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Design and efficient synthesis of novel GM2 analogues with respect to the elucidation of the function of GM2 activator

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Abstract To elucidate the mechanism underlying the hydrolysis of the GalNAcβ1→4Gal linkage in ganglioside GM2 [GalNAcβ1→4(NeuAcα2→3)Galβ1→4Glcβ1→1′Cer] by β-hexosaminidase A (Hex A) with GM2 activator protein, we designed and synthesized two kinds of GM2 linkage analogues—6′-NeuAc-GM2 and α-GalNAc-GM2. In this paper, the efficient and systematic synthesis of these GM2 analogues was described. The highlight of our synthesis process is that the key intermediates, newly developed sialyllactose derivatives, were efficiently prepared in sufficient quantities; these derivatives directly served as highly reactive glycosyl acceptors and coupled with GalNTroc donors to furnish the assembly of GM2 tetrasaccharides in large quantities.

Keywords GM2 analogue · GM2 gangliosidosis · Tay-Sachs disease · β-hexosaminidase A · GM2 activator

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Introduction

The field of glycobiology has witnessed extensive advancement during the last two decades, and glycosphingolipids (GSLs) have received particular attention. GSLs are characteristic membrane components of eukaryotic cells and are found in the glycocalyx of the cell. They provide binding sites for toxins, viruses, and bacteria as well as mediate cell adhesion processes and other intercellular communication events. Among the different classes of GSLs, gangliosides, in particular, have been increasingly noticed for their biological roles as molecules responsible for cell–cell and cell–ligand interactions in the immune system, nervous system, etc. [1–3]. Gangliosides are characterized by the content of sialic acid, mainly *N*-acetyl neuraminic acid (NeuAc) and *N*-glycolyl-neuraminic acid (NeuGc), in their oligosaccharide moiety.

Depending on the accumulation of GSLs in the metabolic pathway, paticular GSL storage diseases such as GM1, GM2, and GM3 gangliosidosis have been reported. With the exception of GM3 gangliosidosis that occurs due to the deficiency of GM2 synthetase, most of these diseases are caused due to the lack of glycosidase [4, 5].

GM2 gangliosidosis is a congenital glycosphingolipid storage disease [4, 6]. It has been shown that in the absence of the GM2 activator protein, the terminal GalNAc and NeuAc residues in GM2 [GalNAcβ1→4(NeuAcα2→3)Galβ1→4Glcβ1→1′Cer] are resistant to β-hexosaminidase

A (Hex A) and sialidase, respectively. The GM2 activator is a protein cofactor that assists Hex A and sialidase in hydrolyzing the β-linked *N*-acetylgalactosamine (GalNAc) and α-linked NeuAc, respectively [7, 8]. Recently, Li *et al.* reported that the GM2 activator renders GalNAc and NeuAc accessible to Hex A and sialidase, respectively, by loosening the firm GM2 epitope from the enzymatic degradation of 6′-GalNAc-GM2 [9, 10] (Fig. 1). To verify this hypothesis, we designed and synthesized two kinds of GM2 linkage analogues—6′-NeuAc-GM2 [GalNAcβ1→4(NeuAcα2→6)Galβ1→4Glcβ1→1′Cer] **1** and α-GalNAc-GM2 [GalNAcα1→4(NeuAcα2→3)Galβ1→4Glcβ1→1′Cer] **2** (Fig. 2).

Results and discussion

The strategy applied for the synthesis of target compounds **1** and **2** is illustrated in Scheme 1. We initially used the suitably protected lactose acceptor **3** [11, 12] to accomplish an efficient construction of the oligosaccharide moieties of the GM2 analogues. The glycosylation of **3**, which is protected by the 2-(trimethylsilyl)ethyl (SE) group in the anomeric center, with phenyl 2-thioglycoside of the Neu5Troc donor **5** [13, 14] in $EtCN/CH_2Cl_2$ (10/1) at −60°C to −50°C in the presence of *N*-iodosuccinimide (NIS)-trifluoromethanesulfonic acid (TfOH) [15] afforded the desired Neu5Troc2→6LacSE **6** in 55% yield; its anomer ratio (α/β) was 10/1. Similarly, the glycosylation of **4** [12] with **5** produced Neu5Troc2→3LacSE **7** in 83% yield; its anomer ratio (α/β) was 5/1 (Scheme 2).

As shown in Scheme 3, the GalNTroc donors **8** and **10** were efficiently prepared. The treatment of phenyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbamoyl)-β-D-galactopyranoside (**8**) [16] with NaOMe in MeOH afforded a completely deacetylated crystalline compound **9** in 92% yield. Compound **9** when treated with di-*tert*-butylsilyl bis(trifluoromethanesulfonate) [DTBS $(TfO)_2$] in pyridine formed 4,6-*O*-di-*tert*-butylsilylene (DTBS) derivative; the subsequent addition of Ac_2O afforded the desired GalNTroc donor **10** in 88% yield.

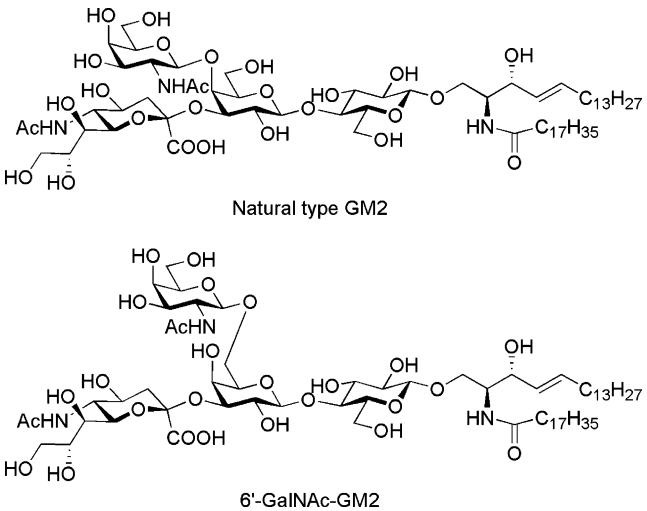


Fig. 1 Structure of GM2 and 6′-GalNAc-GM2

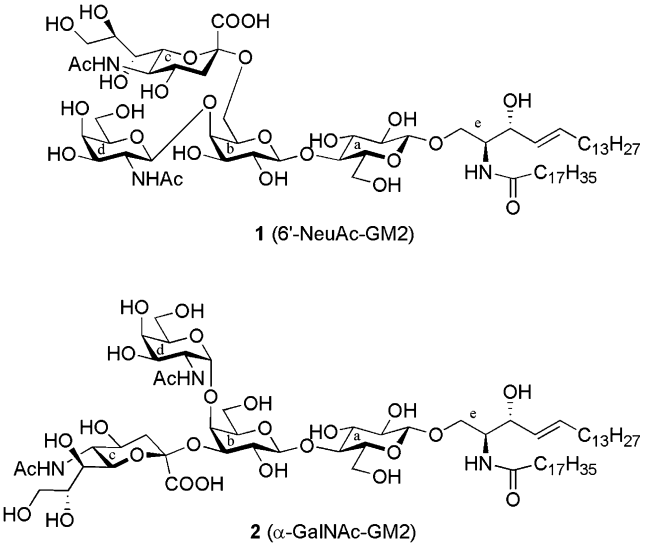
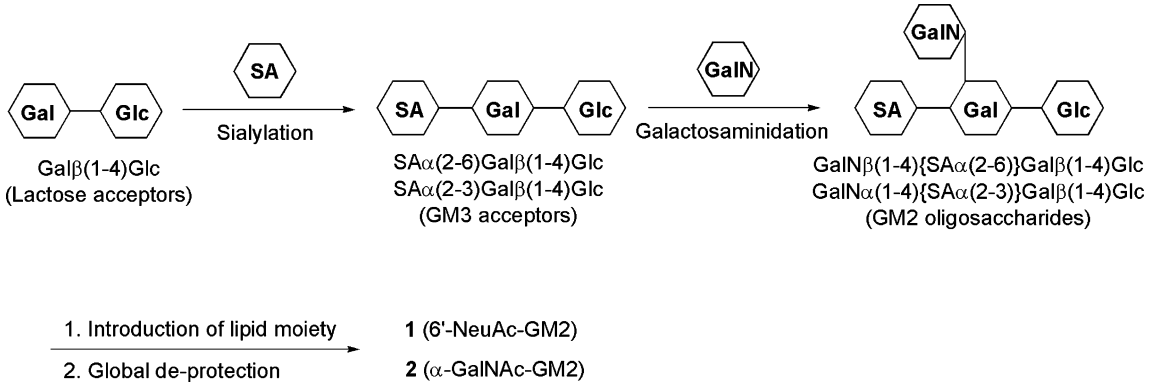


Fig. 2 Structure of synthetic GM2 analogues (6′-NeuAc- and α-GalNAc-GM2)

NIS-TfOH mediated the glycosylation of **6** with **8** in CH_2Cl_2 at 0°C and resulted in the formation of the desired tetrasaccharide [GalNTrocβ1→4(Neu5Trocα2→6)LacSE] **11** in 91% yield (Scheme 4). Efficient construction of α-galactosaminide is an important issue in the synthesis of analogue **2**. Hence, we applied a highly α-selective glycosylation with DTBS-protected galactosamine donor for the synthesis of analogue **2**, which was carried out in our laboratory [17–19]. It is noteworthy that the glycosylation of **7** with **10** provided the desired α-galactosaminide [GalNTrocα1→4(Neu5Trocα2→3)LacSE] **12** in 88% yield; the β isomer was absolutely non-isolated in spite of the neighboring effect by *N*-Troc group at the C-2 position of donor. The removal of the DTBS group from **12** with TBAHF [20] and subsequent acetylation of the resultant 4,6-diol produced compound **13** in 79% yield (Scheme 4).

The preparation of trichloroacetimidate donors **17** and **21** was easily accomplished by the application of simple protecting group chemistry. The conversion of Troc carbamates in **11** and **13** into acetamido groups was carried out by using the Zn–Cu couple [21] (and the Zn–Cu was prepared according to [22]) in AcOH/1,2-dichloroethane (2/1) at 40°C; subsequent acetylation by using conventional methods afforded **14** and **18** along with inseparable by-products, respectively. The hydrogenolytic removal of the benzyl groups in **14** and **18** by using 20% $Pd(OH)_2$ on carbon in a solvent mixture of EtOH/THF, followed by

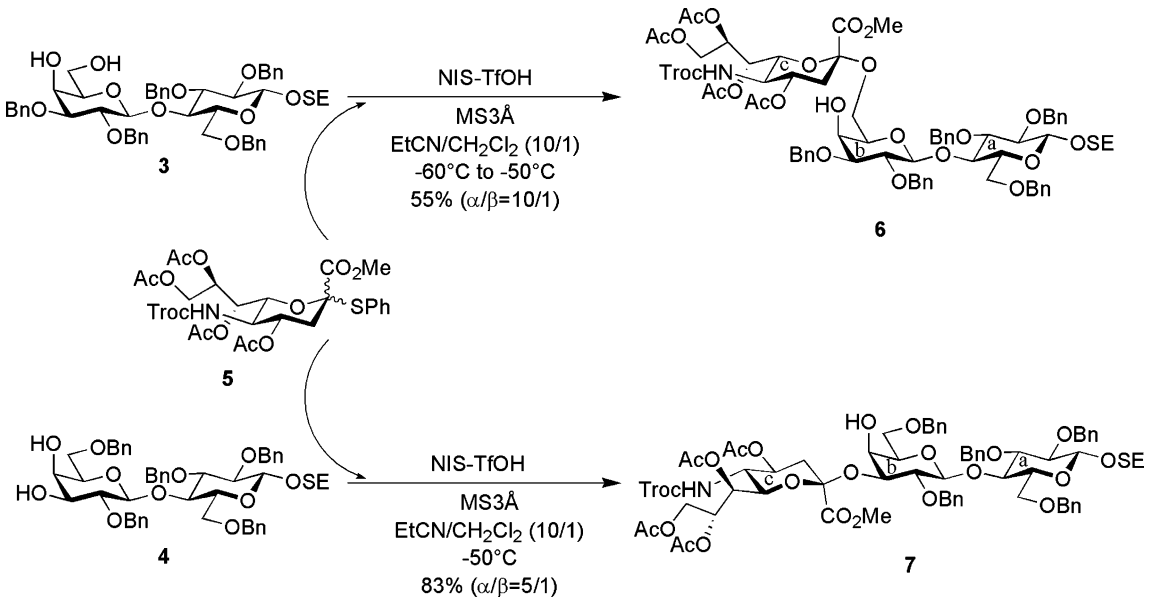


Scheme 1 Systematic strategy for the synthesis of target GM2 analogues

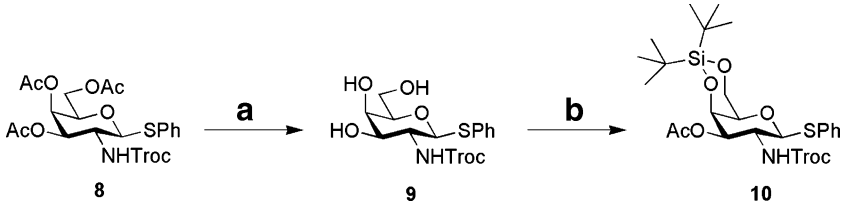
treatment with Ac_2O and DMAP in pyridine afforded the completely acetylated GM2 tetrasaccharides **15** and **19** (four steps), with an overall 74% and 55% yield, respectively. The 2-(trimethylsilyl)ethyl group in **15** and **19** was selectively cleaved by treatment with TFA/CH_2Cl_2 (1/3) [23] to afford the 1-hydroxy derivatives **16** and **20**; these compounds were further treated with trichloroacetonitrile and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 [24] to afford the trichloroacetimidate donors **17** and **21** in 90% and 88% yield (two steps), respectively (Scheme 5).

