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Stereocontrolled Synthesis of Novel Phytosphingosine-type Glucosaminocerebrosides[1]

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Abstract: D-*ribo*-Phytosphingosine **1** was conveniently synthesized from *N*-benzoyl-D-glucosamine **3** by an improved route in which regioselective *O*-methanesulfonation and diastereoselective Grignard addition are involved as key steps. Using a synthetic intermediate of **1**, novel D-*ribo*-phytosphingosine-type glycolipids **2a** and **2b**, unnatural homologues of antifungal cerebrosides Halicylindrosides, were efficiently synthesized in a stereocontrolled manner. © 1999 Elsevier Science Ltd. All rights reserved.

Key words: Glycolipids; Glucosamine; Oxazolines; Stereocontrol

INTRODUCTION

D-*ribo*-C_{18}-Phytosphingosine [(2*S*, 3*S*, 4*R*)-2-aminooctadecane-1,3,4-triol] (**1**) and its C_{16}-C_{22} homologues have been found as backbone components of glycosphingolipids[2] isolated from fungi,[3] plants,[4] marine organisms,[5] and mammalian tissues.[6] Recently, it has been reported that relatively simple mono-glycosylceramides (cerebrosides) containing phytosphingosine in the hydrophobic moiety exhibit significant biological activities. For example, Agelasphins, α-galactosylceramides from the marine sponge *Agelas mauritianus*, showed antitumor and immunostimulatory activities,[7] and Halicylindrosides, β-glucosaminyl-ceramides from the sponge *Halichondria cylindrata*, showed moderate antifungal and cytotoxic activities.[8] Due to the scarcity in nature, phytosphingosines have been important synthetic targets and a variety of synthetic methods of **1** have been developed either by starting from natural chiral pools,[9] mainly from carbohydrates,[10-12] or by using asymmetric reactions.[13,14] However, most of these approaches are lengthy, and there have been only several reports on the synthesis of phytosphingosine-type glycolipids.[15] In addition, glucosaminylceramides such as Halicylindrosides, in which D-glucosamine residue directly binds to the hydrophobic moiety,[16] have not been synthesized.[17] The structural feature as well as the biological activities of Halicylidrosides prompted us to investigate their synthesis.

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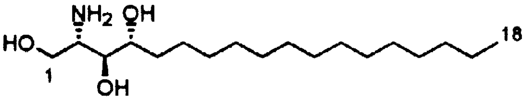
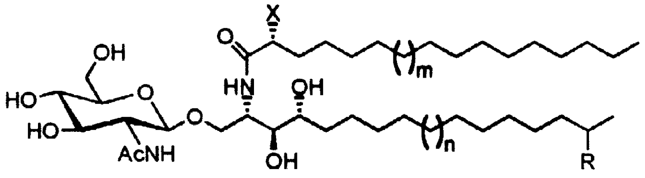
In this paper, we report an improved synthesis of phytosphingosine **1**, utilizing diastereoselective addition of a Grignard reagent to an oxazoline-aldehyde derived from *N*-benzoyl-D-glucosamine. We also describe an efficient synthesis of novel glucosamino-cerebrosides **2a** and **2b**, unnatural homologues of Halicylindrosides A and B having C_{18}-straight-chain sphingosine moiety[18] and C_{16}-fatty acids.



D-*ribo*-C_{18}-phytosphingosine (**1**)



Halicylindrosides A (X = H, R = CH_3, m = 7,8,9; n = 2,3)
Halicylindrosides B (X = OH, R = CH_3, m = 7,8; n = 0,1,2,3)

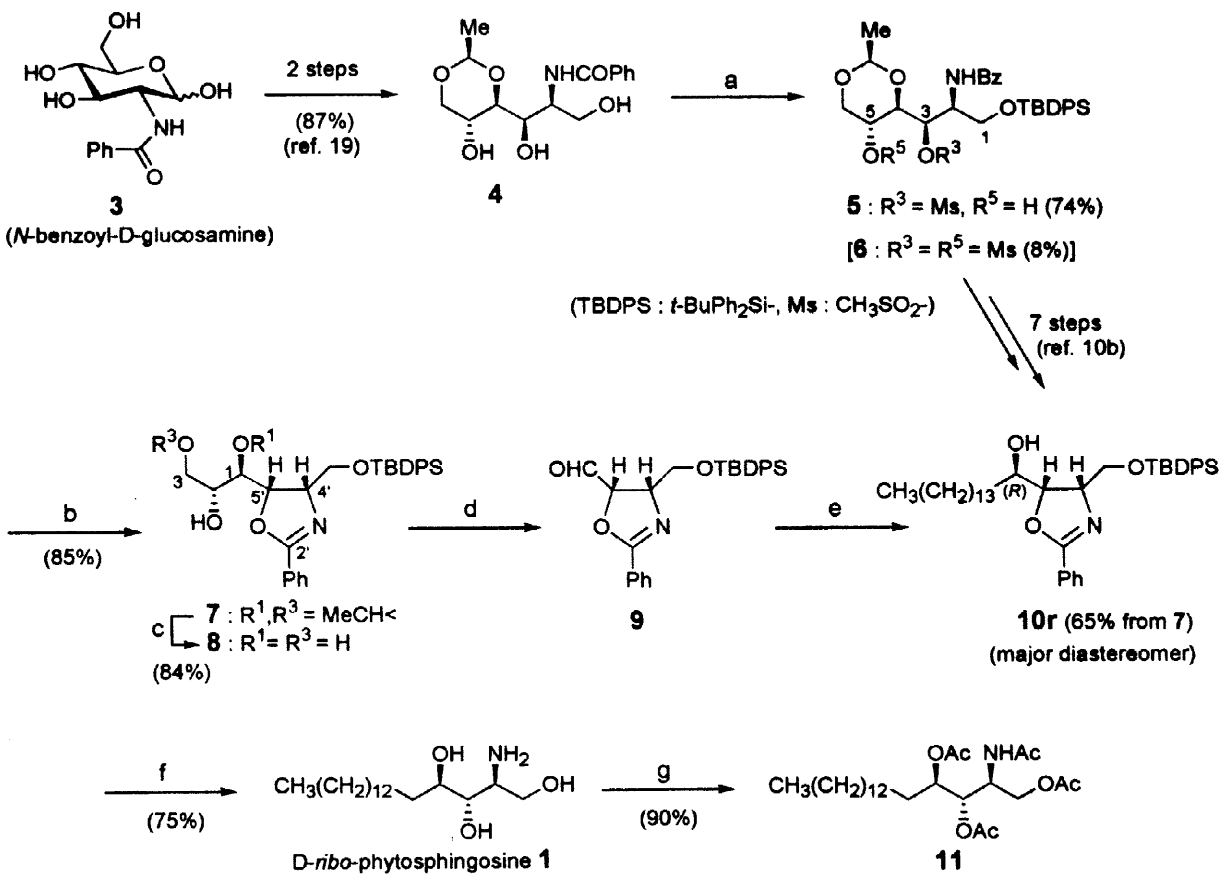
2a (X = H, R = H, m = 1; n = 3)
2b (X = OH, R = H, m = 1; n = 3)

RESULTS AND DISCUSSION

Improved synthesis of phytosphingosine

We already reported[10b] a stereocontrolled synthesis of D-*ribo*-C_{18}-phytosphingosine **1** from D-glucosamine, though the route was rather lengthy. An improved approach to **1** has been developed as shown in Scheme 1. *N*-Benzoyl-D-glucosamine **3** was converted into 2-benzamido-2-deoxy-4,6-*O*-ethylidene-D-glucitol **4** in 2 steps as previously reported.[19] Treatment of **4** with *t*-butyldiphenylsilyl (TBDPS) chloride (1.2 equiv.) in the presence of pyridine gave 1-*O*-TBDPS ether, which was treated *in situ* with methanesulfonyl chloride (1.4 equiv.) to give 1-*O*-TBDPS-3-*O*-monomesylate **5** as a predominant product (74%). The structure of the monomesylate was deduced from its ^1H NMR spectrum, in which the C-3 and C-5 protons were observed at δ 5.45 ppm (dd, J = 2.6, 8.6 Hz) and at δ 3.80 ppm (m, overlapping with the C-1 proton), respectively. A small amount of 3,5-di-*O*-mesylate **6**, which had been a predominant product from the reaction of the 1-*O*-TBDPS ether with excess mesyl chloride and triethylamine, was also obtained, but 5-*O*-monomesylate (R^3 = H, R^5 = Ms) was not detected. The crystalline monomesylate **5** was heated in pyridine at 110 °C for 24 h to effect conversion into the 2-phenyl-2-oxazoline derivative **7** (^1H NMR: $J_{4',5'}$ = 9.2 Hz). The ethylidene acetal in **7** was cleaved with $TiCl_4$ and thiophenol in CH_2Cl_2 at -10 °C to give the triol **8** in 84% yield. The acetal was also removed with $BF_3 OEt_2$ instead of $TiCl_4$, though the reaction proceeded at higher temperature (at 5 - 10 °C) and the yield slightly decreased (72%).

