythro*-C18-sphingosine (**2**), L-*erythro*-C18-dihydrosphingosine (**25**),[15] and *N,O,O*-triacetyl-L-*erythro*-C18-dihydrosphingosine (**25a**)[16] were prepared from **23** through reaction sequences similar to those used for the synthesis of D-*erythro*-C18-sphingosine (**1**) and its derivatives (**20**, **20a**) from **18**.

Syntheses of D-*threo*- and L-*threo*-C18-Sphingosines For the syntheses of D-*threo*-C18-sphingosine (**3**) and L-*threo*-C18-sphingosine (**4**), at first, *Z*-type C4-epoxides [(−)-**11a** and (+)-**11a**] were taken as the starting compounds. When (−)-**11a** was treated with the titanium reagent,[10] a 1,3-diol (**26**) was obtained as a single product in 83% yield and the expected 1,2-diol was not obtained. The structure of **26** was confirmed by ^{1}H-NMR spin-decoupling experiments on its dibenzoate derivative (**26a**).

It was found that the regioselectivity in the epoxide-ring opening of the *Z*-epoxide (−)-**11a** was not the same as that in the case of the *E*-epoxide (+)-**10a**, which gave the 1,2-diol (**12**) as the major product and the 1,3-diol (**13**) as a minor one. The reason may be as follows. In the case of (+)-**10a**, an azide anion is considered to attack principally at the C-3 position in a presumably reasonable conformer C. In

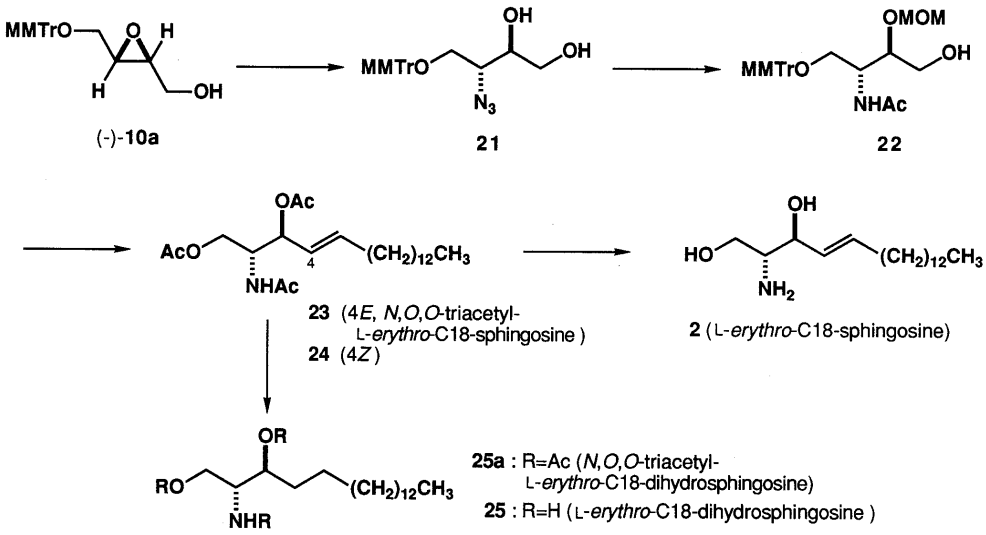

Chart 4

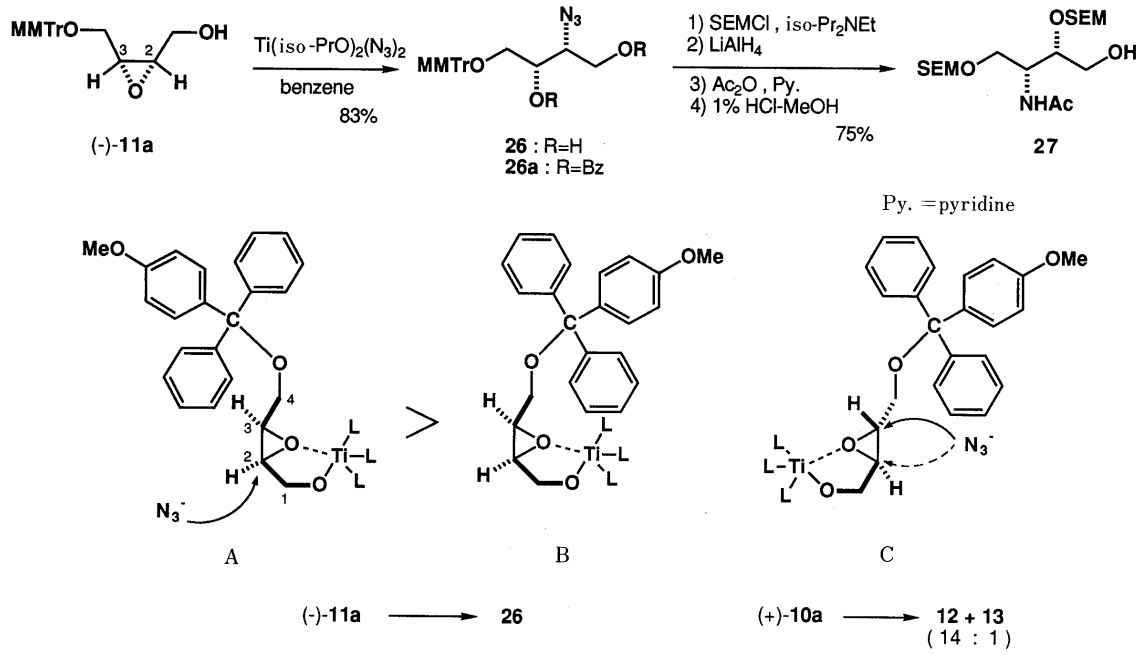

Chart 5

contrast, a favorable conformation of (−)-**11a** may be conformer A rather than conformer B, since the spatial interaction between the MMTr group and the titanium atom, which possesses three ligands, seems to be larger in conformer B than that in conformer A. Furthermore, in conformer A, the attack of an azide anion at the C-3 position may be obstructed by the MMTr group, so that the introduction of the azide group occurred at the C-2 position of (−)-**11a** to provide the 1,3-diol (**26**) as a single product.

Therefore, the 1,3-diol (**26**) was utilized for synthesizing D-*threo*- and L-*threo*-C18-sphingosines (**3**, **4**). Thus, **26** was converted to a D-*threo*-hydroxy-amide (**27**) through the following reaction sequence: i) trimethylsilylethoxymethylation of two hydroxyl groups, ii) reduction of the azide group, iii) acetylation of the resulting amino group, and finally iv) removal of the MMTr group.

The hydroxy-amide (**27**) was then converted to a 1:4 mixture of *N*-acetyl-D-*threo*-C18-sphingosine (**28**) and its 4*Z*-isomer (**29**) through successive reactions: i) Swern oxidation, ii) Wittig reaction and iii) acidic hydrolysis. The resulting mixture was then irradiated with a 500 W high-pressure mercury lamp in a Pyrex tube in the presence of diphenyldisulfide (1 eq) to give a mixture which was separated by HPLC with a normal phase adsorbent to afford **28** (69%) and **29** (6%). The structures of **28** and **29** were substantiated by the ^{13}C-NMR chemical shift of C-6 (δ_C 32.6 for **28**, δ_C 28.1 for **29**).

Treatment of **28** with 80% hydrazine hydrate provided D-*threo*-C18-sphingosine (**3**) in 61% yield, and **3** was acetylated to furnish *N*,*O*,*O*-triacetyl-D-*threo*-C18-sphingosine (**3a**). Further, **28** was subjected to catalytic hydrogenation followed by hydrazine treatment to furnish D-*threo*-C18-dihydrosphingosine (**30**),[15] which was acetylated to give *N*,*O*,*O*-triacetyl-D-*threo*-C18-dihydrosphingosine (**30a**).[15]

In a similar manner, the chiral C4-epoxide (+)-**11a**, which

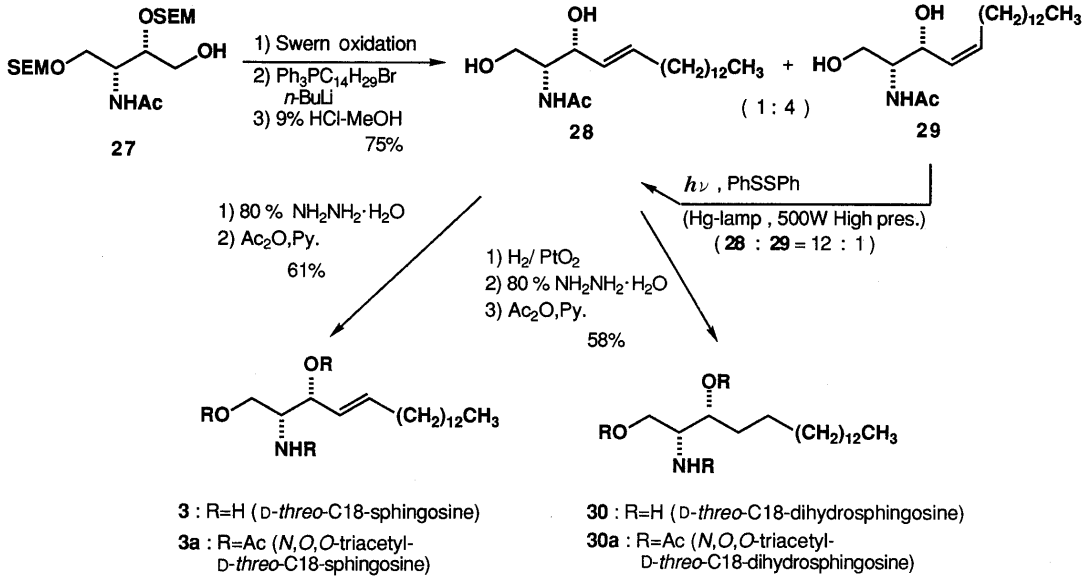

Chart 6

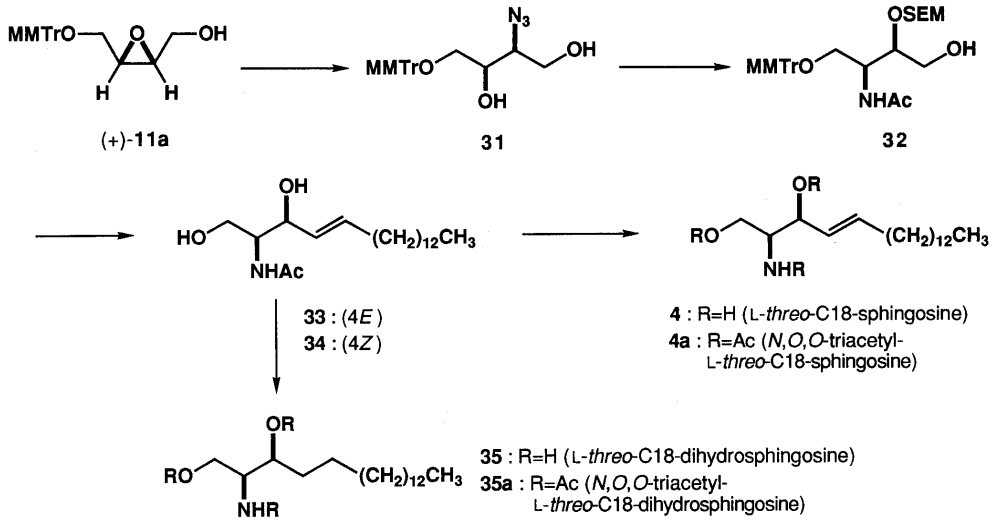

Chart 7

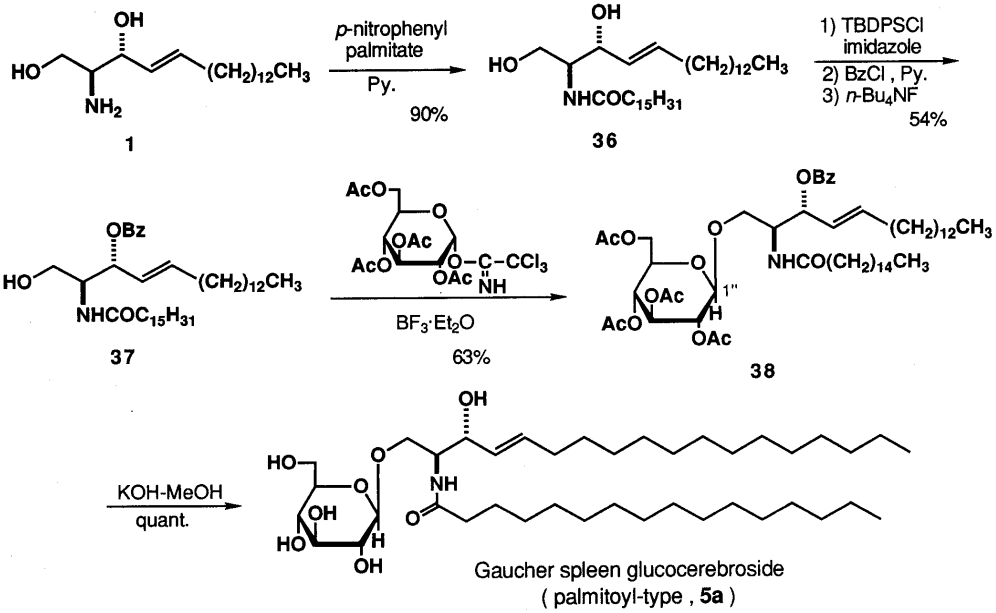

Chart 8

is an enantiomer of (−)-**11a**, was transformed into *N*-acetyl-L-*threo*-C18-sphingosine (**33**) *via* a 1,2-diol (**31**) and a hydroxy-amide (**32**). L-*threo*-C18-Sphingosine (**4**), *N*,*O*,*O*-triacetyl-L-*threo*-C18-sphingosine (**4a**), L-*threo*-C18-dihydrosphingosine (**35**),[15] and *N*,*O*,*O*-triacetyl-L-*threo*-C18-dihydrosphingosine (**35a**)[16] were thus obtained from **33** by a procedure similar to those used for the synthesis of D-*threo*-C18-sphingosine (**3**) and its derivatives (**3a**, **30**, **30a**) from **28**.