With regard to synthesizing the ganglio-series gangliosides, it is well known that glycosidation of oligosaccharide donor with a ceramide acceptor results in a low yield due to the low reactivity of its acceptor. Consequently, we adopted the azido-sphingosine acceptor as the ceramide precursor because it provides a better yield on coupling than when a ceramide acceptor is used, although the resulting azido-sphingosine requires further transformation to ceramide. In our laboratory, 3-*O*-Bz-protected [25] or 3-*O*-TBDPS-protected [26] azido-sphingosine acceptor has been frequently used for gangliosides syntheses; however, we adopted the 3-*O*-PMB-protected azido-sphingosine acceptor **22** [27]; this acceptor is prepared from the unprotected azido-sphingosine [28, 29] in three steps and is more reactive due to the nucleophilicity of the acceptor alcohol, which is enhanced by the electron-donating PMB group. The use of this acceptor led to the formation of β-glycosyl lipid. Glycosidation of **17** and **21** with **22** in the presence of TMSOTf in CH_2Cl_2 at 0°C produced the desired β-glycosyl azido-sphingosines **23** and **24** in 20% and 23% yield, respectively (Scheme 6).

The remaining steps involved the generation of an amino group from azide, amido formation with stearic acid, and global deprotection (Scheme 7). The azide function in the protected glycolipids **23** and **24** was reduced to that of an amine by triphenylphosphine dissolved in a small amount of water, in benzene at 50°C [30]; subsequent condensation with stearic acid by EDC and DMAP in 1,2-



Scheme 2 Preparation of sialyllactose acceptors



8 9 10

Scheme 3 Preparation of DTBS-protected GalNTroc donor. Reagents and conditions: **a** NaOMe, MeOH, r. t., 92% (as crystalline); **b** DTBS $(OTf)_2$, pyridine., then Ac_2O, 88%

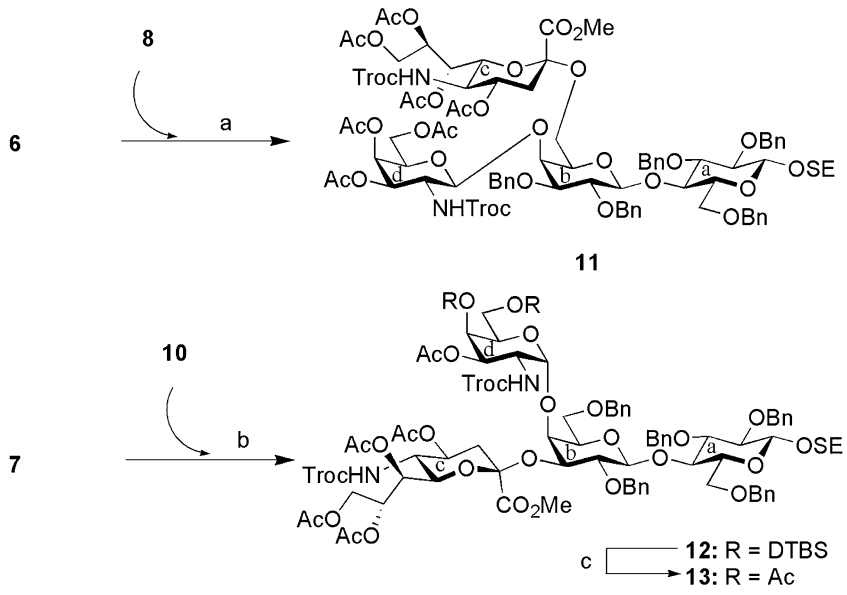
dichloroethane at 40°C afforded the protected GM2 analogues **26** and **29** in 88% and 79% yield (two steps), respectively. The cleavage of the PMB group proceeded smoothly due to the use of TFA in CH_2Cl_2. Finally, the removal of all the acetyl-protecting groups under Zemplén's condition and saponification of methyl ester provided the desired GM2 analogues **1** and **2**, in 66% and 79% yield (two steps), respectively.

In summary, we successfully constructed tetrasaccharide backbone of target GM2 analogues by using the newly developed sialyllactose acceptors (Neu5Trocα2→6LacSE and Neu5Trocα2→3LacSE), which were further glycosylated with GalNTroc donors. The introduced azido-sphingosine moiety, azido reduction, amidation, and deprotection afforded two kinds of target GM2 analogues. Moreover, the new synthetic unit (Neu5Trocα2→3LacSE; **7**) was applicable for the efficient synthesis of a-series gangliosides, modified GM3 analogues, and *N*-glycolyl-GM2, which is expected to be a type of cancer-associated antigen; the syntheses of these compounds are currently in progress in our laboratory. The relationship between enzymatic degradation fashion of these GM2 analogues and conformation, which means whether hydrolyzed by Hex A and sialidase in the absence of GM2 activator protein or not, will be reported in due course.

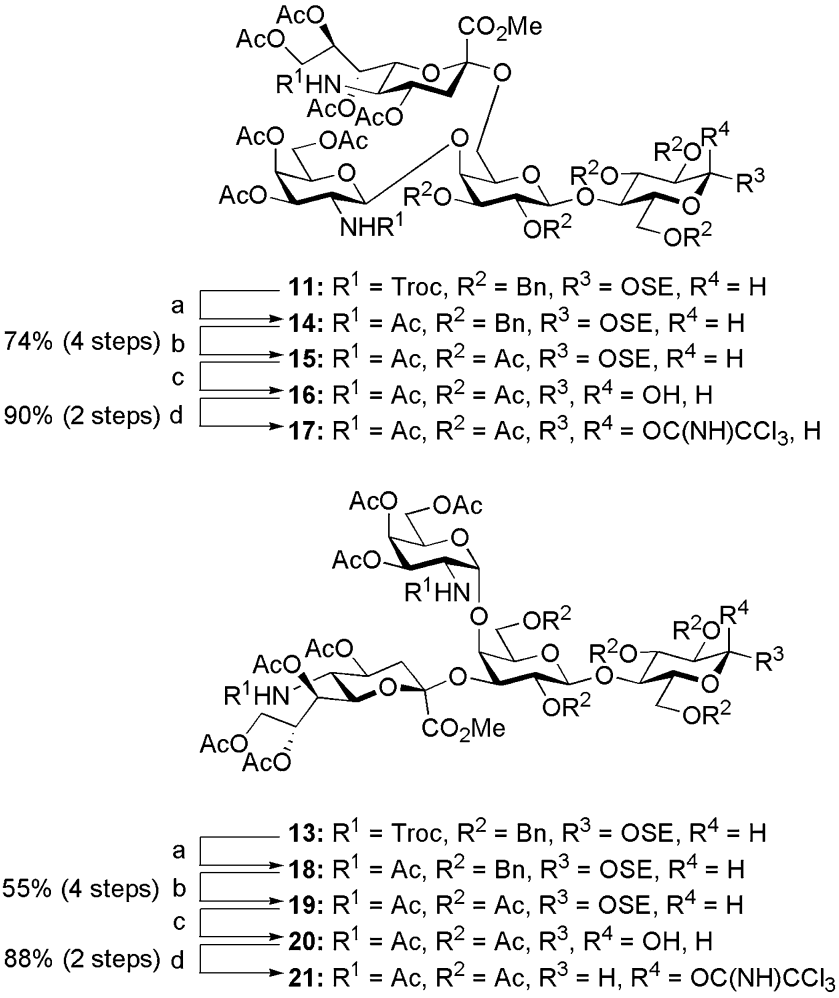
Experimental section

General procedures

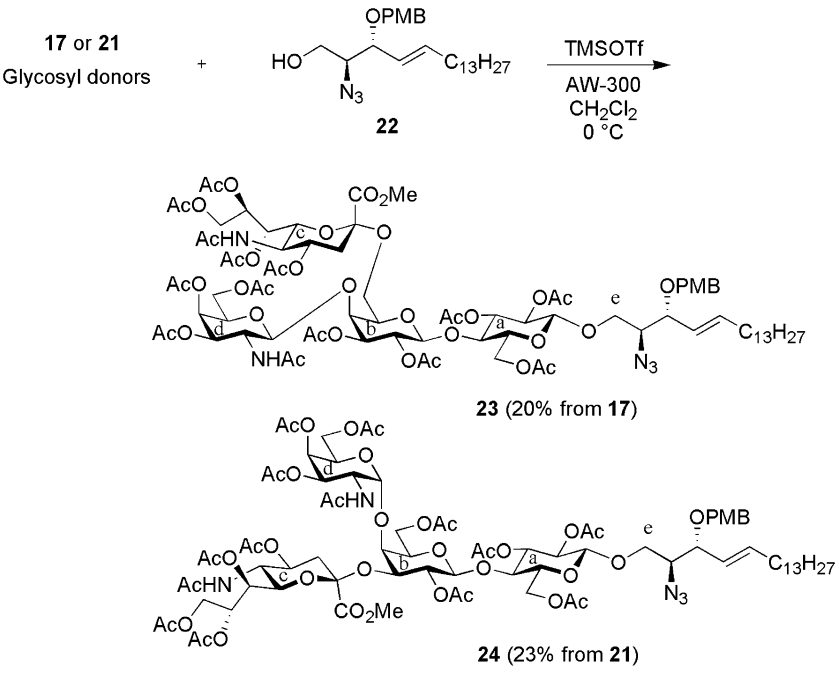
All reactions were carried out under a positive pressure of argon, unless otherwise noted. All chemicals were purchased from commercial suppliers and used without further purification, unless otherwise noted. Molecular sieves were purchased from Wako Chemicals Inc. and dried at 300°C for 2 h in muffle furnace prior to use. ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 300 K with a Varian Unity Inova 400/500 spectrometer and a JEOL ECA 400/500/600 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Data are presented as follow: (s=singlet, d=doublet, t=triplet, q=qultet, dd=double of doublet, dt=double of triplet, m=multiplet and/or multiple resonances), integration, coupling constant in Hertz (Hz). MALDI-TOF MS spectra were recorded in positive or negative ion mode on a Bruker