The triol **8** was treated with $NaIO_4$ in aqueous MeOH to give the aldehyde **9**. Without purification, the crude **9** was treated with tetradecylmagnesium chloride in tetrahydrofuran (THF) to afford a separable mixture of the diastereomeric (*R*)-alcohol **10r** and (*S*)-alcohol **10s** in a ratio of 7:1. The structures of the products were easily determined since we had prepared[10b] the (*R*)-alcohol **10r** from the di-mesylate **6**. The influence of additives in this reaction was then examined. As shown in Table 1, the (*R*)-alcohol **10r** was the major product in all cases. The diastereoselectivity of the reaction slightly increased in the presence of $CeCl_3$, and decreased in the presence of $ZnCl_2$. The high stereoselectivity of the Grignard addition can be explained by Felkin-Anh transition state model. However, chelation control is not ruled out since the oxazoline-nitrogen in **9** has much higher coordination ability than the oxazoline-oxygen or the silylated-oxygen to form

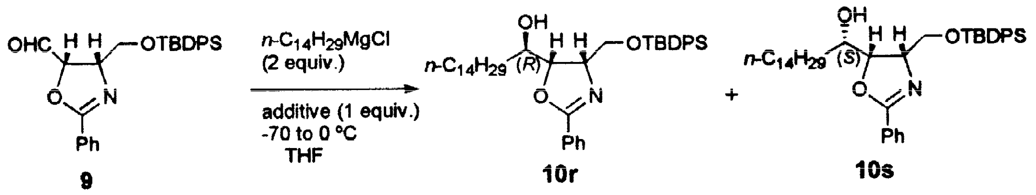


Scheme 1. *Reagents and conditions:* a) *t*-$BuPh_2SiCl$ (1.2 equiv.), pyridine, CH_2Cl_2, r. t., 24 h; then $MeSO_2Cl$ (1.4 equiv.), 0 to 5 °C, 5 h; b) pyridine, toluene, 110 °C, 24 h; c) $TiCl_4$, PhSH, CH_2Cl_2, -10 °C, 1 h; d) $NaIO_4$, aq. MeOH, 5 °C, 2 h; e) *n*-$C_{14}H_{29}MgCl$, THF, -70 to -20 °C; f) 2 M aq. HCl, THF, r. t., 5 h, then NaOH, aq. EtOH, 95 °C, 12 h; g) Ac_2O, pyridine, DMAP, CH_2Cl_2.

Table 1. Effect of Additives in the Grignard Reaction

Entry	Additive	Yield[a]	(%)	Ratio
	(1 equiv. to 9)	**10r**	**10s**	**10r** : **10s**
1	none	65	9	7 : 1
2	$BF_3 \cdot OEt_2$	71	10	7 : 1
3	$ZnCl_2$	50	27	2 : 1
4	$CeCl_3$	68	6	11 : 1

a. Isolated yield. In all cases, the reduction product (RCH_2OH) of **9** was obtained in 5 – 10% yields.



a chelate ring with metal cation and the aldehyde-oxygen. This chelated intermediate should produce **10r** preferentially. For practical synthesis, no additive is necessary since the diastereoselectivity did not improved much and the reactivity decreased in the presence of any additive.

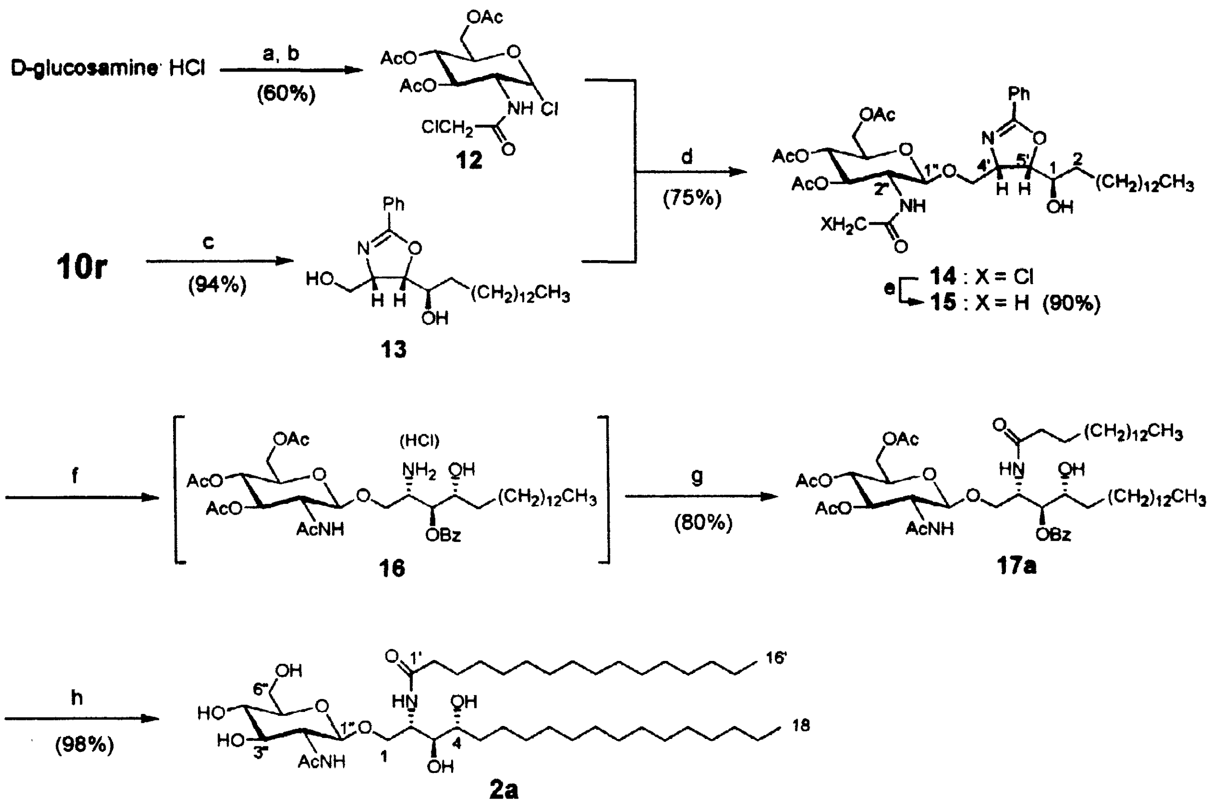
Deprotection of the (*R*)-alcohol **10r** was achieved by two-step hydrolysis to afford D-*ribo*-C_{18}-phytosphingosine **1** in 75% yield. The structure of **1** was further confirmed by its conversion into the known tetraacetyl-phytosphingosine **11**, the physical data of which were almost identical with those reported.[9-14] Thus the present synthetic route could provide the protected phytosphingosine **10r** from **3** in 7 reaction steps, which is fewer by 3 steps than our previous route,[10b] with 30% overall yield.

Glycosidation and Synthesis of Halicylidrosides A Homologue

Having phytosphingosine derivatives with natural (2*S*, 3*S*, 4*R*)-stereochemistry in hand, we turned our attention to the glycosidation. A number of procedures for the synthesis of 2-acetamido-2-deoxy-β-D-glucopyranosides have been developed in recent years.[20,21] However, most methods still suffer from drawbacks. For example, often employed *N*-phthaloyl (Phth)-protected donors have difficulty in converting to the *N*-acetyl group after glycosidation. To avoid harsh conditions required for removal of Phth group, tetrachloro-Phth-[21c] and dichloro-Phth-protected[21h] donors have been developed. In contrast, glycosidation with *N*-acetyl-protected donors directly provide 2-acetamido-2-deoxy-β-D-glucopyranosides, but these donors usually show insufficient reactivities due to the formation of oxazoline intermediate. To increase the reactivity, *N*-haloacetyl-glucosamine derivatives have been employed.[21b,22]

We sought a more efficient glucosamine donor with ready accessibility, and eventually employed 2-chloroacetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl chloride (**12**). To our knowledge, **12** has not been used as a glycosyl donor except for the reaction with excess methanol in the presence of Ag_2CO_3.[23] Although the previous synthesis[23a] of **12** required 5 steps from glucosamine, we could prepare it in a straightforward manner according to the synthetic procedures of *N*-acetyl-[24a] and *N*-pent-4-enoyl-glucosamine[24b] derivatives. (Scheme 2) The oxazoline-diol **13**, readily obtained by desilylation of **10r**, was chosen as glycosyl acceptor. Coupling of **12** and **13** was performed using silver trifluoromethanesulfonate (AgOTf) as the promoter at 70 °C to afford the desired β-glucoside **14** in 75% yield. In the course of the reaction, TLC showed the formation of an intermediate 2-chloromethyl-2-oxazoline derivative and the disappearance of **12** within 1 h. However, the reaction of the oxazoline with **13** proceeded rather slowly. This moderate reactivity eliminates the formation of the diglycosylated product of **13**. The chloroacetyl group in **14** was reduced with *n*-Bu_3SnH to give the acetamide **15**. Glycosidation of **13** with *N*-acetyl analogue of **12** was also examined under similar reaction conditions.[21d] The reaction proceeded more slowly than the former glycosidation and the product **15** was contaminated with several impurities even after chromatography. Thus the former two-step procedure was proved effective and would be applicable to the synthesis of *N*-acetylglucosaminides of reactive alcohols.

