Synthesis of 3-Deoxy Analogs of Sphingolipids†

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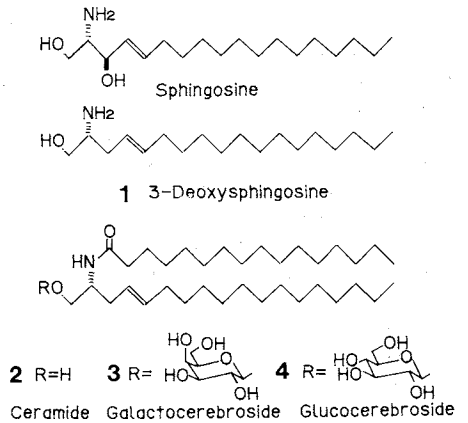
To clarify the role of hydroxyl group at C-3 position in sphingolipid, 3-deoxy analogs of sphingolipids were synthesized employing enzymatic resolution of α-amino acid as the key step.

All naturally occurring long-chain bases in sphingolipids that have ever been discovered have hydroxyl groups at the C-1 and C-3 positions.[1] The role of the primary hydroxyl group at C-1 is to form the glycosyl bond with sugars in glycosphingolipids. The meaning of the secondary hydroxyl group, however, remains unclear. In the case of glycosphingolipids, there may be some interaction between the C-3 hydroxyl group and the sugar moiety to influence the conformation of the molecule. From this point of view, it would be useful to investigate the properties of sphingolipids without the C-3 hydroxyl group, and their biological effects against various biosystems. Here are described a synthesis of optically active 3-deoxysphingosine **1**, and its conversion to deoxyceramide **2**, and deoxycerebrosides **3** and **4**.



The synthesis of **1** was achieved by employing the enzymatic resolution of (±)-*N*-acetyl-α-amino acid **11** with amino acylase as the key step. The starting material for our synthesis was propargyl alcohol tetrahydropyranyl ether **5**. The lithium salt of **5** was alkylated with tridecyl bromide to **6**, which was deprotected to give alkynol **6′** (93% from **5**). Reduction of **6′** with lithium aluminum hydride afforded (*E*)-alkenol **7**, whose tretment with triphenylphosphine in carbon tetrachloride gave allylic chloride **8** in quantitative yield (2 steps). Alkylation of the anion prepared from diethyl acetaminomalonate with **8** yielded **9** in 95% yield. Decarboethoxylation by the method reported by Krapcho *et al.*[2] gave α-acetamino ester **10**. This was hydrolyzed by an alkaline treatment to give (±)-**11**. Asymmetric hydrolysis of (±)-**11** with *Aspergillus* amino acylase[3] effectively gave (*S*)-**12** as a precipitate and unhydrolyzed (*R*)-**11** in the solution. These were readily separable by filtration.

(*R*)-**11** was then esterified to methyl ester **13** according to Rachele.[4] This was reduced with lithium borohydride-methanol[5] to give alcohol **14**, whose deacetylation afforded the desired amino alcohol **1** (deoxysphingosine) in 69% yield from (*R*)-**11**.

Enantiomer (*S*)-**1** was also synthesized by a

† Synthesis of Sphingosine Relatives. Part VIII. For Part VII, see K. Mori and T. Kinsho, *Liebigs Ann. Chem.*, **1988**, 807. 1988.

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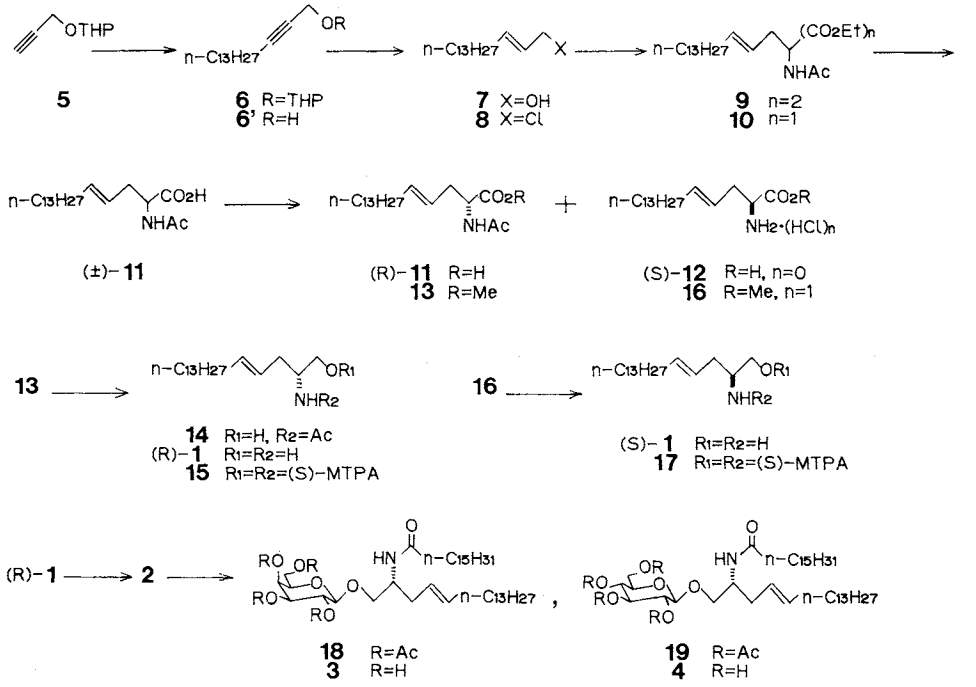

lithium aluminum hydride reduction of methyl ester hydrochloride **16** obtained from (*S*)-**14**. The optical purities of both enantiomers (*R*)- and (*S*)-**1** were estimated by an HPLC analysis of their corresponding bis-(*S*)-MTPA derivatives **15** and **17**, and revealed to be almost 100% *e.e.*