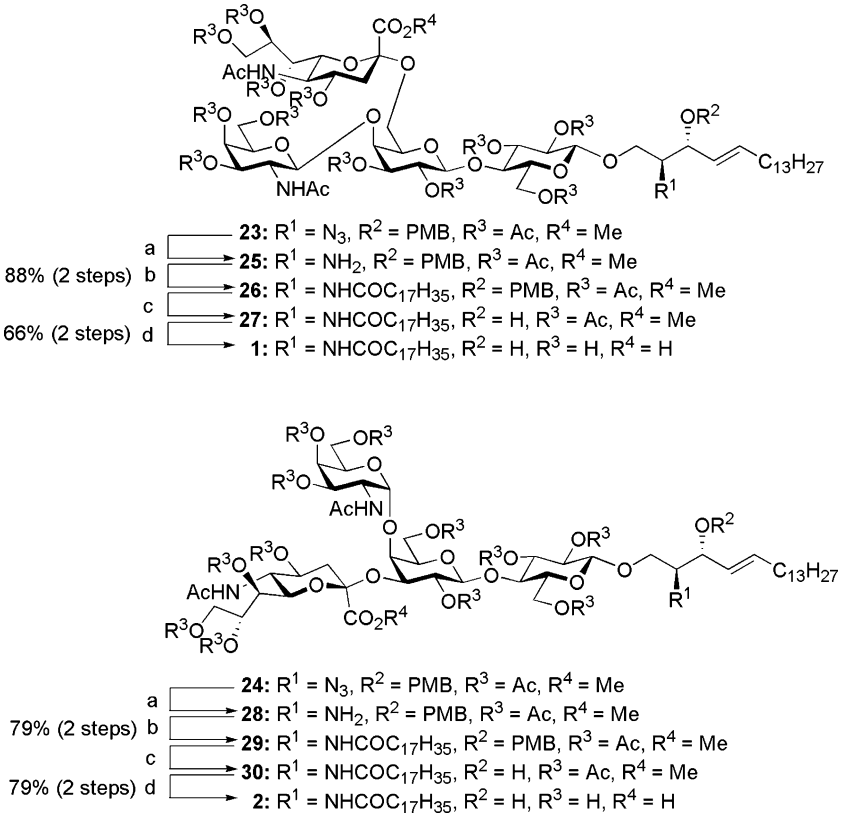
Scheme 4 Assembly of tetrasaccharide moieties of GM2 analogues. Reagents and conditions: **a** NIS-TfOH, MS4Å, CH_2Cl_2, 0°C, 91%; **b** NIS-TfOH, MS4Å, CH_2Cl_2, −20°C, 88%; **c** (1) TBAHF, r. t.; (2) Ac_2O, DMAP, pyridine., r. t., 79% (two steps)



Scheme 5 Conversion of tetrasaccharide into the corresponding glycosyl trichloroacetimidates. Reagents and conditions: **a** (1) Zn-Cu, AcOH/1,2-dichloroethane (2/1), 40°C; (2) Ac_2O, DMAP, pyridine., r.t.; **b** 1) 20% Pd $(OH)_2/C$, H_2 gas, THF/EtOH, 40°C; (2) Ac_2O, DMAP, pyridine., r. t.; **c** TFA/CH_2Cl_2 (1/3), r. t.; **d** CCl_3CN, DBU, CH_2Cl_2, 0°C to r.t



Scheme 6 Glycosidation of tetrasaccharide donors with the azido-sphingosine acceptor



Scheme 7 Conversion into ceramide and global de-protection. Reagents and conditions: **a** PPh_3, H_2O, benzene, 50°C; **b** stearic acid, EDC, DMAP, 1,2-dichloroethane, 40°C; **c** TFA, CH_2Cl_2, r. t.; **d** NaOMe, MeOH, then H_2O, 60°C

Autoflex with the use of α-cyano-4-hydroxy-cinnamic acid (CHCA) as a matrix. Specific rotations were determined with a Horiba SEPA-300 high-sensitive polarimeter. Silica gel (80 mesh and 300 mesh) manufactured by Fuji Silysia Co. was used for flash column chromatography. The quantity of silica gel was usually estimated as 300–400-fold weight of sample to be charged. TLC analysis was conducted on Merck TLC (Silica Gel $60F_{254}$ on glass plate). Compounds were visualized either by exposure to UV light or spraying with a solution of 10% H_2SO_4 in EtOH. Organic solutions were concentrated by rotary evaporation below 40°C under reduced pressure. Solvent systems in chromatography are specified in *v/v*.

2-(Trimethylsilyl)ethyl [methyl 4,7,8,9-tetra-O-acetyl-3,5-dideoxy-5-(2,2,2-trichloroethoxycarbamoyl)-D-glycero-α-D-galacto-2-nonulopyranosylonate]-(2→6)-2,3-di-O-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**6**) A suspension of compound **5** (161 mg, 224 μmol), compound **3** (100 mg, 112 μmol), and molecular sieves 3 Å (260 mg) in dry EtCN/CH_2Cl_2 (10/1, 2.0 ml) was stirred at room temperature for 1.5 h. To the mixture was added NIS (100 mg, 448 μmol). After cooled to −60°C, TfOH (4.0 μl, 44.8 μmol) was added through syringe. The reaction mixture was stirred at −60°C for 2.5 h and for another 1 h at −50°C, with monitoring of the reaction by TLC (EtOAc/$PhCH_3$=1:3). Triethylamine was added to quench the reaction. The mixture was filtered through Celite bed, the combined filtrate and washings was evaporated, and diluted with $CHCl_3$. The organic layer was washed with satd. aq. Na_2CO_3, satd. aq. $Na_2S_2O_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/$PhCH_3$=1:8) to give **6α** (83 mg, 50%), and the corresponding β-isomer **6β** (9 mg, 5%); **6α**: $[\alpha]_D$=+4.2 (*c* 0.52, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.40–7.15 (m, 25 H, 5 Ph), 5.37 (dd, 1 H, $J_{6,7}$=1.5 Hz, H-7c), 5.36–5.33 (m, 1 H, H-8c), 4.99–4.94 (m, 1 H, H-4c), 4.95 (d, 1 H, J_{gem}=11.0 Hz, OCH_2), 4.90–4.87 (m, 3 H, NH-c, 2 OCH_2), 4.77–4.70 (m, 3 H, 3 OCH_2), 4.75 and 4.62 (2 d, 2 H, J_{gem}=12.0 Hz, OCH_2), 4.69 (d, 1 H, J_{gem}=11.0 Hz, OCH_2), 4.49 and 4.39 (2 d, 2 H, J_{gem}=11.5 Hz, OCH_2), 4.47 (d, 1 H, OCH_2), 4.45 (d, 1 H, $J_{1,2}$=8.0 Hz, H-1b), 4.36 (d, 1H, $J_{1,2}$=8.5 Hz, H-1a), 4.30 (dd, 1 H, J_{gem}=12.5 Hz, $J_{8,9}$=2.5 Hz, H-9c), 4.13 (dd, 1 H, $J_{5,6}$=10.5 Hz, $J_{6,7}$= 1.5 Hz, H-6c), 4.08 (dd, 1 H, J_{gem}=12.5 Hz, $J_{8,9'}$ = 4.5 Hz, H-9′c), 4.01 (br s, 1 H, H-4b), 3.98 (m, 1 H, CH_2CH$_2$SiMe$_3$), 3.88 (t, 1 H, H-3a), 3.75 (s, 3 H, COOMe), 3.75–3.54 (m, 7 H, H-4a, 6a, 6′a, 2b, 6b, 6′b, CH_2CH$_2$SiMe$_3$), 3.63 (q, 1 H, $J_{5,6}$=10.5 Hz, H-5c), 3.40–3.35 (m, 3 H, H-2a, 5a, 3b), 3.25 (q, 1 H, H-5b), 2.58 (br s, 1 H, OH-4b), 2.50 (dd, 1 H, J_{gem}=12.6 Hz, $J_{3eq,4}$=4.6 Hz,

H-3eq-c), 2.09, 2.07, 2.00, 1.94, (4 s, 12 H, 4 Ac), 1.81 (t, 1 H, J_{gem}=12.6 Hz, H-3ax-c), 1.00 (m, 2 H, $CH_2CH_2SiMe_3$), 0.00 (s, 9 H, $CH_2CH_2Si\mathit{Me}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.7, 170.3, 170.0, 169.8, 167.7, 154.0, 139.2, 138.7, 138.6, 138.4, 138.1, 128.3, 128.2, 128.0, 128.0, 127.9, 127.8, 127.6, 127.4, 127.4, 127.3, 127.2, 103.0, 102.5, 98.7, 95.3, 82.7, 81.9, 81.1, 79.3, 76.8, 75.2, 75.0, 74.9, 74.7, 74.4, 73.0, 72.1, 72.0, 71.6, 68.6, 68.5, 67.5, 67.3, 64.9, 62.1, 61.9, 52.9, 51.5, 36.5, 29.6, 21.0, 20.8, 20.6, 18.4, −1.4; MALDI-TOF MS: *m/z*: calcd for $C_{73}H_{90}Cl_3NO_{24}SiNa$: 1520.45; found: 1520.44 $[M+Na]^+$.

2-(Trimethylsilyl)ethyl [methyl 4,7,8,9-tetra-O-acetyl-3,5-dideoxy-5-(2,2,2-trichloroethoxycarbamoyl)-D-glycero-α-D-galacto-2-nonulopyranosylonate]-(2→3)-2,6-di-O-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**7**) A suspension of compound **5** (200 mg, 280 μmol), compound **4** (100 mg, 112 μmol), and molecular sieves 3 Å (300 mg) in dry $EtCN/CH_2Cl_2$ (10/1, 2.5 ml) was stirred at room temperature for 1 h. To the mixture was added NIS (126 mg, 560 μmol). After cooled to −50°C, TfOH (5.0 μl, 56.0 μmol) was added through syringe. The reaction mixture was stirred at −50°C for 2 h, with monitoring of the reaction by TLC ($EtOAc/PhCH_3$= 1:2). Triethylamine was added to quench the reaction. The mixture was filtered through Celite bed, the combined filtrate and washings was evaporated, and diluted with $CHCl_3$. The organic layer was washed with satd. aq. $NaHCO_3$, satd. aq. $Na_2S_2O_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($EtOAc/PhCH_3$=1:7) to give **7α** (115 mg, 69%), and the corresponding β-isomer **7β** (23 mg, 14%); **7α**: $[\alpha]_D$=+7.6° (*c* 0.70, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.38–7.11 (m, 25 H, 5 Ph), 5.39 (m, 1 H, H-8c), 5.33 (dd, 1 H, $J_{6,7}$=1.3 Hz, $J_{7,8}$=8.2 Hz, H-7c), 4.95 and 4.73 (2 d, 2 H, J_{gem}=10.9 Hz, OCH_2), 4.93 (dt, 1 H, $J_{3eq,4}$=4.8 Hz, H-4c), 4.88 and 4.69 (2 d, 2 H, J_{gem}= 11.7 Hz, OCH_2), 4.85 (d, 1 H, NH-c), 4.85 and 4.46 (2 d, 2 H, J_{gem}=12.3 Hz, OCH_2), 4.75 and 4.66 (2 d, 2 H, J_{gem}= 11.7 Hz, OCH_2), 4.56 (d, 1 H, $J_{1,2}$=8.2 Hz, H-1b), 4.49 and 4.45 (2 d, 2 H, J_{gem}=11.7 Hz, OCH_2), 4.40 and 4.31 (2 d, 2 H, J_{gem}=12.3 Hz, OCH_2), 4.34 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1a), 4.25 (dd, 1 H, J_{gem}=12.4 Hz, H-9c), 4.06 (near d, 1 H, H-6c), 4.01 (dd, 1 H, H-3b), 3.98–3.94 (m, 2 H, H-9′c, $CH_2CH_2SiMe_3$), 3.93 (t, 1 H, H-3a), 3.81 (br s, 1 H, H-4b), 3.76–3.74 (m, 4 H, H-5b, COOMe), 3.70–3.63 (m, 2 H, H-6b, 5c), 3.59–3.50 (m, 4 H, H-4a, 6a, 2b, $CH_2CH_2SiMe_3$), 3.45–3.43 (m, 2 H, H-5a, 6′b), 3.38–3.35 (m, 2 H, H-2a, 6′ a), 2.67 (br s, 1 H, OH-4b), 2.54 (dd, 1 H, $J_{3eq,4}$=4.8 Hz, H-3eq-c), 2.06, 1.96, 1.84, (3 s, 12 H, 4 Ac), 1.96 (t, 1 H, H-3ax-c), 1.00 (m, 2 H, $CH_2CH_2SiMe_3$), 0.00 (s, 9 H, $CH_2CH_2Si\mathit{Me}_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 170.1, 169.8, 168.1, 154.1, 139.1, 138.8, 138.7, 138.5, 138.2, 128.9, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.9, 127.4, 127.3, 127.2, 127.1, 125.2, 103.0, 102.3, 98.1, 95.2, 82.9, 81.9, 78.3, 77.2, 76.5, 76.3, 75.2, 75.0, 74.8, 74.4, 73.2, 72.9, 72.3, 72.2, 68.5, 68.4, 68.3, 67.8, 67.2, 62.0, 53.0, 51.4, 36.4, 29.6, 21.3, 21.0, 20.7, 20.6, 20.4, 18.4, −1.4; MALDI-TOF MS: *m/z*: calcd for $C_{73}H_{90}Cl_3NO_{24}SiNa$: 1520.45; found: 1520.57 $[M+Na]^+$.