The synthesis of **2a** was completed as follows. Acid catalyzed ring opening of the oxazoline **15** gave the 2-amino-3-*O*-benzoate hydrochloride **16**, which was treated with palmitoyl chloride to afford the amide **17a**. Finally deacylation of **17a** with NaOMe in methanol-THF furnished the glycolipids **2a**. Its physical data were very close to those reported for the natural Halicylindrosides A_1-A_4.[8]



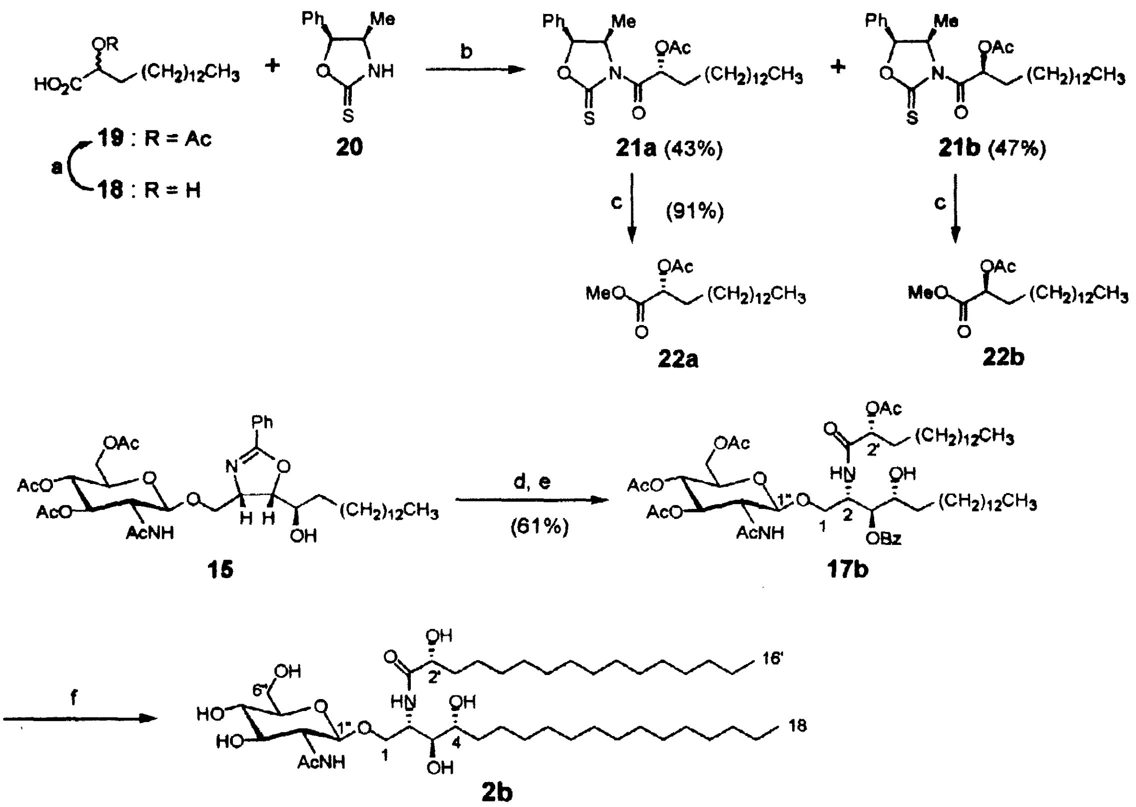
Scheme 2. *Reagents and conditions:* a) NaOMe (1 equiv.), MeOH; then $(ClCH_2CO)_2O$, Et_3N, MeOH, 0 °C, 1 h; b) AcCl, r. t., 24 h; c) $(n\text{-}Bu)_4NF$, THF, r. t., 1 h; d) AgOTf, M.S.4A, $ClCH_2CH_2Cl$, 70 °C, 15 h; e) $(n\text{-}Bu)_3SnH$, AIBN, toluene, 80 °C, 1 h; f) 1M-HCl, THF, r. t., 3 h; g) $n\text{-}C_{15}H_{31}COCl$, Et_3N, CH_2Cl_2, 0 °C; h) NaOMe, MeOH, THF, 5 °C, 2 h.

Synthesis of Halicylidrosides B Homologue

Natural glycosphingolipids generally possess two types of amide-linked fatty acids: non-hydroxy fatty acids (NFA) and (2*R*)-hydroxyfatty acids (HFA). Hence preparation of optically active (2*R*)-HFA derivatives and subsequent coupling with sphingosine amino group are indispensable for glycolipids synthesis. Several syntheses of the ceramides bearing (2*R*)-hydroxypalmitoyl (HOpal) residue have been reported.[15a,25] However, those syntheses required several steps for the preparation of 2-HOpal derivatives[26] suitable for the coupling with sphingosines. We planned to develop a facile preparation of such a (2*R*)-HOpal derivative from commercially available 2(*RS*)-hydroxypalmitic acid **18** by using a simultaneous optical resolution and carboxyl-activation method.

As shown in Scheme 3, 2(*RS*)-acetoxypalmitic acid **19** [25a] was treated with (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione **20** derived from (-)-norephedrin according to the method of Fujita *et al.*[27] The diastereomeric coupling products **21a** and **21b** were readily separated by silica-gel chromatography. For structural determination, each diastereomer was treated with a catalytic amount of K_2CO_3 in methanol to give the methyl ester. The optical rotation of the methyl ester **22a** derived from the more polar isomer **21a** was identical with that reported[28] for methyl (2*R*)-acetoxypalmitate. Thus the required (2*R*)-acetoxypalmitoyl imide **21a**, which can readily react with amines to give the amides, was prepared from 2(*RS*)-hydroxypalmitic acid **18** in 2 steps.

With **21a** in hand, we accomplished the synthesis of **2b** as follows. The oxazoline-glucoside **15** was



Scheme 3. *Reagents and conditions:* a) Ac_2O, pyridine, CH_2Cl_2, r.t.; b) dicyclohexylcarbodiimide, DMAP, CH_2Cl_2, r. t., 1 h; c) K_2CO_3 (cat.), MeOH, 0 °C, 15 min; d) 1M-HCl, THF, r. t., 3 h; e) **21a**, $EtN(i\text{-}Pr)_2$, DMF, 90 °C, 20 h; f) NaOMe, MeOH, THF, 5 °C, 2 h.

converted to the amino-benzoate hydrochloride **16**, which was treated with **21a** in the presence of a tertiary amine. The reaction proceeded sluggishly in CH_2Cl_2 [26] or THF, but moderately in DMF at 90 °C to afford the amide **17b**. Finally **17b** was deacylated with NaOMe in methanol-THF to afford the glycolipids **2b**. Their physical data were very similar to those reported for the natural Halicylindrosides B_1-B_6.[8]

CONCLUSIONS

D-*ribo*-Phytosphingosine **1** was conveniently synthesized from *N*-benzoyl-D-glucosamine **3** by a new, short route featuring regioselective *O*-mesylation and diastereoselective Grignard addition. Glycosidation of the protected phytosphingosine **13** with **12** followed by reductive dechlorination afforded the glucoside **15**, which was converted to a novel glucosamino-cerebroside **2a**, a homologue of Halicylindrosides A. Also Halicylindrosides B homologue **2b** bearing (2*R*)-hydroxypalmitoyl residue was synthesized from **15** by utilizing the simultaneous optical resolution and carboxyl activation method. The use of the 2-*N*,3-*O*-oxazoline-protected sphingosine **13** as a glycosyl acceptor has an advantage that various fatty acids can be installed onto the sphingosine amino group after glycosidation. This glycosidation strategy would be widely applicable to the synthesis of related cerebrosides.

EXPERIMENTAL

General

Melting points were determined with a Yanaco melting point apparatus MP-500D and are uncorrected. Optical rotations were measured with a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded at 270 and 67.8 MHz on a JEOL JNM-GSX-270 spectrometer for solutions in $CDCl_3$ unless otherwise noted. Tetramethylsilane (TMS) was used as internal standard (δ_H = 0) for ^{1}H NMR and $CDCl_3$ served as internal standard (δ_C = 77.0) for ^{13}C NMR. When pyridine-d_5 was used, pyridine-d_5 served as internal standard (δ_H = 7.19, δ_C = 123.5). Infrared (IR) spectra were mesured for samples as KBr pellets with a JASCO FT-IR 620 spectrophotometer. Elemental analyses were performed by the analytical center in this Institute (NIMC). High-resolution mass spectra (HRMS) and FAB mass spectra (FABMS) were obtained on a Hitachi M-80B and a JEOL DX-303 mass spectrometers, respectively. Thin layer chromatography (TLC) was performed on Merck pre-coated silica gel $60F_{254}$ plates. Column chromatography was performed on silica gel (Wako gel C-200). Organic solutions after extractive work-up were dried over Na_2SO_4, filtered through a cotton plug, and evaporated under reduced pressure. Tetradecylmagnesium chloride (1.0 M solution in THF) and molecular sieves 4A (powder) were purchased from Aldrich Chemical Co., and the latter was dried *in vacuo* at 110 °C for 2 h before use.

