Synthesis of a New Cerebroside from a *Chondropsis* sp. Sponge[1,2]

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A cerebroside, 1-*O*-(β-D-galactopyranosyloxy)-(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-hydroxytetracosanoylamino]-17-methyl-6-octadecene-3,4-diol (2), was asymmetrically synthesized from isobutyraldehyde. On the basis of a comparison of the physical data, the absolute structure of a new cerebroside 1b from a *Chondropsis* sp. sponge is thought to be the same as that of 2.

Keywords glycosphingolipid; asymmetric synthesis; absolute stereochemistry; phytosphingosine; galactosyl ceramide; hystidine decarboxylase; hypotensive activity; (*R*)-benzyl-2,3-epoxypropyl ether; sponge; *Chondropsis* sp.

Recently, a mixture of new galactosyl ceramides (**1a** and **1b**) was separated from a sea sponge, *Chondropsis* sp., and was shown to inhibit hystidine decarboxylase as well as to have hypotensive activity in anesthetized rats.[2] The mixture was characterized by acid hydrolysis, ozonolysis, and gas chromatography-mass spectrometry (GC-MS) analysis and found to be composed of D-galactose, α-hydroxytetracosanoic acid, and C_{17}- and C_{18}-phytosphingosines bearing a *trans*-double bond and an iso-type terminal in the long chain, as illustrated in Chart 1. However, neither the determination of the absolute stereochemistry nor the isolation of the pure cerebrosides **1a** and **1b** was achieved.

As a part of our studies on glycosphingolipids from starfishes, we were primarily interested in the absolute structure and biological activities of the new cerebrosides **1a** and **1b**. While the syntheses of many kinds of ceramides and cerebrosides have been achieved,[3] there seems to be no documentation of the synthesis of a phytosphingosine-type cerebroside possessing a hydroxy fatty acid, except for one example by our group.[4] For the synthesis of the new cerebrosides **1a** and **1b**, we focused on the synthesis of the ceramide, (2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-hydroxytetracosanoylamino]-17-methyl-6-octadecene-1,3,4-triol (**2**), which contains the most common configurations among naturally occurring phytosphingosines and α-hydroxy fatty acids. The design of the synthesis of **2** is retrosynthetically outlined in Chart 1. The chiralities on the phytosphingosine were successively introduced into the C-4, C-3, and C-2 positions by utilizing the chiral synthon (*R*)-benzyl-2,3-epoxypropyl ether (**7**), asymmetric epoxidation, and amination with a regioselective epoxide opening, leading to **5**. (*R*)-2-Hydroxytetracosanoic acid (**4**) has been prepared by our group.[4a] The acid **4** and the phytosphingosine **5** were converted into the cerebroside **2** after glycosidation of the ceramide **3** with D-galactose.

Isobutyraldehyde (**9**) was used for the construction of the iso-type terminal of a phytosphingosine, (2*S*,3*S*,4*R*,6*E*)-2-amino-17-methyl-6-octadecene-1,3,4-triol (**5**). A Wittig reaction of **9** with α,α-dibromomethylenetriphenylphosphorane[5] gave an olefinic dibromide **10** in an 88% yield. The dibromide **10** was treated first with *n*-butyllithium and then bromooctane to afford an alkyne **11** in a 70% yield. Hexamethylphosphoric triamide (HMPA) and three equivalents of *n*-butyllithium are necessary for this alkylation. The migration of the internal triple bond of **11** with potassium aminopropylamide (KAPA)[6] resulted in the alkyne **8**, of which the terminals were an iso-type moiety and a triple bond. The alkyne **8** was treated with *n*-butyllithium and then (*R*)-benzyl-2,3-epoxypropyl ether (**7**)[7] to produce a chiral alcohol, which was protected as the methoxymethoxy (MOM) ether (**12**) with chloromethyl methyl ether (MOMCl) and *N*,*N*-diisopropylethylamine in a 64% yield from **8**. Debenzylation and the reduction of the MOM ether **12** with lithium in ethylamine and *tert*-

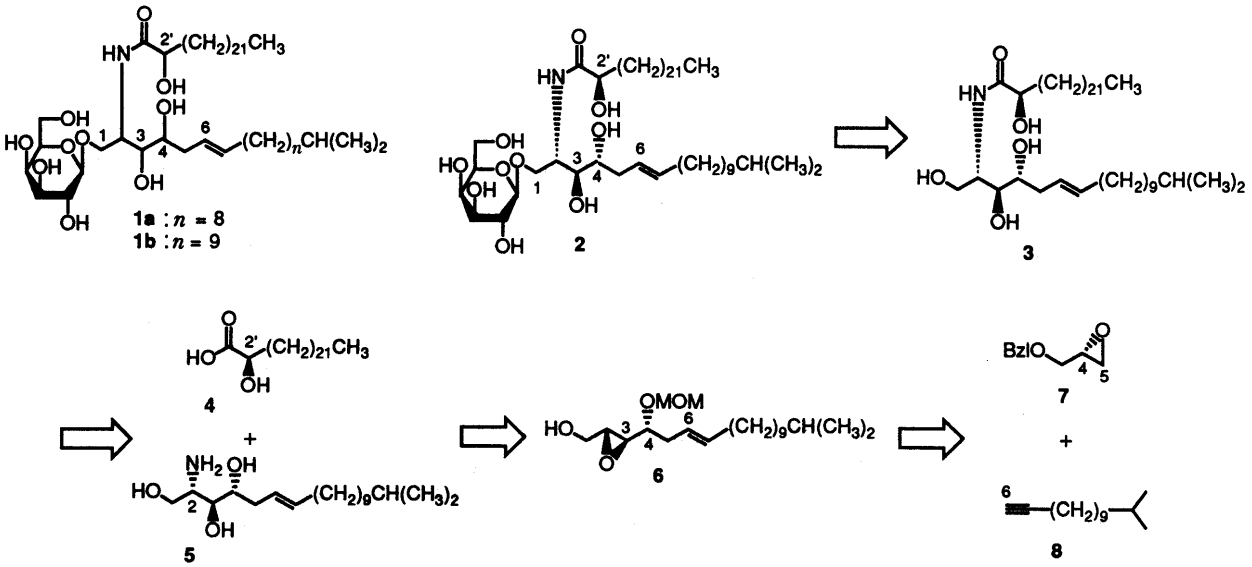

Chart 1

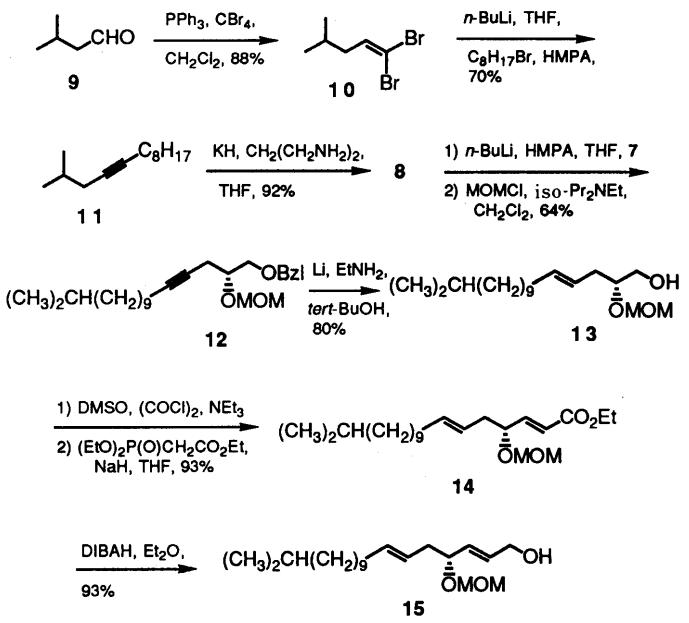

Chart 2

butanol gave an alcohol (**13**) bearing a *trans*-double bond in an 80% yield. Swern oxidation[8] of **13** followed by Horner–Emmons reaction afforded a *trans*-α,β-unsaturated ester **14** in a 93% yield. The ester **14** was reduced with diisobutylaluminum hydride (DIBAH) to give the (4*R*)-allylic alcohol **15** in a 93% yield.

Asymmetric epoxidation[9] of **15**, using (−)-diisopropyl tartrate (DIPT) as a chiral auxiliary, gave a mixture of the (2*R*,3*R*,4*R*)-epoxy alcohol **6** and the (2*S*,3*S*,4*R*)-epoxy alcohol **16** in a ratio of 3 : 1.[10] The formation of the diastereomeric epoxy alcohols was confirmed by a comparison of the epoxy alcohol prepared by epoxidation of **15** with vanadyl acetylacetonate [$VO(acac)_2$] and *tert*-butyl hydroperoxide (TBHP).[11] The configurations of **6** and **16** were determined by examination of the phytosphingosine tetraacetates **23** and **26**, as described later. The mixture of **6** and **16** was converted into the urethanes **17** and **18**, which were subjected to an intramolecular base-catalyzed epoxide opening with sodium hydride in tetrahydrofuran (THF)[12] to give *N*-benzyloxazolidinones **19** and **20** in 63 and 23% yields from **6** and **16**, respectively, after separation by silica gel chromatography.