Synthesis of a Palmitoyl Analogue of Gaucher Spleen Glucocerebroside We next utilized the above-mentioned D-*erythro*-C18-sphingosine (**1**), a natural type C18-sphingosine, for the synthesis of a palmitoyl analogue (**5a**) of Gaucher spleen glucocerebroside (**5**).[5]

Treatment of **1** with *p*-nitrophenyl palmitate[17] gave a ceramide (**36**) in a good yield. Then, the ceramide (**36**) was converted to a monobenzoyl ceramide (**37**) by i) *tert*-butyldiphenylsilylation (TBDPS) of the primary hydroxyl group, ii) benzoylation of the remaining secondary hydroxyl group, and iii) removal of the TBDPS residue. Glycosidation of **37** with *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)trichloroacetimide in the presence of boron trifluoride etherate[18] provided an acetylated β-glucoside (**38**) in 63% yield. The β-configuration at C-1″ of **38** was substantiated by the ^{1}H-NMR coupling constant (J=8.0 Hz) of the anomeric proton. Finally, the acetylated β-glucoside (**38**) was subjected to alkaline hydrolysis to afford a palmitoyl analogue (**5a**) of Gaucher spleen glucocerebroside (**5**) in quantitative yield. The physical data for **5a** was identical with those reported in the literature.[19]

Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and recorded as observed. Optical rotations were measured in a 0.5 dm tube with a JASCO DIP-370 polarimeter. Electron impact mass spectra (EI-MS) were taken on a JEOL JMS-D300 spectrometer. Fast atom bombardment (FAB)-MS were taken on a JEOL JMS-SX102 spectrometer. Infrared (IR) spectra were taken on a Hitachi 260-30 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on JEOL FX-90Q (90 MHz) and GX-500 (500 MHz) spectrometers with tetramethylsilane (TMS) as an internal standard. Chemical shifts are given on the δ scale (ppm). The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet and br=broad. Coupling constants (J values) are given in herts (Hz). HPLC was carried out on Shimadzu LC-5A, LC-6A and Waters C-201 chromatographs. Column chromatography was performed on Kieselgel 60 (Merck, 70—230 mesh). Thin-layer chromatography (TLC) was carried out with pre-coated Kieselgel 60F_{254} plates (Merck). All reactions were carried out under a nitrogen or an argon atmosphere.

The *Z*-Diol Monopropionate (*Z*-7) A solution of (2*Z*)-2-butene-1,4-diol (**6**, 26.7 g, 0.30 mol) in dry acetone (120 ml) was treated with propionic anhydride (39 ml, 0.03 mol) and the mixture was heated under reflux for 10 h. After cooling, the solvent was removed under reduced pressure and the residue was extracted with ether. The ether extract was washed with aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent gave a product (25 g), which was purified by column chromatography (SiO_2 300 g, *n*-hexane : EtOAc = 2 : 1) to afford the *Z*-monopropionate (*Z*-**7**, 23.8 g, 0.17 mol, 55%).

Z-**7**: Colorless oil. IR (film) cm^{-1}: 3430, 1729. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.13 (3H, t, J=7.5 Hz), 2.34 (2H, q, J=7.5 Hz), 4.26 (2H, d, J=6.5 Hz), 4.48 (2H, d, J=6.0 Hz), 5.6—5.9 (2H, m). FAB-MS m/z: 145 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_7H_{12}O_3$+H: 145.0865. Found: 145.0845 $(M+H)^+$.

The *E*-Diol Monopropionate (*E*-7) A solution of the *Z*-monopropionate (*Z*-**7**, 18.5 g, 130 mmol) in dry CH_2Cl_2 (40 ml) was added to a stirred suspension of pyridinium chlorochromate (41.5 g, 190 mmol) in dry CH_2Cl_2 (180 ml) and the mixture was stirred at room temperature for 1 h. After addition of ether (500 ml) to the reaction mixture, the whole was passed through a Florisil column (100 g). The eluate was evaporated under reduced pressure to give an aldehyde (18.2 g). The aldehyde (18.2 g) was dissolved in ether (100 ml) and MeOH (10 ml), and the mixture was stirred in an ice-water bath for 30 min. The reaction mixture was poured into ice-water and extracted with ether. The ether extract was washed with 5% aqueous HCl, aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (17.5 g), which was purified by column chromatography (SiO_2 300 g, *n*-hexane : EtOAc = 2 : 1) to afford the *E*-monopropionate (*E*-**7**, 13.3 g, 72.3 mmol, 72%).

E-**7**: Colorless oil. IR (film) cm^{-1}: 3420, 1731. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 1.23 (3H, t, J=7.5 Hz), 2.35 (2H, q, J=7.5 Hz), 4.15 (2H, br t), 4.59 (2H, d, J=4.0 Hz), 5.6—5.9 (2H, m). EI-MS m/z: 144 (M^+, 2), 57 (100). High-resolution MS m/z: Calcd for $C_7H_{12}O_3$: 144.0787. Found: 144.0798 (M^+).

The *E*-Diol Mono-MMTr Ether (8a) Monomethoxytrityl chloride (2.81 g, 9.09 mmol) was added to a stirred solution of the *E*-diol monopropionate (*E*-**7**, 875 mg, 6.06 mmol) in dry pyridine (10 ml), and the whole mixture was stirred at room temperature for 1.5 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The EtOAc extract was washed with 5% aqueous HCl, aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave an *E*-MMTr-propionate (3.56 g). A stirred solution of the *E*-MMTr-propionate (3.56 g) in MeOH (10 ml) was treated with 10% KOH–MeOH (10 ml), and the whole mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and extracted with EtOAc. The EtOAc extract was washed with brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product (3.56 g), which was purified by column chromatography (SiO_2 90 g, *n*-hexane : EtOAc = 3 : 1) to afford the *E*-diol mono-MMTr ether (**8a**, 1.74 g, 4.82 mmol, 80%).

8a: Colorless oil. IR (film) cm^{-1}: 3360, 3020, 2930, 2860. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.6—3.7 (2H, m), 3.78 (3H, s), 4.1—4.2 (2H, m), 5.6—6.2 (2H, m), 6.8—7.5 (14H, m). EI-MS m/z (%): 360 (M^+, 5), 273 (MMTr, 100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{24}O_3$: 360.1725. Found: 360.1735 (M^+).

The *E*-Diol Monobenzyl Ether (8b) A solution of the *E*-diol mono-MMTr ether (**8a**, 380 mg, 1.06 mmol) was added to a suspension of 60% sodium hydride (66 mg, 1.65 mmol) in dry 1,2-dimethoxyethane (10 ml), and the mixture was stirred at 40 °C for 30 min. After cooling, benzyl bromide (0.14 ml, 1.21 mmol) was added to the reaction mixture, and the whole was stirred at room temperature for a further 1 h. Work-up of the mixture in a usual manner gave a benzyl-MMTr ether (600 mg). A solution of the benzyl-MMTr ether (600 mg) was treated with 5% aqueous HCl (0.5 ml), and the whole mixture was stirred at room temperature for 5 h. Work-up of the reaction mixture gave a product (600 mg), which was purified by column chromatography (SiO_2 20 g, *n*-hexane : EtOAc = 3 : 2) to afford the *E*-diol monobenzyl ether (**8b**, 153 mg, 0.86 mmol, 81%).

8b: Colorless oil. IR (film) cm^{-1}: 3390, 3055, 3020, 744, 694, ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 4.08 (2H, d, J=4 Hz), 4.1—4.2 (2H, m), 4.54 (2H, s), 5.8—6.0 (2H, m), 7.35 (5H, br s). FAB-MS m/z: 179 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_{11}H_{14}O_2$+H: 179.1072. Found: 179.1072 $(M+H)^+$.

The *E*-Diol Monomethoxymethyl Ether (8c) A solution of *E*-**7** (500 mg, 3.47 mmol) in dry CH_2Cl_2 (5.0 ml) was treated with diisopropylethylamine (1.2 ml, 6.94 mmol) and chloromethyl methyl ether (0.4 ml, 5.21 mmol). The mixture was stirred at room temperature for 30 min. Work-up of the reaction mixture gave a MOM-propionate (650 mg). A solution of the MOM-propionate (650 mg) in MeOH (5 ml) was treated with 10% KOH–MeOH (5 ml), and the whole mixture was stirred at room temperature for 30 min. Work-up of the reaction mixture in a usual manner gave a product (450 mg), which was purified by column chromatography (SiO_2 9 g, *n*-hexane : EtOAc = 2 : 1) to afford the *E*-diol monomethoxymethyl ether (**8c**, 390 mg, 2.95 mmol, 85%).

8c: Colorless oil. IR (film) cm^{-1}: 3420. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.35 (3H, s), 4.0—4.2 (2H, s), 5.7—5.9 (2H, m). FAB-MS m/z: 139 $(M+Li)^+$, 133 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_6H_{12}O_3$+H: 133.0865. Found: 133.0892 $(M+H)^+$.

The *E*-Diol Mono-*tert*-butyldimethylsilyl Ether (8d) A solution of *E*-**7** (500 mg, 3.47 mmol) in dry dimethylformamide (DMF) (3 ml) was treated with *tert*-butyldimethylsilyl chloride (628 mg, 4.17 mmol) and imidazole (567 mg, 8.33 mmol), and the whole mixture was stirred at room temperature for 10 min. The reaction mixture was poured into ice-water, and extracted with EtOAc. The EtOAc extract was washed with 5% aqueous HCl, aqueous saturated $NaHCO_3$ and brine. Removal of the

solvent under reduced pressure gave a TBDMS-propionate (1.1 g). A solution of the TBDMS-propionate (1.1 g) in MeOH (4.0 ml) was treated with 10% KOH–MeOH (4.0 ml), and the whole mixture was stirred at room temperature for 30 min. Work-up of the reaction mixture in a usual manner gave a product (1.0 g). Purification of the product by column chromatography (SiO_2 30 g, *n*-hexane : EtOAc = 3 : 1) furnished the *E*-mono-*tert*-butyldimethylsilyl ether (**8d**, 685 mg, 3.39 mmol, 98%).

8d: Colorless oil. IR (film) cm^{-1}: 3400, 1254. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.09 (6H, s), 0.93 (9H, s), 4.0—4.2 (4H, m), 5.7—5.9 (2H, m). FAB-MS *m/z*: 203 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{10}H_{22}O_2Si+H$: 203.1467. Found: 203.1445 $(M+H)^+$.

The *Z*-Diol Mono-MMTr Ether (9a) Compound **9a** (2.28 g, 6.61 mmol, 95% yield) was obtained from *Z*-**7** (1.0 g, 6.97 mmol) through a procedure similar to that used to synthesize **8a** from *E*-**7**.

9a: Colorless oil. IR (film) cm^{-1}: 3400, 3060, 3010, 2930. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.71 (2H, m), 3.81 (3H, s), 4.04 (2H, m), 5.76 (2H, m), 6.8—7.5 (14H, m). EI-MS *m/z* (%): 360 (M^+, 3), 273 (MMTr, 100). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{24}O_3$: 360.1725. Found: 360.1735 (M^+).

The *Z*-Diol Monobenzyl Ether (9b) Compound **9b** (226 mg, 1.49 mmol, 79% yield) was obtained from **9a** (680 mg, 1.89 mmol) through a procedure similar to that used for **8b** from **8a**.