2-Benzamido-2-deoxy-1-*O*-*t*-butyldiphenylsilyl-4,6-*O*-ethylidene-3-*O*-methylsulfonyl-D-glucitol (5)

To an ice-cooled solution of the triol 4[19] (1.74 g, 5.6 mmol) and pyridine (5 ml, 62 mmol) in CH_2Cl_2 (30 ml) was added dropwise a solution of *t*-butyldiphenylchlorosilane (1.85 g, 6.7 mmol) in CH_2Cl_2 (10 ml), and the mixture was stirred at room temperature for 24 h. To this solution was added a solution of methanesulfonyl chloride (905 mg, 7.9 mmol) in CH_2Cl_2 (8 ml) at 0 °C. After being stirred for 5 h in an ice- bath, the mixture was diluted with CH_2Cl_2 (30 ml) and treated with cold aq. $NaHCO_3$ (30 ml), and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 40 ml) and the combined organic layers were successively washed with H_2O and brine, and then dried. Removal of the solvent gave an yellow residue, which was purified by column chromatography with hexane-AcOEt (3:2) as eluent to give the di-mesylate **6** (306 mg, 7.8%) as a colorless oil: R_f 0.36 (hexane-AcOEt, 3:2); $[\alpha]_D^{23}$ −5.0° (*c* 0.92, $CHCl_3$). Further elution with hexane-AcOEt (1:1) afforded the mono-mesylate **5** (2.60 g, 74%): m.p. 143-145 °C (colorless needles from AcOEt-hexane); R_f 0.23 (hexane-AcOEt, 3:2); $[\alpha]_D^{24}$ +6.3° (*c* 1.0, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 1.09 (9H, s, *t*-Bu), 1.24 (1H, d, *J* = 5.0 Hz, CH_3CH), 1.88 (1H, br s, OH), 3.06 (3H, s, CH_3SO_2), 3.35 (1H, t, *J* = 10.5 Hz, 6-H^{ax}), 3.46 (1H, dd, *J* = 2.7, 9.0 Hz, 4-H), 3.76 (1H, dd, *J* = 3.0, 10.9 Hz, 1-Ha), 3.80 (1H, m, 5-H), 3.97 (1H, dd, *J* = 3.3, 11.2 Hz, 1-Hb), 4.14 (1H, dd, *J* = 5.2, 10.7 Hz, 6-H^{eq}), 4.30 (1H, q, *J* = 5.0 Hz, $CHCH_3$), 4.76 (1H, tt, *J* = 3.0, 8.6 Hz, 2-H), 5.45 (1H, dd, *J* = 2.6, 8.6 Hz, 3-H), 6.92 (1H, d, *J* = 8.8 Hz, NH), 7.27-7.83 (15H, m, Ph); δ_C (67.8 MHz, $CDCl_3$) 19.2, 20.3, 26.9, 38.3 (CH_3SO_2), 51.0 (C-2), 61.4, 63.0, 70.2, 76.5, 79.3 (C-3), 99.3, 127.0, 127.9, 128.0, 128.7, 130.0, 130.1, 131.8, 132.4, 132.5, 133.8, 135.5, 135.8, 167.0 (C=O); ν_{max} 3402, 2932, 2858, 1654, 1523, 1349, 1174, 1105, 702 cm^{-1}; Anal. Calcd for $C_{32}H_{41}NO_8SiS$: C, 61.22; H, 6.58; N, 2.23; S, 5.11. Found: C, 61.17; H, 6.62; N, 2.32; S, 5.22.

2-Phenyl-4,5-dihydrooxazole (2-phenyl-2-oxazoline) derivative (7)

A mixture of **5** (1.89 g, 3.0 mmol), pyridine (10 ml), triethylamine (3.0 ml) in toluene (20 ml) was stirred at 110 °C for 24 h. The resulting solution was diluted with AcOEt (50 ml) and aq. $NaHCO_3$ (30 ml), and the layers were separated. The aqueous layer was extracted with AcOEt (2 x 30 ml) and the combined organic layers were successively washed with H_2O and brine, and then dried. Removal of the solvent gave an yellow residue, which was purified by column chromatography with hexane-AcOEt (3:1) as eluent to give the oxazoline **7** (1.35 g, 85%) as a colorless foam: R_f 0.32 (hexane-AcOEt, 2:1); $[\alpha]_D^{27}$ −124.8° (*c* 1.0, $CHCl_3$); δ_H 0.91 (9H, s), 1.21 (3H, d, *J* = 5.0 Hz), 2.99 (1H, br d), 3.38 (1H, t, *J* = 10.4 Hz), 3.86, (1H, m), 4.04 (2H, m), 4.20 (1H, dd, *J* = 5.3, 10.9 Hz), 4.26 (1H, t, *J* = 8.7 Hz), 4.28 (1H, q, *J* = 5.0 Hz), 4.43 (1H, dt, *J* = 2.3, 9.2 Hz), 4.65 (1H, t, *J* = 9.2 Hz), 7.35-7.51 (9H, m), 7.64-7.71 (4H, m), 7.95 (2H, m); HRMS (EI) Calcd for $C_{31}H_{38}NO_5Si$ $(M + H)^+$: 532.2517. Found: 532.2480.

(1*R*,2*R*,4'*S*,5'*S*)-1-[4'-(*t*-Butyldiphenylsilyl)oxymethyl-2'-phenyl-4',5'-dihydrooxazol-5'-yl]propane-1,2,3-triol (8)

To a solution of **7** (425 mg, 0.80 mmol) and thiophenol (0.7 ml, 6.8 mmol) in CH_2Cl_2 (8 ml) under nitrogen at −15 °C was added dropwise a 1.0 M solution of $TiCl_4$ in CH_2Cl_2 (2.4 ml, 2.4 mmol) over 5 min, and the stirring was continued for 1 h at −15 to −10 °C. The resulting brown suspension was diluted with CH_2Cl_2 (10 ml) and quenched by the addition of a cooled solution of saturated aq. $NaHCO_3$ (10 ml) while being vigorously stirred. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried and concentrated to give a pale-yellow oil, which was purified by column chromatography with hexane-AcOEt (3:1) as eluent affording the triol **8** (340 mg, 84%) as a colorless foam: R_f 0.28 (hexane-AcOEt, 1:3); $[\alpha]_D^{25}$ −82.7° (*c* 0.70, $CHCl_3$); δ_H 1.06 (9H, s, *t*-Bu), 2.65 (1H, br, 3-OH), 3.08 (1H, d, *J* = 6.3 Hz, 2-OH), 3.80 (1H, dd, *J* = 9.6, 11.2 Hz, 4'-C*Ha*Hb), 3.90 (1H, m, 2-H) 3.93 (1H, dd, *J* = 3.3, 11.2 Hz, 4'-CHa*Hb*), 4.06 (2H, m, 3-H_2), 4.40 (1H, dt, *J* = 3.0, 9.8 Hz, 1-H), 4.62 (1H, dt, *J* = 3.0, 9.0 Hz, 4'-H), 4.76 (1H, t, *J* = 9.3 Hz, 5'-H), 4.88 (1H, d, *J* = 3.2 Hz, 1-OH), 7.34-7.50 (9H, m, Ph), 7.68 (4H, m, Ph), 7.81 (2H, m, Ph); δ_C 19.0, 26.7, 62.8, 63.0, 69.1, 71.1, 72.5, 81.1, 126.8, 127.99, 128.04, 128.2, 128.4, 130.2, 130.3, 131.7, 131.8, 131.9, 135.5, 135.6, 164.2; ν_{max} 3377 (broad), 2931, 2857, 1648, 1428, 1361, 1112, 1066, 699 cm^{-1}; HRMS Calcd for $C_{29}H_{36}NO_5Si$ $(M + H)^+$: 506.2362. Found: 506.2276.

(4*S*,5*S*)-4-(*t*-Butyldiphenylsilyl)oxymethyl-2-phenyl-4,5-dihydrooxazole-5-carbaldehyde (9)

Solid $NaIO_4$ (190 mg, 0.91 mmol) was added to a stirred, ice-cooled solution of the triol **8** (202 mg, 0.40 mmol) in MeOH (4 ml) and H_2O (1 ml) and the mixture was stirred for 2 h at 5-10 °C. The white precipitate formed was filtered off and washed thoroughly with AcOEt. To the filtrate were added AcOEt (20 ml) and half-saturated brine (20 ml) and the layers were separated. The aqueous layer was extracted with AcOEt (2 x 20 ml) and the combined organic layers were washed with H_2O and brine (20 ml each), and dried. The organic layer was concentrated, coevaporated with toluene, and dried *in vacuo* to give crude aldehyde **9** as a colorless oil (192 mg), which was used in the next step without further purification: R_f 0.37 (hexane-AcOEt, 3:1); δ_H 0.89 (9H, s, *t*-Bu), 3.90 (2H, d, *J* = 2.2 Hz, 4-CH_2), 4.71 (1H, dt, *J* = 2.3, 10.8 Hz, 4-H), 4.93 (1H, dd, *J* = 1.7, 10.8 Hz, 5-H), 7.34-7.42 (6H, m, Ph), 7.47 (2H, m, Ph), 7.53 (1H, m, Ph), 7.58 (2H, m, Ph), 7.65 (2H, m, Ph), 8.05 (2H, m, Ph), 10.12 (1H, d, *J* = 1.7 Hz, HC=O); δ_C 18.9, 26.5, 61.6, 73.4, 83.2, 127.0, 127.6, 127.8, 128.4, 129.7, 129.8, 131.8, 132.3, 132.9, 135.4, 135.8, 163.8, 200.9.