Phenyl 2-deoxy-1-thio-2-(2,2,2,-trichloroethoxycarbamoyl)-β-D-galactopyranoside (**9**) To a solution of compound **8** (19.1 g, 33.4 mmol) in dry MeOH (334 ml) was added a catalytic amount of NaOMe, and the mixture was stirred at room temperature for 5 h, with the monitoring of the reaction by TLC ($CHCl_3$/MeOH=5:1). The mixture was neutralized with IR-120 (H^+), filtered through cotton, and the combined filtrate and washings was concentrated. The residue was recrystallized from hot EtOH to give **9** (13.7 g, 92%); mp: 197 to 199°C; $[\alpha]_D$=+33.3° (*c* 1.0, MeOH); ^{1}H-NMR (500 MHz, CD_3OD): δ 7.54–7.24 (m, 5 H, Ph), 4.91 and 4.76 (2 d, 2 H, J_{gem}=12.1 Hz, OCH_2), 4.81 (d, 1 H, $J_{1,2}$=10.5 Hz, H-1), 3.94 (d, 1 H, $J_{3,4}$=3.2 Hz, H-4), 3.84 (t, 1 H, $J_{1,2}$=10.5 Hz, $J_{2,3}$=10.0 Hz, H-2), 3.82 (dd, 1 H, J_{gem}=11.7 Hz, $J_{5,6'}$ = 6.8 Hz, H-6′), 3.76 (dd, 1 H, J_{gem}= 11.7 Hz, $J_{5,6}$=5.2 Hz, H-6), 3.67 (dd, 1 H, $J_{2,3}$=10.0 Hz, $J_{3,4}$=3.2 Hz, H-3), 3.59 (dt, $J_{5,6}$=5.2 Hz, $J_{5,6'}$ = 6.8 Hz, H-5); ^{13}C-NMR (100 MHz, CD_3OD): δ 156.9, 136.2, 132.0, 129.8, 128.0, 97.1, 89.2, 80.6, 75.5, 73.8, 69.7, 62.5, 54.7; MALDI-TOF MS: *m/z*: calcd for $C_{15}H_{18}Cl_3NO_6SNa$: 467.98; found: 468.01 $[M+Na]^+$.

Phenyl 3-O-acetyl-4,6-O-di-tert-butylsilylene-1,2-dideoxy-1-thio-2-(2,2,2-trichloroethoxycarbamoyl)-β-D-galactopyranoside (**10**) To a solution of compound **9** (7.0 g, 15.7 mmol) in pyridine (160 ml) was added di-*tert*-butylsilyl bis(trifluoromethanesulfonate) (4.5 ml, 12.5 mmol) at 0°C, and the mixture was stirred at room temperature for 1 h. Then to the mixture, $DTBS(OTf)_2$ (1.1 ml, 3.14 mmol) was added, and the resulting mixture was stirred for another 1.5 h. After the complete consumption of the starting material was confirmed on TLC analysis ($CHCl_3$/MeOH=10:1), Ac_2O (2.9 ml, 31.4 mmol) was added and stirred for 2 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=30:1). Then MeOH was added at 0°C, reaction mixture was co-evaporated with toluene, and diluted with $CHCl_3$. The organic layer was washed with 2 M HCl, H_2O, satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane=1:6) to give **10** (8.68 g, 88%); $[\alpha]_D$=+38.5° (*c* 1.0, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.49–7.24 (m, 5 H, Ph), 5.21 (d, 1 , $J_{2,NH}$=9.6 Hz, NH), 4.97 (br d, 1 H, H-3), 4.90 (d, 1 H, $J_{1,2}$= 10.9 Hz, H-1), 4.75 (2 d, 2 H, OCH_2), 4.62 (d, 1 , $J_{3,4}$= 2.7 Hz, H-4), 4.22 (s, 2 H, H-6, 6′), 4.14 (q, 1 H, $J_{1,2}$=

10.9 Hz, $J_{2,NH}$=9.6 Hz, H-2), 3.47 (s, 1 H, H-5), 2.09 (s, 3 H, Ac), 1.11 and 1.01 (2 s, 18 H, 2 ^{t}Bu); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 170.9, 154.0, 133.8, 132.2, 128.9, 127.7, 95.5, 87.8, 74.7, 74.4, 73.5, 69.8, 67.1, 50.9, 27.5, 27.4, 23.2, 20.8, 20.6; MALDI-TOF MS: *m/z*: calcd for $C_{25}H_{36}Cl_3NO_7SSiNa$: 650.09; found: 650.18 $[M+Na]^+$.

2-(Trimethylsilyl)ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2,-trichloroethoxycarbamoyl)-β-D-galactopyranosyl-(1→4)-{methyl 4,7,8,9-tetra-O-acetyl-3,5-dideoxy-5-(2,2,2-trichloroethoxycarbamoyl)-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→6)}-2,3-di-O-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**11**) A suspension of compound **8** (699 mg, 1.22 mmol), compound **6** (610 mg, 407 μmol), and molecular sieves 4 Å (1.3 g) in dry CH_2Cl_2 (16 ml) was stirred at room temperature for 1 h. To the mixture was added NIS (549 mg, 2.44 mmol). After cooled to 0°C, TfOH (21.5 μl, 244 μmol) was added through syringe. The reaction mixture was stirred at 0°C for 1 h, with monitoring of the reaction by TLC (EtOAc/$PhCH_3$=1:1). The mixture was filtered through Celite bed. The combined filtrate and washings was extracted with $CHCl_3$, and the organic layer was washed with satd. aq. $NaHCO_3$, satd. aq. $Na_2S_2O_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:$PhCH_3$=1:4) to give **11** (727 mg, 91%); $[\alpha]_D$= −13.2° (*c* 0.67, $CHCl_3$); ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.55 (d, 2 H, NH-c, NH-d), 7.42–7.20 (m, 25 H, 5 Ph), 5.25 (d, 1 H, $J_{3,4}$=3.0 Hz, H-4d), 5.20 (m, 1 H, H-8c), 5.15 (dd, 1 H, H-7c), 5.12 (dd, 1 H, $J_{3,4}$=3.0 Hz, H-3d), 4.91 (d, 1 H, $J_{1,2}$=8.1 Hz, H-1d), 4.90 and 4.55 (2 d, 2 H, J_{gem}=10.0 Hz, OCH_2), 4.83–4.75 (m, 5 H, H-4c, 4 OCH_2), 4.67–4.59 (m, 5 H, 5 OCH_2), 4.45 (d, 1 H, $J_{1,2}$= 8.5 , H-1b), 4.44 (d, 1 H, $J_{1,2}$=9.5 , H-1a), 4.41 (d, 1 H, OCH_2), 4.32 (d, 2 H, 2 OCH_2), 4.20 (dd, 1 H, $J_{8,9}$=2.5 Hz, J_{gem}=12.0 Hz, H-9c), 4.15 (br s, 1 H, H-4b), 4.13 (t, 1 H, H-4a), 4.05 (dd, 1 H, H-6a), 4.00 (dd, 1 H, $J_{8,9'}$ = 6.0 Hz, J_{gem}=12.0 Hz, H-9′c), 3.95–3.93 (m, 2 H, H-3a, 6c), 3.86 (m, 1 H, CH_2CH$_2$SiMe$_3$), 3.71 (s, 3 H, COOMe), 3.71–3.50 (m, 11 H, H-2a, 5a, 3b, 6b, 6′b, 5c, 2d, 5d, 6d, 6′d, CH_2CH$_2$SiMe$_3$), 3.41 (t, 1 H, H-5b), 3.35–3.29 (m, 1 H, H-6′a), 3.16 (t, 1 H, $J_{1,2}$=8.5 Hz,H-2b), 2.51 (dd, 1 H, J_{gem}= 12.4 Hz, H-3eq-c), 2.07, 2.00, 1.99, 1.96, 1.90, 1.87, 1.83, (7 s, 21 H, 7 Ac), 1.59 (t, 1 H, J_{gem}=12.4 Hz, H-3ax-c), 0.91 (m, 2 H, CH$_2$CH_2SiMe$_3$), 0.01 (s, 9 H, CH$_2$CH$_2$Si*Me$_3$*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.5, 170.3, 170.2, 170.0, 169.9, 169.6, 167.6, 154.0, 138.9, 138.5, 137.3, 129.0, 128.6, 128.3, 128.2, 128.2, 128.0, 127.9, 127.8, 127.6, 127.4, 127.3, 127.1, 103.1, 102.0 101.6, 99.2, 95.3, 82.3, 81.9, 80.5, 75.5, 75.2, 74.7, 74.4, 74.2, 73.1, 72.1, 71.9, 70.6, 68.8, 68.5, 68.3, 67.5, 67.3, 66.4, 63.1, 62.1, 60.7, 52.8, 52.7, 51.6, 37.6, 29.6, 20.9, 20.8, 20.6, 20.6, 20.5, 18.4, −1.4; MALDI-TOF MS: *m/z*: calcd for $C_{88}H_{108}Cl_6N_2O_{33}SiNa$: 1981.46; found: 1981.63 $[M+Na]^+$.

2-(Trimethylsilyl)ethyl 3-O-acetyl-2-deoxy-4,6-O-di-tert-butylsilylene-2-(2,2,2,-trichloroethoxycarbamoyl)-α-D-galactopyranosyl-(1→4)-{methyl 4,7,8,9-tetra-O-acetyl-3,5-dideoxy-5-(2,2,2-trichloroethoxycarbamoyl)-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→3)}-2,6-di-O-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**12**) A suspension of compound **10** (116 mg, 185 μmol), compound **7** (92 mg, 61 μmol), and molecular sieves 4 Å (220 mg) in dry CH_2Cl_2 (2.5 ml) was stirred at room temperature for 2 h. To the mixture was added NIS (85 mg, 369 μmol). After cooled to −20°C, TfOH (3.3 μl, 37 μmol) was added through syringe. The reaction mixture was stirred at −20°C for 1.5 h, with the monitoring of the reaction by TLC (EtOAc/$PhCH_3$=1:3). Triethylamine was added to quench the reaction. The mixture was filtered through Celite bed. The combined filtrate and washings was extracted with $CHCl_3$, and the organic layer was washed with satd. aq. $NaHCO_3$, satd. aq. $Na_2S_2O_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc:$PhCH_3$=1:7) to give **12** (109 mg, 88%); $[\alpha]_D$= +40.7° (*c* 1.0, $CHCl_3$); ratio of rotamer A/B=6.2/1; rotamer A: ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.64–7.16 (m, 25 H, 5 Ph), 5.60–5.58 (m, 2 H, H-8c, NH-d), 5.33 (dd, 1 H, $J_{6,7}$= 2.0 Hz, H-7c), 5.04 (d, 1 H, $J_{1,2}$=3.4 Hz, H-1d), 4.97 (d, 1 H, OCH_2), 4.95–4.84 (m, 7 H, H-1b, 4c, 3d, 4 OCH_2), 4.75 (d, 1 H, NH-c), 4.66–4.61 (m, 3 H, 3 OCH_2), 4.51 (d, 1 H, OCH_2), 4.47 (dt, 1 H, $J_{1,2}$=3.4 Hz, H-2d), 4.43 (d, 1 H, OCH_2), 4.32 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1a), 4.28 and 4.21 (2 d, 2 H, J_{gem}=12.4 Hz, OCH_2), 4.25–4.11 (m, 4 H, H-3b, 9c, 2 OCH_2), 3.99–3.95 (m, 2 H, H-4d, CH_2CH$_2$SiMe$_3$), 3.92 (dd, 1 H, H-9′c), 3.88 (dd, 1 H, $J_{6,7}$= 2.0 Hz, H-6c), 3.83–3.79 (m, 2 H, H-4a, 6d), 3.68–3.61 (m, 3 H, H-4b, 5b, 5c), 3.61 (s, 3 H, COOMe), 3.59–3.53 (m, 4 H, H-3a, 5a, 6b, CH_2CH$_2$SiMe$_3$), 3.48–3.42 (m, 5 H, H-6a, 2b, 6′b, 5d, 6′d), 3.38 (t, 1 H, $J_{1,2}$=7.5 Hz, H-2a), 3.14 (dd, 1 H, H-6′a), 2.42 (dd, 1 H, J_{gem}=12.4 Hz, H-3eq-c), 2.11, 2.05, 2.02, 1.98, 1.65 (5 s, 15 H, 5 Ac), 1.82 (t, 1 H, J_{gem}=12.4 Hz, H-3ax-c), 1.08 and 1.01 (2 s, 18 H, 2 ^{t}Bu), 1.03 (m, 2 H, CH$_2$CH_2SiMe$_3$), 0.00 (s, 9 H, CH$_2$CH$_2$Si*Me$_3$*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.9, 170.4, 170.1, 169.9, 169.7, 167.6, 154.1, 154.0, 139.4, 139.3, 138.7, 138.5, 137.5, 128.2, 128.1, 128.1, 128.0, 128.0, 127.7, 127.6, 127.4, 127.4, 127.2, 127.1, 127.0, 126.9, 102.7, 98.2, 97.3, 95.5, 95.2, 82.3, 81.9, 79.0, 78.2, 77.1, 75.4, 74.9, 74.6, 74.5, 74.2, 74.0, 72.8, 72.8, 71.7, 71.2, 70.1, 69.7, 68.4, 67.7, 67.2, 66.9, 66.0, 61.9, 52.7, 51.3, 49.3, 37.4, 29.6, 27.5, 27.4, 27.3, 27.2, 23.1, 21.2, 20.9, 20.8, 20.7, 20.7, 20.2, 18.4, −1.4; MALDI-TOF MS: *m/z*: calcd for $C_{92}H_{120}Cl_6N_2O_{31}Si_2Na$: 2037.54; found: 2037.52 $[M+Na]^+$.