Debenzylation of the *N*-benzyloxazolidinone **19** afforded an oxazoline **21** which was subjected to alkaline hydrolysis and cleavage of the MOM protective group to produce the phytosphingosine **5**. Acetylation of **5** to **23** and subsequent hydrogenation gave the phytosphingosine tetraacetate **25**. A comparison of the ^1H- and ^{13}C-nuclear magnetic resonance (NMR) data of **25** with those of authentic (2*S*,3*S*,4*R*)-phytosphingosine tetraacetate given in the literature[4b] revealed that the absolute structure of phytosphingosine **5** was (2*S*,3*S*,4*R*)-2-amino-17-methyl-6-octadecene-1,3,4-triol. The isomeric *N*-benzyloxazolidinone **20** was also converted sequentially into **22**, **24**, and **26** in a similar manner to that described above. The configurations of **24** were 2*R*, 3*R*, and 4*R* on the basis of a comparison of the ^1H- and ^{13}C-NMR data on **26** with those of authentic phytosphingosine tetraacetate, (2*R*,3*R*,4*R*)-2-acetamido-1,3,4-triacetoxyhexadecane.[4b]

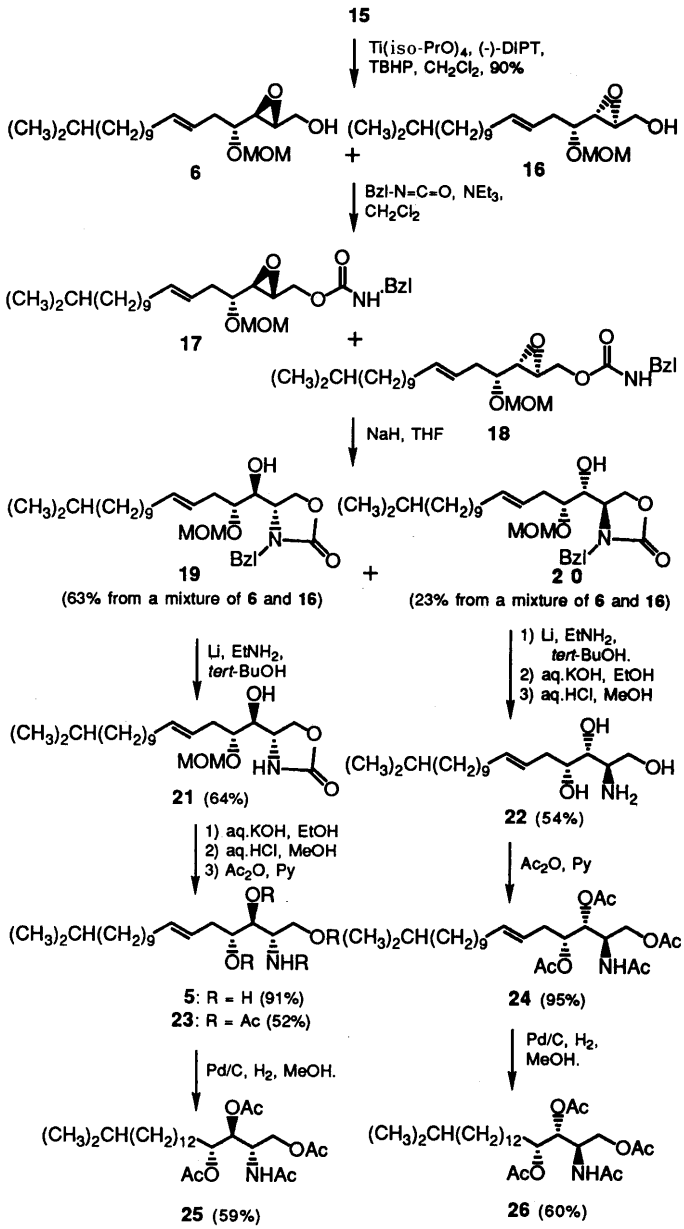

Chart 3

The amidation of **5** and (*R*)-2-(methoxymethoxy)tetracosanoic acid (**27**) was carried out with dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in THF[13] to give **28** in a 76% yield. The MOM protective group of **28** was removed with 1,2-ethanedithiol and boron trifluoride etherate[14] to give the ceramide **3** in a 76% yield. At this point, we could introduce all chiralities, the *trans*-double bond, and the iso-type terminal of the ceramide, requisite for synthesis of the cerebroside **2**. The secondary hydroxy groups of **3** were protected as benzoyl esters (except for the primary hydroxy group) by successive tritylation, benzoylation, and detritylation to afford **31** in an 84% yield. Glycosidation of **31** and a D-galactosyl imidate **32** in the presence of boron trifluoride etherate and 4 Å molecular sieves in dichloromethane[15] gave **33** together with **34**, which was also formed in the glycosidation of a pentaacetylglucosyl imidate.[3b,4b] Finally, deacylation of **33** with a methanolic potassium carbonate solution gave the D-galactosyl ceramide **2**. All of the NMR data of **2**

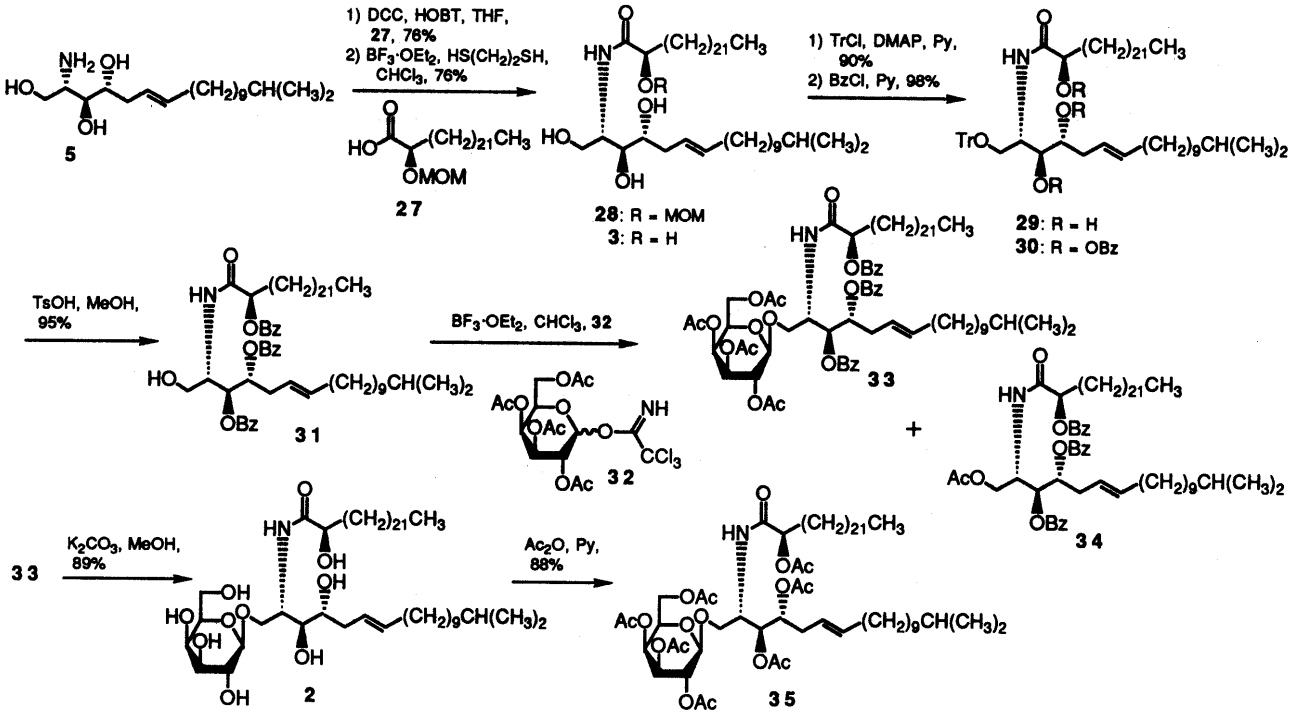

Chart 4

were in good agreement with those of the mixture of **1a** and **1b**.[2] Consequently, the first asymmetric synthesis of the new cerebroside **1b** with hystidine decarboxylase-inhibitory activity has been accomplished from isobutyraldehyde (**9**) in 22 steps. The cerebroside **2** was converted into a heptaacatate **35** in the usual manner. The ^{1}H- and ^{13}C-NMR spectra of **35** were also in good agreement with those of the mixture of acetyl derivatives of **1a** and **1b**.[2]

On the basis of the above results, the absolute structure of **1b** is thought to be 1-*O*-(β-D-galactopyranosyloxy)-(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-hydroxytetracosanoylamino]-17-methyl-6-octadecene-3,4-diol (**2**) and the other component of the mixture, **1a**, which has the same absolute stereochemistry is considered to consist of a nor-phytosphingosine residue with the same hydroxytetracosanoyl group.

Experimental

Melting points were determined with a Yanaco micro melting point apparatus (MP-3). Optical rotations: Jasco DIP-360 polarimeter. Infrared (IR) spectra: Jasco IR-810 spectrometer. ^{1}H-NMR spectra: 90 MHz, JEOL FX-90Q spectrometer; 270 MHz, JEOL GX-270 spectrometer; 400 MHz, JEOL GX-400 spectrometer. ^{13}C-NMR spectra: 67.8 MHz, JEOL GX-270 spectrometer; 100 MHz, JEOL GX-400 spectrometer. NMR spectra were obtained by using $CDCl_3$, C_6D_6, or pyridine-d_5 (C_5D_5N) as the solvent and tetramethylsilane as an internal standard. Field desorption mass spectra (FD-MS) and fast atom bombardment MS (FAB-MS): JEOL JMS-DX300/JMA-3500 data system. Electron impact MS (EI-MS) and high-resolution EI-MS: JEOL JMS-DX300/JMA-3100 data system. Silica gel column chromatography: Kieselgel 60 (70—230 mesh, No. 7734, Merck) if not otherwise specified, or Silica gel BW-300 (200—400 mesh, Fuji Davison Co., Ltd.). All solvents were distilled before use. Anhydrous THF and ether were distilled from sodium and benzophenone. Other anhydrous solvents were distilled from calcium hydride and stored over activated 4-Å molecular sieve pellets. Reactions were carried out under argon, as required.