Deoxysphingosine (*R*)-**1** was selectively *N*-acylated by treating with *p*-nitrophenyl palmitate in pyridine to give deoxyceramide **2** in 90% yield. Glycosylation of **2** with tetra-*O*-acetylgalactopyranosyl bromide under Königs-Knorr conditions[6] and subsequent deacetylation gave the desired deoxygalactocerebroside **3** (80% from **2**). Glucoside **4** was also synthesized in the same manner, using tetra-*O*-acetylglucopyranosyl bromide.

Biological studies employing these synthetic materials are underway by Prof. Y. Nagai in the Faculty of Medicine, the University of Tokyo.

Experimental

All bps and mps were uncorrected. IR spectra were measured as films for oils, and as KBr discs for solids, on a Jasco A-102 spectrophotometer. ^{1}H-NMR spectra were recorded with the TMS as internal standard at 100 MHz on a JEOL JNM FX-100, or at 400 MHz on a JEOL JNM GX-400. ^{13}C-NMR spectra were recorded with the TMS as internal standard at 100 MHz on a JEOL JNM GX-400. Optical rotations were measured on a JASCO DIP-140 polarimeter.

2-Hexadecyn-1-ol (**6'**). A solution of *n*-butyllithium in *n*-hexane (1.54 M, 130 ml, 200 mmol) was added dropwise to a solution of propargyl alcohol tetrahydropyranyl ether (**5**, 25.2 g, 180 mmol) in tetrahydrofuran (250 ml) with stirring at −20°C under argon. After stirring for 2 hr at −20°C, a solution of 1-bromotridecane (51.5 g, 196 mmol) in hexamethylphosphoric triamide (100 ml) was added to the mixture. Stirring was continued for 2 hr at −20°C and for another 1 hr at room temperature. The mixture was then poured into ice-cooled water and extracted with ether. The ether solution was washed with water and brine, dried with magnesium sulfate and concentrated *in vacuo* to give 59.3 g (quantitative) of **6**. This was dissolved in methanol 1000 ml), and *p*-toluenesulfonic acid monohydrate (500 mg) was added to the solution. The mixture was stirred for 18 hr at room temperature, before being poured into ice-cooled water and extracted with ether. The ether solution was washed with saturated sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated *in vacuo*. The residual solid was recrystallized from *n*-hexane to give 39.7 g (93%) of **6**, mp 49.5~50.0°C; IR ν_{max} cm^{-1} 3320 (s), 3200 (s), 2220 (w), 1470 (s), 1025 (s), 715 (s); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J=6.0 Hz), 1.27 (20H, br. s), 1.35~1.60 (3H,

m), 2.08 ~ 2.32 (2H, m), 4.26 (2H, t, J = 2.0 Hz); GLC (column, 5% PEG, 2 m × 4 mm at 220°C: carrier gas, nitrogen, 1.2 kg/cm^2): t_R = 9.41 min (99.6%). *Anal.* Found: C, 80.72; H, 12.59. Calcd. for $C_{16}H_{30}O$: C, 80.60; H, 12.68%.

(E)-2-Hexadecen-1-ol (**7**). A solution of **6′** (37.0 g, 155 mmol) in tetrahydrofuran (500 ml) was added dropwise to an ice-cooled suspension of lithium aluminum hydride (22.0 g, 580 mmol) in tetrahydrofuran (300 ml). The mixture was stirred for 20 hr at room temperature. With ice-cooling and vigorous stirring, ice-cooled water (22 ml), a 15% aqueous solution of sodium hydroxide (22 ml) and more ice-cooled water (66 ml) were added in succession. After stirring for 30 min at room temperature, the precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residual solid was recrystallized from *n*-hexane to give 37.3 g (quantitative) of **7** as plates, mp 30.0 ~ 31.0°C; IR ν_{max} cm^{-1} 3330 (s), 1460 (s), 1085 (s), 1005 (s), 965 (s), 710 (s); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.0 Hz), 1.27 (22H, br. s), 1.53 (1H, s), 2.03 (2H, m), 4.06 (2H, m), 5.66 (2H, m); GLC (column, 5% PEG, 2 m × 4 mm at 220°C; carrier gas, nitrogen, 1.1 kg/cm^2): t_R = 5.81 min (98.8%). *Anal.* Found: C, 79.64; H, 13.10. Calcd. for $C_{16}H_{32}O$: C, 79.93; H, 13.42%.