9b: Colorless oil. IR (film) cm^{-1}: 3425, 3055, 3020, 744, 694. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 4.10 (2H, d, J=5 Hz), 4.15 (2H, d, J=5 Hz), 4.53 (2H, s), 5.6—5.9 (2H, m), 7.35 (5H, br s). FAB-MS *m/z*: 179 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{11}H_{14}O_2+H$: 179.1072. Found: 179.1078 $(M+H)^+$.

The *Z*-Diol Monomethoxymethyl Ether (9c) Compound **9c** (380 mg, 2.88 mmol, 83%, yield) was obtained from *Z*-**7** (500 mg, 3.47 mmol) through a procedure similar to that used for **8c** from *E*-**7**.

9c: Colorless oil. IR (film) cm^{-1}: 3400. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.38 (3H, s), 4.1—4.3 (4H, m), 4.64 (2H, s), 5.5—6.0 (2H, m). FAB-MS *m/z*: 139 $(M+Li)^+$, 133 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_6H_{12}O_3+H$: 133.0865. Found: 133.0890 $(M+H)^+$.

The *Z*-Diol Mono-*tert*-butyldimethylsilyl Ether (9d) Compound **9d** (678 mg, 3.36 mmol, 97% yield) was obtained from *Z*-**7** (500 mg, 3.47 mmol) through a procedure similar to that used for **8d** from *E*-**7**.

9d: Colorless oil. IR (film) cm^{-1}: 3350, 1255. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.09 (6H, s), 0.91 (9H, s), 4.1—4.3 (4H, m), 5.8—6.0 (2H, m). FAB-MS *m/z*: 203 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{10}H_{22}O_2Si+H$: 203.1467. Found: 203.1465 $(M+H)^+$.

Asymmetric Epoxidation of 8a Giving (−)-10a Titanium tetraisopropoxide (1.95 ml, 6.56 mmol) and diethyl L-(+)-tartrate (1.12 ml, 6.56 mmol) were added sequentially to dry CH_2Cl_2 (40 ml) with stirring at −20 °C and the whole mixture was stirred for 30 min. Then, a solution of **8a** (2.36 g, 6.56 mmol) in dry CH_2Cl_2 (15 ml) was added and the resulting mixture was stirred at −20 °C for 30 min. Further, *tert*-butylhydroperoxide in isooctane (3.0 M, 4.37 ml, 13.1 mmol) was added dropwise to the reaction mixture at a moderate rate (over *ca.* 5 min). Stirring was continued at −20 °C for 11 h, then the reaction mixture was treated with 10% aqueous tartaric acid (15 ml) and stirred again at −20 °C for 30 min and at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, then dried over $MgSO_4$, and evaporated to give a residue. The residue, dissolved into ether (48 ml), was treated with 1 N aqueous NaOH (18 ml) in an ice-water bath for 30 min. The whole was extracted with ether. The combined organic phase was washed with brine, and dried over $MgSO_4$. Removal of the solvent gave a product (2.5 g), which was purified by column chromatography (SiO_2 60 g, *n*-hexane : EtOAc = 2 : 1) to afford (−)-**10a** (2.07 g, 5.51 mmol, 84%).

(−)-**10a**: Colorless oil. $[\alpha]_D^{24}$ +7.2° (*c*=1.1, MeOH). IR (film) cm^{-1}: 3400. ^{1}H-NMR (90 MHz, C_6D_6) δ: 2.6—2.8 (1H, m), 3.0—3.4 (5H, m), 3.28 (3H, s), 6.7—7.7 (14H, m). EI-MS *m/z* (%): 376 (M^+, 11), 273 (100). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{24}O_4$: 376.1674. Found: 376.1675 (M^+).

Asymmetric Epoxidation of 8a Giving (+)-10a Titanium tetraisopropoxide (1.46 ml, 4.95 mmol) and diethyl D-(−)-tartrate (0.86 ml, 4.94 mmol) were added sequentially to dry CH_2Cl_2 (35 ml) with stirring at −20 °C and the mixture was stirred for 30 min. Then, a solution of **8a** (1.78 g, 4.94 mmol) in dry CH_2Cl_2 (12 ml) was added and the resulting mixture was stirred at −20 °C for 30 min. Further, *tert*-butylhydroperoxide in isooctane (3.0 M, 3.29 ml, 9.88 mmol) was added dropwise to the reaction mixture at a moderate rate (over *ca.* 4 min). The resulting mixture was stirred further at −20 °C for 12 h, and 10% aqueous tartaric acid (11 ml) was added, then the whole was stirred at −20° C for 30 min and at room temperature for 1 h. The reaction mixture was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, then dried over $MgSO_4$, and evaporated to give a residue. The residue, dissolved into ether (35 ml), was treated with 1 N aqueous NaOH (13 ml) in an ice-water bath for 30 min. The whole was extracted with ether. The combined organic phase was washed with brine and dried over $MgSO_4$. Removal of the solvent gave a product (2.0 g), which was purified by column chromatography (SiO_2 60 g, *n*-hexane : EtOAc = 2 : 1) to afford (+)-**10a** (1.47 g, 3.91 mmol, 79%).

(+)-**10a**: Colorless oil. $[\alpha]_D^{23}$ +7.2° (*c*=1.1, MeOH). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{24}O_4$: 376.1674. Found: 376.1675 (M^+). IR, ^{1}H-NMR and EI-MS data for (+)-**10a** were identical with those for (−)-**10a**.

Asymmetric Epoxidation of 8b Giving (−)-10b Compound (−)-**10b** (84 mg, 0.43 mmol, 86% yield) was obtained from **8b** (90 mg, 0.51 mmol) through a procedure similar to that used for (−)-**10a** from **8a**.

(−)-**10b**: Colorless oil. $[\alpha]_D^{23}$ −21.4° (*c*=1.1, MeOH). IR (film) cm^{-1}: 3430, 3079, 3029. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.0—3.3 (2H, m), 3.4—3.9 (4H, m), 4.59 (2H, s), 7.35 (5H, s). FAB-MS *m/z*: 217 $(M+Na)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{11}H_{14}O_3+Na$: 217.0851. Found: 217.0823 $(M+Na)^+$.

Asymmetric Epoxidation of 8b Giving (+)-10b Compound (+)-**10b** (87 mg, 0.45 mmol, 89% yield) was obtained from **8b** (90 mg, 0.51 mmol) through a procedure similar to that used for (+)-**10a** from **8a**.

(+)-**10b**: Colorless oil. $[\alpha]_D^{23}$ +21.2° (*c*=1.0, MeOH). High-resolution FAB-MS *m/z*: Calcd for $C_{11}H_{14}O_3+Na$: 217.0841. Found: 217.0824 $(M+Na)^+$. IR, ^{1}H-NMR and FAB-MS data for (+)-**10b** were identical with those for (−)-**10b**.

Asymmetric Epoxidation of 8c Giving (−)-10c Using Diethyl L-(+)-Tartrate Compound (−)-**10c** (55 mg, 0.37 mmol, 62% yield) was obtained from **8c** (80 mg, 0.61 mmol) through a procedure similar to that described for (−)-**10a** from **8a**.

(−)-**10c**: Colorless oil. $[\alpha]_D^{23}$ −26.0° (*c*=1.3, MeOH). IR (film) cm^{-1}: 3450, 3005. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 3.0—3.3 (2H, m), 3.38 (3H, s), 3.5—4.0 (4H, m), 4.66 (2H, m). FAB-MS *m/z*: 149 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_6H_{12}O_4+H$: 149.0814. Found: 149.0838 $(M+H)^+$.

Asymmetric Epoxidation of 8c Giving (−)-10c Using Diisopropyl L-(+)-Tartrate Titanium tetraisopropoxide (0.066 ml, 0.22 mmol) and diisopropyl L-(+)-tartrate (0.056 ml, 0.26 mmol) were added sequentially to a stirred suspension of molecular sieves 4A (132 mg) in dry CH_2Cl_2 (17.5 ml) at −25 °C and the mixture was stirred at the same temperature for 30 min. Then, a solution of **8c** (582 mg, 4.41 mmol) in dry CH_2Cl_2 (5 ml) was added and the resulting mixture was stirred at −25 °C for 30 min. Further, *tert*-butylhydroperoxide in isooctane (3.0 M, 2.90 ml, 8.82 mmol) was added dropwise to the reaction mixture at a moderate rate (over *ca.* 4 min). The resulting mixture was stirred further at −25 °C for 20 h, and a solution of citric acid monohydrate (46 mg) in acetone–ether (1 : 9, 6.7 ml) was added, then the whole was stirred at room temperature for 30 min. The reaction mixture was passed through a Celite column and the eluate was evaporated to give a product (750 mg). Purification of the product by column chromatography (SiO_2 20 g, *n*-hexane : EtOAc = 2 : 3) afforded (−)-**10c** (542 mg, 3.66 mmol, 83%).

Asymmetric Epoxidation of 8c Giving (+)-10c Using Diethyl D-(−)-Tartrate Compound (+)-**10c** (57 mg, 0.39 mmol, 64% yield) was obtained from **8c** (80 mg, 0.61 mmol) through a procedure similar to that described for **10a** from **8a**.

(+)-**10c**: Colorless oil. $[\alpha]_D^{23}$ +25.4° (*c*=1.0, MeOH). High-resolution FAB-MS *m/z*: Calcd for $C_6H_{12}O_4+H$: 149.0814. Found: 149.0788 $(M+H)^+$. IR, ^{1}H-NMR and FAB-MS data for (+)-**10c** were identical with those for (−)-**10c**.

Asymmetric Epoxidation of 8c Giving (+)-10c Using Diisopropyl D-(−)-Tartrate Titanium tetraisopropoxide (0.059 mmol, 0.20 mmol, 0.05 eq) and diisopropyl D-(−)-tartrate (0.050 ml, 0.24 mmol, 0.06 eq) were added sequentially to a suspension of molecular sieves 4A (119 mg) in dry CH_2Cl_2 (15.7 ml) with stirring at −25 °C and the mixture was stirred for 30 min. Then, a solution of **8c** (523 mg, 3.96 mmol) in dry CH_2Cl_2 (5 ml) was added and the resulting mixture was stirred at −25 °C for 30 min. Further, *tert*-butylhydroperoxide in isooctane (3.0 M, 2.60 ml, 8.82 mmol) was added to the reaction mixture at a moderate rate (over *ca.* 4 min). The resulting mixture was stirred further at −25°C for 20 h, and a solution of citric acid monohydrate (41 mg) in acetone–ether (1 : 9, 6.0 ml) was added, then the whole was stirred at room temperature for 30 min. The reaction mixture was passed through a Celite column and the eluate was evaporated to give a product (670 mg). Purification of the product by column chromatography (SiO_2 20 g, *n*-hexane : EtOAc = 2 : 3) afforded (+)-**10c** (480 mg, 3.24 mmol, 82%).

Asymmetric Epoxidation of 8d Giving (−)-10d Compound (−)-**10d** (81 mg, 0.37 mmol, 75% yield) was obtained from **8d** (100 mg, 0.50 mmol) through a procedure similar to that used for (−)-**10a** from **8a**.

(−)-**10d**: Colorless oil. $[\alpha]_D^{24}$ −11.6° (c=0.9, MeOH). IR (film) cm^{-1}: 3400, 1253. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.12 (6H, s), 0.92 (9H, s), 2.4—2.6 (1H, m), 2.80 (1H, d-like), 3.95 (2H, br s), 4.09 (2H, s). FAB-MS m/z: 219 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_{10}H_{22}O_3Si+H$: 219.1416. Found: 219.1394 $(M+H)^+$.

Asymmetric Epoxidation of 8d Giving (+)-10d Compound (+)-**10d** (82 mg, 0.38 mmol, 76% yield) was obtained from **8d** (100 mg, 0.50 mmol) through a procedure similar to that used for (+)-**10a** from **8a**.

(+)-**10d**: Colorless oil. $[\alpha]_D^{23}$ +10.9° (c=1.0, MeOH). High-resolution FAB-MS m/z: Calcd for $C_{10}H_{22}O_3Si+H$: 219.1416. Found: 219.1382 $(M+H)^+$. IR, ^{1}H-NMR and FAB-MS data for (+)-**10d** were identical with those for (−)-**10d**.

Asymmetric Epoxidation of 9a Giving (−)-11a Compound (−)-**11a** (845 mg, 2.25 mmol, 81% yield) was obtained from **9a** (1.0 g, 2.78 mmol) through a procedure similar to that described for (−)-**10a** from **8a**.

(−)-**11a**: Colorless oil. $[\alpha]_D^{24}$ −16° (c=1.2, MeOH). IR (film) cm^{-1}: 3540, 3066. ^{1}H-NMR (90 MHz, C_6D_6) δ: 2.8—3.0 (2H, m), 3.0—3.5 (4H, m), 3.27 (3H, s), 6.6—7.6 (14H, m). EI-MS m/z (%): 376 (M^+, 6), 273 (100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{24}O_4$: 376.1672. Found: 376.1661 (M^+).