1,1-Dibromo-4-methyl-1-pentene (10) Carbon tetrabromide (12.4 g, 37.4 mmol) was added at 0 °C to a solution of triphenylphosphine (19.6 g, 74.6 mmol) in CH_2Cl_2 (37 ml). The reaction mixture was stirred at room temperature for 1 h and isobutyraldehyde **9** (2.0 ml, 18.7 mmol) was added at 0 °C to the vigorously stirred mixture. Stirring was continued at room temperature for 1 h, then the mixture was diluted with hexane (400 ml) and the resulting precipitate was filtered off through a cotton plug. The filtrate was concentrated under atmospheric pressure and distilled to give **10** (3.98 g, 16.4 mmol, 88%) as a colorless oil, bp 96 °C (46 Torr). IR (neat): 2950 (C–H), 1615 (C=C), 1383 and 1365 [CH–$(CH_3)_2$] cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 6.40 (1H, t, *J*=7.1 Hz, 2-H), 2.00 (2H, m, 3-H), 1.73 (1H, m, 4-H), 0.93 (6H, d, *J*=6.3 Hz, 5-H and $CHCH_3$). *Anal.* Calcd for $C_6H_{10}Br_2$: C, 29.79; H, 4.17. Found: C, 29.63; H, 3.97.

2-Methyl-4-tridecyne (11) *n*-Butyllithium (73.2 ml, 110 mmol, 1.5 M in hexane) was added at −78 °C to a solution of **10** (8.57 g, 35.4 mmol) in THF (71 ml). The reaction mixture was allowed to warm to room temperature over 1.5 h and then cooled to −78 °C. A solution of 1-bromononane (6.44 ml, 37.2 mmol) in HMPA (71 ml) was added at −78 °C to the mixture. After being stirred at −78 °C for 30 min, the mixture was allowed to warm to room temperature over 1.5 h, diluted with hexane, and washed with water. The aqueous layer was extracted with hexane. The combined hexane layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was distilled to give **11** (4.85 g, 70% yield) as a colorless oil, bp 125 °C (17 Torr). IR (neat): 2955 (C–H), 2930, 2850, 1383 and 1365 [CH–$(CH_3)_2$] cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 2.08 (4H, m, 3-H and 6-H), 1.38 (12H, m), 0.96 (6H, d, *J*=6.4 Hz, 1-H and $CHCH_3$). EI-MS *m/z* (%): 194 (M^+, 2), 151 ($M^+-C_3H_7$, 5), 81 ($M^+-C_8H_{17}$, 100). *Anal.* Calcd for $C_{14}H_{26}$: C, 86.51; H, 13.48. Found: C, 86.55; H, 13.48.

12-Methyl-1-tridecyne (8) 1,3-Diaminopropane (31 ml) was added to KH (2.24 g, 55.9 mmol; 20—25% wt. KH dispersion in mineral oil was washed 3 times with hexane and dried) under stirring and cooling in an ice bath. The reaction mixture was stirred at room temperature for 1 h and **11** (5.97 g, 30.7 mmol) was added dropwise to the vigorously stirred mixture. Stirring was continued at room temperature for 5 min, then the reaction mixture was quenched with water and extracted with hexane. The extracts were washed consecutively with water, 10% aqueous HCl, and water, dried (Na_2SO_4), filtered, and concentrated under atmospheric pressure. The residue was distilled to give **8** (5.50 g, 92% yield) as a colorless oil, bp 85 °C (1 Torr). IR (neat): 3315 (≡C–H), 2955 (C–H), 2930, 2855, 2120 (C≡C), 1383 and 1365 [CH–$(CH_3)_2$] cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 2.18 (2H, dd, *J*=7.0, 2.6 Hz, 3-H), 1.93 (1H, t, *J*=2.6, 1-H), 1.27 (10H, m), 0.86 (6H, d, *J*=6.6 Hz, 13-H and $CHCH_3$). EI-MS *m/z* (%): 194 (M^+, 1), 179 (M^+-CH_3, 3), 151 ($M^+-C_3H_7$, 5), 109 ($M^+-C_6H_{13}$, 100). *Anal.* Calcd for $C_{14}H_{26}$: C, 86.51; H, 13.48. Found: C, 86.48; H, 13.30.

(2*R*)-1-Benzyloxy-2-(methoxymethoxy)-15-methyl-4-hexadecyne (12) *n*-Butyllithium (5.37 ml, 8.06 mmol, 1.5 M hexane solution) was added at −25 °C to a solution of **8** (2.0 ml, 8.06 mmol) in THF (8 ml) and the

mixture was allowed to warm to room temperature over 10 min. The epoxide **7** (1.48 ml, 8.07 mmol) and HMPA (16 ml) were added at −25 °C to the mixture. After being stirred at room temperature for 30 min, the reaction mixture was diluted with hexane–Et_2O (2 : 1), washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 8 : 2) to give a mixture (2.55 g) of the desired alcohol and a trace of unreacted **7**. Chloromethyl methyl ether (812 μl, 10.7 mmol) and *N,N*-diisopropylethylamine (2.11 ml, 12.1 mmol) were added to the mixture (2.55 g). After being stirred at room temperature for 20 h, the reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (hexane–AcOEt, 85 : 15) to give **12** (2.16 g, 64% yield from **8**) as a colorless oil. $[\alpha]_D^{26}$ −5.68° (c=2.66, $CHCl_3$). IR (neat): 2920 (C–H), 2930, 2855, 735 and 790 (Ar–H) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 7.32 (5H, s, aromatic H), 4.74 (2H, s, OCH_2O), 4.57 (2H, s, benzylic H), 3.85 (1H, m, 2-H), 3.62 (2H, dd, J=4.9, 1.1 Hz, 1-H), 3.38 (3H, s, OCH_3), 2.48 (2H, m, 3-H), 2.11 (2H, br s, 6-H), 1.25 (m), 0.86 (6H, d, J=6.1 Hz, 16-H and $CHC\underline{H}_3$). EI-MS m/z (%): 402 (M^+, 4), 357 ($M^+-CH_2OCH_3$, 93), 207 ($M^+-C_{11}H_{15}O_3$, 100). *Anal.* Calcd for $C_{26}H_{42}O_3$: C, 77.56; H, 10.51. Found: C, 77.32; H, 10.35.

(2*R*)-2-(Methoxymethoxy)-15-methyl-4-hexadecen-1-ol (13) Liquid $EtNH_2$ (50 ml) was added at 0 °C to a solution of **12** (2.05 g, 5.09 mmol) in *tert*-BuOH (10 ml), then several pieces of lithium (300 mg) were added at −20 °C. The blue-colored mixture was stirred at −20 °C for 10 min and quenched with ammonium chloride. The unreacted lithium was removed, then the mixture was concentrated to half the original volume, diluted with ether, washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 7 : 3) to give **13** (1.28 g, 80% yield) as a colorless oil. $[\alpha]_D^{26}$ −20.0° (c=2.72, $CHCl_3$). IR (neat): 3440 (O–H), 2920 (C–H), 2855, 1381 and 1362 [CH–$(CH_3)_2$] cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 4.71 (2H, s, OCH_2O), 3.54 (3H, m, 1-H and 2-H), 3.42 (3H, s, OCH_3), 2.82 (1H, m, OH), 2.22 (2H, m, 3-H), 1.99 (2H, m, 6-H), 1.25 (m), 0.86 (6H, d, J=6.1 Hz, 16-H and $CHC\underline{H}_3$). FD-MS m/z (%): 315 (M^++H, 100), 105 (50). *Anal.* Calcd for $C_{19}H_{38}O_3$: C, 72.56; H, 12.18. Found: C, 72.27; H, 12.23.

Ethyl (2*E*,4*R*,6*E*)-4-(Methoxymethoxy)-17-methyl-2,6-octadecadien-1-ate (14) Dimethyl sulfoxide (DMSO) (549 μl, 7.74 mmol) was added at −60 °C to a solution of oxalyl chloride (506 μl, 5.80 mmol) in CH_2Cl_2 (9.67 ml). The mixture was stirred at −60 °C for 2 min and a solution of **13** (1.21 g, 3.87 mmol) in CH_2Cl_2 (3.87 ml) was added. After being stirred at −50 to −60 °C for 15 min, the mixture was treated with triethylamine (3.24 ml, 23.2 mmol), stirred at −60 °C for 10 min, and then allowed to warm to room temperature over 1 h. The reaction mixture was diluted with ether, washed consecutively with 5% aqueous H_3PO_4, water, and aqueous saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was used for the next reaction without further purification. NaH (242 mg, 6.05 mmol, 60% wt. dispersion in mineral oil) was added to a solution of triethyl phosphonoacetate (1.26 ml, 6.35 mmol) in THF (8 ml) under cooling with a water bath. A solution of the residue in THF (8 ml) was added to the mixture. After being stirred at room temperature for 20 min, the mixture was diluted with ether, washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting residue was chromatographed on silica gel (hexane–AcOEt, 8 : 2) to give **14** (1.38 g, 93% yield) as a colorless oil. $[\alpha]_D^{27}$ +16.8° (c=5.66, $CHCl_3$). IR (neat): 2920 (C–H), 2850, 1722 (C=O), 1566 (C=C) cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 6.83 (1H, dd, J=15.6, 6.0 Hz, 3-H), 5.97 (1H, dd, J=15.8, 1.1 Hz, 2-H), 5.51 (1H, d, J=5.5 Hz, 6-H), 5.39 (1H, d, J=5.3 Hz, 7-H), 4.62 (2H, s, OCH_2O), 4.20 (2H, q, J=7.1 Hz, $OC\underline{H}_2CH_3$), 3.37 (3H, s, OCH_3), 2.31 (2H, m, 5-H), 1.99 (2H, m, 8-H), 1.26 (m), 0.86 (6H, d, J=6.1 Hz, 18-H and $CHC\underline{H}_3$). FD-MS m/z (%): 382 (M^+, 30), 173 (100). *Anal.* Calcd for $C_{23}H_{42}O_4$: C, 72.20; H, 11.06. Found: C, 71.97; H, 11.06.