(E)-1-Chloro-2-hexadecene (**8**). A mixture of **7** (4.09 g, 17.0 mmol) and triphenylphosphine (6.10 g, 25.6 mmol) in carbon tetrachloride (20 ml) was stirred for 13 hr under reflux. After cooling, the mixture was filtered through silica gel (75 g) and eluted with carbon tetrachloride to remove the triphenylphosphine oxide. The filtrate was concentrated *in vacuo* and the residue was chromatographed over silica gel (75 g). Elution with *n*-hexane gave 4.40 g (quantitative) of **8** as an oil, n_D^{21} = 1.4544; IR ν_{max} cm^{-1} 1665 (m), 1460 (s), 1440 (s), 1250 (s), 965 (s), 720 (m), 680 (s); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.0 Hz), 1.27 (22H, br. s), 2.06 (2H, m), 4.05 (2H, d, J = 6.2 Hz), 5.56 (1H, dt, J = 15.0, 6.2 Hz), 5.80 (1H, dt, J = 15.0, 6.0 Hz). *Anal.* Found: C, 73.89; H, 11.80. Calcd. for $C_{16}H_{31}Cl$: C, 74.23; H, 12.07%.

Diethyl (E)-2-acetamino-2-(2′-hexadecenyl)malonate (**9**). Diethyl acetaminomalonate (24.4 g, 112 mmol) in absolute ethanol (400 ml) was added to a solution of sodium ethoxide [prepared from sodium metal (2.48 g, 108 mg atom)] in absolute ethanol (130 ml). After stirring for 30 min at room temperature, **8** (22.3 g, 86.1 mmol was added to the mixture. The mixture was stirred for 4 hr under reflux and then for 18 hr at room temperature, before the solvent was removed *in vacuo*. The residue was diluted with ice-cooled water and extracted with ether. The ether solution was washed with brine and concentrated *in vacuo*. The residual solid was recrystallized from ethyl acetate–*n*-hexane (1 : 1) to give 36.1 g (95%) of **9** as granules, mp 55.5 ~ 56.0°C; IR ν_{max} cm^{-1} 3250 (s), 1750 (s), 1735 (s), 1645 (s), 1530 (s), 1300 (s), 1225 (s), 970 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.0 Hz), 1.24 (22H, br. s), 1.26 (6H, t, J = 7.0 Hz), 1.80 ~ 2.06 (2H, m), 2.04 (3H, s), 3.00 (2H, d, J = 7.2 Hz), 4.25 (4H, q, J = 7.0 Hz), 5.12 (1H, dt, J = 15.0, 7.5 Hz), 5.52 (1H, dt, J = 15.0, 7.0 Hz), 6.63 (1H, br.). *Anal.* Found: C, 68.49; H, 10.25; N, 3.14. Calcd. for $C_{25}H_{45}O_5N$: C, 68.30; H, 10.32; N, 3.19%.

Ethyl (E)-2-acetamino-4-octadecenoate (**10**). A mixture of **9** (37.3 g, 84.8 mmol) and sodium chloride (5.28 g, 90.3 mmol) in dimethyl sulfoxide (190 ml) and water (3.10 ml) was stirred under reflux for 18 hr. It was then poured into ice-cooled water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried with magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel (200 g). Elution with *n*-hexane–ethyl acetate (3 : 1) gave 25.7 g (82%) of **10** as needles, mp 53.0 ~ 54.0°C; IR ν_{max} cm^{-1} 3250 (s), 1745 (s), 1635 (s), 1550 (s), 1470 (s), 1375 (s), 1195 (s), 965 (s), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.0 Hz), 1.24 (22H, br. s), 1.26 (3H, t, J = 7.5 Hz), 1.73 ~ 2.20 (2H, m), 2.01 (3H, s), 2.50 (2H, t, J = 6.0 Hz), 4.20 (2H, q, J = 7.1 Hz), 4.62 (1H, dt, J = 7.8, 5.7 Hz), 5.24 (1H, dt, J = 15.2, 6.7 Hz), 5.53 (1H, dt, J = 15.2, 6.0 Hz), 6.00 (1H, d, J = 7.8 Hz). *Anal.* Found: C, 72.35; H, 11.26; N, 4.21. Calcd. for $C_{22}H_{41}O_3N$: C, 71.88; H, 11.24; N, 3.81%.