Asymmetric Epoxidation of 9a Giving (+)-11a Compound (+)-**11a** (815 mg, 2.17 mmol) was obtained from **9a** (1.0 g, 2.78 mmol) through a procedure similar to that described for (+)-**10a** from **8a**.

(+)-**11a**: Colorless oil. $[\alpha]_D^{23}$ +16° (c=1.0, MeOH). High-resolution EI-MS m/z: Calcd for $C_{24}H_{24}O_4$: 376.1675. Found: 376.1677 (M^+). IR, ^{1}H-NMR and EI-MS data for (+)-**11a** were identical with those for (−)-**11a**.

Asymmetric Epoxidation of 9b Giving (−)-11b Compound (−)-**11b** (80 mg, 0.37 mmol, 74% yield) was obtained from **9b** (100 mg, 0.50 mmol) through a procedure similar to that used for (−)-**10b** from **8b**.

(−)-**11b**: Colorless oil. $[\alpha]_D^{24}$ −10.5° (c=0.9, MeOH). IR (film) cm^{-1}: 3400, 3082, 3056, 3028, 736, 697. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.12 (1H, t, J=6 Hz), 3.1—3.4 (2H, m), 3.6—3.8 (4H, m), 4.51, 4.67 (2H, ABq, J=12 Hz), 7.35 (5H, s). FAB-MS m/z: 217 $(M+Na)^+$, 195 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_{11}H_{14}O_3+H$: 195.1021. Found: 195.0973 $(M+H)^+$.

Asymmetric Epoxidation of 9b Giving (+)-11b Compound (+)-**11b** (83 mg, 0.38 mmol, 77% yield) was obtained from **9b** (100 mg, 0.50 mmol) through a procedure similar to that used for (+)-**10b** from **8b**.

(+)-**11b**: Colorless oil. $[\alpha]_D^{24}$ +10.4° (c=0.9, MeOH). High-resolution FAB-MS m/z: Calcd for $C_{11}H_{14}O_3+H$: 195.1021. Found: 195.0980 $(M+H)^+$. IR, ^{1}H-NMR and FAB-MS data for (+)-**11b** were identical with those for (−)-**11b**.

Asymmetric Epoxidation of 9c Giving (−)-11c Compound (−)-**11c** (58 mg, 0.39 mmol, 65% yield) was obtained from **9c** (80 mg, 0.61 mmol) through a procedure similar to that used for the synthesis of (−)-**10c** from **8c** using diethyl L-(+)-tartrate.

(−)-**11c**: Colorless oil. $[\alpha]_D^{22}$ −18.6° (c=1.1, MeOH). IR (film) cm^{-1}: 3450, 3005. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.36 (1H, t, J=6 Hz), 3.2—3.3 (2H, m), 3.40 (3H, s), 3.6—3.9 (4H, m), 4.68 (2H, s). FAB-MS m/z: 149 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_6H_{12}O_4+H$: 149.0814. Found: 149.0784 $(M+H)^+$.

Asymmetric Epoxidation of 9c Giving (+)-11c Compound (+)-**11c** (54 mg, 0.36 mmol, 60% yield) was obtained from **9c** (80 mg, 0.61 mmol) through a procedure similar to that employed for (+)-**10c** from **8c** using diethyl L-(+)-tartrate.

(+)-**11c**: Colorless oil. $[\alpha]_D^{24}$ +17.9° (c=0.9, MeOH). High-resolution FAB-MS m/z: Calcd for $C_6H_{12}O_4+H$: 149.0814. Found: 149.0795 $(M+H)^+$. IR, ^{1}H-NMR and FAB-MS data for (+)-**11c** were identical with those for (−)-**11c**.

Asymmetric Epoxidation of 9d Giving (−)-11d Compound (−)-**11d** (82 mg, 0.42 mmol, 84% yield) was obtained from **9d** (90 mg, 0.51 mmol) through a procedure similar to that employed for (−)-**10d** from **8d**.

(−)-**11d**; Colorless oil. $[\alpha]_D^{23}$ −12.3° (c=1.0, MeOH). IR (film) cm^{-1}: 3400, 3001, 1254. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.11 (6H, s), 0.91 (9H, s), 2.19 (1H, t, J=6.5 Hz), 3.1—3.3 (2H, m), 3.6—3.9 (4H, m). FAB-MS m/z: 241 $(M+Na)^+$, 219 $(M+H)^+$. High-resolution FAB-MS m/z: Calcd for $C_{10}H_{22}O_3Si+H$: 219.1416. Found: 219.1378 $(M+H)^+$.

Asymmetric Epoxidation of 9d Giving (+)-11d Compound (+)-**11d** (87 mg, 0.45 mmol, 89% yield) was obtained from **9d** (90 mg, 0.51 mmol) through a procedure similar to that used for (+)-**10d** from **8d**.

(+)-**11d**: Colorless oil. $[\alpha]_D^{23}$ +11.8° (c=1.1, MeOH). High-resolution FAB-MS m/z: Calcd for $C_{10}H_{22}O_3Si+H$: 219.1416. Found: 219.1386 $(M+H)^+$. IR, ^{1}H-NMR and FAB-MS data for (+)-**11d** were identical with those for (−)-**11d**.

Preparation of 12 and 13 from (+)-10a A solution of titanium tetraisopropoxide (2.4 ml, 7.98 mmol) and trimethylsilyl azide (2.1 ml, 16.0 mmol) in dry benzene (50 ml) was heated under reflux for 6 h. After cooling of the reaction mixture to 40 °C, a solution of (+)-**10a** (2.0 g, 5.32 mmol) in dry benzene (26 ml) was added dropwise over a period of 10 min, and the resulting mixture was stirred at 40 °C for 30 min. After cooling, the reaction mixture was evaporated, the residue was dissolved in ether (110 ml), and the whole was stirred at room temperature for 1 h. The organic phase was separated and washed with aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent gave a product (2.5 g), which was purified by column chromatography (SiO_2 50 g, n-hexane : EtOAc = 2 : 1→3 : 2) to afford a 1,2-diol (**12**, 1.67 g, 4.13 mmol, 78%) and a 1,3-diol (**13**, 0.12 g, 0.29 mmol, 6%).

12: Colorless oil. $[\alpha]_D^{25}$ +5.9° (c=1.6, MeOH). IR (CCl_4) cm^{-1}: 3400, 2100. ^{1}H-NMR (90 MHz, C_6D_6) δ: 3.25 (3H, s), 3.2—3.6 (6H, m), 6.6—7.7 (14H, m). EI-MS m/z (%): 419 (M^+, 4), 273 (100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{25}N_3O_4$: 419.1842. Found: 419.1827 (M^+).

13: Colorless oil. $[\alpha]_D^{22}$ +16° (c=2.0, MeOH). IR (CCl_4) cm^{-1}: 3400, 2100. ^{1}H-NMR (90 MHz, C_6D_6) δ: 3.28 (3H, s), 3.2—3.7 (6H, m), 6.6—7.6 (14 H, m). EI-MS m/z (%): 419 (M^+, 4), 273 (100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{25}N_3O_4$: 419.1842. Found: 419.1820 (M^+).

Benzoylation of 12 Giving 12a Benzoyl chloride (0.2 ml, 1.17 mmol) was added to a solution of **12** (10 mg, 0.023 mmol) in pyridine (0.5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and extracted with EtOAc. The EtOAc extract was washed with 5% aqueous HCl, aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (20 mg), which was purified by column chromatography (SiO_2 1 g, n-hexane : EtOAc = 6 : 1) to afford **12a** (13 mg, 0.021 mmol, 87%).

12a: Colorless oil. $[\alpha]_D^{24}$ −11° (c=1.0, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2100, 1720. ^{1}H-NMR (500 MHz, C_6D_6) δ: 3.22 (3H, s, OMe), 3.48 (2H, m), 3.5—3.8 (1H, m), 4.42 (1H, dd, J=6.0, 12.0 Hz), 4.70 (1H, dd, J=4.0, 12.0 Hz), 5.70 (1H, m), 6.6—8.1 (24H, m). FAB-MS m/z: 650 $(M+Na)^+$, 627 (M^+). High-resolution FAB-MS m/z: Calcd for $C_{38}H_{33}N_3O_6$: 627.2368. Found: 627.2390 (M^+).

Benzoylation of 13 Giving 13a Compound **13a** (14 mg, 0.022 mmol, 94% yield) was obtained from **13** (10 mg, 0.023 mmol) through a procedure similar to that used for **12a** from **12**.

13a: Colorless oil. $[\alpha]_D^{23}$ −12° (c=1.8, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2100, 1720. ^{1}H-NMR (500 MHz, C_6D_6) δ: 3.22 (3H, s), 3.55 (1H, dd, J=5.0, 11.0 Hz), 3.63 (1H, dd, J=4.0, 11.0 Hz), 4.19 (1H, ddd, J=7.5, 3.5, 5.0 Hz), 4.28 (1H, dd, J=7.5, 11.5 Hz), 4.56 (1H, dd, J=3.5, 11.5 Hz), 5.53 (1H, m), 6.8—8.3 (24 H, m). FAB-MS m/z: 650 $(M+Na)^+$, 627 (M^+). High-resolution FAB-MS m/z: Calcd for $C_{38}H_{33}N_3O_6$: 627.2368. Found: 627.2398 (M^+).

Monobenzoylation of 12 Followed by Methoxymethylation Giving 14 Benzoyl chloride (1.3 ml, 11.1 mmol, 1.5 eq) was added at 0 °C to a solution of **12** (3.09 g, 7.37 mmol) and triethylamine (10.3 ml, 73.7 mmol, 10 eq) in dry CH_2Cl_2 (80 ml), and the whole mixture was stirred at the same temperature for 1 h. Work-up of the reaction mixture in a usual manner gave a product (4.5 g), which was purified by column chromatography (SiO_2, 90 g, n-hexane : EtOAc = 6 : 1) to yield a monobenzoate (3.39 g, 6.5 mmol). Diisopropylethylamine (7.97 ml, 45.4 mmol, 7.0 eq) and chloromethyl methyl ether (1.97 ml, 25.9 mmol, 4.0 eq) were added to a solution of the monobenzoate (3.39 g) in dry CH_2Cl_2 (30 ml) and the resulting mixture was heated under reflux for 4 h. After cooling, the reaction mixture was worked up in the usual manner to give a product (3.4 g). Purification of the product by a column chromatography (SiO_2 60 g, n-hexane : EtOAc = 4 : 1) afforded **14** (3.49 g, 6.16 mmol, 84%).

14: Colorless oil. $[\alpha]_D^{23}$ +15° (c=1.8, MeOH). IR (CCl_4) cm^{-1}: 2085, 1725. ^{1}H-NMR (90 MHz, C_6D_6) δ: 2.97 (3H, s), 3.25 (3H, s), 3.2—3.8 (4H, m), 4.33 (2H, s), 4.2—4.7 (2H, m), 6.6—8.2 (19H, m). EI-MS m/z (%): 567 (M^+, 3), 273 (100). High-resolution EI-MS m/z: Calcd for $C_{33}H_{33}N_3O_6$: 567.2307. Found: 567.2292 (M^+).

$LiAlH_4$ Reduction of 14 Followed by Acetylation A suspension of $LiAlH_4$ (535 mg, 14.1 mmol) in dry tetrahydrofuran (THF) (25 ml) was treated with a solution of **14** (2.0 g, 3.53 mmol) in dry THF (15 ml), and the mixture was stirred at room temperature for 30 min. The reaction was quenched by adding ether saturated with water and 4 N aqueous NaOH, and the precipitate was removed by filtration. The filtrate was evaporated to give an aminoalcohol (2.0 g). Acetic anhydride (3.5 ml, 35 mmol) was

added to a solution of the aminoalcohol (2.0 g) in MeOH (30 ml), and the whole mixture was stirred at room temperature for 10 min. Removal of the solvent from the mixture gave a product (2.2 g), which was purified by column chromatography (SiO_2 50 g, $CHCl_3 \rightarrow CHCl_3$: MeOH = 20 : 1) to afford a hydroxyamide (**15**, 1.39 g, 2.9 mmol, 82%).

15: Colorless oil. $[\alpha]_D^{23}$ +30° (c = 1.9, MeOH). IR (film) cm^{-1}: 3300, 3055, 2925, 2880, 1670. ^{1}H-NMR (90 MHz, C_6D_6) δ; 1.51 (3H, s), 3.12 (3H, s), 3.29 (3H, s), 3.5—3.8 (5H, m), 4.51, 4.59 (2H, ABq, J = 7.0 Hz), 4.3—4.6 (1H, m), 5.55 (1H, br d, amide proton), 6.6—7.6 (14H, m). EI-MS m/z (%): 479 (M^+, 0.2), 273 (100). High-resolution EI-MS m/z: Calcd for $C_{28}H_{33}NO_6$: 479.2305. Found: 479.2297 (M^+).