(2*E*,4*R*,6*E*)-4-(Methoxymethoxy)-17-methyl-2,6-octadecadien-1-ol (15) A DIBAH solution (12.7 ml, 12.7 mmol, 1.0 M in hexane) was added at −25 °C to a solution of **14** (1.22 g, 3.20 mmol) in ether (12.8 mmol). The reaction mixture was allowed to warm to room temperature and stirred at ambient temperature for 12 h. After dropwise addition of a 5% aqueous H_3PO_4 solution, the mixture was extracted with ether. The extracts were acidified with aqueous 5% H_3PO_4, washed with brine and aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (BW-300, hexane–AcOEt, 7 : 3) to give **15** (1.01 g, 93% yield) as a colorless oil. $[\alpha]_D^{27}$ +30.5° (c=0.78, $CHCl_3$). IR (neat): 3420 (O–H), 2930 (C–H), 2855 cm^{-1}. ^{1}H-NMR (90 MHz, $CDCl_3$) δ: 5.71 (2H, m, 2-H and 3-H), 5.46 (2H, m, 6-H and 7-H), 4.69 (1H, d, J=6.8 Hz, OCH_aO), 4.53 (1H, d, J=6.6 Hz, OCH_bO), 3.35 (3H, s, OCH_3), 2.26 (2H, m, 5-H), 1.99 (2H, m, 8-H), 1.25 (m), 0.85 (6H, d, J=6.1 Hz, 18-H and $CHC\underline{H}_3$). FD-MS m/z (%): 341 (M^++H, 2), 131 (100). *Anal.* Calcd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84. Found: C, 73.89; H, 11.87.

(2*R*,3*R*,4*R*,6*E*)-2,3-Epoxy-4-(methoxymethoxy)-17-methyl-6-octadecen-1-ol (6) and Its (2*S*,3*S*,4*R*,6*E*) Isomer (16) A mixture of titanium tetraisopropoxide (325 μl, 1.09 mmol) and powdered 4-Å molecular sieves (400 mg) in CH_2Cl_2 was cooled to −30 °C. (−)-Diisopropyl tartrate (290 μl, 1.37 mmol) and a *tert*-butyl hydroperoxide solution (1.68 ml, 4.10 mmol, 2.44 M in CH_2Cl_2) were added dropwise at −30 °C, sequentially. The reaction mixture was stirred at −25 °C for 30 min and a solution of **15** (931 mg, 2.74 mmol) in CH_2Cl_2 (11 ml) was added dropwise. The resulting mixture was stored at −20 °C for 15 h in a refrigerator and quenched with water (6.5 ml). The mixture was allowed to warm to room temperature over 1 h while being stirred vigorously, and filtered through a pad of Celite 545. The filtrate was treated with an aqueous 1 N KOH solution (5.5 ml) saturated with NaCl, stirred vigorously for 30 min, and filtered through a pad of Celite 545. The filtrate was extracted with $CHCl_3$. The extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 7 : 3) to give a mixture of **6** and **16** (854 mg, 88% yield) as a colorless oil. $[\alpha]_D^{27}$ +4.65° (c=2.69, $CHCl_3$). IR (neat): 3440 (O–H), 2930 (C–H), 2855 cm^{-1}. FD-MS m/z (%): 357 (M^++H, 66), 147 (100). *Anal.* Calcd for $C_{21}H_{40}O_4$: C, 70.74; H, 11.31. Found: C, 70.56; H, 11.41.

(2*R*,3*R*,4*R*,6*E*)-1-[(Benzylcarbamoyl)oxy]-2,3-epoxy-4-(methoxymethoxy)-17-methyl-6-octadecene (17) and Its (2*S*,3*S*,4*R*,6*E*) Isomer (18) Triethylamine (962 μl, 6.90 mmol) and benzyl isocyanate (426 μl, 3.45 mmol) were added sequentially to a solution of a mixture of **6** and **16** (820 mg, 2.30 mmol) in CH_2Cl_2 (9.2 ml). The whole was stirred at room temperature for 15 h, then treated with water (83 μl, 4.6 mmol) and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 3 : 1) to give a mixture of **17** and **18** (1.09 g, 97% yield) as a colorless oil. $[\alpha]_D^{27}$ +13.0° (c=2.66, $CHCl_3$). IR (CCl_4): 2930 (C–H), 2855, 1735 (C=O) cm^{-1}. FAB-MS m/z (%): 490 (M^++H, 25), 91 ($PhCH_2^+$, 100). *Anal.* Calcd for $C_{29}H_{47}NO_5$: C, 71.13; H, 9.67; N, 2.86. Found: C, 71.39; H, 9.69; N, 2.83.

(4*S*,1′*S*,2′*R*,4′*E*)-3-Benzyl-4-[1′-hydroxy-2′-(methoxymethoxy)-15′-methyl-4′-hexadecenyl]-2-oxazolidinone (19) and Its (4*R*,1′*R*,2′*R*,4′*E*) Isomer (20) A solution of a mixture of **17** and **18** (1.03 g, 2.11 mmol) in THF (42 ml) was added to NaH (146 mg, 3.65 mmol, 60% wt. oil suspension), and the mixture was stirred at 50 °C for 1 h. Then the reaction was quenched with 5% aqueous H_3PO_4 and the mixture was extracted with $CHCl_3$. The extracts were washed with aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 63 : 35—6 : 4) to give **19** (683 mg, 66% yield) and **20** (249 mg, 24% yield).

19: Viscous colorless oil. $[\alpha]_D^{27}$ −19.3° (c=2.02, $CHCl_3$). IR (CCl_4): 3380 (O–H), 2930 (C–H), 2855, 1738 (C=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.32 (5H, m, aromatic H), 5.40 (1H, dt, J=14.6, 7.1 Hz, 4′-H), 5.22 (1H, dt, J=14.8, 7.3 Hz, 5′-H), 4.70 (1H, d, J=15.5 Hz, benzylic H_a), 4.57 (1H, d, J=6.4 Hz, OCH_aO), 4.53 (1H, d, J=6.6 Hz, OCH_bO), 4.47 (1H, dd, J=8.9, 7.4 Hz, 5-H_a), 4.25 (1H, d, J=15.2 Hz, benzylic H_b), 4.23 (1H, t, J=8.9 Hz, 5-H_b), 3.90 (1H, dd, J=7.5, 1.5 Hz, 4-H), 3.81 (1H, m, 1′-H), 3.57 (1H, dd, J=5.8, 5.8 Hz, 2′-H), 3.29 (3H, s, OCH_3), 2.87 (1H, d, J=5.3 Hz, OH), 2.12 (2H, m, 3′-H), 1.95 (2H, m, 6′-H), 1.51 (1H, dqq, J=6.5, 6.5, 6.5 Hz, 15′-H), 1.26 (m), 0.86 (6H, d, J=6.6 Hz, 16′-H and $CHC\underline{H}_3$). FD-MS m/z (%): 490 (M^++H, 98), 489 (M^+, 100). *Anal.* Calcd for $C_{29}H_{47}NO_5$: C, 71.13; H, 9.67; N, 2.86. Found: C, 71.01; H, 9.75; N, 2.71.

20: Viscous colorless oil. $[\alpha]_D^{27}$ +5.99° (c=1.74, $CHCl_3$). IR (CCl_4): 3410 (O–H), 2930 (C–H), 2855, 1740 (C=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.32 (5H, m, aromatic H), 5.40 (1H, dt, J=14.6, 7.1 Hz, 4′-H), 5.20 (1H, dt, J=14.7, 7.4 Hz, 5′-H), 4.80 (1H, d, J=15.2 Hz, benzylic H_a), 4.64 (1H, d, J=6.9 Hz, OCH_aO), 4.60 (1H, d, J=6.8 Hz, OCH_bO), 4.48 (1H, dd, J=8.7, 6.8 Hz, 5-H_a), 4.21 (1H, t, J=8.8 Hz, 5-H_b), 4.18 (1H, d, J=15.7 Hz, benzylic H_b), 3.87 (1H, m, 1′-H), 3.71 (1H, dd, J=7.1, 1.7 Hz, 4-H), 3.34 (3H, s, OCH_3), 3.15 (1H, d, J=3.6 Hz, OH), 2.25 (2H, m, 3′-H), 2.11 (2H, m, 6′-H), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 15′-H), 1.26 (m), 0.86 (6H, d, J=6.6 Hz, 16′-H and $CHC\underline{H}_3$). FD-MS m/z (%): 490 (M^++H, 93), 489 (M^+, 100). *Anal.* Calcd for $C_{29}H_{47}NO_5$: C, 71.13; H, 9.67; N, 2.86. Found: C, 71.01; H, 9.61; N, 2.84.