(E)-Acetamino-4-octadecenoic acid ((±)-**11**). A solution of potassium hydroxide (5.64 g, 101 mmol) in water (100 ml) was added to a solution of **10** (23.5 g, 63.9 mmol) in tetrahydrofuran (200 ml). The mixture was stirred and heated under reflux for 5 hr, before solvent was removed *in vacuo*. The residue was diluted with ice-cooled water (100 ml), acidified by adding 2 N hydrochloric acid to pH 4, and extracted with ether. The ether solution was washed with water, dried with magnesium sulfate, and concentrated *in vacuo*. The residual solid was recrystallized from ethyl acetate–*n*-hexane (2 : 1) to give 18.8 g (87%) of (±)-**11** as plates, mp 108 ~ 109°C; IR ν_{max} cm^{-1} 3300 (vs), 2600 ~ 2200 (br.), 1710 (s), 1580 (vs), 1530 (vs), 1450 (m), 1420 (m), 1365 (s), 1330 (m), 1210 (m), 950 (m), 705 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J = 6.0 Hz), 1.24 (22H, br. s), 1.90 ~ 2.14 (2H, m), 2.07 (3H, s), 2.54 (2H, t, J = 6.0 Hz), 3.85 (1H, br., disappeared by D_2O replacement), 4.60 (1H, dt, J = 8.0, 6.0 Hz), 5.30 (1H, dt, J = 16.0, 6.5 Hz), 5.49 (1H, dt, J = 16.0, 6.0 Hz), 5.99 (1H, d, J = 8.0 Hz). *Anal.* Found: C, 70.70; H, 10.82; N, 4.06. Calcd. for $C_{20}H_{37}O_3N$: C, 70.75; H, 10.99; N, 4.13%.

(2R,4E)-2-Acetamino-4-octadecenoic acid ((*R*)-**11**) *and (2S,4E)-2-amino-4-octadecenoic acid* ((*S*)-**12**) *by enzymatic resolution of* (±)-**11** *with amino acylase.* Amino acylase (from *Aspergillus*, 10,000 units/g, Tokyo Kasei Co., 3.8 g) and cobaltous chloride (*ca.* 10 mg) were added to a solution of (±)-**11** (18.7 g, 55.1 mmol) in water (3100 ml) that was adjusted to pH 7.1 by adding sodium hydroxide. The solution was left to stand for 2 days at 37°C. The resulting turbid mixture was then acidified by the addition

of 2 N hydrochloric acid to pH 3. The precipitated solid was collected on a filter, and washed with hot ethyl acetate (300 ml × 4). The insoluble precpitate was washed with water, methanol and ether, and dried over phosphorous pentoxide to give 8.20 g (quantitative) of crude (*S*)-**12** as an amorphous solid, mp 177 ~ 182°C (decomposition point); IR ν_{max} cm^{-1} 3300 (br.), 1580 (s), 1500 (m), 1465 (m), 1415 (m), 1400 (s), 1140 (m), 965 (s), 720 (m). This material was employed in the next step without further purification.

The ethyl acetate solution was dried with magnesium sulfate and concentrated *in vacuo*. The residual solid was recrystallized from ethyl acetate–*n*-hexane (1 : 5) to give 6.06 g (65%) of (*R*)-**11** as fine needles, mp 104 ~ 105°C; $[\alpha]_D^{23}$ −45.0° (*c* = 0.50, $CHCl_3$); IR ν_{max} cm^{-1} 3360 (s), 2600 (m), 2460 (m), 1710 (s), 1630 (s), 1555 (s), 1470 (s), 1270 (s), 1240 (s), 965 (s), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.0 Hz), 1.27 (22H, br. s), 1.78 ~ 2.10 (2H, m), 2.06 (3H, s), 2.54 (2H, br. t, *J* = 6.0 Hz), 3.07 (1H, br., disappeared by D_2O replacement), 4.58 (1H, dt, *J* = 7.2, 6.1 Hz), 5.29 (1H, dt, *J* = 15.0, 6.2 Hz), 5.60 (1H, dt, *J* = 15.0, 6.0 Hz), 5.96 (1H, d, *J* = 7.2 Hz). *Anal.* Found: C, 71.04; H, 10.95; N, 4.13. Calcd. for $C_{20}H_{37}O_3N$: C, 70.75; H, 10.99; N, 4.13%.

Methyl (2R,4E)-2-acetamino-4-octadecenoate ((*R*)-**13**). To a solution of (*R*)-**11** (3.00 g, 8.84 mmol) in 2,2-dimethoxypropane (100 ml) was added concentrated hydrochloric acid (8.84 ml). The mixture was stirred for 18 hr at room temperature, before the solvent was removed *in vacuo*, and the residue was chromatographed over silica gel (60 g). Elution with *n*-hexane–ether (1 : 2) gave crude (*R*)-**13**, which was recrystallized from *n*-hexane to give 2.85 g (96%) of (*R*)-**13** as fine needles, mp 69.0 ~ 70.5°C; $[\alpha]_D^{17}$ −41.6° (*c* = 0.60, $CHCl_3$); IR ν_{max} cm^{-1} 3280 (s), 1730 (s), 1660 (s), 1550 (s), 1460 (m), 1430 (m), 1375 (m), 1300 (m), 965 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.4 Hz), 1.27 (22H, br. s), 1.85 ~ 2.04 (2H, m), 2.02 (3H, s), 2.47 (2H, br. t, *J* = 6.2 Hz), 3.74 (3H, s), 4.63 (1H, dt, *J* = 8.0, 6.0 Hz), 5.23 (1H, dt, *J* = 15.0, 6.9 Hz), 5.54 (1H, dt, *J* = 15.0, 6.2 Hz), 5.94 (1H, d, *J* = 8.0 Hz). *Anal.* Found: C, 71.26; H, 11.16; N, 4.01. Calcd. for $C_{21}H_{39}O_3N$: C, 71.34; H, 11.12; N, 3.96%.