(1*S*,4'*S*,5'*S*)- and (1*R*,4'*S*,5'*S*)-1-[4'-(*t*-Butyldiphenylsilyl)oxymethyl-2'-phenyl-4',5'-dihydrooxazol-5'-yl]pentadecan-1-ol (10s) and (10r)

A 1.0 M solution of tetradecylmagnesium chloride in THF (0.8 ml, 0.8 mmol) was added dropwise over 5 min to a stirred solution of the aldehyde **9** (192 mg, 0.40 mmol) in THF (5 ml) at -70 °C under nitrogen. The resulting pale yellow solution was stirred at -70 to -50 °C for 30 min and was then allowed to warm. At *ca.* -20°C, this solution was treated with saturated aq. NH_4Cl (2 ml), followed by AcOEt (15 ml) and H_2O (5 ml). The layers were separated and the aqueous phase was extracted with AcOEt (2 x 15 ml). The organic layer was successively washed with H_2O and brine, dried and concentrated. The residue was chromatographed on a column with hexane-AcOEt (5:1) as eluent to afford the (1*S*)-alcohol **10s** (23 mg, 9% yield) as a colorless oil: R_f 0.40 (hexane-AcOEt, 4:1); $[\alpha]_D^{25}$ -37.6° (*c* 1.4, $CHCl_3$); δ_H 0.88 (3H, t, *J* = 6.8 Hz, CH_3), 1.00 (9H, s, *t*-Bu), 1.26 (24H, s-like, 12 x CH_2), 1.67 (2H, m, 2-H_2), 3.00 (1H, d, *J* = 4.3 Hz, OH), 4.01 (1H, dd, *J* = 3.3, 10.9 Hz, 4'-C*Ha*Hb), 4.11 (1H, dd, *J* = 6.2, 10.9 Hz, 4'-CHa*Hb*), 4.24 (1H, m, 1-H), 4.36 (1H, ddd, *J* = 3.3, 6.4, 9.7 Hz, 4'-H), 4.64 (1H, dd, *J* = 3.1, 9.7 Hz, 5'-H), 7.35-7.48 (9H, m, Ph), 7.68 (2H, m, Ph), 7.72 (2H, m, Ph), 7.97 (2H, m, Ph); δ_C 14.1, 19.1, 22.7, 26.0, 26.8, 29.4, 29.68, 29.72, 31.9, 34.8, 62.8, 68.9, 69.4, 84.2, 127.67, 127.73, 127.8, 128.28, 128.30, 129.8, 129.9, 131.4, 132.5, 133.0, 135.6, 135.8, 164.4.

Further elution with hexane-AcOEt (4:1) afforded the (1*R*)-alcohol **10r** (167 mg, 65%) as a colorless oil: R_f 0.25 (hexane-AcOEt, 4:1); $[\alpha]_D^{24}$ -62.6° (*c* 1.3, $CHCl_3$); δ_H 0.88 (3H, t, *J* = 6.8 Hz, CH_3), 1.07 (9H, s, *t*-Bu), 1.26 (24H, s-like, 12 x CH_2), 1.66 (2H, m, 2-H_2), 3.78 (1H, dd, *J* = 8.9, 10.9 Hz, 4'-C*Ha*Hb), 3.90 (1H, dd, *J* = 3.0, 11.0 Hz, 4'-CHa*Hb*), 4.17 (1H, m, 1-H), 4.37 (1H, br s, OH), 4.58 (1H, t, *J* = 8.6 Hz, 5'-H), 4.64 (1H, dt, *J* = 2.6, 8.2 Hz, 4'-H), 7.34-7.47 (9H, m, Ph), 7.68 (4H, m, Ph), 7.87 (2H, m, Ph); δ_C 14.1, 19.0, 22.7, 25.2, 26.8, 29.4, 29.7, 29.8, 31.9, 34.4, 62.7, 68.3, 68.7, 84.9, 127.1, 127.9, 128.0, 128.3, 130.1, 130.2, 131.8, 131.9, 132.0, 135.6, 165.0; HRMS Calcd for $C_{41}H_{60}NO_3Si$ $(M + H)^+$: 642.4342. Found: 642.4352.

D-*ribo*-C_{18}-Phytosphingosine [(2*S*, 3*S*, 4*R*)-2-aminooctadecane-1,3,4-triol] (1)

To a stirred solution of **10r** (70 mg, 0.11 mmol) in THF (3.6 ml) was added 2.0 M aq. HCl (0.4 ml), and the mixture was stirred for 5 h at room temperature. To this solution was added a solution of NaOH (200 mg, 4.0 mmol) in H_2O (1.0 ml) and EtOH (1.0 ml), and the mixture was heated at 95 °C for 12 h. The cooled reaction mixture was diluted with H_2O (10 ml) and extracted with Et_2O (3 x 10 ml). The organic layer was dried and concentrated to give a yellow solid, which was subjected to column chromatography, with CH_2Cl_2-MeOH (9:1), then with CH_2Cl_2-MeOH-10% aq. NH_4OH (40:10:1) as eluent, to afford phytosphingosine **1** (26 mg, 75%) as a colorless solid: m.p. 98-101 °C; $[\alpha]_D^{24}$ +8.7° (*c* 0.80, pyridine) {lit.[11b] m.p. 95 °C; $[\alpha]_{578}^{23}$ +8.5° (*c* 1, pyridine), lit.[11d] m.p. 98-100 °C; $[\alpha]_D^{20}$ +8.9° (*c* 0.6, pyridine), lit.[12a] m.p. 103 °C; $[\alpha]_D^{20}$ +7.9° (*c* 1.0, pyridine), lit.[12e] m.p. 95.4-98.5 °C; $[\alpha]_D^{27}$ +7.3° (*c* 0.99, pyridine)}; δ_H (pyridine-d_5/D_2O) 0.83 (3H, t, *J* = 6.7 Hz, 18-Me), 1.21 (21H, s-like), 1.37 (1H, m), 1.66 (1H, m), 1.78-1.95 (2H, m), 2.16-2.30 (1H, m), 3.52 (1H, br, 2-H), 3.97 (1H, t, *J* = 7.1 Hz, 3-H), 4.19 (1H, m, 4-H), 4.22 (1H, dd, *J* = 6.1, 9.3 Hz, 1-H), 4.32 (1H, br, 1-H); HRMS Calcd for $C_{18}H_{40}NO_3$ $(M + H)^+$: 318.3008. Found: 318.3030.

Tetraacetyl-D-*ribo*-C$_{18}$-phytosphingosine (11)

To an ice-cooled solution of phytosphingosine **1** (21 mg, 0.07 mmol) in CH_2Cl_2 (2 ml) were added pyridine (0.1 ml) and acetic anhydride (0.1 ml), and the mixture was stirred at room temperature. After 2 h, 4-(dimethylamino)pyridine (2 mg) was added to the mixture to complete the acetylation. After extractive work-up, the organic layer was dried and concentrated to give a white solid, which was purified by chromatography to afford tetraacetyl-phytosphingosine **11** (29 mg, 90%) as a colorless solid: m.p. 34-37 °C; $[\alpha]_D^{24}$ +28.0° (*c* 1.30, $CHCl_3$) {lit.[9b] $[\alpha]_D^{23}$ +26.2° (*c* 0.1, $CHCl_3$), lit.[9d] $[\alpha]_D$ +24.7° (*c* 0.5, $CHCl_3$), lit.[9f] $[\alpha]_D^{19}$ +24.7° (*c* 1.14, $CHCl_3$), lit.[12a] m.p. 48 °C; $[\alpha]_D^{20}$ +26.3° (*c* 2, $CHCl_3$), lit.[12g] $[\alpha]_D^{21}$ +28.9° (*c* 0.95, $CHCl_3$)}; R_f 0.34 (hexane-AcOEt, 1:1); δ_H 0.88 (3H, t, J = 6.8 Hz, 18-Me), 1.25 (24H, s-like, 6 to 17-CH_2), 1.65 (2H, m, 5-H_2), 2.03 (3H, s, CH_3CO), 2.05 (6H, s, CH_3CO), 2.08 (3H, s, CH_3CO), 4.00 (1H, dd, J = 3.0, 11.7 Hz, 1-Ha), 4.29 (1H, dd, J = 4.8, 11.7 Hz, 1-Hb), 4.47 (1H, m, 2-H), 4.93 (1H, dt, J = 3.3, 9.6 Hz, 4-H), 5.11 (1H, dd, J = 3.0, 8.3 Hz, 3-H), 6.01 (1H, d, J = 9.4 Hz, NH); δ_C 14.1, 20.69, 20.73, 21.0, 22.6, 23.2, 25.5, 28.1, 29.25, 29.32, 29.45, 29.54, 29.58, 29.61, 29.63, 31.9, 47.6, 62.8, 71.9, 73.0, 169.7, 170.1, 170.8, 171.2; ν_{max} 3300, 2920, 2851, 1731, 1659, 1550, 1376, 1264, 1227, 1042 cm^{-1}; Anal. Calcd for $C_{26}H_{47}NO_7$: C, 64.30; H, 9.75; N, 2.88. Found: C, 64.40; H, 9.93; N, 2.82.