2-(Trimethylsilyl)ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2,-trichloroethoxycarbamoyl)-α-D-galactopyranosyl-(1→4)-{methyl 4,7,8,9-tetra-O-acetyl-3,5-dideoxy-5-(2,2,2-trichloroethoxycarbamoyl)-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→3)}-2,6-di-O-benzyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-benzyl-β-D-glucopyranoside (**13**) A solution of compound **12** (946 mg, 469 μmol) in TBAHF 1M solution (10 ml, 10 mmol) was stirred at room temperature for 2 h, observing TLC ($CHCl_3$/MeOH=25:1), and the solvent was evaporated. The residue was then dissolved in pyridine (10 ml). To the mixture, Ac_2O (1.0 ml, 10.5 mmol) and a catalytic amount of DMAP were added, and the resulting mixture was stirred at room temperature for 19 h, with the monitoring of the reaction by TLC ($CHCl_3$/MeOH=40:1). Then MeOH was added at 0°C, the reaction mixture was co-evaporated with toluene, and diluted with EtOAc. The organic layer was washed with 2 M HCl, H_2O, satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/$PhCH_3$=1:3) to give **13** (723 mg, 79%); $[\alpha]_D$=+22.4° (*c* 0.52, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 7.43–7.16 (m, 25 H, 5 Ph), 5.81 (d, 1 H, NH-d), 5.59 (m, 1 H, H-8c), 5.34 (dd, 1 H, $J_{6,7}$=2.0 Hz, H-7c), 5.33 (br s, 1 H, H-4d), 5.11 (dd, 1 H, H-3d), 5.10 (d, 1 H, $J_{1,2}$=3.0 Hz, H-1d), 5.05 and 4.69 (2 d, 2 H, J_{gem}=13.0 Hz, OCH_2), 4.93–4.85 (m, 6 H, H-1b, 4c, 4 OCH_2), 4.76 (d, 1 H, NH-c), 4.62 and 4.47 (2 d, 2 H, J_{gem}= 13.0 Hz, OCH_2), 4.61 (d, 1 H, OCH_2), 4.44 (d, 1 H, OCH_2), 4.37 (dd, 1 H, H-6d), 4.32 (d, 1 H, $J_{1,2}$=8.0 Hz, H-1a), 4.30–4.18 (m, 7 H, H-3b, 9c, 2d, 4 OCH_2), 4.08 (t, 1 H, H-5d), 4.00–3.94 (m, 3 H, H-9′c, 6′d, $CH_2CH_2SiMe_3$), 3.91 (dd, 1 H, $J_{6,7}$=2.0 Hz, H-6c), 3.84–3.79 (m, 2 H, H-4a, 6b), 3.70–3.60 (m, 3 H, H-4b, 5b, 5c), 3.64 (s, 3 H, COOMe), 3.58–3.41 (m, 6 H, H-3a, 5a, 6a, 2b, 6′b, $CH_2CH_2SiMe_3$), 3.36 (t, 1 H, $J_{1,2}$=8.0 Hz, H-2a), 3.17 (dd, 1 H, H-6′a), 2.62 (dd, 1 H, J_{gem}=12.5 Hz, H-3eq-c), 2.14, 2.13, 1.99, 1.95, 1.94, 1.66, 1.63(7 s, 21 H, 7 Ac), 1.82 (t, 1 H, J_{gem}=12.5 Hz, H-3ax-c), 1.00 (m, 2 H, $CH_2CH_2SiMe_3$), 0.00 (s, 9 H, $CH_2CH_2SiMe_3$); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 170.5, 170.3, 170.2, 170.0, 169.9, 169.9, 169.7, 167.9, 154.2, 154.0, 139.4, 139.3, 138.7, 138.5, 137.4, 129.0, 128.3, 128.1, 128.1, 128.1, 128.0, 127.8, 127.4, 127.4, 127.2, 127.0, 127.0, 126.9, 126.8, 125.2, 102.7, 98.0, 97.4, 95.4, 95.3, 82.4, 82.2, 78.9, 78.1, 75.6, 74.9, 74.6, 74.6, 74.5, 74.3, 74.2, 73.2, 72.8, 72.8, 71.8, 71.1, 69.7, 68.5, 68.4, 67.8, 67.2, 67.0, 66.9, 66.6, 65.8, 61.9, 60.4, 52.7, 51.2, 50.3, 37.3, 29.6, 21.3, 20.7, 20.7, 20.5, 20.1, 18.4, −1.4; MALDI-TOF MS: *m/z*: calcd for $C_{88}H_{108}Cl_6N_2O_{33}SiNa$: 1981.46; found: 1981.44 $[M+Na]^+$.

2-(Trimethylsilyl)ethyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→6)}-2,3-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside (**15**) To a solution of compound **11** (185 mg, 94 μmol) in AcOH/1,2-dichloroethane (2/1, 5.0 ml) was added Zn–Cu (920 mg). The suspension was vigorously stirred at 40°C for 50 min, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=20:1). The mixture was filtered through Celite bed and the combined filtrate and washings was evaporated. The residue was dissolved in pyridine (3.0 ml). To the mixture, Ac_2O (1.0 ml) and a catalytic amount of DMAP were added at 0°C and the resulting mixture was stirred at room temperature for 12 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=20:1). Then MeOH was added at 0°C, the reaction mixture was co-evaporated with toluene, and diluted with $CHCl_3$. The organic layer was washed with 2 M HCl, H_2O, satd. aq. Na_2CO_3, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=35:1) to give **14** with inseparable by-product. To a solution of crude compound **14** in EtOH/THF (5/4 ml) was added 20% $Pd(OH)_2$ on carbon (134 mg). The suspension was stirred at 40°C under H_2 atmosphere for 13 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=10:1). The reaction mixture was filtered through Celite bed and, the combined filtrate and washings were concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=10:1). Then the residue was dissolved in pyridine (4 ml). To the mixture, Ac_2O (0.5 ml) and a catalytic amount of DMAP were added at 0°C and the resulting mixture was stirred at room temperature for 12 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH= 10:1). Then MeOH was added at 0°C, the reaction mixture was co-evaporated with toluene, and diluted with $CHCl_3$. The organic layer was washed with 2 M HCl, H_2O, satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=30:1) to give **15** (103 mg, 74%); $[\alpha]_D$=−33.1° (*c* 0.86, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.17 (d, 1 H, NH-d), 5.94 (dd, 1 H, $J_{2,3}$= 10.9 Hz, $J_{3,4}$=3.4 Hz, H-3d), 5.40 (d, 1 H, $J_{3,4}$=3.4 Hz, H-4d), 5.34 (dd, 1 H, H-7c), 5.29 (m, 1 H, H-8c), 5.18 (d, 1 H, NH-c), 5.17 (t, 1 H, H-3a), 5.15 (d, 1 H, $J_{1,2}$=8.0 Hz, H-1d), 5.10 (t, 1 H, $J_{1,2}$=7.4 Hz, $J_{2,3}$=10.3 Hz, H-2b), 4.94 (dd, 1 H, $J_{2,3}$=10.3 Hz, $J_{3,4}$=2.3 Hz, H-3b), 4.90 (t, 1 H, $J_{1,2}$=8.0 Hz, H-2a), 4.86 (dt, 1 H, $J_{3eq,4}$=4.6 Hz, H-4c), 4.58 (d, 1 H, $J_{1,2}$=7.4 Hz, H-1b), 4.48 (d, 1 H, $J_{1,2}$=8.0 Hz, H-1a), 4.45 (dd, 1 H, J_{gem}=9.5 Hz, H-6d), 4.29 (dd, 1 H, J_{gem}=12.0 Hz, H-9c), 4.21 (dd, 1 H, J_{gem}=9.5 Hz, H-6′d), 4.18 (dd, 1 H, $J_{3,4}$=2.3 Hz, H-4b), 4.15 (dd, 1 H, J_{gem}= 12.0 Hz, H-9′c), 4.12–3.98 (m, 4 H, H-6a, 5c, 6c, 5d), 3.94–3.91 (m, 3 H, H-4a, 6′a, $CH_2CH_2SiMe_3$), 3.87 (s, 3 H, COOMe), 3.73–3.72 (m, 2 H, H-5a, 6b), 3.67 (t, 1 H, H-5b), 3.57–3.52 (m, 2 H, H-6′b, $CH_2CH_2SiMe_3$), 3.30 (m,

1 H, H-2d), 2.57 (dd, 1 H, J_{gem}=13.2 Hz, $J_{3eq,4}$=4.6 Hz, H-3eq-c), 2.18, 2.17, 2.11, 2.10, 2.09, 2.06, 2.04, 2.03, 2.02, 2.00, 1.99, 1.88 (12 s, 42 H, 14 Ac), 1.91 (t, 1 H, J_{gem}= 13.2 Hz, H-3ax-c), 0.89 (m, 2 H, $CH_2CH_2SiMe_3$), 0.00 (s, 9 H, $CH_2CH_2Si(Me)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 171.3, 170.8, 170.6, 170.5, 170.4, 170.4, 170.3, 170.1, 170.1, 169.9, 169.8, 169.6, 169.6, 169.4, 167.8, 99.9, 99.6, 99.5, 98.5, 77.1, 75.4, 73.2, 72.8, 72.5, 72.5, 72.4, 71.9, 71.5, 70.1, 70.0, 68.6, 68.0, 67.2, 66.9, 66.8, 62.6, 62.5, 62.2, 60.9, 53.6, 52.9, 49.4, 37.8, 29.6, 23.3, 23.1, 21.0, 20.8, 20.7, 20.7, 20.6, 20.6, 20.6, 20.5, 20.5, 17.8, −1.4; MALDI-TOF MS: *m/z*: calcd for $C_{61}H_{90}N_2O_{36}SiNa$: 1477.49; found: 1477.44 $[M+Na]^+$.