(2R,4E)-2-Acetamino-4-octadecen-1-ol ((*R*)-**14**). A mixture of (*R*)-**13** (2.85 g, 8.06 mmol) and lithium borohydride (0.96 g, 44.1 mmol) in ether (100 ml) was stirred and heated under reflux. To this was added methanol (0.495 ml, 8.11 mmol) dropwise over 70 min. After stirring for 30 min under reflux, the mixture was cooled in an ice bath, and the excess lithium borohydride was quenched by the addition of 2 N hydrochloric acid. The mixture was then diluted with ice-cooled water and extracted with chloroform. The chloroform solution was washed with brine, dried with magnesium sulfate and concentrated *in vacuo*. The residue was chromatographed over silica gel (75 g), and elution with ether gave crude (*R*)-**14**, which was recrystallized from *n*-hexane–ether (5 : 1) to give 1.87 g (71%) of (*R*)-**14** as an amorphous solid, mp 71.0 ~ 72.0°C; $[\alpha]_D^{17}$ −5.06° (*c* = 0.78, $CHCl_3$); IR ν_{max} cm^{-1} 3310 (s), 1650 (s), 1555 (s), 1465 (m), 1425 (m), 1370 (m), 1035 (m), 965 (m), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.0 Hz), 1.28 (22H, br. s), 1.97 (2H, m), 2.02 (3H, s), 2.24 (2H, br. t, *J* = 7.0 Hz), 2.88 (1H, br.), 3.50 ~ 3.67 (1H, m), 3.67 ~ 4.28 (2H, m), 5.34 (1H, dt, *J* = 15.2, 6.2 Hz), 5.56 (1H, dt, *J* = 15.2, 6.4 Hz), 5.88 (1H, d, *J* = 7.0 Hz). *Anal.* Found: C, 73.27; H, 11.75; N, 4.24. Calcd. for $C_{20}H_{39}O_2N$: C, 73.79; H, 12.08; N, 4.30%.

(E)-2-Amino-4-octadecen-1-ol ((*R*)-**1**). A mixture of (*R*)-**14** (1.30 g, 4.00 mmol) and 2 N hydrochloric acid was stirred for 30 min under reflux. It was then diluted with ice-cooled water, neutralized with 2 N ammonia water to pH 8, and extracted with methylene chloride. The methylene chloride solution was washed with brine and concentrated *in vacuo*. The residue was chromatographed over silica gel (20 g), and elution with chloroform–methanol (9 : 1) gave 1.13 g (quantitative) of crude (*R*)-**1**. This material was employed in the next step without further purification.

For use in the bioassay and analysis, a part of this material was further purified by adding an ion-exchange resin (Amberlyst IRA-400 OH^- form, 40.5 ml, 56.7 mmol) to a solution of crude (*R*)-**1** (126 mg, 0.390 mmol) in 99% ethanol (600 ml). After stirring for 1 hr, the resin was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was chromatographed over neutral alumina (grade IV, 20 g), and elution with 99% ethanol gave 88 mg of (*R*)-**1** as an amorphous solid, mp 56.0 ~ 57.5°C; IR ν_{max} cm^{-1} 3440 (s), 1600 (m), 1570 (m), 1465 (s), 1015 (m), 970 (s), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.0 Hz), 1.27 (22H, br. s), 1.60 ~ 2.30 (7H, m, the integral value decreased by D_2O replacement), 2.70 ~ 3.72 (3H, m), 5.32 (1H, dt, *J* = 16.0, 5.9 Hz), 5.54 (1H, dt, *J* = 16.0, 5.9 Hz).

The optical purity of (*R*)-**1** was estimated by an HPLC analysis of the corresponding bis[(*S*)-MTPA] derivative **15** (column, Senshu Pak silica-1251-N, 25 cm × 4.6 mm; solvent, *n*-hexane–tetrahydrofuran = 15 : 1; flow rate, 1.0 ml/min) t_R = 14.4 min (100%). The peak due to **17** at t_R = 13.3 min was not detected; therefore, our (*R*)-**1** was of almost 100% *e.e.*

Methyl (2S,4E)-2-amino-4-octadecenoate hydrochloride (**16**). A mixture of (*S*)-**12** (4.00 g, 13.4 mmol) and concentrated hydrochloric acid (13.4 ml, 162 mmol) in 2,2-dimethoxypropane–methanol (5 : 1, 84 ml) was stirred for 15 min under reflux at 70°C and for 12 hr at room temperature. The solvent was then removed *in vacuo* and the residual solid was recrystallized from methanol–ether (1 : 1) to give 3.23 g (69%) of **16** as fine needles, mp 112 ~ 113°C; IR ν_{max} cm^{-1} 1745 (s), 1595 (w), 1500 (s), 1465 (s), 1245 (s), 975 (s), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, *J* = 6.2 Hz), 1.27 (22H, br. s), 2.30 (2H, m), 2.76 (2H, m), 3.81 (3H, s), 3.85 ~ 4.25 (3H, br., the

integral value decreased by D_2O replacement), 5.43 (1H, m), 5.70 (1H, m). *Anal.* The hydrochloride content varied from 1.2 to 1.6. Found: C, 63.32; H, 10.66; N, 4.16. Calcd. for $C_{19}H_{37}O_2N \cdot 1.34HCl$: C, 63.33; H, 10.72; N, 3.89%. Found: C, 61.91; H, 10.47; N, 3.89. Calcd. for $C_{19}H_{37}O_2N \cdot 1.57HCl$: C, 61.89; H, 10.54; N, 3.80%. This material was employed in the next step without further purification.