3,4,6-Tri-*O*-acetyl-2-chloroacetamido-2-deoxy-α-D-glucopyranosyl chloride (12)

To an ice-cooled, stirred solution of 1.0 M NaOMe in MeOH (5 ml, 5 mmol) was added D-glucosamine hydrochloride (1.08 g, 5.0 mmol) and the mixture was stirred for 20 min. The precipitated NaCl was removed by filtration through Celite and the filter cake was rinsed with MeOH (1 ml). The filtrate was placed in an ice bath, and chloroacetic anhydride (1.0 g, 5.8 mmol) and triethylamine (0.80 ml, 5.7 mmol) were added alternatively in several portions. After being stirred for 1 h, the solution was concentrated and dried *in vacuo*. Since *N*-chloroacetylglucosamine formed [R_f 0.24 (CH_2Cl_2-MeOH, 4:1)] was not crystallized, this residue was used in the next step without purification. To the crude *N*-chloroacetyl-D-glucosamine was added acetyl chloride (10 ml), and the mixture was stirred in a sealed flask for 24 h. The reaction mixture was diluted with AcOEt (50 ml), cooled by an ice-water bath, and treated with cold saturated aq. $NaHCO_3$ (30 ml). The phases were separated, and the organic phase was washed successively with ice-cooled saturated aq. $NaHCO_3$ and H_2O. The combined aqueous layers were extracted with AcOEt (2 x 20 ml), and the organic extracts were dried and concentrated. The dark brown residue was purified by chromatography with hexane-AcOEt (3:2→1:1) containing 0.5% Et_3N as eluent to give the glucosyl chloride **12** (1.20g, 60%) as a colorless solid: m.p. 133-135 °C (decomp.); $[\alpha]_D^{24}$ +121.6° (*c* 1.40, $CHCl_3$) {lit.[23a] m.p. 143 °C (decomp.); $[\alpha]_D^{22}$ +115.4° (*c* 1.43, $CHCl_3$)}; R_f 0.50 (hexane-AcOEt, 1:1); δ_H 2.05 (3H, s, CH_3CO), 2.06 (3H, s, CH_3CO), 2.11 (3H, s, CH_3CO), 4.02 (2H, AB-type, CH_2Cl), 4.14 (1H, m, 5-H), 4.30 (2H, m, 6-H_2), 4.49 (1H, ddd, J = 4.0, 8.6, 10.6 Hz, 2-H), 5.23 (1H, t, J = 9.6 Hz, 4-H), 5.40 (1H, dd, J = 9.6, 10.6 Hz, 3-H), 6.21 (1H, d, J = 4.0 Hz, 1-H), 6.86 (1H, d, J = 8.2 Hz, NH); δ_C 20.49, 20.55, 20.62, 42.1, 53.9, 61.0, 66.8, 69.7, 70.9, 92.7, 166.4, 169.1, 170.5, 171.1; ν_{max} 3250, 3222, 2998, 1741, 1663, 1553, 1372, 1226, 1125, 1044 cm^{-1}; Anal. Calcd for $C_{14}H_{19}NO_8Cl_2$: C, 42.04; H, 4.78; N, 3.50. Found: C, 42.22; H, 4.67; N, 3.33.

(1*R*,4'*S*,5'*S*)-1-[4'-Hydroxymethyl-2'-phenyl-4',5'-dihydrooxazol-5'-yl]pentadecan-1-ol (13)

To a stirred solution of **10r** (180 mg, 0.28 mmol) in THF (4.0 ml) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.5 ml, 0.5 mmol) at room temperature. After 1 h, a drop of aq. NH_4Cl was added to the mixture, and the solvent was removed to dryness. Purification by chromatography with hexane-AcOEt (1:2) gave the diol **13** (104 mg, 92%) as a colorless solid: m.p. 90-92 °C; $[\alpha]_D^{24}$ –25.5° (*c* 1.3, $CHCl_3$); δ_H ($CDCl_3/CD_3OD$) 0.88 (3H, t, *J* = 6.8 Hz, CH_3), 1.26 (24H, s-like, 12 x CH_2), 1.60 (1H, m, 2-Ha), 1.83 (1H, m, 2-Hb), 3.75 (1H, dd, *J* = 8.6, 11.2 Hz, 4'-C*Ha*Hb), 3.86 (1H, dd, *J* = 3.3, 11.9 Hz, 4'-CHa*Hb*), 4.04 (1H, dt, *J* = 2.7, 8.6 Hz, 1-H), 4.47 (1H, dt, *J* = 2.6, 8.6 Hz, 4'-H), 4.54 (1H, t, *J* = 8.9 Hz, 5'-H), 7.42 (2H, m, Ph), 7.50 (1H, m, Ph), 7.89 (2H, m, Ph); ν_{max} 3418, 3246 (broad), 2916, 2849, 1643, 1469, 1367, 1092, 959, 692 cm^{-1}; Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found: C, 74.40; H, 10.08; N, 3.45.

(1*R*,4'*S*,5'*S*)-1-[4'-(3",4",6"-Tri-*O*-acetyl-2"-chloroacetamido-2"-deoxy-β-D-glucopyranosyl)oxymethyl-2'-phenyl-4',5'-dihydrooxazol-5'-yl]pentadecan-1-ol (14)

A solution of diol **13** (95 mg, 0.23 mmol), glucosyl chloride **12** (178 mg, 0.44 mmol), molecular sieves 4A (150 mg) in dichloroethane (8 ml) was stirred under argon at room temperature for 30 min. To this suspension was added AgOTf (132 mg, 0.51 mmol), and the mixture was stirred at 70 °C for 15 h. The resulting suspension was diluted with AcOEt, and the insoluble material was filtered off and washed thoroughly with AcOEt. The filtrate was washed with aq. $NaHCO_3$, H_2O, and brine. Combined aqueous layers were extracted with AcOEt (2 x 20 ml), and the organic extracts were dried and concentrated. The residue was purified by chromatography eluting with hexane-AcOEt (1:2→1:3→0:1) to afford the glycoside **14** (135 mg, 75%) as a colorless solid: m.p. 179-181 °C; R_f 0.27 (hexane-AcOEt, 1:2); $[\alpha]_D^{25}$ –29.7° (*c* 1.0, $CHCl_3$); δ_H 0.88 (3H, t, *J* = 6.6 Hz, 15-CH_3), 1.26 (24H, s-like, 12 x CH_2), 1.58 (2H, m, 2-H_2), 2.02 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO), 2.11 (3H, s, CH_3CO), 3.14 (1H, d, *J* = 4.0 Hz, OH), 3.71 (1H, dd, *J* = 7.9, 10.6 Hz, 4'-C*Ha*Hb), 3.73 (1H, m, 5"-H), 3.86 (2H, AB-type, CH_2Cl), 3.91 (1H, dt, *J* = 8.6, 10.6 Hz, 2"-H), 3.95 (1H, m, 1-H), 4.16 (1H, dd, *J* = 2.3, 12.2 Hz, 6"-Ha), 4.23 (1H, dd, *J* = 2.6, 10.4 Hz, 4'-CHa*Hb*), 4.29 (1H, dd, *J* = 4.9, 12.2 Hz, 6"-Hb), 4.44 (1H, t, *J* = 9.1 Hz, 5'-H), 4.55 (1H, dt, *J* = 2.6, 8.2 Hz, 4'-H), 4.83 (1H, d, *J* = 8.6 Hz, 1"-H), 5.08 (1H, t, *J* = 9.6 Hz, 4"-H), 5.30 (1H, dd, *J* = 9.2, 10.6 Hz, 3"-H), 6.57 (1H, d, *J* = 8.9 Hz, NH), 7.42 (2H, m, Ph), 7.50 (1H, m, Ph), 7.90 (2H, m, Ph); δ_C 14.2, 20.6, 20.7, 20.9, 22.8, 25.2, 29.4, 29.7, 29.8, 29.9, 32.0, 34.8, 42.4, 54.9, 61.8, 66.6, 67.4, 68.3, 68.7, 71.4, 72.2, 84.1, 100.2, 127.1, 128.1 (2C), 128.3 (2C), 131.7, 164.5, 166.7, 169.1, 170.5, 170.6; ν_{max} 3500, 3344, 2922, 2851, 1747, 1662, 1536, 1372, 1257, 1231, 1088, 692 cm^{-1}; Anal. Calcd for $C_{39}H_{59}N_2O_{11}Cl$: C, 61.04; H, 7.75; N, 3.65. Found: C, 60.91; H, 7.90; N, 3.60.

(1*R*,4'*S*,5'*S*)-1-[4'-(2"-Acetamido-3",4",6"-tri-*O*-acetyl-2"-deoxy-β-D-glucopyranosyl)oxymethyl-2'-phenyl-4',5'-dihydrooxazol-5'-yl]pentadecan-1-ol (15)

To a solution of **14** (85 mg, 0.11 mmol), 2,2'-azobis(isobutyronitrile) (4 mg, 24 μmol) in toluene (4 ml) under argon was added tributyltin hydride (50 μl, 0.17 mmol), and the mixture was stirred at 80 °C for 1 h. Removal of the solvent gave a colorless oil, which was purified by column chromatography eluting with AcOEt to give the acetamide **15** (73 mg, 90%) as a colorless solid: m.p. 165-168 °C; $[\alpha]_D^{25}$ –37.0° (*c* 1.1,

$CHCl_3$); δ_H 0.88 (3H, t, J = 6.8 Hz, 15-CH_3), 1.26 (24H, s-like, 12 x CH_2), 1.58 (2H, m, 2-H_2), 1.78 (3H, s, CH_3CONH), 2.00 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.10 (3H, s, CH_3CO), 3.34 (1H, br s, OH), 3.72 (1H, m, 5"-H), 3.76 (1H, dd, J = 7.6, 10.6 Hz, 4'-C*Ha*Hb), 3.86 (1H, dt, J = 8.6, 10.6 Hz, 2"-H), 3.97 (1H, m, 1-H), 4.15 (1H, dd, J = 2.3, 12.2 Hz, 6"-Ha), 4.23 (1H, dd, J = 2.6, 10.6 Hz, 4'-CHa*Hb*), 4.27 (1H, dd, J = 4.8, 12.4 Hz, 6"-Hb), 4.45 (1H, t, J = 8.9 Hz, 5'-H), 4.55 (1H, dt, J = 2.3, 8.1 Hz, 4'-H), 4.80 (1H, d, J = 8.2 Hz, 1"-H), 5.06 (1H, t, J = 9.6 Hz, 4"-H), 5.22 (1H, dd, J = 9.2, 10.6 Hz, 3"-H), 5.68 (1H, d, J = 8.9 Hz, NH), 7.42 (2H, m, Ph), 7.51 (1H, m, Ph), 7.91 (2H, m, Ph); δ_C 14.2, 20.7, 20.8, 22.7, 23.1, 25.2, 29.4, 29.7, 29.9, 31.9, 35.0, 54.6, 61.9, 66.8, 67.1, 68.4, 68.6, 72.0, 72.2, 84.1, 100.5, 127.1, 128.1 (2C), 128.3 (2C), 131.7, 164.4, 169.1, 170.4, 170.6, 170.7; Anal. Calcd for $C_{39}H_{60}N_2O_{11}{\cdot}H_2O$: C, 62.38; H, 8.32; N, 3.73. Found: C, 62.58; H, 8.20; N, 3.67.