(4*S*,1′*S*,2′*R*,4′*E*)-4-[1′-Hydroxy-2′-(methoxymethoxy)-15′-methyl-4′-hexadecenyl]-2-oxazolidinone (21) Liquid $EtNH_2$ (30 ml) was added at 0 °C to a solution of **19** (631 mg, 5.09 mmol) in *tert*-BuOH (6.3 ml). Several pieces of lithium (100 mg) were added at −78 °C to the mixture. The blue-colored mixture was stirred at −78 °C for 10 min and the reaction

was quenched with ammonium chloride. After removal of the unreacted lithium, the mixture was concentrated to half of the original volume, diluted with ether, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 3:7) to give **21** (356 mg, 69% yield) as a colorless oil. $[\alpha]_D^{27}$ −26.6° (c=2.08, $CHCl_3$). IR (CCl_4): 3400 and 3280 (O–H and N–H), 2930 (C–H), 2850, 1752 (C=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.37 (1H, s, NH), 5.54 (1H, dt, J=14.4, 7.0 Hz, 4′-H), 5.39 (1H, dt, J=14.7, 7.2 Hz, 5′-H), 4.63 (2H, s, OCH_2O), 4.52 (1H, dd, J=8.9, 6.3 Hz, 5H$_a$), 4.41 (1H, t, J=8.7 Hz, 5-H$_b$), 4.08 (1H, m, 4-H), 3.68 (1H, t, J=4.6 Hz, 1′-H), 3.61 (1H, dt, J=3.1, 3.1 Hz, 2′-H), 3.37 (3H, s, OCH_3), 2.31 (2H, m, 3′-H), 2.00 (2H, m, 6′-H), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 15′-H), 1.26 (m), 0.86 (6H, d, J=6.6 Hz, 16′-H and CHC$\underline{H}_3$). FD-MS m/z (%): 400 (M^++H, 100). *Anal.* Calcd for $C_{22}H_{41}NO_5$: C, 66.13; H, 10.34; N, 3.51. Found: C, 65.91; H, 10.43; N, 3.50.

(2*S*,3*S*,4*R*,6*E*)-2-Amino-17-methyl-6-octadecene-1,3,4-triol (5) An aqueous 2 N KOH solution (3.52 ml, 7.04 mmol) was added to a solution of **21** (282 mg, 70.6 μmol) in EtOH (3.5 ml). The reaction mixture was heated for 5 h at reflux, cooled to room temperature, and extracted with Et_2O. The extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue (268 mg) was dissolved in 2 N HCl in MeOH (2 ml). The resulting mixture was heated for 5 h at reflux and alkalinized with a 0.1 M solution of K_2CO_3 in MeOH. The precipitate was filtered off through a cotton plug. The filtrate was concentrated by blowing a stream of nitrogen gas over it. The residue was chromatographed on silica gel (BW-300, $CHCl_3$–MeOH–H_2O, 7:3:0.5) to give crude **5** (515 mg), which was passed through a Sephadex LH-20 column (MeOH as the eluent). The obtained **5** (212 mg, 91% yield) was a viscous colorless oil. ^{1}H-NMR (270 MHz, C_5D_5N) δ: 5.91 (1H, dt, J=14.8, 7.3 Hz, 6-H), 5.67 (1H, dt, J=14.6, 7.1 Hz, 7-H), 4.78 (1H, dd, J=8.7, 3.3 Hz, 3-H), 4.72 (2H, m, 1-H), 4.27 (1H, dt, J=8.4, 2.8 Hz, 4-H), 3.05 (1H, m, 5-H$_a$), 2.61 (1H, quint., J=7.3 Hz, 5-H$_b$), 2.00 (2H, q, J=6.6 Hz, 8-H), 1.24 (m), 0.87 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). ^{13}C-NMR (67.8 MHz, C_5D_5N) δ: 133.2 (d, (C7)), 127.4 (d, (C6)), 73.4 (d, (C3 and C4)), 60.0 (t, (C1)), 56.7 (d, (C2)), 39.2 (t), 38.6 (t, (C5)), 33.1 (t, (C8)), 30.2 (t), 30.0 (t), 29.9 (t), 29.8 (t), 29.6 (t), 28.2 (d, (C17)), 27.7 (t), 22.8 (q, (C18 and CH$\underline{C}H_3$)). FD-MS m/z (%): 330 (M^++H, 100). This product was used in the next reaction without further purification.

(2*S*,3*S*,4*R*,6*E*)-2-Acetamido-17-methyl-1,3,4-triacetoxy-6-octadecene (23) Acetic anhydride (147 μl, 1.56 mmol) and pyridine (127 μl, 1.57 mmol) were added to **5** (34.3 mg, 104 μmol). The reaction mixture was stirred at 50 °C for 1 h and at room temperature for 15 h, then concentrated by blowing nitrogen gas over it. The residue was chromatographed on silica gel (BW-300, hexane–AcOEt, 2:3) to give **23** (26.8 mg, 52% yield) as a colorless viscous oil. $[\alpha]_D^{26}$ +9.76° (c=1.24, $CHCl_3$). IR (CCl_4): 3370 (N–H), 2930 (C–H), 2855, 1755 (OC=O), 1690 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.06 (1H, d, J=9.4 Hz, NH), 5.49 (1H, dt, J=14.7, 7.2 Hz, 6-H), 5.28 (1H, dt, J=14.7, 7.3 Hz, 7-H), 5.09 (1H, dd, J=7.6, 3.4 Hz, 3-H), 4.96 (1H, dt, J=9.1, 3.8 Hz, 4-H), 4.51 (1H, m, 2-H), 4.26 (1H, dd, J=11.7, 5.0 Hz, 1-H$_a$), 4.01 (1H, dd, J=11.6, 3.4 Hz, 1-H$_b$), 2.43 (1H, m, 5-H$_a$), 2.28 (1H, m, 5-H$_b$), 2.09 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 1.96 (2H, m, 8-H), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.25 (m), 0.86 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 170.9 (s, $\underline{C}OCH_3$), 170.2 (s, $\underline{C}OCH_3$), 169.7 (s, $\underline{C}OCH_3$), 134.7 (d, (C6)), 124.0 (d, (C7)), 72.5 (d, (C4)), 72.2 (d, (C3)), 62.8 (t, (C1)), 47.7 (d, (C2)), 39.1 (t), 32.6 (t), 32.1 (t, (C5)), 30.0 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.2 (t), 28.0 (d, (C17)), 27.4 (t), 23.3 (q, $\underline{C}OCH_3$), 22.7 (q, (C18 and CH$\underline{C}H_3$)), 21.0 (q, $\underline{C}OCH_3$), 20.8 (q, $\underline{C}OCH_3$). FD-MS m/z (%): 498 (M^++H, 100). *Anal.* Calcd for $C_{27}H_{47}NO_7$: C, 65.16; H, 9.52; N, 2.81. Found: C, 64.83; H, 9.40; N, 2.77.

(2*S*,3*S*,4*R*)-2-Acetamido-17-methyl-1,3,4-triacetoxyoctadecane (25) A suspension of **23** (23.8 mg, 47.8 μmol) and 10% palladium on carbon (22.4 mg) in MeOH (2.4 ml) was stirred for 7 h under a hydrogen atmosphere. The mixture was filtered through a pad of Celite 545 and concentrated *in vacuo*. The residue was chromatographed on silica gel (BW-300, hexane–AcOEt, 2:3) to give **25** (14.2 mg, 59% yield) as a colorless oil. $[\alpha]_D^{26}$ +26.1° (c=0.71, $CHCl_3$). IR (CCl_4): 3350 (N–H), 2930 (C–H), 2855, 1750 (OC=O), 1690 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.00 (1H, d, J=9.4 Hz, NH), 5.11 (1H, dd, J=8.3, 3.1 Hz, 3-H), 4.93 (1H, dt, J=9.3, 3.5 Hz, 4-H), 4.47 (1H, m, 2-H), 4.29 (1H, dd, J=11.6, 4.9 Hz, 1-H$_a$), 4.00 (1H, dd, J=11.6, 3.1 Hz, 1-H$_b$), 2.08 (3H, s, CH_3CO), 2.05 (6H, s, CH_3CO × 2), 2.03 (3H, s, CH_3CO), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.25 (m), 0.86 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 171.2 (s, $\underline{C}OCH_3$), 170.9 (s, $\underline{C}OCH_3$), 170.1 (s, $\underline{C}OCH_3$), 169.7 (s, $\underline{C}OCH_3$), 73.0 (d, (C3)), 72.0 (d, (C4)), 62.9 (t, (C1)), 47.6 (d, (C2)), 39.1 (t), 30.0 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.3 (t), 28.2 (d), 28.0 (d, (C17)), 27.4 (t), 25.5 (d), 23.3 (q, $\underline{C}OCH_3$), 22.7 (q, (C18 and CH$\underline{C}H_3$)), 21.0 (q, $\underline{C}OCH_3$), 20.7 (q, $\underline{C}OCH_3$). FD-MS m/z (%): 500 (M^++H, 100). *Anal.* Calcd for $C_{27}H_{49}NO_7$: C, 64.90; H, 9.88; N, 2.80. Found: C, 64.51; H, 9.77; N, 2.71.

(2*R*,3*R*,4*R*,6*E*)-2-Amino-17-methyl-6-octadecene-1,3,4-triol (22) According to the procedures described for the preparation of **5** from **19**, compound **20** (332 mg) was converted into **22** (120 mg, 54% yield) as a colorless viscous oil. ^{1}H-NMR (270 MHz, C_5D_5N) δ: 5.64 (1H, dt, J=14.5, 7.1 Hz, 7-H), 2.78 (2H, t, J=6.7 Hz, 5-H), 2.00 (2H, q, J=6.8 Hz, 8-H), 1.49 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.25 (m), 0.87 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). FD-MS m/z (%): 330 (M^++H, 100). This product was used in the next reaction without further purification.