For analytical use, the free amine of **16** was prepared from a mixture of hydrochloride **16** (940 mg, 2.70 mmol) and potassium carbonate (400 mg, 2.89 mmol) in methanol–tetrahydrofuran (1 : 1, 30 ml), which was stirred for 24 hr at room temperature. It was then diluted with ether and filtered through Celite to remove the salts. The filtrate was dried with magnesium sulfate and concentrated *in vacuo*. The oily residue was chromatographed over silica gel (10 g), and elution with *n*-hexane–ether (1 : 1) gave 740 mg (88%) of the free amine as an oil, IR ν_{max} cm^{-1} 3400 (m), 1740 (s), 1200 (s), 1170 (s), 965 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (3H, t, J=6.2 Hz), 1.27 (22H, br. s), 1.70 (2H, br. s), 1.95 (2H, m), 2.38 (2H, m), 3.53 (1H, t, J=6.0 Hz), 3.74 (3H, s), 5.30 (1H, dt, J=15.0, 6.0 Hz), 5.57 (1H, dt, J=15.0, 6.0 Hz). *Anal.* Found: C, 73.48; H, 11.51; N, 4.41. Calcd. for $C_{19}H_{37}O_2N$: C, 73.26; H, 11.97; N, 4.50%.

(2S,4E)-2-Amino-4-octadecen-1-ol ((*S*)-**1**). A solution of **16** (200 mg, 0.575 mmol) in tetrahydrofuran (25 ml) was added dropwise to an ice-cooled suspension of lithium aluminum hydride (120 mg, 3.16 mmol) in tetrahydrofuran (1 ml). The mixture was stirred for 16 hr at room temperature. With ice-cooling and vigorous stirring, water (0.12 ml), a 15% aqueous solution of sodium hydroxide (0.12 ml), and more water (0.36 ml) were added in succession. After stirring for 30 min at room temperature, the precipitate was filtered off. The filtrate was dried with magnesium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel (15 g), and elution with chloroform–methanol (9 : 1) gave 130 mg (80%) of (*S*)-**1** as an amorphous solid, mp 55.5 ~ 59.0°C. Its IR and NMR spectra were identical with those of (*R*)-**1**. The optical purity of (*S*)-**1** was estimated in the same manner as that described for **15** by an HPLC analysis of the corresponding bis[(*S*)-MTPA] derivative **17**, t_R=13.3 min (100%). The peak due to **15** at t_R=14.4 min was not detected; therefore, our (*S*)-**1** was of almost 100% *e.e.*

(2R,4E)-2-N-Hexadecanoylamino-4-octadecen-1-ol (**2**). A solution of crude (*R*)-**1** (220 mg, *ca.* 770 mmol) and *p*-nitrophenyl hexadecanoate (380 mg, 1.01 mmol) in pyridine (10 ml) was stirred for 2 hr at 50°C and for 16 hr at room temperature. The solvent was removed *in vacuo*, and the residue was chromatographed over silica gel (25 g). Elution with *n*-hexane–ether (2 : 1) gave crude **2**, which was recrystallized from ether to give 365 mg (90%) of **2** as cubes, mp 71.5 ~ 72.0°C; $[\alpha]_D^{20}$ −3.62° (c=0.57, $CHCl_3$); IR ν_{max} cm^{-1} 3450 (s), 3330 (s), 3280 (s), 1645 (s), 1605 (s), 1550 (s), 1465 (s), 965 (s), 720 (s); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (6H, t, J=6.0 Hz, 18-H_3, 16′-H_3), 1.27 (48H, br. s), 1.57 (1H, br., OH), 1.85 ~ 2.32 (6H, m, 3-H_2, 6-H_2, 2′-H_2), 3.40 ~ 4.06 (3H, m, 1-H_2, 2-H), 5.33 (1H, dt, J= 15.0, 6.0 Hz, 5-H), 5.54 (1H, dt, J=15.0, 6.0 Hz, 4-H), 5.68 (1H, d, J=8.0 Hz, NH); FD-MS m/z: 522 $(M+H)^+$. *Anal.* Found: C, 78.20; H, 12.58; N, 2.66. Calcd. for $C_{34}H_{67}O_2N$: C, 78.26; H, 12.92; N, 2.68%.