2-(Trimethylsilyl)ethyl 2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→3)}-2,6-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranoside (**19**) To a solution of compound **13** (598 mg, 304 μmol) in AcOH/1,2-dichloroethane (2/1, 12 ml) was added Zn–Cu (5.0 g). The suspension was vigorously stirred at 40°C for 3 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=40:1). The mixture was filtered through Celite bed and the combined filtrate and washings were evaporated. The residue was dissolved in pyridine (12 ml). To the mixture, Ac_2O (4 ml) and a catalytic amount of DMAP were added at 0°C and the resulting mixture was stirred at room temperature for 17 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=30:1). Then MeOH was added at 0°C, the reaction mixture was co-evaporated with toluene, and diluted with $CHCl_3$. The organic layer was washed with 2 M HCl, H_2O, satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=50:1) to give **18** with inseparable by-product. To a solution of crude compound **18** in EtOH/THF (10/10 ml) was added 20% $Pd(OH)_2$ on carbon (420 mg) was added. The suspension was stirred at 40°C under H_2 atmosphere for 12 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=10:1). The reaction mixture was filtered through Celite bed and the combined filtrate and washings was concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=15:1). Then the residue was dissolved in pyridine (6 ml). To the mixture, Ac_2O (1.5 ml) and a catalytic amount of DMAP were added at 0°C and the resulting mixture was stirred at room temperature for 12 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=10:1). Then MeOH was added at 0°C, the reaction mixture was co-evaporated with toluene, and diluted with $CHCl_3$. The organic layer was washed with 2 M HCl, H_2O, satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=35:1) to give **19** (245 mg, 55%); $[\alpha]_D$=+17.8° (*c* 0.55, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 6.09 (d, 1 H, NH-d), 5.64 (m, 1 H, H-8c), 5.46 (d, 1 H, H-4d), 5.32 (dd, 1 H, H-7c), 5.23–5.20 (m, 3 H, H-3a, 3d, NH-c), 4.98 (t, 1 H, $J_{1,2}$=8.2 Hz, $J_{2,3}$=10.2 Hz, H-2b), 4.93 (d, 1 H, $J_{1,2}$= 3.4 Hz, H-1d), 4.84 (t, 1 H, $J_{1,2}$=8.2 Hz, H-2a), 4.82 (d, 1 H, $J_{1,2}$=8.2 Hz, H-1b), 4.80 (dt, 1 H, $J_{3eq,4}$=4.1 Hz, H-4c), 4.54 (dt, 1 H, $J_{1,2}$=3.4 Hz, H-2d), 4.49 (d, 1 H, $J_{1,2}$= 8.2 Hz, H-1a), 4.45 (dd, 1 H, H-6d), 4.42 (dd, 1 H, J_{gem}= 11.7 Hz, H-6a), 4.37 (dd, 1 H, H-9c), 4.30 (dd, 1 H, H-6b), 4.27 (dd, 1 H, $J_{2,3}$=10.2 Hz, H-3b), 4.19 (dd, 1 H, J_{gem}= 11.7 Hz, H-6′a), 4.16 (t, 1 H, H-5d), 4.06–4.02 (m, 2 H, H-5c, 6′d), 3.97–3.90 (m, 3 H, H-4a, 9′c, $CH_2CH_2SiMe_3$), 3.85 (t, 1 H, H-5b), 3.77 (s, 3 H, COOMe), 3.75–3.73 (m, 2 H, H-6′b, 6c), 3.65 (m, 1 H, H-5a), 3.57 (m, 1 H, $CH_2CH_2SiMe_3$), 3.36 (d, 1 H, H-4b), 2.58 (dd, 1H, J_{gem}= 12.3 Hz, $J_{3eq,4}$=4.1 Hz, H-3eq-c), 2.26, 2.12, 2.11, 2.09, 2.08, 2.07, 2.05, 2.02, 2.00, 1.99, 1.98, 1.85 (12 s, 42 H, 14 Ac), 1.73 (t, 1 H, J_{gem}=12.3 Hz, H-3ax-c), 0.92 (m, 2 H, $CH_2CH_2SiMe_3$), 0.00 (s, 9 H, $CH_2CH_2Si(Me)_3$); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 170.7, 170.5, 170.5, 170.4, 170.3, 170.1, 170.0, 170.0, 169.8, 169.7, 169.6, 169.4, 168.0, 101.1, 99.5, 98.9, 97.0, 77.2, 77.1, 74.5, 74.2, 72.6, 72.2, 72.1, 71.9, 71.1, 69.2, 68.7, 67.6, 67.2, 66.9, 66.8, 66.5, 62.8, 62.6, 60.9, 59.7, 52.7, 48.9, 48.7, 37.1, 29.5, 23.0, 21.2, 20.7, 20.6, 20.6, 20.5, 20.4, 17.7, −1.5; MALDI-TOF MS: *m/z*: calcd for $C_{61}H_{90}N_2O_{36}SiNa$: 1477.49; found: 1477.61 $[M+Na]^+$.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→6)}-2,3-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-D-glucopyranosyl Trichloroacetimidate (**17**) To a solution of compound **15** (232 mg, 159 μmol) in dry CH_2Cl_2 (3.8 ml) was added TFA (1.3 ml) at 0°C. The mixture was stirred at room temperature for 4 h, until disappearance of the starting material on TLC ($CHCl_3$/MeOH=10:1), and then solvent was co-evaporated with toluene. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=25:1) to give **16**. To a solution of compound **16** in dry CH_2Cl_2 (5 ml) were added CCl_3CN (320 μl, 3.18 mmol) and DBU (29 μl, 191 μmol) at 0°C. The mixture was stirred at 0°C to room temperature for 2.5 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=10:1), and then solvent was evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=30:1) to give **17** (216 mg, α/β=10:1, 90%); **17**α: ^{1}H-NMR (500 MHz, $CDCl_3$): δ 8.67 (s, 1 H, C= NH), 6.49 (d, 1 H, $J_{1,2}$=3.4 Hz, H-1a), 6.33 (d, 1 H, NH-d), 5.90 (dd, 1 H, $J_{3,4}$=4.0 Hz, H-3d), 5.47 (t, 1 H, $J_{2,3}$= 10.3 Hz, H-3a), 5.39 (dd, 1 H, $J_{3,4}$=4.0 Hz, H-4d), 5.38 (d,

1 H, NH-c), 5.33 (d, 1 H, H-7c), 5.29 (m, 1 H, H-8c), 5.16 (d, 1 H, $J_{1,2}$=9.9 Hz, H-1d), 5.14 (t, 1 H, $J_{1,2}$=7.4 Hz, H-2b), 5.09 (dd, 1 H, $J_{1,2}$=3.4 Hz, $J_{2,3}$=10.3 Hz, H-2a), 4.95 (dd, 1 H, H-3b), 4.87 (dt, 1 H, $J_{3eq,4}$=4.6 Hz, H-4c), 4.58 (d, 1 H, $J_{1,2}$=7.4 Hz, H-1b), 4.51 (d, 1 H, H-6d), 4.31 (d, 1 H, J_{gem}= 10.8 Hz, H-9c), 4.20 (br s, 1 H, H-4b), 4.14 (dd, 1 H, J_{gem}= 10.8 Hz, H-9′c), 4.11–3.97 (m, 6 H, H-4a, 6a, 6′a, 5c, 6c, 6′ d), 3.94 (t, 1 H, H-5d), 3.86 (m, 4 , H-5b, COOMe), 3.73–3.70 (m, 2 H, H-5a, 6b), 3.61 (dd, 1 H, H-6′b), 3.34 (m, 1 H, H-2d), 2.58 (dd, 1 H, J_{gem}=12.4 Hz, $J_{3eq,4}$=4.6 Hz, H-3eq-c), 2.17, 2.15, 2.11, 2.10, 2.06, 2.05, 2.05, 2.03, 2.01, 1.99, 1.88 (11 s, 42 H, 14 Ac), 1.91 (t, 1 H, J_{gem}=12.4 Hz, H-3ax-c).

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→3)}-2,6-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-α-D-glucopyranosyl Trichloroacetimidate (**21**) To a solution of compound **19** (55 mg, 38 μmol) in dry CH_2Cl_2 (1.5 ml) was added TFA (0.50 ml) at 0°C. The mixture was stirred at room temperature for 3 h, until disappearance of the starting material on TLC ($CHCl_3$/MeOH=10:1), and then solvent was co-evaporated with toluene. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=25:1) to give **20**. To a solution of compound **20** in dry CH_2Cl_2 (2.0 ml) were added CCl_3CN (75 μl, 750 μmol) and DBU (7.2 μl, 49 μmol) at 0°C. The mixture was stirred at room temperature for 2.5 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=10:1), and then solvent was evaporated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=30:1) to give **21** (49 mg, 88%); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 8.66 (s, 1 H, C=NH), 6.47 (d, 1 H, $J_{1,2}$=4.1 Hz, H-1a), 6.05 (d, 1 H, NH-d), 5.58 (m, 1 H, H-8c), 5.56 (t, 1 H, $J_{2,3}$=9.6 Hz, H-3a), 5.21 (dd, 1 H, H-3d), 5.16 (d, 1 H, NH-c), 5.06 (dd, 1 H, $J_{1,2}$=4.1 Hz, $J_{2,3}$=9.6 Hz, H-2a), 5.01 (t, 1 H, $J_{1,2}$= 7.5 Hz, $J_{2,3}$=10.3 Hz, H-2b), 4.95 (d, 1 H, $J_{1,2}$=3.4 Hz, H-1d), 4.83 (dt, 1 H, $J_{3eq,4}$=4.1 Hz, H-4c), 4.82 (d, 1 H, $J_{1,2}$= 7.5 Hz, H-1b), 4.54 (dt, 1 H, $J_{1,2}$=3.4 Hz, H-2d), 4.46–4.43 (m, 2 H, H-6a, 6d), 4.38 (dd, 1 H, H-9c), 4.32 (dd, 1 H, H-6b), 4.27 (dd, 1 H, $J_{2,3}$=10.3 Hz, H-3b), 4.22 (dd, 1 H, H-6′ a), 4.19–4.16 (m, 2 H, H-6c, 5d), 4.05–3.94 (m, 4 H, H-4a, 5c, 9′c, 6′d), 3.90 (t, 1 H, H-5b), 3.79 (s, 3 H, COOMe), 3.77–3.73 (m, 2 H, H-5a, 6′b), 3.38 (d, 1 H, H-4b), 2.59 (dd, 1 H, J_{gem}=12.3 Hz, $J_{3eq,4}$=4.1 Hz, H-3eq-c), 2.26, 2.24, 2.13, 2.12, 2.11, 2.09, 2.07, 2.06, 2.02, 2.01, 2.00, 1.86 (12 s, 42 H, 14 Ac), 1.74 (t, 1 H, J_{gem}=12.3 Hz, H-3ax-c); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 170.8, 170.6, 170.5, 170.5, 170.4, 170.4, 170.2, 170.1, 170.0, 169.8, 169.6, 169.3, 169.1, 168.1, 160.9, 101.3, 98.8, 97.0, 92.8, 90.6, 76.4, 74.3, 72.8, 71.9, 71.2, 70.7, 70.6, 70.0, 69.2, 68.7, 67.7, 67.3, 66.8, 66.8, 66.7, 62.3, 62.0, 61.1, 59.8, 52.7, 49.0, 48.8, 37.2, 29.6, 23.0, 23.0, 21.3, 20.8, 20.7, 20.6, 20.6, 20.5, 20.5, 20.4; MALDI-TOF MS: *m/z:* calcd for $C_{58}H_{78}Cl_3N_3O_{36}Na$: 1520.33; found: 1520.34 $[M+Na]^+$.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→6)}-2,3-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-2-azido-3-O-(4-methoxybenzyl)-4-octadecen-1,3-diol (**23**) A suspension of compound **17** (216 mg, 144 μmol), compound **22** (197 mg, 443 μmol), and molecular sieves AW-300 (500 mg) in dry CH_2Cl_2 (7 ml) was stirred at room temperature for 2 h. After cooled to 0°C, TMSOTf (5.2 μl, 29 μmol) was added. The reaction mixture was stirred at 0°C for 7 h, then TMSOTf (5.2 μl, 29 μmol) was added, and stirred at 0°C for another 17 h to cleave orthoester, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). Triethylamine was added to quench the reaction. The mixture was filtered through Celite bed. The combined filtrate and washings was extracted with $CHCl_3$, the organic layer was washed with satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH= 40:1→30:1) to give **23** (51 mg, 20%); $[\alpha]_D$=−31.3° (*c* 0.59, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.21 and 6.86 (2 d, 4 H, *Ph*OMe), 6.28 (d, 1 H, NH-d), 5.94 (dd, 1 H, $J_{2,3}$=11.0 Hz, $J_{3,4}$=3.4 Hz, H-3d), 5.72 (m, 1 H, H-5e), 5.39 (d, 1 H, $J_{3,4}$=3,4 Hz, H-4d), 5.36 (m, 1 H, H-4e), 5.33 (dd, 1 H, $J_{6,7}$=2.1 Hz, H-7c), 5.29 (m, 1 H, H-8c), 5.18 (d, 1 H, NH-c), 5.16 (t, 1 H, $J_{2,3}$=9.6 Hz, H-3a), 5.15 (d, 1 H, $J_{1,2}$= 8.2 Hz, H-1d), 5.11 (t, 1 H, $J_{1,2}$=7.5 Hz, $J_{2,3}$=10.3 Hz, H-2b), 4.94 (dd, 1 H, $J_{2,3}$=10.3 Hz, H-3b), 4.93 (t, 1 H, $J_{1,2}$=7.5 Hz, $J_{2,3}$=9.6 Hz, H-2a), 4.86 (dt, 1 H, $J_{3eq,4}$= 4.8 Hz, H-4c), 4.58 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1b), 4.50 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1a), 4.49 and 4.26 (2 d, 2 H, J_{gem}= 11.7 Hz, O*CH*$_2$PhOMe), 4.45 (dd, 1 H, J_{gem}=11.7 Hz, H-6d), 4.29 (dd, 1 H, H-9c), 4.21 (dd, 1 H, J_{gem}=11.7 Hz, H-6′d), 4.18 (d, 1 H, H-4b), 4.15 (dd, 1 H, H-9′c), 4.10 (t, 1 H, H-5d), 4.07 (dd, 1 H, $J_{6,7}$ = 2.1 Hz, H-6c), 4.04–3.98 (m, 2 H, H-5b, 5c), 3.96–3.92 (m, 3 H, H-4a, 6b, 1e), 3.86 (s, 3 H, OMe), 3.81 (t, 1 H, H-3e), 3.80 (s, 3 H, OMe), 3.74–3.71 (m, 2 H, H-6a, 6′b), 3.68 (m, 1 H, H-5a), 3.63 (dd, 1 H, H-1′e), 3.57 (dd, 1 H, H-6′a), 3.49 (m, 1 H, H-2e), 3.29 (m, 1 H, H-2d), 2.56 (dd, 1 H, J_{gem}=13.0 Hz, $J_{3eq,4}$=4.8 Hz, H-3eq-c), 2.16, 2.15, 2.11, 2.10, 2.05, 2.04, 2.03, 2.02, 2.00, 1.99, 1.99, 1.88 (12 s, 42 H, 14 Ac), 2.10–2.08 (m, 2 H, H-6e, 6′e), 1.90 (t, 1 H, J_{gem}=13.0 Hz, H-3ax-c), 1.40 (m, 2 H, H-7e, 7′e), 1.34–1.25 (m, 20 H, –CH_2–), 0.87 (t, 3 H, –CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 171.3, 170.8, 170.6, 170.5, 170.4, 170.3, 170.1, 170.1, 169.9, 169.9, 169.7, 169.6,