(2*R*,3*R*,4*R*,6*E*)-2-Acetamido-17-methyl-1,3,4-triacetoxy-6-octadecene (24) According to the procedures described for the preparation of **23**, compound **22** (49.1 mg) was converted into **24** (70.1 mg, 95% yield) as a colorless oil. $[\alpha]_D^{27}$ −2.14° (c=1.00, $CHCl_3$). IR (CCl_4): 3320 (N–H), 2930 (C–H), 2855, 1745 (OC=O), 1695 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.73 (1H, d, J=9.9 Hz, NH), 5.48 (1H, dt, J=14.6, 7.1 Hz, 6-H), 5.27 (1H, dt, J=14.9, 7.4 Hz, 7-H), 4.54 (1H, m, 2-H), 4.22 (1H, dd, J=11.7, 4.5 Hz, 1-H$_a$), 3.96 (1H, dd, J=11.7, 3.3 Hz, 1-H$_b$), 2.13 (3H, s, CH_3CO), 2.08 (3H, s, CH_3CO), 2.07 (3H, s, CH_3CO), 1.98 (3H, s, CH_3CO), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.25 (m), 0.86 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 170.8 (s, $\underline{C}OCH_3$), 170.4 (s, $\underline{C}OCH_3$), 170.3 (s, $\underline{C}OCH_3$), 169.6 (s, $\underline{C}OCH_3$), 135.3 (d, (C6)), 123.3 (d, (C7)), 71.6 (d, (C4)), 70.9 (d, (C3)), 63.1 (t, (C1)), 47.5 (d, (C2)), 39.1 (t), 34.4 (t, (C5)), 32.6 (t), 29.9 (t), 29.7 (t), 29.5 (t), 29.4 (t), 29.2 (t), 28.0 (d, (C17)), 27.4 (q, $\underline{C}OCH_3$), 23.3 (q, $\underline{C}OCH_3$), 22.7 (q, (C18 and CH$\underline{C}H_3$)), 21.0 (q, $\underline{C}OCH_3$), 20.8 (q, $\underline{C}OCH_3$). FD-MS m/z (%): 498 (M^++H, 100). *Anal.* Calcd for $C_{27}H_{47}NO_7$: C, 65.16; H, 9.52; N, 2.81. Found: C, 64.97; H, 9.43; N, 2.75.

(2*R*,3*R*,4*R*)-2-Acetamido-17-methyl-1,3,4-triacetoxyoctadecane (26) According to the procedures described for the preparation of **25**, compound **24** (36.3 mg) was converted into **26** (21.7 mg, 60% yield) as a colorless powder. mp 77 °C. $[\alpha]_D^{27}$ −3.09° (c=1.09, $CHCl_3$). IR (CCl_4): 3380 (N–H), 2920 (C–H), 2850, 1745 (OC=O), 1690 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.79 (1H, d, J=9.7 Hz, NH), 5.09 (2H, m, 3-H and 4-H), 4.53 (1H, m, 2-H), 4.23 (1H, dd, J=11.7, 4.6 Hz, 1-H$_a$), 3.97 (1H, dd, J=11.7, 3.3 Hz, 1-H$_b$), 2.13 (3H, s, CH_3CO), 2.09 (6H, s, CH_3CO × 2), 2.07 (3H, s, CH_3CO), 1.98 (3H, s, CH_3CO), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.24 (m), 0.86 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). ^{1}H-NMR (400 MHz, C_6D_6) δ: 5.30 (1H, d, J=9.9 Hz, NH), 5.23 (1H, ddd, J=8.1, 5.4, 2.6 Hz, 4-H), 4.80 (1H, ddt, J=9.6, 5.1, 3.2 Hz, 3-H), 4.25 (1H, dd, J=11.7, 5.1 Hz, 1-H$_a$), 3.90 (1H, dd, J=11.7, 3.2 Hz, 1-H$_b$), 1.99 (3H, s, CH_3CO), 1.78 (6H, s, CH_3CO × 2), 1.73 (3H, s, CH_3CO), 1.66 (3H, s, CH_3CO), 1.31 (m), 0.91 (6H, d, J=6.6 Hz, 18-H and CHC$\underline{H}_3$). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 170.7 (s, $\underline{C}OCH_3$), 170.6 (s, $\underline{C}OCH_3$), 170.3 (s, $\underline{C}OCH_3$), 169.6 (s, $\underline{C}OCH_3$), 71.9 (d, (C3)), 71.2 (d, (C4)), 63.2 (t, (C1)), 47.5 (d, (C2)), 39.1 (t), 30.9 (t), 30.0 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 28.0 (d, (C17)), 27.4 (t), 25.2 (d), 23.3 (q, $\underline{C}OCH_3$), 22.7 (q, (C18 and CH$\underline{C}H_3$)), 21.0 (q, $\underline{C}OCH_3$), 20.75 (q, $\underline{C}OCH_3$), 20.70 (q, $\underline{C}OCH_3$). ^{13}C-NMR (100 MHz, C_6D_6) δ: 170.4 (s, $\underline{C}OCH_3$), 170.2 (s, $\underline{C}OCH_3$), 169.1 (s, $\underline{C}OCH_3$), 71.9 (d, (C3)), 70.8 (d, (C4)), 63.6 (t, (C1)), 47.5 (d, (C2)), 39.5 (t), 31.6 (t), 30.4 (t), 30.2 (t), 30.1 (t), 30.0 (t), 27.9 (t), 25.9 (d, (C17)), 22.9 (q, (C18, $\underline{C}OCH_3$, and CH$\underline{C}H_3$)), 20.9 (q, $\underline{C}OCH_3$), 20.4 (q, $\underline{C}OCH_3$), 20.2 (q, $\underline{C}OCH_3$). FD-MS m/z (%): 500 (M^++H, 100). *Anal.* Calcd for $C_{27}H_{49}NO_7$: C, 64.90; H, 9.88; N, 2.80. Found: C, 64.79; H, 9.83; N, 2.77.

(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-(Methoxymethoxy)tetracosanoylamino]-17-methyl-6-octadecene-1,3,4-triol (28) A solution of DCC (44.8 mg, 217 μmol) in THF (1.5 ml) was added to a mixture of **5** (47.7 mg, 145 μmol), **27** (62.2 mg, 145 μmol), and HOBT (33.3 mg, 217 μmol). The reaction mixture was stirred at room temperature for 2 d and filtered through a cotton plug. The filtrate was concentrated and chromatographed on silica gel (BW-300, $CHCl_3$–acetone–water, 85:15:0.3) gave **28** (80.9 mg, 76% yield) as a colorless powder. mp 67.5 °C. $[\alpha]_D^{27}$ +9.08° (c=1.96, $CHCl_3$). IR (CCl_4): 3420 (O–H and N–H), 2930 (C–H), 2850, 1655 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.41 (1H, d, J=7.6 Hz, NH), 5.60 (1H, dt, J=14.6, 7.1 Hz, 6-H), 5.41 (1H, dt, J=15.0, 7.4 Hz, 7-H), 4.69 (2H, s, OCH_2O), 4.17 (1H, m, 2-H), 4.07 (1H, t, J=5.6 Hz, 2′-H), 3.94 (1H, dd, J=11.9, 2.3 Hz, 1-H$_a$), 3.74 (1H, dd, J=11.9, 4.9 Hz, 1-H$_b$), 3.56 (2H, m, 3-H and 4-H), 3.41 (3H, s, CH_3O), 2.56 (1H, m, 5-H$_a$), 2.17 (1H, quint., J=7.5 Hz, 5-H$_b$), 2.03 (2H, q, J=6.8 Hz, 8-H), 1.77 (2H, m, 3′-H), 1.51 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.25 (m), 0.864 (3H, t, J=4.1 Hz,

24'-H), 0.860 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). FAB-MS m/z (%): 740 (M^+, 14), 708 (M^+-CH_3OH, 21). *Anal.* Calcd for $C_{45}H_{89}NO_6$: C, 73.02; H, 12.12; N, 1.89. Found: C, 72.77; H, 12.02; N, 1.88.

(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-Hydroxytetracosanoylamino]-17-methyl-6-octadecene-1,3,4-triol (3) $BF_3\cdot OEt_2$ (38.2 μl, 311 μmol) was added to a solution of **28** (76.7 mg, 104 μmol) in 1,2-ethanedithiol (1 ml) and $CHCl_3$ (1 ml), and the mixture was stirred at room temperature for 30 min. The reaction was quenched with triethylamine (144 μl, 1.0 mmol), and the mixture was concentrated by blowing a stream of nitrogen gas over it. The residue was chromatographed on silica gel (BW-300, $CHCl_3$–acetone–water, 65:35:0.7) to give **3** (54.5 mg, 76% yield) as a colorless powder. mp 125—126 °C. $[\alpha]_D^{27}$ +2.89° (c=1.06, $CHCl_3$). IR (CCl_4): 3360 (O–H and N–H), 2925 (C–H), 2850, 1642 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, C_5D_5N) δ: 8.59 (1H, d, J=8.9 Hz, NH), 5.99 (1H, dt, J=14.8, 7.3 Hz, 6-H), 5.74 (1H, dt, J=14.7, 7.2 Hz, 7-H), 5.13 (1H, m, 2-H), 4.62 (1H, dd, J=7.6, 3.6 Hz, 2'-H), 4.51 (1H, dd, J=10.6, 4.76 Hz, 1-H_a), 3.07 (1H, m, 5-H_a), 2.72 (1H, quint., J=7.1 Hz, 5-H_b), 2.23 (1H, m, 3'-H_a), 1.50 (1H, dqq, J=6.6, 6.6, 6.6 Hz, 17-H), 1.32 (m), 1.26 (m), 0.88 (3H, t, J=6.6 Hz, 24'-H), 0.86 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). ^{13}C-NMR (67.8 MHz, C_5D_5N) δ: 175.3 (s, CO), 132.8 (d, (C7)), 128.3 (d, (C6)), 76.3 (d, (C3)), 73.3 (d, (C4)), 42.5 (d, (C2')), 62.0 (t, (C1)), 52.9 (d, (C2)), 39.3 (t), 37.7 (t), 33.2 (t, (C8)), 32.1 (t), 30.2 (t), 30.0 (t), 29.9 (t), 29.6 (t), 28.2 (t), 27.7 (d, (C17)), 25.8 (t), 22.9 (t), 22.8 (q, (C18 and $CHC\underline{H}_3$)), 14.3 (q, (C24')). FD-MS m/z (%): 696 (M^++H, 100), 678 (M^+-H_2O, 42). *Anal.* Calcd for $C_{43}H_{85}NO_5$: C, 74.19; H, 12.31; N, 2.01. Found: C, 74.11; H, 12.23; N, 2.05.