*(2′R,4′E)-1-O-(2′-Hexadecanoylamino-4′-octadecenyl)-2,3,4,6-tetra-O-acetyl-β-*D*-galactopyranoside* (**18**). Dry benzene (20 ml) was added to a solution of **2** (600 mg, 1.15 mmol) in nitromethane–acetonitrile (7 : 2, 45 ml), and the solution was stirred and heated at 110°C to remove the moisture azeotropically with benzene. The mixture was concentrated to the volume of *ca.* 30 ml, and cooled under argon. To the solution was added 2,3,4,6-tetra-*O*-acetylgalactopyranosyl bromide (710 mg, 1.73 mmol) and mercuric cyanide (434 mg, 1.72 mmol), and the mixture was stirred for 2 hr under reflux at 100°C under argon. After cooling, the mixture was diluted with chloroform. The chloroform solution was washed with saturated hydrogen sulfide solution, and the black precipitate of mercuric sulfide was filtered off over Celite. The filtrate was washed with saturated sodium hydrogen carbonate solution and brine, dried with sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed over silica gel (50 g). Elution with chloroform–ethyl acetate (49 : 1) gave crude **18**, which was recrystallized from *n*-hexane to give 881 mg (90%) of **18** as rods, mp 72.0 ~ 72.5°C; $[\alpha]_D^{27}$ −2.96° (c=0.38, $CHCl_3$); IR ν_{max} cm^{-1} 3450 (s), 3300 (s), 1760 (vs), 1645 (s), 1550 (s), 1470 (s), 1370 (s), 1280 ~ 1210 (vs, br.), 1080 (s), 1060 (s), 960 (m), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (6H, t, J= 6.0 Hz), 1.27 (48H, br. s), 2.00 ~ 2.35 (6H, m), 2.00 (3H, s), 2.06 (6H, s), 2.16 (3H, s), 3.54 (1H, dd, J=4.5, 9.5 Hz), 3.68 ~ 4.00 (2H, m), 4.01 ~ 4.25 (3H, m), 4.44 (1H, d, J= 7.0 Hz), 5.01 (1H, dd, J=3.5, 10.0 Hz), 5.08 ~ 5.66 (5H, m). *Anal.* Found: C, 67.25; H, 10.11; N, 1.61. Calcd. for $C_{48}H_{85}O_{11}N$: C, 67.65; H, 10.05; N, 1.64%.

*(2′R,4′E)-1-O-(2′-Hexadecanoylamino-4′-octadecenyl)-β-*D*-galactopyranoside* (**3**). Sodium methoxide in methanol (28%, 0.20 ml, 0.98 mmol) was added to a solution of **18** (400 mg, 0.496 mmol) in methanol–tetrahydrofuran (4 : 3, 35 ml). The mixture was stirred for 1.5 hr at room temperature. It was then neutralized by addition of ion-exchange resin (Amberlyst-15, 2.50 g, 1.00 mmol) and stirred for 30 min at room temperature. After filtration through Celite, the filtrate was concentrated *in vacuo*. The residue was chromatographed over silica gel (40 g). Elution with chloroform–methanol (9 : 1) gave 285 mg (89%) of **3** as white granules, mp 144 ~ 146°C; $[\alpha]_D^{23}$ −11.7° (c=0.20, CH_3OH); IR ν_{max} cm^{-1} 3400 (s), 3300 (vs), 2960 (s), 2930 (vs), 2860 (vs), 1650 (vs), 1555 (s), 1470 (s), 1440 (w), 1420 (w), 1370 (m), 1120 (m), 1075 (vs), 1160 (s), 1150 (s), 1020 (m), 980 (m), 960 (m), 860 (w), 785 (m), 715 (s); NMR δ_H

(400 MHz, C_5D_5N) 0.877 (6H, t, J=7.0 Hz, 18′-H_3, 16″-H_3), 1.27 (44H, br.), 1.35 (2H, m), 1.73～1.89 (2H, m, 3″-H_2), 1.996 (2H, q-like, J=5.5 Hz, 6′-H_2), 2.377 (2H, t, J=7.5 Hz, 2″-H_2), 2.451 (1H, ddd, J=6.0, 7.8, 13.0 Hz, 3′-H), 2.586 (1H, dt, J=13.0, 5.5 Hz, 3′-H), 3.904 (1H, dd, J=5.5, 10.0 Hz, 1′-H), 4.060 (1H, t-like, J=6.0 Hz, 2-H), 4.148 (1H, dd, J=3.5, 9.5 Hz, 6-H), 4.316 (1H, dd, J=5.0, 10.0 Hz, 1′-H), 4.40～4.48 (2H, m, 3-H, 5-H), 4.477 (1H, dd, J=7.8, 9.5 Hz, 6-H), 4.564 (1H, d-like, J=3.0 Hz, 4-H), 4.621 (1H, m, 2′-H), 4.828 (1H, d, J=7.8 Hz, 1-H), 5.540 (1H, dt, J=15.0, 5.5 Hz, 5′-H), 5.587 (1H, dt, J=15.0, 5.5 Hz, 4′-H), 6.27 (4H, br., OH), 8.200 (1H, d, J=8.8 Hz, NH); δ_C (100 MHz, C_5D_5N) 14.28 (q), 22.95 (t), 26.41 (t), 29.58 (t), 29.62 (t), 29.77 (t), 29.84 (t), 30.00 (t), 32.15 (t), 33.00 (t), 35.48 (t), 36.91 (t), 50.01 (d), 62.40 (t), 70.24 (d), 72.46 (t), 72.75 (d), 75.41 (d), 77.07 (d), 106.35 (d), 126.89 (d), 133.47 (d), 173.02 (s), multiplicities were determined by an INEPT experiment; FD-MS m/z: 684 $(M+H)^+$, 706 $(M+Na)^+$. *Anal.* Found: C, 70.23; H, 11.11; N, 2.07. Calcd. for $C_{40}H_{77}O_7N$: C, 70.23; H, 11.35; N, 2.05%.