Swern Oxidation of 15 Followed by Wittig Reaction and Acidic Hydrolysis A solution of DMSO (0.075 ml, 0.97 mmol, 2.2 eq) in dry CH_2Cl_2 (0.22 ml) was mixed with a solution of oxalyl chloride (0.044 ml, 0.48 mmol, 1.1 eq) in dry CH_2Cl_2 (1.1 ml), and the whole was stirred at −78 °C for 15 min. Then, a solution of **15** (209 mg, 0.44 mmol) in dry CH_2Cl_2 (1.0 ml) was added. The reaction mixture was stirred at −78 °C for a further 30 min, then triethylamine (0.3 ml, 2.2 mmol, 5.0 eq) was added and the whole was warmed to room temperature, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave an aldehyde (210 mg). The aldehyde in dry THF (1.5 ml) was treated at −78 °C with a tetradecyltriphenylphosphorane reagent [prepared from triphenylphosphine tetradecylbromide (712 mg, 1.3 mmol, 3.0 eq), n-butyl lithium (1.6 M solution in n-hexane, 0.41 ml, 0.66 mmol, 1.5 eq), and dry THF (1.0 ml)]. The reaction mixture was further stirred at 0 °C for 4 h. Work-up of the reaction mixture in a usual manner gave a product (950 mg), which was purified by column chromatography (SiO_2 5 g, n-hexane : EtOAc = 2 : 3) to furnish a C18 compound (244 mg, 0.37 mmol). This product was treated with 9% HCl–MeOH (2.5 ml) at room temperature for 3 h. The reaction mixture was neutralized with a silver carbonate powder, and the precipitate was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product (250 mg), which was purified by column chromatography (SiO_2 6 g, $CHCl_3$: MeOH = 50 : 1) to afford a mixture (110 mg, 0.32 mmol, 78%) of N-acetyl-D-*erythro*-C18-sphingosine (**16**) and its 4Z-isomer (**17**). The ratio (1 : 2) of **16** and **17** was determined by ^{1}H-NMR analysis (500 MHz, $CDCl_3$).

Photoisomerization of a Mixture of 16 and 17 A solution of the mixture of **16** and **17** (1 : 2, 50 mg, 0.15 mmol) and diphenyl disulfide (33 mg, 0.15 mmol) in dry dioxane (2.0 ml)–dry cyclohexane (8.0 ml) was irradiated by a 500 W high-pressure mercury lamp through a Pyrex filter at 20—30 °C for 6 h. The reaction mixture was concentrated under reduced pressure and the residue was treated with acetic anhydride (0.2 ml) and pyridine (0.5 ml) at room temperature for 2 h. The whole mixture was evaporated to give a product (96 mg). Purification of the product by column chromatography (SiO_2 3 g, n-hexane : EtOAc = 1 : 2) furnished N,O,O-triacetyl-D-*erythro*-C18-sphingosine (**18**, 51 mg, 0.12 mmol, 82%) and **19** (10 mg, 0.02 mmol, 16%).

18: Colorless needles, mp 101—102 °C (n-hexane–EtOAc). $[\alpha]_D^{24}$ −11.4° (c = 1.2, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3455, 1733, 1672, 969. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, J = 7.0 Hz, 18-H_3), 1.26 (22H, s, $CH_2 \times 11$), 1.99, 2.07, 2.08 (3H each, all s, $COCH_3 \times 3$), 2.0—2.1 (2H, m, 6-H), 4.05 (1H, dd, J = 4.0, 12.0 Hz, 1-H_a), 4.31 (1H, dd, J = 6.0, 12.0 Hz, 1-H_b), 4.44 (1H, m, 2-H), 5.28 (1H, dd, J = 7.0, 7.5 Hz, 3-H), 5.39 (1H, dd, J = 15.0, 7.5 Hz, 4-H), 5.66 (1H, d, J = 9.0 Hz, amide proton), 5.80 (1H, dt, J = 15.0, 7.0 Hz, 5-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.2 (C-18), 20.9, 21.2 ($COCH_3 \times 2$), 22.8 (C-17), 23.4 ($NHCOCH_3$), 29.0, 29.2, 29.4, 29.5, 29.7 (totally 9C, C-7—15), 32.0 (C-16), 32.3 (C-6), 50.8 (C-2), 62.7 (C-1), 73.9 (C-3), 124.2 (C-5), 137.5 (C-4), 169.7, 170.0, 171.0 ($COCH_3 \times 3$). EI-MS m/z (%): 425 (M^+, 0.2), 366 (3), 144 (100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{43}NO_5$: 425.3138. Found: 425.3128 (M^+).

19: Colorless needles, mp 84—85 °C (n-hexane–EtOAc). $[\alpha]_D^{24}$ +4.3° (c = 0.9, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3455, 1735, 1676. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, J = 7.0 Hz, 18-H_3), 1.25 (22H, s, $CH_2 \times 11$), 1.98, 2.05, 2.07 (3H each, all s, $COCH_3 \times 3$), 2.1—2.3 (2H, m, 6-H), 4.04 (1H, dd, J = 4.0, 11.5 Hz, 1-H_a), 4.33 (1H, dd, J = 6.5, 11.5 Hz, 1-H_b), 4.4—4.5 (1H, m, 2-H), 5.32 (1H, dd, J = 9.0, 11.0 Hz, 3-H), 5.6—5.8 (3H, m, 4-H, 5-H, amide proton). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.2 (C-18), 20.9, 21.1 ($COCH_3 \times 2$), 22.7 (C-17), 23.4 ($NHCOCH_3$), 28.1 (C-6), 29.4, 29.5, 29.6, 29.7 (totally 9C, C-7—15), 32.0 (C-16), 51.2 (C-2), 62.7 (C-1), 69.7 (C-3), 123.9 (C-5), 137.1 (C-4), 169.8, 170.0, 171.1 ($COCH_3 \times 3$). FAB-MS m/z: 448 ($M+Na$)$^+$, 426 ($M+H$)$^+$. High-resolution FAB-MS m/z: Calcd for $C_{24}H_{43}NO_5+H$: 426.3220. Found: 426.3269 ($M+H$)$^+$.

Preparation of D-*erythro*-C18-Sphingosine (1) from 18 A solution of **18** (40.5 mg, 0.10 mmol) in dry MeOH (4.0 ml) was treated with 10% KOH–MeOH (5 drops) at room temperature for 20 min. The reaction mixture was neutralized with Dowex 50W × 8 (H^+ form). The resin was removed by filtration and evaporation of the solvent from the filtrate under reduced pressure gave an N-acetyl compound (37.2 mg). The N-acetyl compound was dissolved into 80% hydrazine hydrate (10 ml) and the solution was heated at 90 °C in a sealed tube for 20 h. After cooling, the reaction mixture was concentrated under reduced pressure to give a product (28 mg). Purification of the product by column chromatography (SiO_2 1 g, $CHCl_3$: MeOH : H_2O = 13 : 6 : 1) afforded D-*erythro*-C18-sphingosine (**1**, 17.1 mg, 0.06 mmol, 60%).

1: Colorless needles, mp 81—82 °C ($CHCl_3$–MeOH). $[\alpha]_D^{24}$ −2.8° (c = 1.0, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3400, 970. ^{1}H-NMR (500 MHz, d_5-pyridine) δ: 0.84 (3H, t, J = 7.0 Hz, 18-H_3), 1.23 (22H, s, $CH_2 \times 11$), 2.0—2.1 (2H, m, 6-H), 3.5—3.6 (1H, m, 2-H), 4.23 (1H, dd, J = 7.0, 11.0 Hz, 1-H_a), 4.29 (1H, dd, J = 4.0, 11.0 Hz, 1-H_b), 4.75 (1H, dd, J = 5.0, 5.0 Hz, 3-H), 5.9—6.0 (2H, m, 4-H, 5-H). ^{13}C-NMR (125 MHz, d_5-pyridine) δ_C: 14.2 (C-18), 22.8 (C-17), 30.0—29.3 (totally 9C, C-7—15), 32.0 (C-16), 32.4 (C-6), 56.3 (C-2), 63.5 (C-1), 74.8 (C-3), 129.0 (C-5), 134.7 (C-4). EI-MS m/z (%): 299 (M^+, 5), 267 (100). High-resolution EI-MS m/z: Calcd for $C_{18}H_{37}NO_2$: 299.2824. Found: 299.2825 (M^+).

Catalytic Hydrogenation of 18 Giving 20a A solution of **18** (15 mg, 0.035 mmol) in MeOH (1.3 ml) was treated with PtO_2 (20 mg) and the mixture was stirred vigorously under an H_2 atmosphere at room temperature for 3 h. After removal of the catalyst by filtration, the solvent was evaporated off to yield a product (26 mg). Purification of the product by column chromatography (SiO_2 1 g, n-hexane : EtOAc = 2 : 3) afforded N,O,O-triacetyl-D-*erythro*-C18-dihydrosphingosine (**20a**, 14 mg, 0.033 mmol, 94%).

20a: Colorless needles, mp 95—96 °C (n-hexane–EtOAc). $[\alpha]_D^{24}$ +16° (c = 1.0, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 1735, 1677. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, J = 7.0 Hz, 18-H_3), 1.26 (28H, m, $CH_2 \times 14$), 2.01, 2.07, 2.08 (3H each, all s, $COCH_3 \times 3$), 4.06 (1H, dd, J = 3.5, 11.5 Hz, 1-H_a), 4.26 (1H, dd, J = 6.0, 11.5 Hz, 1-H_b), 4.40 (1H, m, 2-H), 4.91 (1H, dt, J = 8.0, 5.0 Hz, 3-H), 5.86 (1H, br d, J = *ca.* 9.0 Hz, amide proton). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.2 (C-18), 20.9, 21.1 ($COCH_3 \times 2$), 22.8 (C-17), 23.4 ($NHCOCH_3$), 25.5 (C-5), 29.4, 29.5, 29.6, 29.7, 29.8 (totally 10C, C-6—15), 31.6 (C-16), 32.0 (C-4), 50.6 (C-2), 62.7 (C-1), 74.1 (C-3), 169.8, 171.0, 171.1 ($COCH_3 \times 3$). EI-MS m/z (%): 427 (M^+, 0.3), 84 (100). High-resolution EI-MS m/z: Calcd for $C_{24}H_{45}NO_5$: 427.3296. Found: 427.3296 (M^+).

Preparation of D-*erythro*-C18-Dihydrosphingosine (20) from 20a A solution of **20a** (20.0 mg, 0.05 mmol) in dry MeOH (2.0 ml) was treated with 10% KOH–MeOH (2 drops) at room temperature for 30 min. After neutralization of the reaction mixture with Dowex 50W × 8 (H^+ form), the resin was removed by filtration. The solvent was removed from the filtrate under reduced pressure to afford an N-acetate (19.5 mg). The N-acetate (19.5 mg) was treated with 80% hydrazine hydrate (5 ml) at 90 °C in a sealed tube for 20 h. After cooling, the reaction mixture was concentrated under reduced pressure to give a product (16 mg). Purification of the product by column chromatography (SiO_2 1 g, $CHCl_3$: MeOH : H_2O = 13 : 6 : 1) afforded D-*erythro*-C18-dihydrosphingosine (**20**, 8.5 mg, 0.03 mmol, 60%).

20: Colorless needles, mp 77—78 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ +5.5° (c = 1.1, $CHCl_3$: MeOH = 10 : 1). IR (KBr) cm^{-1}: 3330, 2918, 2850. ^{1}H-NMR (500 MHz, d_5-pyridine) δ: 0.84 (3H, t, J = 7.0 Hz, 18-H_3), 1.1—1.9 (28H, m, $CH_2 \times 14$), 3.60 (1H, m, 2-H), 4.3—4.5 (3H, m, 1-H_2, 3-H). ^{13}C-NMR (125 MHz, d_5-pyridine) δ_C: 14.2 (C-18), 22.9 (C-17), 26.7 (C-5), 29.6, 29.9, 30.0 (totally 10C, C-6—15), 32.1 (C-16), 34.2 (C-4), 58.6 (C-2), 61.2 (C-1), 71.4 (C-3). EI-MS m/z (%): 301 (M^+, 0.1), 60 (100). High-resolution EI-MS m/z: Calcd for $C_{18}H_{39}NO_2$: 301.2981. Found: 301.2984 (M^+).

Preparation of 21 from (−)-10a The 1,2-diol **21** (1.50 g, 3.73 mmol, 78% yield) was obtained together with the 1,3-diol (0.11 g, 6% yield) from (−)-**10a** (1.8 g, 4.79 mmol) through a procedure similar to that used for the synthesis of **12** from (+)-**10a**.

21: Colorless oil. $[\alpha]_D^{24}$ −5.9° (c = 2.8, MeOH). High-resolution EI-MS m/z: Calcd for $C_{24}H_{25}N_3O_4$: 419.1842. Found: 419.1799 (M^+). IR, ^{1}H-NMR and EI-MS data for **21** were identical with those for **12**.