(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-Hydroxytetracosanoylamino]-17-methyl-1-(triphenylmethyloxy)-6-octadecene-3,4-diol (29) Compound **3** (18.6 mg, 26.7 μmol), trityl chloride (73.2 mg, 263 μmol), and dimethylaminopyridine (DMAP) (21.4 mg, 175 μmol) were dissolved in pyridine (534 μl). After being stirred at 60 °C for 4 h, the reaction mixture was diluted with $CHCl_3$, washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel ($CHCl_3$–MeOH–H_2O, 6:4:0.8) to give **29** (15.8 mg, 90% yield) as a colorless viscous oil. $[\alpha]_D^{25}$ +16.0° (c=0.725, $CHCl_3$). IR (CCl_4): 3410 (O–H and N–H), 3060 and 3030 (Ar–H), 2930 (C–H), 2855, 1660 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 7.41 (6H, m, aromatic H), 7.27 (9H, m, aromatic H), 7.12 (1H, d, J=8.6 Hz, NH), 5.53 (1H, dt, J=14.6, 7.1 Hz, 6-H), 5.34 (1H, dt, J=14.6, 7.3 Hz, 7-H), 4.25 (1H, m, 2-H), 4.07 (1H, t, J=5.6 Hz, 2'-H), 4.00 (1H, m, 2'-H), 3.62 (1H, m, 3-H), 3.52 (1H, dd, J=11.9, 2.3 Hz, 1-H_a), 3.43 (1H, dd, J=9.9, 4.0 Hz, 1-H_b), 3.26 (1H, m, 4-H), 2.47 (1H, m, 5-H_a), 2.02 (2H, m, 8-H), 1.26 (m), 0.86 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). Negative FAB-MS m/z (%): 936 (M^+−H, 4), 694 (M^+-CPh_3, 19), 424 (41), 153 (100). *Anal.* Calcd for $C_{62}H_{99}NO_5$: C, 79.35; H, 10.63; N, 1.49. Found: C, 79.38; H, 10.57; N, 1.45.

(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-Benzoyloxytetracosanoylamino]-3,4-dibenzoyloxy-17-methyl-1-(triphenylmethyloxy)-6-octadecene (30) Benzoyl chloride (95.0 μl, 820 μmol) was added to a solution of **29** (44.2 mg, 47.1 μmol) and DMAP (99.8 mg, 820 μmol) in pyridine (1.6 ml). After being stirred at 70—75 °C for 15 h, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extracts were washed with water, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 3:1) to give **30** (58.0 mg, 98% yield) as a colorless viscous oil. $[\alpha]_D^{29}$ +30.9° (c=2.43, $CHCl_3$). IR (CCl_4): 3060 and 3030 (Ar–H), 2920 (C–H), 2850, 1725 (OC=O), 1682 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.05 (2H, d, J=7.6 Hz, aromatic H), 7.96 (2H, d, J=7.6 Hz, aromatic H), 7.86 (2H, d, J=7.6 Hz, aromatic H), 7.52 (3H, m, aromatic H), 7.39 (4H, t, J=7.6 Hz, aromatic H), 7.27 (2H, t, J=7.8 Hz, aromatic H), 7.12 (6H, m, aromatic H), 7.00 (9H, m, aromatic H), 5.85 (1H, dd, J=8.2, 3.3 Hz, 3-H), 5.57 (1H, t, J=5.8 Hz, 2'-H), 5.53 (1H, m, 6-H), 5.39 (1H, m, 4-H), 5.34 (1H, m, 7-H), 4.64 (1H, m, 2-H), 3.24 (d, J=3.3 Hz, 2H, 1-H), 2.66 (m, 1H, 5-H_a), 2.49 (1H, m, 5-H_b), 2.06 (2H, m, 3'-H), 1.87 (2H, m, 8-H), 1.26 (m), 0.88 (3H, t, J=6.3 Hz, $CH_2C\underline{H}_3$), 0.85 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). Negative FAB-MS m/z (%): 1248 (M^+−H, 1.2), 486 (1.1). *Anal.* Calcd for $C_{83}H_{111}NO_8$: C, 79.70; H, 8.94; N, 1.12. Found: C, 79.83; H, 8.94; N, 1.12.

(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-Benzoyloxytetracosanoylamino]-3,4-dibenzoyloxy-17-methyl-6-octadecen-1-ol (31) A solution of $TsOH\cdot H_2O$ (17.7 mg, 93 μmol) in $CHCl_3$ (1.25 ml) and MeOH (0.6 ml) was added to **30** (58.0 mg, 46.4 μmol). After being stirred at room temperature for 8 h, the mixture was concentrated to 1/4 of the original volume by blowing a stream of nitrogen gas over it, and the concentrate was chromatographed on silica gel (hexane–AcOEt, 7:3) to give **31** (44.3 mg, 95% yield) as a colorless viscous oil. $[\alpha]_D^{26}$ +43.7° (c=1.88, $CHCl_3$). IR (CCl_4): 3520 and 3420 (O–H and N–H), 3060 and 3030 (Ar–H), 2930 (C–H), 2850, 1725 (OC=O), 1685 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.14 (2H, d, J=7.9 Hz, aromatic H), 8.01 (2H, d, J=8.2 Hz, aromatic H), 7.96 (2H, d, J=8.4 Hz, aromatic H), 7.45 (9H, m, aromatic H), 7.13 (1H, d, J=9.2 Hz, NH), 5.65—5.35 (5H, m, 3-H, 4-H, 6-H, 7-H, and 2'-H), 4.44 (1H, m, 2-H), 3.64 (2H, br s, 1-H), 2.78 (1H, m, 5-H_a), 2.65 (1H, m, 5-H_b), 2.07 (2H, m), 2.92 (2H, m), 1.26 (m), 0.88 (3H, t, J=6.6 Hz, $CH_2C\underline{H}_3$), 0.86 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). FAB-MS m/z (%): 1008 (M^++H, 11), 990 (M^+−OH, 16), 886 (M^+−PhCOO, 100). *Anal.* Calcd for $C_{64}H_{97}NO_8$: C, 76.22; H, 9.70; N, 1.39. Found: C, 75.97; H, 9.67; N, 1.42.

1-*O*-(2,3,4,6-Tetra-*O*-acetoxy-β-D-galactopyranosyloxy)-(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-benzoyloxytetracosanoylamino]-3,4-dibenzoyloxy-17-methyl-6-octadecene (33) and (2*S*,3*S*,4*R*,6*E*)-1-Acetoxy-2-[(*R*)-2-benzoyloxytetracosanoylamino]-3,4-dibenzyloxy-17-methyl-6-octadecane (34) A suspension of **31** (15.9 mg, 15.8 μmol), **32** (25.3 mg, 53.1 μmol), and 4 Å molecular sieves (38.9 mg) in CH_2Cl_2 (315 μl) was stirred at room temperature for 1 h and boron trifluoride etherate (5.82 μl, 47.3 μmol) was added at −25 °C. After being stirred at −25 °C for 1 h, the reaction mixture was allowed to warm to room temperature over 1 h and stirred at ambient temperature for 1 h. The mixture was diluted with $CHCl_3$, washed with aqueous saturated $NaHCO_3$, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–AcOEt, 8:2—7:3) to give **33** (15.7 mg, 74% yield) and **34** (4.2 mg, 25% yield).

33: $[\alpha]_D^{27}$ +24° (c=0.82, $CHCl_3$). IR (CCl_4): 2930 (C–H), 2850, 1755 and 1725 (OC=O), 1685 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.16 (2H, dd, J=7.8, 1.7 Hz, aromatic H), 8.00 (2H, dd, J=5.9, 1.3 Hz, aromatic H), 7.97 (2H, dd, J=9.8, 1.8 Hz, aromatic H), 7.60 (3H, m, aromatic H), 7.45 (6H, m, aromatic H), 6.07 (1H, d, J=8.9 Hz, NH), 5.60 (1H, dd, J=7.89, 4.0 Hz, 6-H), 4.63 (1H, m, 2-H), 4.38 (1H, d, J=7.9 Hz, 1''-H), 2.07 (3H, s, Ac), 1.96 (3H, s, Ac), 1.91 (3H, s, Ac), 1.71 (3H, s, Ac), 1.25 (m), 0.88 (3H, t, J=6.8 Hz, $CH_2C\underline{H}_3$), 0.85 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). FAB-MS m/z (%): 1338 (M^++H, 2.0), 1216 (M^+−PhCOO, 3.5), 990 (M^+−tetraacetylgalactose unit, 8.4). This product was used in the next reaction without further purification.