(2*S*,3*S*,4*R*)-1-*O*-(2"-Acetamido-3",4",6"-tri-*O*-acetyl-2"-deoxy-β-D-glucopyranosyl)-3-*O*-benzoyl-2-hexadecanoylaminooctadecane-1,3,4-triol (17a)

To a stirred solution of **15** (40 mg, 0.054 mmol) in THF (2.5 ml) was added 2.0 M aq. HCl (0.2 ml), and the mixture was stirred for 3 h at room temperature. To this solution were added CH_2Cl_2 (10 ml) and H_2O (10 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 10 ml). The combined organic extracts were dried and concentrated under reduced pressure to give 2-amino-3-*O*-benzoate **16** (43 mg) as a colorless foam. To an ice-cooled solution of the crude **16** (43 mg) in CH_2Cl_2 (2 ml) was added dropwise a solution of hexadecanoyl chloride (20 mg, 0.072 mmol) in CH_2Cl_2 (1 ml), and then Et_3N (10 mg, 0.10 mmol). After being stirred for 10 min, the reaction mixture was diluted with AcOEt and H_2O (10 ml), and extracted with AcOEt (3 x 10 ml). The combined organic layers were dried and concentrated to give a white solid, which was purified by chromatography with hexane-AcOEt (1:2) to give **17a** (43 mg, 80%) as a colorless solid: m.p. 122-125 °C; R_f 0.37 (hexane-AcOEt, 1:2); $[\alpha]_D^{23}$ -11.1° (c 0.80, $CHCl_3$); δ_H 0.88 (6H, t, J = 6.6 Hz, 18- and 16'-CH_3), 1.25 (48H, s-like, 24 x CH_2), 1.52-1.66 (4H, m, 5- and 3'-CH_2), 1.93 (3H, s, CH_3CO), 2.01 (3H, s, CH_3CO), 2.02 (3H, s, CH_3CO), 2.03 (3H, s, CH_3CO), 2.20 (2H, t, J = 7.8 Hz, 2'-H_2), 3.24 (1H, d, J = 6.3 Hz, OH), 3.68 (1H, ddd, J = 2.6, 4.6, 9.9 Hz, 5"-H), 3.80-3.95 (4H, m, 1-Ha, 1-Hb, 4-H, 2"-H), 3.99 (1H, dd, J = 2.3, 12.2 Hz, 6"-Ha), 4.15 (1H, dd, J = 4.6, 12.5 Hz, 6"-Hb), 4.67 (1H, dt, J = 3.6, 8.6 Hz, 2-H) 4.71 (1H, d, J = 8.2 Hz, 1"-H), 5.05 (1H, t, J = 9.7 Hz, 4"-H), 5.07 (1H, t, J = 5.0 Hz, 3-H), 5.17 (1H, dd, J = 9.2, 10.6 Hz, 3"-H), 5.99 (1H, d, J = 8.2 Hz, NH), 6.64 (1H, d, J = 8.2 Hz, NH), 7.46 (2H, m, Ph), 7.60 (1H, m, Ph), 8.04 (2H, m, Ph); δ_C 14.2, 20.7 (broad), 22.7, 23.4, 25.7, 25.9, 29.4, 29.5, 29.6, 29.66, 29.71, 29.8, 32.0, 33.5, 36.7, 48.4, 54.5, 61.9, 67.8, 68.3, 71.3, 71.9, 72.6, 73.9, 100.4, 128.4 (2C), 129.4, 129.7 (2C), 133.4, 166.3, 169.2, 170.5, 170.6, 170.8, 173.7; ν_{max} 3326, 2919, 2850, 1747, 1646, 1551, 1376, 1242, 1049, 713 cm^{-1}; FAB-MS (positive) *m/z* (rel intensity, %) 1011 $(M + Na)^+$ (26), 642 (12), 330 (62), 105 (100).

(2*S*,3*S*,4*R*)-1-*O*-(2"-Acetamido-2"-deoxy-β-D-glucopyranosyl)-2-hexadecanoylaminooctadecane-1,3,4-triol (2a)

To a stirred solution of **17a** (28 mg, 28 μmol) in MeOH (1 ml) and THF (1 ml) was added 1.0 M solution of NaOMe in MeOH (30 μl, 30 μmol), and the mixture was stirred for 30 min at room temperature. Acetic acid (10 mg) was added and the solvent was removed. Addition of MeOH gave a colorless solid, which was filtered off and washed with a small amount of MeOH, then with CH_2Cl_2, and dried *in vacuo* to afford the cerebroside **2a** (18 mg) as a colorless solid. The filtrate was purified by column chromatography eluting with CH_2Cl_2–MeOH (7:1) to give additional **2a** (3 mg, total 21 mg, 98%): m.p. 176-178 °C; $[\alpha]_D^{24}$ -18.0° (*c* 0.25, pyridine); R_f 0.32 (CH_2Cl_2-MeOH, 6:1); δ_H (270 MHz; pyridine-d_5/CD_3OD) 0.84 (6H, t-like, *J* = 6.6 Hz, 18- and 16'-CH_3), 1.22 (46H, s-like, 23 x CH_2), 1.62 (1H, m), 1.70-1.95 (4H, m), 2.10-2.20 (1H, m), 2.16 (3H, s, CH_3CO), 2.45 (2H, t, *J* = 7.6 Hz, 2'-CH_2), 3.83 (1H, ddd, *J* = 2.5, 5.8, 9.6 Hz, 5"-H), 4.10 (1H, t, 9.1 Hz, 4"-H), 4.15 (1H, m, 4-H), 4.19 (1H, t, *J* = 9.6 Hz, 3"-H), 4.23 (1H, m, 6"-Ha), 4.28 (1H, t, *J* = 6.3 Hz, 3-H), 4.44 (1H, dd, *J* = 2.4, 11.8 Hz, 6"-Hb), 4.50 (1H, m, 2"-H), 4.52 (1H, dd, *J* = 5.0, 10.6 Hz, 1-Ha), 4.59 (1H, dd, *J* = 6.3, 10.5 Hz, 1-Hb), 5.10 (1H, d, *J* = 8.6 Hz, 1"-H), 8.55 (1H, d, *J* = 9.2 Hz, NH), 9.02 (1H, d, *J* = 8.2 Hz, NH) (2-H was not observed due to the overlapping with HOD peak at 5.05 ppm); δ_C (67.8 MHz, pyridine-d_5/CD_3OD) 14.2, 22.9, 23.1, 23.5, 26.5, 26.6, 29.8-30.4 (highest), 32.3, 36.9, 51.4, 57.5, 62.7, 68.8, 72.1, 72.4, 75.5, 78.1, 78.5, 101.8, 172.0, 173.8; ν_{max} 3307 (broad), 2919, 2849, 1651, 1552, 1468, 1380, 1082 cm^{-1}; FAB-MS (positive) *m/z* 759 (M^+), 299; Anal. Calcd for $C_{42}H_{82}N_2O_9 \cdot H_2O$: C, 64.91; H, 10.89; N, 3.60. Found: C, 64.83; H, 11.10; N, 3.41.

(4*R*,5*S*,2'*R*)-3-(2'-Acetoxyhexadecanoyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (21a) and (4*R*,5*S*,2'*S*)-3-(2'-Acetoxyhexadecanoyl)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione (21b)

To an ice-cooled solution of 2-acetoxyhexadecanoic acid **19** (944 mg, 3 mmol), (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione **20** (637 mg, 3.3 mmol), and 4-dimethylaminopyridine (25 mg, 0.2 mol) in CH_2Cl_2 (15 ml) was added *N,N'*-dicyclohexylcarbodiimide (650 mg, 3.5 mmol), and the resulting suspension was stirred for 3 h at room temperature. The solvent was removed and AcOEt (10 ml) was added. The insoluble white solid (dicyclohexylurea) was filtered off and washed thoroughly with AcOEt. The filtrate was concentrated *in vacuo* to give a yellowish oil, which was chromatographed on silica gel. Elution with hexane-AcOEt (10:1→ 9:1) afforded the (2'*S*)-isomer **21b** (690 mg, 47%) as a colorless solid: $[\alpha]_D^{24}$ -97.7° (*c* 1.0, $CHCl_3$); R_f 0.33 (hexane-AcOEt, 10:1); δ_H 0.88 (3H, t, *J* = 6.8 Hz, 16'-CH_3), 0.95 (3H, d, *J* = 6.6 Hz, 4-CH_3), 1.26 (24H, s-like, 12 x CH_2), 1.53 (2H, m, 3'-CH_2), 2.15 (3H, s, CH_3CO), 4.98 (1H, quint, *J* = 7.4 Hz, 4-H), 5.80 (1H, d, *J* = 7.3 Hz, 5-H), 6.77 (1H, dd, *J* = 2.6, 9.6 Hz, 2'-H), 7.32-7.44 (5H, m, Ph); δ_C 13.8, 14.1, 20.5, 22.7, 25.5, 29.2, 29.37, 29.40, 29.5, 29.7, 30.8, 31.9, 59.2, 73.1, 83.6, 125.9, 128.8, 129.0, 132.1, 170.8, 171.6, 184.3 (C=S); ν_{max} 2925, 2853, 1737, 1710, 1456, 1373, 1197 cm^{-1}; HRMS Calcd for $C_{28}H_{43}NO_4S$ $(M)^+$: 489.2913. Found: 489.2924.