Preparation of 22 from 21 A hydroxy-amide **22** (2.52 g, 5.26 mmol, 69% yield) was obtained from **21** (3.20 g, 7.64 mmol) through a procedure similar to that used for **15** from **12**.

22: Colorless oil. $[\alpha]_D^{24}$ −32° (c = 1.3, MeOH). High-resolution EI-MS m/z: Calcd for $C_{28}H_{33}NO_6$: 479.2307. Found: 479.2307 (M^+). IR, ^{1}H-NMR and EI-MS data for **22** were identical with those for **15**.

Preparation of 23 and 24 from 22 N,O,O-Triacetyl-L-*erythro*-C18-

sphingosine (**23**, 272 mg, 0.64 mmol, 64% yield) and its 4*Z*-isomer (**24**, 53 mg, 0.12 mmol, 12% yield) were obtained from **22** (480 mg, 1.00 mmol) through a procedure similar to that for the synthesis of **18** and **19** from **15**.

23: Colorless needles, mp 101—102 °C (*n*-hexane–EtOAc). $[\alpha]_D^{23}$ +12.1° (c=1.1, $CHCl_3$). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{43}NO_5$: 425.3138. Found: 425.3131 (M^+). IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS data for **23** were identical with those for **18**.

24: Colorless needles, mp 84—85 °C (*n*-hexane–EtOAc). $[\alpha]_D^{23}$ −4.1° (c=1.1, $CHCl_3$). High-resolution FAB-MS *m/z*: Calcd for $C_{24}H_{43}NO_5$+H: 426.3220. Found: 426.3252 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **24** were identical with those for **19**.

Preparation of L-*erythro*-C18-Sphingosine (2) from 23 L-*erythro*-C18-Sphingosine (**2**, 8.4 mg, 0.03 mmol, 60% yield) was obtained from **23** (20 mg, 0.05 mmol) through a procedure similar to that described for D-*erythro*-C18-sphingosine (**1**) from **18**.

2: Colorless needles, mp 81—82 °C ($CHCl_3$–MeOH). $[\alpha]_D^{24}$ +2.8° (c=0.6, $CHCl_3$). High-resolution EI-MS *m/z*: Calcd for $C_{18}H_{37}NO_2$: 299.2824. Found: 299.2826 (M^+). IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS data for **2** were identical with those for **1**.

Preparation of 25a from 23 *N,O,O*-Triacetyl-L-*erythro*-C18-dihydrosphingosine (**25a**, 49 mg, 0.12 mmol, in quantitative yield) was obtained from **23** (52 mg, 0.12 mmol) through a procedure similar to that described for **20a** from **18**.

25a: Colorless needles, mp 96—97 °C (*n*-hexane–EtOAc). $[\alpha]_D^{23}$ −16.5° (c=1.2, $CHCl_3$). High-resolution BAF-MS *m/z*: Calcd for $C_{24}H_{45}NO_5$+H: 428.3374. Found: 428.3364 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **25a** were identical with those for **20a**.

Preparation of 25 from 25a L-*erythro*-C18-Dihydrosphingosine (**25**, 8.5 mg, 0.03 mmol, 60% yield) was obtained from **25a** (20 mg, 0.05 mmol) through a procedure similar to that employed for **20** from **20a**.

25: Colorless needles, mp 77.5—78.5 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ −5.8° (c=1.0, $CHCl_3$: MeOH = 10 : 1). High-resolution EI-MS *m/z*: Calcd for $C_{18}H_{38}NO_2$: 301.2981. Found: 301.2890 (M^+). IR, ^{1}H-NMR, ^{13}C-NMR and EI-MS data for **25** were identical with those for **20**.

Preparation of 26 from (−)-11a A solution of titanium tetraisopropoxide (2.4 ml, 7.98 mmol) and trimethylsilylazide (2.1 ml, 16.0 mmol) in dry benzene (50 ml) was heated under reflux for 6 h, then cooled to 40 °C. A solution of (−)-**11a** (2.0 g, 5.32 mmol) in dry benzene (26 ml) was added dropwise into the above reaction mixture over 10 min, and the resulting mixture was stirred at 40 °C for 30 min. After cooling, the reaction mixture was evaporated and the residue was dissolved in ether (110 ml), then this solution was stirred at room temperature for 1 h. The organic phase was separated and washed with aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent gave a product (2.5 g), which was purified by column chromatography (SiO_5 50 g, *n*-hexane: EtOAc = 3 : 2) to afford a 1,3-diol (**26**, 1.85 g, 4.42 mmol, 83%).

26: Colorless oil. $[\alpha]_D^{25}$ −8.0° (c=1.7, MeOH). IR (CCl_4) cm^{-1}: 3580, 2118. ^{1}H-NMR (90 MHz, C_6D_6) δ: 3.28 (3H, s), 3.2—3.8 (6H, m), 6.7—7.6 (14H, m). EI-MS *m/z* (%): 419 (M^+, 4), 273 (100). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{25}N_3O_4$: 419.1842. Found: 419.1827 (M^+).

Benzoylation of 26 Giving 26a Benzoyl chloride (0.2 ml) was added to a solution of **26** (10 mg, 0.023 mmol) in pyridine (0.5 ml) and the mixture was stirred at room temperature for 1 h. The reaction mixture was poured into ice-water and the whole was extracted with EtOAc. The EtOAc extract was washed with 5% aqueous HCl, aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (20 mg), which was purified by column chromatography (SiO_2, 1 g, *n*-hexane: EtOAc = 6 : 1) to afford **26a** (13 mg, 0.021 mmol, 87%).

26a: Colorless oil. $[\alpha]_D^{25}$ −16.6° (c=2.8, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 2100, 1728. ^{1}H-NMR (500 MHz, C_6D_6) δ: 3.25 (3H, s, OCH_3), 3.57 (2H, d, J=5.5 Hz, 4-H_2), 3.8—4.0 (1H, m, 2-H), 4.37 (1H, dd, J=7.0, 11.5 Hz, 1-H_a), 4.58 (1H, dd, J=4.5, 11.5 Hz, 1-H_b), 5.73 (1H, m, 3-H), 6.6—8.1 (24H, m, aromatic protons). FAB-MS *m/z*: 627 (M^+). High-resolution FAB-MS *m/z*: Calcd for $C_{38}H_{33}N_3O_6$: 627.2368. Found: 627.2395 (M^+).

Preparation of 27 from 26 Diisopropylethylamine (3.7 ml, 21.5 mmol) and trimethysilylethoxymethyl chloride (2.3 ml, 12.9 mmol) were added to a solution of **26** (900 mg, 2.15 mmol) in dry CH_2Cl_2 (1.1 ml), and the whole mixture was stirred at 40 °C for 5 h. Then aqueous saturated $NaHCO_3$ (5 ml) was added and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (2.3 g), which was purified by column chromatography (SiO_2 30 g, *n*-hexane : EtOAc = 10 : 1) to afford a di-SEM ether (1.39 g, 2.04 mmol). The di-SEM ether (1.39 g) in dry tetrahydrofuran (8.0 ml) was added at 0 °C to a suspension of lithium aluminum hydride (190 mg, 5.00 mmol) in dry THF (8.0 ml), and the whole mixture was stirred at room temperature for 30 min. The reaction mixture was worked up in a usual manner to give an amine compound (1.3 g). The amine compound was treated with acetic anhydride (3.0 ml) and pyridine (6.0 ml) at room temperature for 2 h. Work-up of the reaction mixture yielded an amide (1.54 g), which was treated with 1% KOH–MeOH (10 ml) at room temperature for 15 min. The reaction mixture was neutralized with a silver carbonate powder and the precipitate was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product (1.6 g). Purification of the product by column chromatography (SiO_2 40 g, *n*-hexane : EtOAc = 1 : 2) afforded **27** (685 mg, 1.61 mmol, 75%).

27: Colorless oil. $[\alpha]_D^{25}$ +35.2° (c=1.3, $CHCl_3$). IR (film) cm^{-1}: 3400, 3280, 1650, 1249. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 0.03 (18H, s, $-Si(CH_3)_3\times2$), 2.04 (3H, s, $COCH_3$), 3.4—3.8 (13H, m, $-OCH_2CH_2$-TMS×2, 1-H_2, 3-H, 4-H_2), 4.2—4.4 (1H, m, 2-H), 4.6—4.7 (4H, m, $-OCH_2O-\times2$), 5.67 (1H, d-like, amide proton). FAB-MS *m/z*: 446 $(M+Na)^+$, 424 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{18}H_{41}NO_4Si_2$+H: 424.2551. Found: 424.2548 $(M+H)^+$.

Swern Oxidation of 27 Followed by Wittig Reaction and Acidic Hydrolysis A solution of DMSO (0.21 ml, 2.92 mmol, 2.0 eq) in dry CH_2Cl_2 (4.0 ml) was added to a solution of oxalyl chloride (0.19 ml, 2.19 mmol, 1.5 eq) in dry CH_2Cl_2 (1.7 ml), and the mixture was stirred at −78 °C for 15 min. Then, **27** (620 mg, 1.46 mmol) in dry CH_2Cl_2 (2.0 ml) was added, and the whole was stirred at −78 °C for a further 30 min. The reaction mixture was treated with triethylamine (1.0 ml, 7.29 mmol, 5.0 eq), warmed to room temperature, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with brine and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (700 mg). A solution of the product (700 mg) in dry THF (3.5 ml) was added to a tetradecyltriphenylphosphorane reagent [prepared from triphenylphosphine tetradecylbromide (2.36 g, 26.3 mmol, 3.0 eq), *n*-butyl lithium (1.6 M solution in *n*-hexane, 1.37 ml, 13.1 mmol, 1.5 eq), and dry THF (1.0 ml)] and the whole was stirred at 0 °C for 4 h. Work-up of the reaction mixture in a usual manner gave a product (3.2 g), which was purified by column chromatography (SiO_2, 50 g, *n*-hexane : EtOAc = 2 : 1) to furnish a mixture of C18 compound (701 mg, 1.16 mmol). Then, the C18 compound mixture was treated with 9% HCl–MeOH (5.0 ml) at room temperature for 15 min. The reaction mixture was neutralized with silver carbonate powder, and the precipitate was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product (695 mg), which was purified by column chromatography (SiO_2 20 g, $CHCl_3$: MeOH = 40 : 1) to afford a mixture (373 mg, 1.09 mmol, 75%) of *N*-acetyl-D-*erythro*-C18-sphingosine (**28**) and its 4*Z*-isomer (**29**). The ratio (1 : 4) of **28** and **29** was determined by ^{1}H-NMR analysis (500 MHz, $CDCl_3$).

Photoisomerization of a Mixture of 28 and 29 A solution of the mixture of **28** and **29** (1 : 4, 93 mg, 0.27 mmol) and diphenyl disulfide (59 mg, 0.27 mmol) in dry dioxane (4 ml)–dry cyclohexane (16 ml) was irradiated by a 500 W high-pressure mercury lamp through a Pyrex filter at 20—30 °C for 5 h. The reaction mixture was concentrated under reduced pressure to yield a product (96 mg). Purification of the product by column chromatography (SiO_2 3 g, $CHCl_3$: MeOH = 40 : 1) furnished **28** (86 mg, 0.25 mmol, 92%) and **29** (7 mg, 0.02 mmol, 7%).

28: Colorless needles, mp 65—66 °C ($CHCl_3$–MeOH). $[\alpha]_D^{25}$ +11.0° (c=1.2, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3450, 3400, 1665. ^{1}H-NMR (500 MHz, d_5-pyridine) δ: 0.84 (3H, t, J=6.5 Hz, 18-H_3), 1.22 (33H, s, $CH_2\times11$), 2.03 (2H, dt, J=7.0, 7.0 Hz, 6-H_2), 2.13 (3H, s, $COCH_3$), 4.21 (1H, dd, J=6.0, 10.5 Hz, 1-H_a), 4.33 (1H, dd, J=7.0, 10.5 Hz, 1-H_b), 4.7—4.8 (1H, m, 2-H), 5.04 (1H, t-like, 3-H), 5.9—6.0 (2H, m, 4-H, 5-H). ^{13}C-NMR (125 MHz, d_5-pyridine) δ_C: 14.2 (C-18), 22.9 (C-17), 23.2 ($NHCOCH_3$), 29.4, 29.6, 29.7, 29.8, 29.9, 30.1 (totally 9C, C-7—15), 32.1 (C-16), 32.6 (C-6), 56.9 (C-2), 62.4 (C-1), 71.0 (C-3), 131.6 (C-5), 132.2 (C-4), 170.4 ($NHCOCH_3$). FAB-MS *m/z*: 364 $(M+Na)^+$, 342 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{20}H_{39}NO_3$+H: 342.3008. Found: 432.2982 $(M+H)^+$.