34: $[\alpha]_D^{25}$ +17° (c=0.21, $CHCl_3$). IR (CCl_4): 2925 (C–H), 2850, 1730 (OC=O), 1690 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.10 (2H, dd, J=8.3, 1.3 Hz, aromatic H), 8.00 (2H, dd, J=8.4, 1.5 Hz, aromatic H), 7.96 (2H, dd, J=8.9, 1.5 Hz, aromatic H), 7.59 (3H, m, aromatic H), 7.43 (6H, m, aromatic H), 6.92 (1H, d, J=9.2 Hz, NH), 5.68—5.30 (5H, m, 3-H, 4-H, 6-H, 7-H, and 2'-H), 4.77 (1H, m, 2-H), 4.24 (1H, dd, J=11.7, 5.1 Hz, 1-H_a), 4.16 (1H, dd, J=11.7, 4.1 Hz, 1-H_b), 2.06 (2H, m), 1.88 (2H, m), 1.70 (3H, s, Ac), 1.25 (m), 0.87 (3H, t, J=7.3 Hz, $CH_2C\underline{H}_3$), 0.86 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$). FD-MS m/z (%): 1050 (M^++H, 100). *Anal.* Calcd for $C_{66}H_{99}NO_9$: C, 75.46; H, 9.50; N, 1.33. Found: C, 75.27; H, 9.46; N, 1.29.

1-*O*-(β-D-Galactopyranosyloxy)-(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-hydroxytetracosanoylamino]-17-methyl-6-octadecene-3,4-diol (2) A 0.1 M solution of K_2CO_3 in MeOH (1.2 ml) was added to a solution of **33** (15.7 mg) in MeOH (0.6 ml). After being stirred at room temperature for 30 min, the reaction mixture was concentrated by blowing a stream of nitrogen gas over it, and the residue was chromatographed on silica gel (BW-300, $CHCl_3$–MeOH–H_2O, 85:15:1.5) to give **2** (8.7 mg, 89% yield) as colorless crystals. mp 218—220 °C. $[\alpha]_D^{27}$ +18° (c=0.34, $CHCl_3$–MeOH, 2:1). IR (KBr): 3400 (O–H), 2920 (C–H), 2850 (C–H), 1645 (NC=O), 1540, 1075, 720 cm^{-1}. ^{1}H-NMR (270 MHz, C_5D_5N) δ: 8.57 (1H, d, J=9.6 Hz, NH), 5.99 (1H, dt, J=14.6, 7.2 Hz, 6-H), 5.74 (1H, dt, J=14.5, 7.1 Hz, 7-H), 5.29 (1H, m, 2-H), 4.89 (1H, d, J=7.9 Hz), 4.78 (1H, dd, J=10.6, 6.6 Hz), 4.13 (3H, dd, J=9.2, 3.3 Hz), 4.02 (1H, t, J=5.9 Hz), 3.04 (1H, dd, J=12.5, 6.6 Hz, 5-H_a), 2.70 (1H, quint., J=7.2 Hz, 5-H_b), 1.50 (1H, dqq, J=6.5, 6.6, 6.6 Hz, 17-H), 1.33 (m), 1.27 (m), 0.879 (6H, d, J=6.6 Hz, 18-H and $CHC\underline{H}_3$), 0.877 (3H, t, J=6.9 Hz, 24'-H). ^{13}C-NMR (67.8 MHz, C_5D_5N) δ: 175.7 (s), 132.7 (d), 128.3 (d), 106.3 (d), 77.1 (d), 75.3 (d), 75.2 (d), 72.8 (d), 72.6 (d), 72.4 (d), 70.6 (t), 70.2 (d), 62.4 (t), 51.6 (d), 39.3 (t), 37.5 (t), 35.6 (t), 33.3 (t), 32.1 (t), 30.3 (t), 30.1 (t), 29.9 (t), 29.73 (t), 29.65 (t), 29.6 (t), 28.2 (d), 27.7 (t), 25.9 (t), 22.9 (t), 22.8 (q), 14.3 (q). FD-MS m/z (%): 858 (M^++H, 100), 840 (M^+−OH, 27). *Anal.* Calcd for $C_{64}H_{97}NO_8\cdot 0.5H_2O$: C, 67.86; H, 11.16; N, 1.61. Found: C, 67.79; H, 10.97; N, 1.60. [Spectral data of the mixture of **1a** and **1b**.[2)] IR (KBr): 3361, 1076, and 1047 (O–H), 1656 and 1544 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, C_5D_5N) δ: 5.94 (dt, J=15.4, 8.1 Hz), 5.71 (dt, J=15.4, 8.1 Hz), 4.0—4.7 (sugar protons), 4.87 (d, J=7.5 Hz, anomeric proton), 1.25 (long chain methylene protons), 0.85 (6H, d, J=7.3 Hz, secondary methyls), 0.85 (3H, t, J=7.0 Hz, primary methyl). ^{13}C-NMR (67 MHz, C_5D_5N) δ: 175.61 (carbonyl), 133.67 and 126.60 (olefinic carbons)]. The ^{1}H-NMR spectrum of **2** was superimposable on that of the mixture of **1a** and **1b**

provided by Dr. M. Nakagawa.

1-*O*-(2,3,4,6-Tetra-*O*-acetoxy-β-D-galactopyranosyloxy)-(2*S*,3*S*,4*R*,6*E*)-2-[(*R*)-2-acetoxytetracosanoylamino]-3,4-diacetoxy-17-methyl-6-octadecene (35) Acetic anhydride (175 μl) and pyridine (151 μl) were added to **2** (8.0 mg). After being stirred at 50 °C for 3 h, the reaction mixture was concentrated by blowing a stream of nitrogen gas over it and the residue was chromatographed on silica gel (BW-300, hexane–AcOEt, 6 : 4) to give **35** (9.5 mg, 88% yield) as a colorless viscous oil. $[\alpha]_D^{26}$ +2.8° (c = 0.44, $CHCl_3$). IR (CCl_4): 2925 (C–H), 2850 (C–H), 1755 (OC=O), 1685 (NC=O) cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.78 (1H, d, J = 8.9 Hz, NH), 5.48 (1H, dt, J = 14.6, 7.2 Hz, 6-H), 5.37 (1H, d, J = 2.8 Hz, 4″-H), 5.26 (1H, dt, J = 14.7, 7.3 Hz, 7-H), 5.19—5.08 (2H, m, 3-H, and 2′-H), 5.00 (1H, dd, J = 10.6, 3.3 Hz, 3″-H), 4.92 (1H, dt, J = 9.1, 3.7 Hz, 4-H), 4.45 (1H, d, J = 7.6 Hz, 1″-H), 4.33 (1H, m, 2-H), 4.13 (2H, d, J = 6.6 Hz, 6″-H), 3.90 (1H, dd, J = 7.6, 6.6 Hz, 5″-H), 3.86 (1H, dd, J = 10.9, 3.6 Hz, 1-H_a), 3.68 (1H, dd, J = 10.9, 3.6 Hz, 1-H_b), 2.23 (3H, s, CH_3CO), 2.15 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 2.05 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 1.97 (3H, s, CH_3CO), 1.25 (m), 0.88 (3H, t, J = 6.6 Hz, CH_2CH_3), 0.86 (6H, d, J = 6.6 Hz, 18-H and $CHCH_3$). ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ: 170.7 (s), 170.3 (s), 170.2 (s), 170.1 (s), 170.05 (s), 169.99 (s), 169.8 (s), 169.4 (s), 134.6 (d), 124.0 (d), 100.7 (d), 73.9 (d), 72.6 (d), 72.0 (d), 70.8 (d), 68.6 (d), 67.0 (d), 66.2 (t), 61.1 (t), 48.1 (d), 39.1 (t), 32.6 (t), 32.1 (t), 31.9 (t), 31.8 (t), 30.0 (t), 29.7 (t), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.2 (t), 28.0 (d), 27.4 (t), 24.9 (t), 22.7 (q), 20.99 (q), 20.95 (q), 20.7 (q), 20.6 (q), 20.5 (q), 14.1 (q). FAB-MS m/z (%): 1152 (M^++H, 1.2), 1092 (M^+−AcOH, 1.5), 804 (M^+−tetraacetylgalactose unit, 8.9). *Anal.* Calcd for $C_{64}H_{97}NO_8$: C, 65.65; H, 9.53; N, 1.22. Found: C, 65.38; H, 9.50; N, 1.24. [NMR data of the mixture of acetates of **1a** and **1b**.[16] ^{1}H-NMR (360 MHz, $CDCl_3$) δ: 4.44 (1H, d, J = 7.5 Hz, 1″-H), 3.86 (1H, dd, J = 10.8, 3.0 Hz, 1-H_a), 3.67 (1H, dd, J = 10.8, 3.5 Hz, 1-H_b). ^{13}C-NMR (67 MHz, $CDCl_3$) δ: 134.3 (d), 123.9 (d), 100.6 (d), 73.9 (d), 72.6 (d), 72.1 (d), 70.9 (d), 68.7 (d), 67.0 (d), 66.3 (t), 61.1 (t), 48.2 (d), 39.2 (t), 28.2 (d), 25.1 (t), 22.8 (q), 14.3 (q)]. The ^{13}C- and ^{1}H-NMR spectral data of **35** were superimposable on those of the mixture of acetates of **1a** and **1b** provided by Dr. M. Nakagawa.

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