169.3, 167.8, 159.1, 137.9, 130.0, 129.2, 126.0, 113.7, 100.2, 99.5, 99.5, 98.6, 78.7, 77.2, 75.2, 73.2, 73.0, 72.5, 72.4, 72.3, 71.9, 71.4, 70.1, 70.0, 69.8, 68.6, 68.6, 68.0, 67.0, 66.8, 63.6, 62.6, 62.4, 62.2, 60.9, 55.2, 53.6, 52.9, 49.4, 37.8, 32.3, 31.8, 29.6, 29.6, 29.4, 29.2, 29.1, 29.0, 23.3, 23.1, 22.6, 21.0, 20.8, 20.7, 20.7, 20.6, 20.6, 20.6, 20.5, 20.5, 14.0; MALDI-TOF MS: *m/z*: calcd for $C_{82}H_{119}N_5O_{38}Na$: 1804.74; found: 1804.90 $[M+Na]^+$.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→3)}-2,6-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-2-azido-3-O-(4-methoxybenzyl)-4-octadecen-1,3-diol (**24**) A suspension of compound **21** (213 mg, 142 μmol), compound **22** (194 mg, 435 μmol), and molecular sieves AW-300 (510 mg) in dry CH_2Cl_2 (5 ml) was stirred at room temperature for 2 h. After cooled to 0°C, TMSOTf (2.6 μl, 14 μmol) was added through syringe. The reaction mixture was stirred at 0°C for 17 h, then TMSOTf (5.1 μL, 28 μmol) was added, and stirred at 0°C for another 28 h to cleave orthoester, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). Triethylamine was added to quench the reaction. The mixture was filtered through Celite bed. The combined filtrate and washings was extracted with $CHCl_3$, the organic layer was washed with satd. aq. $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=50:1→40:1→30:1) to give **24** (58 mg, 23%); $[\alpha]_D$=−5.6° (*c* 0.62, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.21 and 6.85 (2d, 4 H, *Ph*OMe), 6.05 (d, 1 H, NH-d), 5.72 (m, 1 H, H-5e), 5.63 (m, 1 H, H-8c), 5.47 (d, 1 H, H-4d), 5.38 (dd, 1 H, H-4e), 5.33 (dd, 1 H, H-7c), 5.23–5.20 (m, 1 H, H-3a, 3d), 5.04 (d, 1 H, NH-c), 4.98 (t, 1 H, $J_{1,2}$=7.5 Hz, H-2b), 4.93 (d, 1 H, $J_{1,2}$= 3.4 Hz, H-1d), 4.86 (t, 1 H, $J_{1,2}$=8.2 Hz, H-2a), 4.82 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1b), 4.81 (dt, 1 H, $J_{3eq,4}$=4.8 Hz, H-4c), 4.54 (dt, 1 H, $J_{1,2}$=3.4 Hz, H-2d), 4.52 (d, 1 H, $J_{1,2}$= 8.2 Hz, H-1a), 4.50 and 4.27 (2 d, 2 H, J_{gem}=11.0 Hz, OC*H*$_2$PhOMe), 4.45 (dd, 1 H, H-6d), 4.42 (dd, 1 H, J_{gem}= 11.7 Hz, H-6a), 4.38 (dd, 1 H, H-9c), 4.31–4.26 (m, 2 H, H-3b, 6b), 4.20 (dd, 1 H, J_{gem}=11.7 Hz, H-6′a), 4.16 (t, 1 H, H-5d), 4.06–4.01 (m, 2 H, H-5c, 6′d), 3.98–3.91 (m, 3 H, H-4a, 9′c, 1e), 3.87–3.72 (m, 4 H, H-5b, 6′b, 6c, 3e), 3.79 and 3.78 (2 s, 6 H, COOMe, PhO*Me*), 3.68–3.64 (m, 2 H, H-5a, 1′e), 3.50 (m, 1 H, H-2e), 3.35 (d, 1 H, H-4b), 2.57 (dd, 1 H, J_{gem}=12.3 Hz, $J_{3eq,4}$=4.8 Hz, H-3eq-c), 2.26, 2.13, 2.11, 2.10, 2.07, 2.05, 2.04, 2.02, 2.01, 2.00, 1.98, 1.85 (12 s, 42 H, 14 Ac), 2.06 (m, 2 H, H-6e, 6′e), 1.74 (t, 1 H, J_{gem}=12.3 Hz, H-3ax-c), 1.40 (m, 2 H, H-7e, 7′e), 1.34–1.25 (m, 20 H, –CH_2–), 0.87 (t, 3 H, –CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 170.8, 170.7, 170.6, 170.6, 170.5, 170.2, 170.2, 170.1, 169.9, 169.8, 169.7, 169.6, 169.5, 168.1, 159.1, 138.0, 130.0, 129.3, 126.0, 113.7, 101.2, 99.9, 99.0, 97.1, 78.7, 74.6, 74.2, 72.7, 72.5, 72.0, 71.9, 71.3, 69.8, 69.3, 68.8, 68.7, 67.7, 67.3, 67.0, 66.9, 66.7, 63.7, 62.8, 62.6, 61.0, 59.8, 55.2, 52.8, 49.1, 48.8, 37.2, 32.3, 31.9, 29.6, 29.6, 29.4, 29.3, 29.1, 29.0, 23.1, 22.6, 21.3, 20.8, 20.8, 20.7, 20.7, 20.7, 20.6, 20.5, 14.1; MALDI-TOF MS: *m/z*: calcd for $C_{82}H_{119}N_5O_{38}Na$: 1804.74; found: 1804.85 $[M+Na]^+$.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→6)}-2,3-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-3-O-(4-methoxybenzyl)-2-octadecanoylamino-4-octadecen-1,3-diol (**26**) To a solution of compound **23** (43 mg, 24 μmol) in benzene (2.8 ml) were added PPh_3 (28 mg, 108 μmol) and trace water, and the mixture was stirred at 50°C for 17 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). Then, the solvent was co-evaporated with toluene. The residue was dissolved in dry 1,2-dichloroethane (2.5 ml), and stearic acid (35 mg, 123 μmol), acatalytic amount of DMAP, and EDC (24 mg, 125 μmol) were added. The reaction mixture was stirred at 40°C for 12 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). The mixture was diluted with $CHCl_3$, the organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$:MeOH=40:1) to give **26** (43 mg, 88%); $[\alpha]_D$=−24.6° (*c* 0.71, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.20 and 6.84 (2d, 4 H, *Ph*OMe), 6.38 (d, 1 H, NH-d), 5.94 (dd, 1 H, $J_{2,3}$=11.7 Hz, $J_{3,4}$=3.4 Hz, H-3d), 5.65 (m, 1 H, H-5e), 5.57 (d, 1 H, NH-e), 5.40 (d, 1 H, $J_{3,4}$=3.4 Hz, H-4d), 5.34 (dd, 1 H, $J_{6,7}$=2.0 Hz, H-7c), 5.33–5.28 (m, 2 H, H-8c, 4e), 5.19 (t, 1 H, $J_{2,3}$= 9.6 Hz, H-3a), 5,17 (d, 1 H, NH-c), 5.15 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1d), 5.11 (t, 1 H, $J_{1,2}$=7.5 Hz, $J_{2,3}$=10.3 Hz, H-2b), 4.93 (dd, 1 H, $J_{2,3}$=10.3 Hz, $J_{3,4}$=2.0 Hz, H-3b), 4.89 (t, 1 H, $J_{1,2}$=8.2 Hz, $J_{2,3}$=9.6 Hz, H-2a), 4.86 (dt, 1 H, $J_{3eq,4}$=4.8 Hz, H-4c), 4.58 (d, 1 H, $J_{1,2}$=7.5 Hz, H-1b), 4.46 and 4.23 (2 d, 2 H, J_{gem}=11.7 Hz, OC*H*$_2$PhOMe), 4.45 (d, 1 H, $J_{1,2}$= 8.2 Hz, H-1a), 4.43 (dd, 1 H, J_{gem}=12.3 Hz, H-6a), 4.29 (dd, 1 H, H-9c), 4.23 (dd, 1 H, J_{gem}=12.3 Hz, H-6′a), 4.18 (dd, 1 H, $J_{3,4}$=2.0 Hz, H-4b), 4.16–3.98 (m, 5 H, H-5c, 6c, 9′c, 5d, 1e, 2e), 3.94–3.90 (m, 2 H, H-4a, 1′e), 3.86 and 3.79 (2 s, 6 H, COOMe, PhO*Me*), 3.77 (t, 1 H, H-3e), 3.74–3.70 (m, 2 H, H-5b, 6b), 3.67 (m, 1 H, H-5a), 3.60–3.55 (m, 3 H, H-6′b, 6d, 6′d), 3.29 (m, 1 H, H-2d), 2.56 (dd, 1 H, J_{gem}=13.0 Hz, $J_{3eq,4}$=4.8 Hz, H-3eq-c), 2.16, 2.15, 2.11, 2.10, 2.04, 2.04, 2.03, 2.03, 2.02, 2.01, 1.99, 1.99, 1.88 (13 s, 42 H, 14 Ac), 2.11–2.02 (m, 4 H, H-6e, 6′e, NHCOC*H*$_2$), 1.90 (t, 1 H, J_{gem}=13.0 Hz, H-3ax-c), 1.54 (m, 2 H, NHCOCH$_2$C*H*$_2$), 1.36

(m, 2 H, H-7e, 7′e), 1.30–1.25 (m, 48 H, –CH_2–), 0.87 (t, 6 H, 2 –CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 172.4, 171.4, 170.8, 170.6, 170.5, 170.4, 170.3, 170.3, 170.1, 169.9, 169.9, 169.7, 169.6, 169.6, 167.8, 159.0, 136.8, 130.4, 129.2, 127.1, 113.6, 100.6, 99.4, 98.6, 79.0, 75.2, 73.2, 73.0, 72.5, 72.0, 71.8, 71.8, 70.2, 70.0, 68.6, 68.0, 66.9, 66.8, 62.6, 62.4, 62.2, 60.9, 55.1, 53.6, 52.9, 51.4, 49.5, 37.9, 36.7, 32.2, 31.8, 29.6, 29.5, 29.4, 29.4, 29.3, 29.3, 29.2, 25.6, 23.3, 23.1, 22.6, 21.0, 20.8, 20.7, 20.7, 20.7, 20.6, 20.6, 20.5, 20.5, 14.0; MALDI-TOF MS: *m/z*: calcd for $C_{100}H_{155}N_3O_{39}Na$: 2045.01; found: 2045.24 $[M+Na]^+$.