*(2′R,4′E)-1-O-(2′-Hexadecanoylamino-4′-octadecenyl)-2,3,4,6-tetra-O-acetyl-β-*D*-glucopyranoside* (**19**). In the same manner as that described for the synthesis of **18**, **2** (300 mg, 0.575 mmol) and tetra-*O*-acetylglucopyranosyl bromide (355 mg, 0.860 mmol) gave 373 mg (76%) of **19** as rods, mp 91.0～91.5°C; $[\alpha]_D^{17}$ +5.60° (c=0.44, $CHCl_3$); IR ν_{max} cm^{-1} 3450 (s), 3340 (s), 1750 (vs), 1645 (s), 1550 (s), 1470 (s), 1380 (s), 1365 (s), 1280～1210 (vs, br.), 1100 (s), 1055 (s), 965 (m), 720 (m); NMR δ_H (100 MHz, $CDCl_3$) 0.88 (6H, t, J=6.0 Hz), 1.27 (48H, br. s), 2.01 (3H, s), 2.04 (3H, s), 2.06 (3H, s), 2.10 (3H, s), 1.85～2.35 (6H, m), 3.45～4.54 (9H, m), 4.85～5.66 (3H, m). *Anal.* Found: C, 67.26; H, 10.05; N, 1.67. Calcd. for $C_{48}H_{85}O_{11}N$: C, 67.65; H, 10.05; N, 1.64%.

*(2′R,4′S)-1-O-(2′-Hexadecanoylamino-4′-octadecenyl)-β-*D*-glucopyranoside* (**4**). In the same manner as that described for the synthesis of **3**, **19** (195 mg, 0.230 mmol) gave 140 mg (89%) of **4** as white granules, mp 125～127°C; $[\alpha]_D^{23}$ −23.1° (c=0.25, CH_3OH); IR ν_{max} cm^{-1} 3450 (s), 3350 (s), 2960 (s), 2930 (vs), 2860 (vs), 1625 (s), 1550 (s), 1470 (s), 1435 (m), 1370 (m), 1160 (m), 1110 (s), 1080 (s), 1035 (s), 965 (m), 720 (m); NMR δ_H (400 MHz, C_5D_5N) 0.875 (6H, t, J=7.0 Hz, 18′-H_3, 16″-H_3), 1.27 (44H, br.), 1.35 (2H, m), 1.73～1.89 (2H, m, 3″-H_2), 2.000 (2H, q-like, J=6.0 Hz, 6′-H_2), 2.395 (2H, t, J=7.5 Hz, 2H, 2″-H_2), 2.468 (1H, ddd, J=6.0, 8.2, 13.0 Hz, 3′-H), 2.615 (1H, dt, J=13.0, 5.5 Hz, 3′-H), 3.901 (1H, dd, J=5.5, 10.2 Hz, 1′-H), 3.92～3.98 (1H, m, 5-H), 4.053 (1H, t-like, J=9.0 Hz, 2-H), 4.19～4.26 (2H, m, 3-H, 4-H), 4.310 (1H, dd, J=5.2, 10.2 Hz, 1′-H), 4.384 (1H, dd, J=5.5, 12.0 Hz, 6-H), 4.544 (1H, dd, J=2.4, 12.0 Hz, 6-H), 4.61～4.70 (1H, m, 2′-H), 4.916 (1H, d, J=7.8 Hz, 1-H), 5.556 (1H, dt, J=15.0, 5.5 Hz, 5′-H), 5.606 (1H, dt, J=15.0, 5.5 Hz, 4′-H), 6.05 (4H, br., 4OH), 8.269 (1H, d, J=8.8 Hz, NH); δ_C (100 MHz, C_5D_5N) 14.28 (q), 22.94 (t), 26.43 (t), 29.62 (t), 30.00 (t), 32.15 (t), 33.00 (t), 35.49 (t), 36.91 (t), 50.01 (d), 62.87 (t), 71.62 (d), 72.61 (t), 75.32 (d), 78.59 (d), 105.83 (d), 122.23 (t), 122.41 (t), 126.86 (d), 133.50 (d), 173.07 (s), multiplicities were determined by an INEPT experiment; FD-MS m/z: 684 $(M+H)^+$, 706 $(M+Na)^+$. *Anal.* Found: C, 70.01; H, 11.21; N, 2.11. Calcd. for $C_{40}H_{77}O_7N$: C, 70.23; H, 11.35; N, 2.05%.

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