29: Colorless needles, mp 70.5—71.5 °C ($CHCl_3$–MeOH). $[\alpha]_D^{24}$ −32.1° (c=0.7, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3460, 3400, 1668. ^{1}H-NMR (500 MHz, d_5-pyridine) δ: 0.84 (3H, t, J=7.0 Hz, 18-H_3), 1.21 (22H, s, $CH_2\times11$), 2.0—2.3 (2H, m, 6-H_2), 2.13 (3H, s, $COCH_3$), 4.19 (1H, dd, J=5.5, 10.5 Hz, 1-H_a), 4.34 (1H, dd, J=7.0, 10.5 Hz, 1-H_b), 4.71 (1H, m, 2-H), 5.42 (1H, dd, J=3.0, 9.0 Hz, 3-H), 5.59 (1H, dt, J=11.0, 7.0 Hz, 5-H), 6.01 (1H, dd, J=11.0, 9.0 Hz, 4-H). ^{13}C-NMR (125 MHz, d_5-pyridine) δ_C: 14.2 (C-18), 22.9 (C-17), 23.2 ($NHCOCH_3$), 28.1 (C-6), 29.5, 29.7, 29.8, 29.9, 30.0 (totally 9C, C-7—15), 32.0 (C-16), 57.3 (C-2), 62.0 (C-1), 65.9 (C-3), 131.8 (C-5), 132.0 (C-4), 170.5 ($NHCOCH_3$). FAB-MS *m/z*: 364

$(M+Na)^+$, 342 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{20}H_{39}NO_3+H$: 342.3008. Found: 342.2988 $(M+H)^+$.

Preparation of D-*threo*-C18-Sphingosine (3) from 28 *N*-Acetyl-D-*threo*-C18-sphingosine (**28**, 20 mg, 0.06 mmol) was treated with 80% hydrazine hydrate (5.0 ml) and heated at 90 °C in a sealed tube for 20 h. After cooling, the reaction mixture was concentrated under reduced pressure to give a product (19 mg). Purification of the product by column chromatography (SiO_2 1 g, $CHCl_3$: MeOH : H_2O = 13 : 6 : 1) afforded D-*threo*-C18-sphingosine (**3**, 10.7 mg, 0.04 mmol, 61%).

3: Colorless needles, mp 84—85 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ +2.8° (*c* = 1.0, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3300, 970. ^{1}H-NMR (500 MHz, d_5-pyridine) δ: 0.84 (3H, t, *J* = 7.0 Hz, 18-H_3), 1.23 (22H, s, $CH_2 \times 11$), 2.01 (2H, dt, *J* = 7.0, 6.5 Hz, 6-H_2), 3.61 (1H, br s, 2-H), 4.23 (1H, dd, *J* = 6.0, 11.0 Hz, 1-H_a), 4.28 (1H, dd, *J* = 3.5, 11.0 Hz, 1-H_b), 4.82 (1H, dd, *J* = 7.0, 7.0 Hz, 3-H), 5.85 (1H, dd, *J* = 15.0, 7.0 Hz, 4-H), 5.96 (1H, dt, *J* = 15.0, 7.0 Hz, 5-H). ^{13}C-NMR (125 MHz, d_5-pyridine) δ_C: 14.2 (18-C), 22.9 (C-17), 29.5, 29.6, 29.8, 29.9 (totally 9C, C-7—15), 32.1 (C-16), 32.6 (C-6), 59.2 (C-2), 61.7 (C-1), 71.4 (C-3), 131.2 (C-5), 133.8 (C-4). FAB-MS *m/z*: 322 $(M+Na)^+$, 300 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{18}H_{37}NO_2+H$: 300.2903. Found: 300.2867 $(M+H)^+$.

Acetylation of 3 Giving 3a D-*threo*-C18-Sphingosine (**3**, 10 mg, 0.03 mmol) was treated with acetic anhydride (0.2 ml) and pyridine (0.4 ml) at room temperature for 3 h. The reaction mixture was worked up in a usual manner to give a product (16 mg). Purification of the product by column chromatography (SiO_2 1 g, *n*-hexane : EtOAc = 1 : 2) afforded *N,O,O*-triacetyl-D-*threo*-C18-sphingosine (**3a**, 14.1 mg, 0.03 mmol, in quantitative yield).

3a: Colorless needles, mp 41—42 °C (*n*-hexane–EtOAc). $[\alpha]_D^{25}$ −8.9° (*c* = 0.9, $CHCl_3$). IR ($CHCl_3$) cm^{-1}: 3450, 1737, 1674, 969. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (3H, t, *J* = 7.0 Hz, 18-H_3), 1.26 (22H, s, $CH_2 \times 11$), 2.00, 2.07, 2.08 (3H each, all s, $COCH_3 \times 3$), 2.0—2.1 (2H, m, 6-H_2), 4.08 (2H, m, 1-H_2), 4.40 (1H, m, 2-H), 5.40 (2H, m, 3-H, 4-H), 5.65 (1H, d, *J* = 9.0 Hz, amide proton), 5.78 (1H, dt, *J* = 15.0, 7.0 Hz, 5-H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.1 (18-C), 21.0, 20.7 ($\underline{C}OCH_3 \times 2$), 22.7 (C-17), 23.2 ($NHCO\underline{C}H_3$), 28.8, 29.1, 29.3, 29.4, 29.6 (totally 9C, C-7—15), 31.9 (C-16), 32.3 (C-6), 50.9 (C-2), 63.1 (C-1), 73.1 (C-3), 124.2 (C-5), 137.3 (C-4), 169.9, 170.0, 170.6 ($\underline{C}OCH_3 \times 3$). FAB-MS *m/z*: 448 $(M+Na)^+$, 426 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{24}H_{43}NO_5+H$: 426.3220. Found: 426.3198 $(M+H)^+$.

Catalytic Hydrogenation of 28 Giving 30 A solution of **28** (30 mg, 0.07 mmol) in MeOH (0.5 ml) was treated with PtO_2 (30 mg) and the mixture was stirred vigorously under an H_2 atmosphere at room temperature for 3 h. After removal of the catalyst by filtration, the solvent was evaporated off to yield a product (32 mg). Purification of the product by column chromatography (SiO_2 1 g, $CHCl_3$: MeOH : H_2O = 13 : 6 : 1) afforded D-*threo*-C18-dihydrosphingosine (**30**, 15.4 mg, 0.05 mmol, 58%).

30: Colorless needles, mp 101—102 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ +10.5° (*c* = 0.9, $CHCl_3$: MeOH = 10 : 1). IR (KBr) cm^{-1}: 3400. ^{1}H-NMR (500 MHz, d_5-pyridine) δ: 0.84 (3H, t, *J* = 7.0 Hz, 18-H_3), 1.24 (28H, br s, $CH_2 \times 14$), 3.44 (1H, d-like, 2-H), 4.14 (1H, dd, *J* = 7.0, 11.0 Hz, 1-H_a), 4.21 (1H, m, 3-H), 4.27 (1H, dd, *J* = 4.0, 11.0 Hz, 1-H_b). ^{13}C-NMR (125 MHz, d_5-pyridine) δ_C: 14.2 (C-18), 22.9 (C-17), 26.3 (C-5), 29.6, 29.9, 30.0 (totally 10C, C-6—15), 32.1 (C-16), 34.9 (C-4), 58.7 (C-2), 62.9 (C-1), 70.2 (C-3). FAB-MS *m/z*: 302 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{18}H_{39}NO_2+H$: 302.3059. Found: 302.3026 $(M+H)^+$.

Acetylation of 30 Giving 30a D-*threo*-C18-Dihydrosphingosine (**30**, 10 mg, 0.03 mmol) was treated with acetic anhydride (0.2 ml) and pyridine (0.4 ml) at room temperature for 3 h. Work-up of the reaction mixture in a usual manner gave a product (15 mg). Purification of the product by column chromatography (SiO_2 1 g, *n*-hexane : EtOAc = 1 : 2) afforded *N,O,O*-triacetyl-D-*threo*-C18-dihydrosphingosine (**30a**, 14.1 mg, 0.03 mmol, in quantitative yield).

30a: Colorless needles, mp 44—45 °C (*n*-hexane–EtOAc). $[\alpha]_D^{24}$ +13.2° (*c* = 0.9, pentane). IR ($CHCl_3$) cm^{-1}: 3450, 1736, 1674. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (3H, t, *J* = 7.0 Hz, 18-H_3), 1.26 (28H, br s, $CH_2 \times 14$), 2.02, 2.06, 2.08 (3H each, all s, $COCH_3 \times 3$), 4.04 (2H, m, 1-H_a, 2-H), 4.41 (1H, m, 1-H_b), 5.07 (1H, m, 3-H), 5.65 (1H, d, *J* = 9.0 Hz, amide proton). ^{13}C-NMR (125 MHz, $CDCl_3$) δ_C: 14.2 (18-C), 20.8, 21.0 ($\underline{C}OCH_3 \times 2$), 22.8 (C-17), 23.3 ($NHCO\underline{C}H_3$), 25.2 (C-5), 29.4, 29.5, 29.6, 29.7, 29.8 (totally 10C, C-6—15), 31.4 (C-16), 32.0 (C-4), 50.2 (C-2), 63.5 (C-1), 72.5 (C-3), 170.0, 170.5, 170.9 ($\underline{C}OCH_3 \times 3$). FAB-MS *m/z*: 450 $(M+Na)^+$, 428 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{24}H_{45}NO_5+H$: 428.3376. Found: 428.3354 $(M+H)^+$.

Preparation of 31 from (+)-11a The 1,3-diol **31** (1.80 g, 4.30 mmol, 83% yield) was obtained from (+)-**11a** (1.95 g, 5.19 mmol) through a procedure similar to that used for **26** from (−)-**11a**.

31: Colorless oil. $[\alpha]_D^{22}$ +8.0° (*c* = 1.9, MeOH). High-resolution EI-MS *m/z*: Calcd for $C_{24}H_{25}N_3O_4$: 419.1842. Found: 419.1840 (M^+). IR, ^{1}H-NMR and EI-MS data for **31** were identical with those for **26**.

Preparation of 32 from 31 The hydroxy-amide **32** (1.14 g, 2.68 mmol, 75% yield) was obtained from **31** (1.50 g, 3.58 mmol) through a procedure similar to that used for **27** from **26**.

32: Colorless oil. $[\alpha]_D^{23}$ −34° (*c* = 0.9, MeOH). High-resolution FAB-MS *m/z*: Calcd for $C_{18}H_{41}NO_4+H$: 424.2552. Found: 424.2565 $(M+H)^+$. IR, ^{1}H-NMR and FAB-MS data for **32** were identical with those for **27**.

Preparation of 33 and 44 from 32 *N*-Acetyl-L-*threo*-C18-sphingosine (**33**, 558 mg, 1.64 mmol, 69% yield) and its 4*Z*-isomer (**34**, 47 mg, 1.36 mmol, 6% yield) were obtained from **32** (1 g, 2.36 mmol) through a procedure similar to those used for the synthesis of **28** and **29** from **27**.

33: Colorless needles, mp 65—66 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ −11.0° (*c* = 0.6, $CHCl_3$). High-resolution FAB-MS *m/z*: Calcd for $C_{20}H_{39}NO_3+H$: 342.3008. Found: 342.2980 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **33** were identical with those for **28**.

34: Colorless needles, mp 70.5—71.5 °C ($CHCl_3$–MeOH). $[\alpha]_D^{24}$ +30.5° (*c* = 1.1, $CHCl_3$). High-resolution FAB-MS *m/z*: Calcd for $C_{20}H_{39}NO_3+H$: 342.3008. Found: 342.2980 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **34** were identical with those for **29**.

Preparation of L-*threo*-C18-Sphingosine (4) from 33 L-*threo*-C18-Sphingosine (**4**, 11 mg, 0.04 mmol, 61% yield) was obtained from **33** (20 mg, 0.06 mmol) through a procedure similar to that used for D-*threo*-C18-sphingosine (**3**) from **28**.

4: Colorless needles, mp 84—85 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ −2.7° (*c* = 1.1, $CHCl_3$). High-resolution FAB-MS *m/z*: Calcd for $C_{18}H_{37}NO_2+H$: 300.2902. Found: 300.2876 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **4** were identical with those for **3**.

Preparation of 4a from 4 *N,O,O*-Triacetyl-L-*threo*-C18-sphingosine (**4a**, 14 mg, 0.03 mmol, in quantitative yield) was obtained from **4** (10 mg, 0.03 mmol) by acetylation as described for the synthesis of **3a** from **3**.

4a: Colorless needles, mp 41—42 °C (*n*-hexane–EtOAc). $[\alpha]_D^{24}$ +8.5° (*c* = 1.0, $CHCl_3$). High-resolution FAB-MS *m/z*: Calcd for $C_{24}H_{43}NO_5$: 426.3220. Found: 426.3248 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **4a** were identical with those for **3a**.