2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-α-D-galactopyranosyl-(1→4)-{methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate-(2→3)}-2,6-di-O-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-3-O-(4-methoxybenzyl)-2-octadecanoylamino-4-octadecen-1,3-diol (**29**) To a solution of compound **24** (95 mg, 53 μmol) in benzene (4.5 ml) were added PPh_3 (56 mg, 213 μmol) and trace water, and the mixture was stirred at 50°C for 19 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). Then, the solvent was co-evaporated with toluene. The residue was dissolved in dry 1,2-dichloroethane (3 ml), and stearic acid (76 mg, 266 μmol), a catalytic amount of DMAP, and EDC (51 mg, 266 μmol) were added. The reaction mixture was stirred at 40°C for 12 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). The mixture was diluted with $CHCl_3$, the organic layer was washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$:MeOH=40:1) to give **29** (85 mg, 79%); $[\alpha]_D$=+8.7° (*c* 0.35, $CHCl_3$); ^{1}H-NMR (600 MHz, $CDCl_3$): δ 7.20 and 6.84 (2 d, 4 H, *Ph*OMe), 5.98 (d, 1 H, NH-d), 5.66–5.61 (m, 2 H, H-8c, 5e), 5.56 (d, 1 H, NH-e), 5.47 (d, 1 H, H-4d), 5.33 (dd, 1 H, H-7c), 5.32 (m, 1 H, H-4e), 5.21 (t, 1 H, H-3a), 5.21 (dd, 1 H, H-3d), 5.14 (d, 1 H, NH-c), 4.98 (t, 1 H, $J_{2,3}$=10.3 Hz, H-2b), 4.94 (d, 1 H, $J_{1,2}$=3.4 Hz, H-1d), 4.84–4.79 (m, 3 H, H-2a, 1b, 4c), 4.54 (dt, 1 H, $J_{1,2}$=3.4 Hz, H-2d), 4.47 and 4.24 (2 d, 2 H, J_{gem}=10.9 Hz, OC*H*$_2$PhOMe), 4.46–4.44 (m, 2 H, H-1a, 6d), 4.42 (dd, 1 H, J_{gem}=11.7 Hz, H-6a), 4.38 (dd, 1 H, H-9c), 4.31 (dd, 1 H, H-6b), 4.26 (dd, 1 H, $J_{2,3}$=10.3 Hz, $J_{3,4}$=2.1 Hz, H-3b), 4.20 (dd, 1 H, J_{gem}=11.7 Hz, H-6′a), 4.17–4.12 (m, 3 H, H-5d, 1e, 2e), 4.06–4.01 (m, 2 H, H-5c, 6′d), 3.95–3,91 (m, 2 H, H-4a, 9′c), 3.86 (t, 1 H, H-5b), 3.81–3.73 (m, 3 H, H-6′b, 6c, 3e), 3.79 and 3.78 (2 s, 6 H, COOMe, PhO*Me*), 3.62–3.59 (m, 2 H, H-5a, 1′e), 3.35 (d, 1 H, $J_{3,4}$=2.1 Hz, H-4b), 2.58 (dd, 1 H, J_{gem}=12.3 Hz, H-3eq-c), 2.26, 2.13, 2.12, 2.10, 2.10, 2.07, 2.05, 2.02, 2.01, 2.01, 2.00, 1.86 (12 s, 42 H, 14 Ac), 2.04 (m, 4 H, H-6e, 6′e, NHCOC*H*$_2$), 1.74 (t, 1 H, J_{gem}=12.3 Hz, H-3ax-c), 1.54 (m, 2 H, NHCOCH$_2$C*H*$_2$), 1.34 (m, 2 H, H-7e, 7′e), 1.31–1.20 (m, 48 H, -CH_2-), 0.87 (t, 6 H, 2 -CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$): δ 172.3, 170.8, 170.6, 170.5, 170.5, 170.4, 170.2, 170.1, 170.0, 169.8, 169.7, 169.7, 169.5, 169.4, 168.1, 159.0, 136.8, 130.3, 129.2, 127.1, 113.6, 101.0, 100.3, 99.0, 97.0, 78.9, 74.6, 73.8, 72.6, 72.5, 72.2, 71.9, 71.2, 69.8, 69.2, 68.7, 68.1, 67.7, 67.2, 66.9, 66.8, 66.6, 62.7, 62.5, 61.0, 59.8, 55.1, 52.7, 51.5, 49.0, 48.9, 37.2, 36.7, 32.2, 31.8, 29.6, 29.4, 29.4, 29.3, 29.3, 29.2, 29.2, 29.2, 25.6, 23.1, 23.0, 22.6, 21.3, 20.8, 20.7, 20.7, 20.6, 20.6, 20.5, 20.4, 14.0; MALDI-TOF MS: *m/z*: calcd for $C_{100}H_{155}N_3O_{39}Na$: 2045.01; found: 2045.22 $[M+Na]^+$.

2-Acetamido-2-deoxy-β-D-galactopyranosyl-(1→4)-{5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylic acid-(2→6)}-β-D-galactopyranosyl-(1→4)-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-2-octadecanoylamino-4-octadecen-1,3-diol (**1**) To a solution of compound **26** (43 mg, 21 μmol) in dry CH_2Cl_2 (1.8 ml) was added TFA (1.3 ml) at 0°C. The resulting mixture was stirred at room temperature for 7 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH=15:1). The reaction mixture was extracted with $CHCl_3$, the organic layer was washed with Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($PhCH_3$/EtOAc/MeOH=30:15:1) to give **27**. To a solution of compound **27** in dry MeOH (1.5 ml) was added a catalytic amount of NaOMe. The resulting mixture was stirred at room temperature for 17 h. Then to the mixture, H_2O was added, the mixture was heated to 60°C, and stirred for 4 days, with monitoring of the reaction by TLC ($CHCl_3$/MeOH/5% aq. $CaCl_2$=5:4:1). After cooled to room temperature, the mixture was neutralized with Dowex (H^+), filtered through cotton, and the combined filtrate and washings was concentrated. The residue was purified by column chromatography on Sephadex LH-20 ($CHCl_3$/MeOH/H_2O=5:5:1) to give **1** (19 mg, 66%); $[\alpha]_D$=–15.0° (*c* 0.10, $CHCl_3$:MeOH:H_2O=5:5:1); ^{1}H-NMR (600 MHz, $CDCl_3$:CD_3OD:D_2O=5:5:1): δ 5.74 (m, 1 H, H-5e), 5.42 (m, 1 H, H-4e), 2.72 (dd, 1 H, J_{gem}=12.3 Hz, H-3eq-c), 2.22–2.17 (m, 2 H, NHCOC*H*$_2$), 2.03 and 2.02 (2 s, 6 H, 2 NH*Ac*), 2.05–2.00 (m, 2 H, H-6e, 6′e), 1.69 (t, 1 H, J_{gem}=12.3 Hz, H-3ax-c), 1.58 (m, 2 H, NHCOCH$_2$C*H*$_2$), 1.37 (m, 2 H, H-7e, 7′e), 1.32–1.27 (m, 48 H, -CH_2-), 0.89 (t, 6 H, 2 -CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$:CD_3OD:D_2O=5:5:1): δ 180.7, 176.1, 175.1, 175.0, 174.0, 170.6, 158.6, 133.4, 129.4, 104.3, 103.3, 101.1, 80.6, 78.7, 77.6, 75.6, 75.5, 75.3, 74.2, 73.8, 73.5, 73.3, 72.8, 72.5, 71.8, 70.3, 69.7, 69.4, 69.4, 68.8, 65.3, 65.0, 63.9, 62.1, 61.0, 53.8, 53.8, 52.8, 41.1, 37.1, 33.1, 32.5, 30.5, 30.4, 30.3, 30.3, 30.2, 30.2, 30.1, 30.0, 29.9, 26.8, 24.2, 23.3, 23.1, 22.9, 14.5; MALDI-TOF MS: *m/z*: calcd for $C_{67}H_{120}N_3O_{26}$: 1382.81; found: 1382.96 $[M-H]^-$.

2-Acetamido-2-deoxy-α-D-galactopyranosyl-(1→4)-{5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylic acid-(2→3)}-β-D-galactopyranosyl-(1→4)-β-D-glucopyranosyl-(1→1)-(2S,3R,4E)-2-octadecanoylamino-4-octadecen-1,3-diol (**2**) To a solution of compound **29** (84 mg, 42 μmol) in dry CH_2Cl_2 (1.4 ml) was added TFA (1.0 ml) at 0°C. The resulting mixture was stirred at 0°C for 2 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH= 15:1). The reaction mixture was extracted with $CHCl_3$, the organic layer was washed with Na_2CO_3 and brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH=30:1) to give **30**. To a solution of compound **30** in dry MeOH (2.5 ml) was added catalytic amount of NaOMe. The resulting mixture was stirred at room temperature for 1 day. Then to the mixture, H_2O was added, the mixture was stirred at room temperature for 17 h, heated to 60°C, and stirred for another 20 h, with monitoring of the reaction by TLC ($CHCl_3$/MeOH/5% aq. $CaCl_2$=5:4:1). After cooled to room temperature, the mixture was neutralized with IR-120 (H^+), filtered through cotton, and the combined filtrate and washings was concentrated. The residue was purified by column chromatography on Sephadex LH-20 ($CHCl_3$/MeOH/H_2O=5:5:1) to give **2** (45 mg, 79%); $[\alpha]_D$=+56.0° (*c* 0.24, $CHCl_3$:MeOH:H_2O=5:5:1); ^{1}H-NMR (600 MHz, $CDCl_3$:CD_3OD:D_2O=5:5:1): δ 5.70 (m, 1 H, H-5e), 5.42 (m, 1 H, H-4e), 4.89 (d, 1 H, $J_{1,2}$=3.4 Hz, H-1d), 4.06 (t, 1 H, H-3e), 2.87 (br d, 1 H, H-3eq-c), 2.17 (t, 2 H, NHCOCH_2), 2.04 and 2.03 (2 s, 6 H, 2 NH*Ac*), 2.04–1.99 (m, 2 H, H-6e, 6′e), 1.69 (m, 1 H, H-3ax-c), 1.56 (m, 2 H, NHCOCH_2CH_2), 1.37 (m, 2 H, H-7e, 7′e), 1.33–1.17 (m, 48 H, -CH_2-), 0.89 (t, 6 H, 2 -CH_3); ^{13}C-NMR (150 MHz, $CDCl_3$:CD_3OD:D_2O=5:5:1): δ 175.5, 175.4, 174.3, 173.5, 135.4, 130.1, 104.4, 103.6, 100.6, 98.2, 79.7, 76.9, 76.1, 75.6, 75.3, 74.2, 74.0, 74.0, 72.4, 72.3, 71.1, 69.9, 69.6, 69.4, 68.4, 68.4, 64.0, 61.6, 60.9, 60.7, 53.8, 52.9, 50.9, 41.1, 37.1, 33.1, 32.5, 30.4, 30.4, 30.3, 30.3, 30.3, 30.2, 30.1, 30.0, 30.0, 26.7, 23.3, 22.7, 22.6, 14.5; MALDI-TOF MS: *m/z*: calcd for $C_{67}H_{121}N_3O_{26}Na$: 1406.81; found: 1406.81 $[M+Na]^+$.

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