Further elution with hexane-AcOEt (8:1) afforded the (2'*R*)-isomer **21a** (635 mg, 43%) as a colorless oil: $[\alpha]_D^{24}$ +19.4° (*c* 1.0, $CHCl_3$); R_f 0.23 (hexane-AcOEt, 10:1); δ_H 0.88 (3H, t, *J* = 6.4 Hz, 16'-CH_3), 0.92 (3H, d, *J* = 6.9 Hz, 4-CH_3), 1.26 (24H, s-like, 12 x CH_2), 1.55 (2H, m, 3'-CH_2), 2.15 (3H, s, CH_3CO), 5.03 (1H, quint, *J* = 6.8 Hz, 4-H), 5.88 (1H, d, *J* = 7.3 Hz, 5-H), 6.47 (1H, dd, *J* = 2.6, 9.6 Hz, 2'-H), 7.32-7.44 (5H, m, Ph); δ_C 14.1, 14.2, 20.5, 22.7, 25.3, 29.2, 29.36, 29.39, 29.5, 29.7, 30.6, 31.9, 58.9, 72.8, 83.8, 125.8, 128.8, 129.0, 132.3, 171.1, 171.5, 184.3 (C=S); ν_{max} 2924, 2853, 1745, 1712, 1456, 1374, 1197 cm^{-1}; HRMS Calcd for $C_{28}H_{43}NO_4S$ $(M)^+$: 489.2913. Found: 489.2988.

Methyl (2*R*)-acetoxyhexadecanoate (22a) and the (2*S*)-enantiomer (22b)

To an ice-cooled solution of **21a** (98 mg, 0.20 mmol) in MeOH (1 ml) and THF (1 ml) was added K_2CO_3 (4 mg, 0.03 mmol), and the mixture was stirred for 40 min. The resulting solution was diluted with AcOEt (10 ml) and aq. NH_4Cl (10 ml), and the layers were separated. The organic layer was washed with half-saturated brine, and the combined aqueous layers were extracted with AcOEt (2 x 10 ml). The organic extracts were dried and concentrated. The residue was purified by column chromatography with hexane-AcOEt (10:1) as eluent to give the methyl ester **22a** (60 mg, 91%) as a colorless oil: $[\alpha]_D^{24}$ +14.1° (*c* 1.75, $CHCl_3$) {lit.[28] $[\alpha]_D^{24}$ +14.5° ($CHCl_3$, estimated value)}; R_f 0.33 (hexane-AcOEt, 10:1); δ_H 0.88 (3H, t, J = 6.6 Hz, 16-CH_3), 1.26 (24H, s-like, 12 x CH_2), 1.82 (2H, q, 3-CH_2), 2.14 (3H, s, CH_3CO), 3.74 (3H, s, CH_3O), 4.98 (1H, t, J = 6.4 Hz, 2-H); HRMS Calcd for $C_{19}H_{37}O_4$ $(M + H)^+$: 329.2691. Found: 329.2684.

Similarly, methyl (2*S*)-acetoxyhexadecanoate **22b** {$[\alpha]_D^{24}$ −13.8° (*c* 2.5, $CHCl_3$)} was obtained from the less-polar isomer **21b**.

(2*S*,3*S*,4*R*,2'*R*)-1-*O*-(2"-Acetamido-3",4",6"-tri-*O*-acetyl-2"-deoxy-β-D-glucopyranosyl)-3-*O*-benzoyl-2-(2'-acetoxyhexadecanoyl)aminooctadecane-1,3,4-triol (17b)

Compound **15** (38 mg, 0.051 mmol) was converted to the amino-benzoate **16** in the same manner as described above. To a solution of the crude **16** (40 mg) and (*R*)-acetoxypalmitoyl imide **21a** (50 mg, 0.10 mmol) in *N*,*N*-dimethylformamide (2 ml) was added *N*-ethyldiisopropylamine (13 mg, 0.10 mmol), and the mixture was stirred at 90 °C for 15 h. The reaction mixture was diluted with AcOEt and H_2O (10 ml), and extracted with AcOEt (3 x 10 ml). The organic extracts were dried and concentrated to give a white solid, which was purified by chromatography with hexane-AcOEt (1:2) to give **17b** (33 mg, 61%) as a colorless solid: $[\alpha]_D^{24}$ +12.3° (*c* 0.60, $CHCl_3$); δ_H 0.88 (6H, t, J = 6.6 Hz, 18- and 16'-CH_3), 1.25 (48H, s-like, 24 x CH_2), 1.40-1.60 (2H, m, 5-CH_2), 1.75-1.90 (2H, m, 3'-CH_2), 1.94 (3H, s, CH_3CO), 2.02 (6H, s, CH_3CO), 2.06 (3H, s, CH_3CO), 2.16 (3H, s, CH_3CO), 2.76 (1H, br, OH), 3.76 (2H, m, 2"- and 5"-H), 3.82 (1H, dd, J = 4.6, 11.5 Hz, 1-Ha), 3.94 (1H, m, 4-H), 3.95 (1H, dd, J = 5.6, 10.9 Hz, 1-Hb), 4.08 (1H, dd, J = 2.3, 12.2 Hz, 6"-Ha), 4.22 (1H, dd, J = 4.5, 12.3 Hz, 6"-Hb), 4.67 (1H, m, 2-H) 4.85 (1H, d, J = 8.6 Hz, 1"-H), 5.02 (1H, t, J = 9.6 Hz, 4"-H), 5.02 (1H, m, 2'-H), 5.09 (1H, dd, J = 4.6, 6.9 Hz, 3-H), 5.27 (1H, t, J = 10.0 Hz, 3"-H), 6.10 (1H, d, J = 8.2 Hz, NH), 7.37 (1H, d, J = 7.9 Hz, NH), 7.48 (2H, m, Ph), 7.62 (1H, m, Ph), 8.03 (2H, m, Ph); δ_C 14.2, 20.67, 20.73, 21.0, 22.7, 23.3, 25.0, 25.6, 29.3, 29.4, 29.5, 29.66, 29.71, 29.75, 31.8, 32.0, 33.5, 49.0, 54.9, 61.8, 68.0, 68.4, 70.6, 71.9, 72.4, 73.9, 78.1, 100.6, 128.5 (2C), 129.0, 129.7 (2C), 133.6, 166.8, 169.2, 170.1, 170.3, 170.5, 170.6, 170.7; FAB-MS (positive) *m/z* 1069 $(M + Na)^+$.

(2*S*,3*S*,4*R*,2'*R*)-1-*O*-(2"-Acetamido-2"-deoxy-β-D-glucopyranosyl)-2-(2'-hydroxyhexadecanoyl)amino-octadecane-1,3,4-triol (2b)

To a stirred solution of **17b** (30 mg, 28 μmol) in MeOH (1 ml) and THF (1 ml) was added 1.0 M solution of NaOMe in MeOH (30 μl, 30 μmol), and the mixture was stirred for 30 min at room temperature. Acetic acid (10 mg) was added and the solvent was removed. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2-MeOH (6:1) to afford the cerebroside **2b** (20 mg, 90%) as a colorless solid: m.p. 194-198 °C; $[\alpha]_D^{22}$ −9.0° (*c* 0.30, pyridine); R_f 0.25 (CH_2Cl_2-MeOH, 6:1); δ_H (270 MHz; pyridine-d_5/CD_3OD) 0.84 (6H, t-like, J = 6.6 Hz), 1.23 (46H, s-like), 1.55-1.75 (3H, m), 1.80-2.05 (3H, m), 2.10-2.25 (2H, m), 2.16 (3H, s, CH_3CO), 3.81 (1H, m, 5"-H), 4.14 (1H, t, J = 8.9 Hz, 4"-H), 4.15 (1H, m, 4-H), 4.22 (1H, m, 3"-H), 4.24 (1H, dd, J = 5.6, 6.6 Hz, 3-H), 4.26 (1H, dd, J = 5.4, 12.0 Hz, 6"-Ha), 4.42 (1H, dd, J = 2.1, 12.0 Hz, 6"-Hb), 4.49 (1H, m, 2"-H), 4.54 (2H, m, 1-Ha, 2'-H), 4.60 (1H, dd, J=7.3, 10.6 Hz, 1-Hb), 5.11 (1H, d, J = 8.3 Hz, 1"-H), 5.20 (1H, m, 2-H), 8.51 (1H, d, J = 8.9 Hz, NH), 8.90 (1H, d, J = 7.8 Hz, NH); δ_C (pyridine-d_5) 14.5, 23.1, 23.6, 26.0, 26.6, 29.8, 30.08, 30.14, 30.3, 30.5 (highest), 32.3, 34.4, 35.7, 50.7, 57.8, 62.4, 69.1, 72.3, 72.57, 72.65, 75.9, 77.2, 78.6, 102.0, 172.0, 175.5; ν_{max} 3330 (broad), 2918, 2850, 1658, 1527, 1468, 1312, 1076 cm^{-1}; FAB-MS (positive) m/z 776 $(M + H)^+$, 573, 299; Anal. Calcd for $C_{42}H_{82}N_2O_{10}\cdot 1.5\ H_2O$: C, 62.89; H, 10.68; N, 3.49. Found: C, 62.60; H, 10.90; N, 3.37.

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