Preparation of 35 from 33 *N,O,O*-Triacetyl-L-*threo*-C18-dihydrosphingosine (**35**, 10 mg, 0.03 mmol, 58% yield) was obtained from **33** (20 mg, 0.06 mmol) by catalytic hydrogenation as described for the synthesis of **30** from **28**.

35: Colorless needles, mp 101—102 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ −11.3° (*c* = 0.9, $CHCl_3$: MeOH = 10 : 1). High-resolution FAB-MS *m/z*: Calcd for $C_{18}H_{39}NO_2+H$: 302.3059. Found: 302.3010 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **35** were identical with those for **30**.

Preparation of 35a from 35 *N,O,O*-Triacetyl-L-*threo*-C18-dihydrosphingosine (**35a**, 14 mg, 0.03 mmol, in quantitative yield) was obtained from **35** (10 mg, 0.03 mmol) by acetylation similar to that for **30a** from **30**.

35a: Colorless needles, mp 44—45 °C (*n*-hexane–EtOAc). $[\alpha]_D^{24}$ −13.2° (*c* = 1.1, pentane). High resolution FAB-MS *m/z*: Calcd for $C_{24}H_{45}NO_5+H$: 428.3376. Found: 428.3346 $(M+H)^+$. IR, ^{1}H-NMR, ^{13}C-NMR and FAB-MS data for **35a** were identical with those for **30a**.

Palmitoylation of 1 Giving 36 D-*erythro*-C18-Sphingosine (**1**, 20 mg, 0.067 mmol) was treated with *p*-nitrophenyl palmitate (33 mg, 0.087 mmol) in pyridine (0.9 ml) at room temperature for 5 h. The reaction mixture was evaporated under reduced pressure to give a product (45 mg). Purification of the product by column chromatography (SiO_2 2 g, $CHCl_3$: MeOH = 60 : 1 → 30 : 1) afforded **36** (32 mg, 0.060 mmol, 90%).

36: Colorless needles, mp 95—96 °C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ −5.4° (*c* = 0.9, $CHCl_3$: MeOH = 9 : 1). IR ($CHCl_3$) cm^{-1}: 3445, 3400, 1655. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.89 (6H, t, *J* = 7.0 Hz, 18-H_3, 16′-H_3), 1.27 (48H, br s, $CH_2 \times 24$), 2.06 (2H, dt, *J* = 7.0, 6.5 Hz, 6-H_2), 2.34 (2H, t, *J* = 7.5 Hz, 2′-H_2), 3.7—4.0 (4H, m, 1-H_2, 2-H, 3-H), 5.54 (1H, dd, *J* = 15.0, 6.0 Hz, 4-H), 5.80 (1H, dt, *J* = 15.0, 6.5 Hz, 5-H), 6.25 (1H, d, *J* = 7.0 Hz, amide proton). FAB-MS *m/z*: 538 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{34}H_{67}NO_3+H$: 538.5199. Found: 538.5191 $(M+H)^+$.

Preparation of 37 from 36 A solution of **36** (30 mg, 0.056 mmol) in dry DMF (0.5 ml) was treated with imidazole (10 mg, 0.15 mmol) and *tert*-butyldiphenylsilyl chloride (0.02 ml, 0.073 mmol). The whole mixture was stirred at 60 °C for 5 h, then poured into ice-water and the whole was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 3% aqueous HCl, aqueous saturated $NaHCO_3$, and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a 1-*O*-TBDPS ether

(45 mg). The 1-*O*-TBDPS ether, dissolved in pyridine (0.8 ml), was treated with benzoyl chloride (4 drops) at room temperature for 30 min. The reaction mixture was worked up in a usual manner to give a product (63 mg). Purification of the product by column chromatography (SiO_2 2 g, *n*-hexane : EtOAc = 15 : 1) afforded a 1-*O*-TBDPS-3-*O*-benzoyl derivative (29 mg, 0.033 mmol). This 1-*O*-TBDPS-3-*O*-benzoyl derivative was dissolved in THF (0.5 ml) and treated with tetra-*n*-butylammonium fluoride (35 mg, 0.13 mmol) at room temperature for 7 h. The reaction mixture was worked up in a usual manner to give a product (38 mg). Purification of the product by column chromatography (SiO_2 2 g, *n*-hexane : EtOAc = 4 : 1) afforded **37** (19.3 mg, 0.030 mmol, 54%).

37: Colorless needles, mp 155—158 °C ($CHCl_3$). $[\alpha]_D^{25}$ −3.8° (*c* = 0.9, $CHCl_3$). IR (KBr) cm^{-1}: 3360, 1720, 1635. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.88 (6H, m, 18-H_3, 16-H_3), 1.1—1.7 (48H, m, $CH_2 \times 24$), 2.05 (2H, m, $CH_2 \times 1$), 2.20 (2H, m, $CH_2 \times 1$), 3.72 (2H, m, 1-H_2), 4.29 (1H, m, 2-H), 5.53 (1H, m, 3-H), 5.61 (1H, dd, *J* = 15.0, 7.5 Hz, 4-H), 5.86 (1H, dt, *J* = 15.0, 7.0 Hz, 5-H), 6.05 (1H, d, *J* = 9.0 Hz, amide proton), 7.47 (2H, m, aromatic protons), 7.60 (1H, m, aromatic proton), 8.04 (2H, m, aromatic protons). FAB-MS *m/z*: 642 $(M+H)^+$. *Anal.* Calcd for $C_{41}H_{71}NO_4$: C, 76.70; H, 11.14; N, 2.18. Found: C, 76.72; H, 11.13; N, 2.20.

Glycosidation of 37 Giving 38 Molecular sieves 4A (180 mg) and *O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-trichloroacetimide (15 mg, 0.030 mmol) were added to a solution of **37** (20 mg, 0.023 mmol) in dry CH_2Cl_2 (1.4 ml) at room temperature, then the mixture was treated with boron trifluoride-etherate (1% solution in dry CH_2Cl_2, 0.08 ml, 0.007 mmol) at −30 °C for 2 h. The reaction mixture was poured into ice-water and the whole was extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with aqueous saturated $NaHCO_3$ and brine, then dried over $MgSO_4$. Removal of the solvent under reduced pressure gave a product (37 mg). Purification of the product by column chromatography (SiO_2 1 g, *n*-hexane : EtOAc = 5 : 3) afforded **38** (13.9 mg, 0.014 mmol, 63%).

38: Colorless needles, mp 198—199°C ($CHCl_3$–MeOH). $[\alpha]_D^{23}$ +4.5° (*c* = 1.1, MeOH). IR (KBr) cm^{-1}: 3360, 2915, 2850, 1735, 1635. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.86 (6H, m, 18-H_3, 16′-H_3), 1.1—1.7 (48H, m, $CH_2 \times 24$), 1.9—2.2 (16H, m, $COCH_3 \times 4$, 6-H_2, 2′-H_2), 3.68 (2H, m, 6″-H_a, 5″-H), 3.90 (1H, dd, *J* = 10.0, 3.0 Hz, 6″-H_b), 4.04 (1H, dd, *J* = 12.0, 2.0 Hz, 1-H_a), 4.23 (1H, dd, *J* = 12.0, 5.0 Hz, 1-H_b), 4.39 (1H, d, *J* = 8.0 Hz, 1″-H), 4.47 (1H, m, 2-H), 5.01 (2H, m, 2″-H, 3″-H), 5.15 (1H, dd, *J* = 7.5, 7.5 Hz, 4″-H), 5.42 (2H, m, 3-H, 4-H), 5.81 (2H, m, 5-H, amide proton), 7.44 (2H, m, aromatic protons), 7.60 (1H, m, aromatic proton), 8.04 (2H, m, aromatic protons). FAB-MS *m/z*: 972 $(M+H)^+$. *Anal.* Calcd for $C_{55}H_{89}NO_{13}$: C, 67.94; H, 9.23; N, 1.44. Found: C, 67.91; H, 9.20; N, 1.47.

Preparation of a Palmitoyl Analogue of Gaucher Spleen Glucocerebroside (5a) from 38 A solution of **38** (10 mg, 0.010 mmol) in MeOH (0.9 ml) was treated with 10% KOH–MeOH (0.1 ml) at room temperature for 5 h. The mixture was neutralized with Dowex 50W × 8 (H^+ form) and the resin was removed by filtration. Removal of the solvent from the filtrate under reduced pressure gave a product (10 mg). Purification of the product by column chromatography (SiO_2 1 g, $CHCl_3$: MeOH = 10 : 1) afforded a palmitoyl analogue of Gaucher spleen glucocerebroside (**5a**, 7.1 mg, 0.010 ml, in quantitative yeild).

5a: Colorless needles, mp 179—180.5 °C (MeOH–H_2O). $[\alpha]_D^{23}$ +3.8° (*c* = 1.1, MeOH). IR (KBr) cm^{-1}: 3360, 1635. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.85 (6H, m, 18-H_3, 16′-H_3), 1.22 (46H, m, $CH_2 \times 23$), 1.45 (2H, m, CH_2), 1.9—2.2 (4H, m, 6-H_2, 2′-H_2), 2.9—3.2 (4H, m), 3.45 (2H, m), 3.5—4.0 (4H, m), 4.09 (1H, d, *J* = 8.0 Hz, 1″-H), 4.50 (1H, t, *J* = 5.0 Hz, OH), 4.92 (3H, m, OH × 3), 5.03 (1H, d, *J* = 4.5 Hz, OH), 5.35 (1H, dd, *J* = 15.0, 6.5 Hz, 4-H), 5.52 (1H, m, 5-H), 7.51 (1H, d, *J* = 8.5 Hz, amide proton). FAB-MS *m/z*: 700 $(M+H)^+$. High-resolution FAB-MS *m/z*: Calcd for $C_{40}H_{77}NO_8$ + H: 700.5727. Found: 700.5696 $(M+H)^+$.

Acknowledgment This work was supported in part by Grants-in-Aid for Scientific Research (No. 02250225, 03236227) from the Ministry of Education, Science and Culture of Japan, to which the authors' thanks are due.

References

1) This paper is Part II of the series "Sphingolipids and Glycerolipids." Part I: H. Shibuya, K. Kawashima, M. Sakagami, H. Kawanishi, M. Shimomura, K. Ohashi, and I. Kitagawa, *Chem. Pharm. Bull.*, **38**, 2933 (1990).
2) S. Hakomori, "Sphingolipid Biochemistry" in Handbook of Lipid Research, Vol. 3, ed. by J. N. Kaufer and S. Hakomori, Plenum Press, New York, 1983.
3) A. H. Merrill, S. Nimkar, D. Menaldino, Y. A. Hannun, C. Loomis, R. M. Bell, S. R. Tyahi, J. D. Lambeth, V. L. Stevens, R. Hunter, and D. C. Liotta, *Biochemistry*, **28**, 3138 (1989).
4) A preliminary report: H. Shibuya, K. Kawashima, M. Ikeda, and I. Kitagawa, *Tetrahedron Lett.*, **30**, 7205 (1989).
5) N. Halliday, J. J. Deurel, Jr., L. J. Tragelman, and W. E. Ward, *J. Biol. Chem.*, **1940**, 132.
6) J. C. Buck, F. Ellis, and P. C. North, *Tetrahedron Lett.*, **23**, 4161 (1982).
7) T. Katsuki and K. B. Sharpless, *J. Am. Chem. Soc.*, **102**, 5974 (1980).
8) Y. Gao, R. M. Hanson, J. M. Klunder, S. Y. Ko, H. Masamune, and K. B. Sharpless, *J. Am. Chem. Soc.*, **109**, 5765 (1987).
9) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
10) M. Caron, P. R. Carlier, and K. B. Sharpless, *J. Org. Chem.*, **53**, 5185 (1988).
11) C. Moussebois and J. Dale, *J. Chem. Soc. (C)*, **1966**, 260.
12) H. E. Carter, W. P. Norris, F. J. Glick, G. E. Phillips, and R. Harris, *J. Biol. Chem.*, **170**, 269 (1947).
13) P. Zimmermann and R. R. Schmidt, *Justus Liebigs Ann. Chem.*, **1988**, 663.
14) C. A. Grob, E. F. Jenny, and H. Utzinger, *Helv. Chim. Acta*, **34**, 2249 (1953).
15) W. Stoffel, *Chem. Phys. Lipids*, **11**, 318 (1973).
16) H. E. Carter and D. Shapiro, *J. Am. Chem. Soc.*, **11**, 318 (1973).
17) T. Kinsho and K. Mori, *Agric. Biol. Chem.*, **53**, 2785 (1989).
18) R. R. Schmidt and M. Stumpp, *Justus Liebigs Ann. Chem.*, **1983**, 249.
19) *a*) R. R. Schmidt and R. Klager, *Angew. Chem. Int. Ed. Engl.*, **24**, 65 (1985); *b*) R. R. Schmidt and P. Zimmermann, *ibid.*, **25**, 725 (1986).