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An efficient short-step total synthesis of ganglioside GM_3: effective usage of the neighbouring group participation strategy

Toshiyuki Tomoo [a], Tadao Kondo [b,*], Hiroyuki Abe [a], Syunji Tsukamoto [a], Minoru Isobe [a], Toshio Goto [a]

[a] *Laboratory of Organic Chemistry, School of Agriculture, Nagoya University, Chikusa, Nagoya 464-01, Japan*

[b] *Chemical Instrument Center, Nagoya University, Chikusa, Nagoya 464-01, Japan*

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Abstract

We have developed an efficient methodology for highly stereoselective sialylation using 3-position substituted sialic acids and have prepared **2a** having a 3β-phenylthio group as a sialic donor. Glycosylation of suitably protected lactoside **3** with **2a** gave only the α-sialyl trisaccharide **16** in good yield. Condensation of the azidosphingosine **4** with the acetate **17** using promotors, DMTST or NIS-TfOH, afforded the glycolipid **18**, which was directly transformed to **20** by reduction with Bu_3P and subsequent acylation with octadecanoic acid in the presence of WSC. Removal of the protecting groups generated ganglioside GM_3 (**1**). © (1996) Elsevier Science Ltd.

Keywords: Ganglioside; Glycolipid; Synthesis; Participation, neighbouring group

1. Introduction

The ganglioside GM_3, first isolated from horse erythrocytes by Yamakawa et al. [1], has recently become well known for its biological importance, namely as a neurofunctional substance [2]. It has been chemically synthesized by a few groups [3–5].

One of the key reactions for synthesis of gangliosides is formation of the thermodynamically unstable α-linkage of *N*-acetylneuraminic acid (NANA). The early attempts

* Corresponding author.

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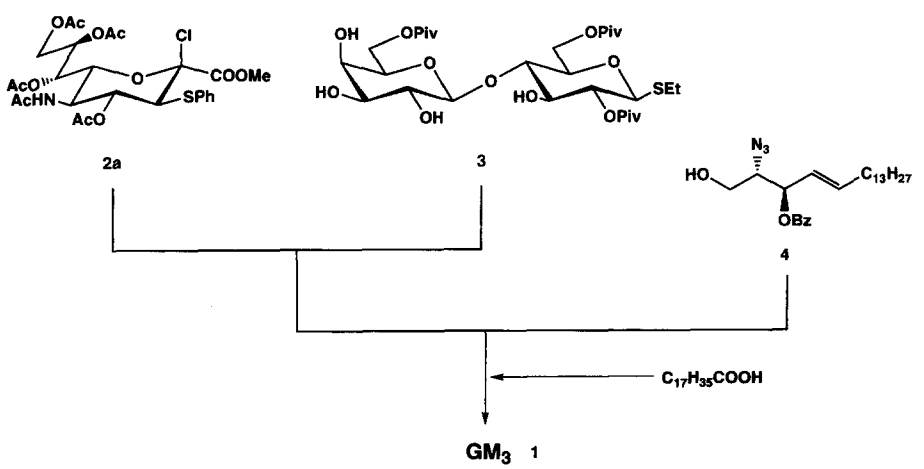
using a sialyl chloride [6] as sialic donor often afforded the 2,3-dehydro product and gave only a few α-sialyl, and/or β-glycoside products [4,7].

An ingenious α-stereocontrolling technique based on nitrile effects [8] has been carried out with thioglycosides [9–13], phosphites and phosphates [14] of neuraminic acid using acetonitrile as solvent to give the α glycosides; however, the α products were usually accompanied by the β isomers. An alternative procedure is introduction of an auxiliary group such as a hydroxyl, phenylthio, or phenylseleno at the 3-position of the sialic acid to regulate stereochemically the anomeric configuration of sialylation and suppress dehydrohalogenation during glycosylation [15–20]. In particular, substitution with a phenylthio group at C-3β of neuraminic acid leads to production of only the α glycoside without the β isomer [16,17]. Ogawa et al. have used the perbenzylated sialyl bromide as a donor, to which transformation from NANA requires multiple steps [17]. Simultaneously, we have developed per-*O*-acetyl-2β-chloro-3β-phenylthioneuraminate (**2a**) by syn-addition of phenylsulfenyl chloride (PhSCl) to the 2,3-dehydrosialate **6** [16]. The chloride **2a** is stable and crystalline.

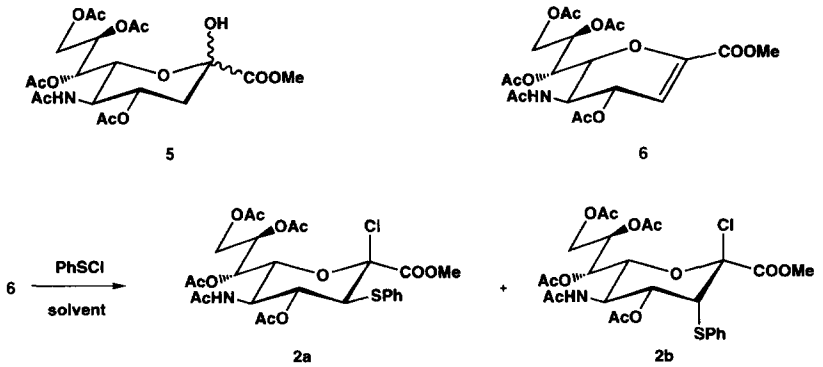
We have accomplished a stereochemically controlled total synthesis of GM_3 **1** on the basis of our simple methodology.

2. Results and discussion

Strategy for the synthesis of GM_3.—Our synthetic strategy for GM_3 is based on two key reactions: (*i*) α-stereoselective sialylation and (*ii*) direct condensation of a sterically hindered lipid with a GM_3 backbone thiosaccharide having glycosyl donor potential. Employment of our α-selective glycosylation method using methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*S*-phenyl-3-thio-D-*erythro*-α-L-*gluco*-2-nonulopyranosyl)onate chloride (**2a**) as a sialyl donor with a sugar efficiently realized formation of its



Scheme 1.



Scheme 2.

sialylsaccharide [16]. The other key reaction is direct β-linkage formation of a hindered lipid, such as a sphingosine, using a thioglycoside with the promoter and prevention from formation of the orthoester and acyl migration. However, until now, only the imidate method, which requires multiple steps for transformation of the reducing terminal protecting group into the imidate, has been reported for such glycosylations [3–5,21,22]. Our use of the ethyl 2-*O*-pivaloylthiolactoside **3** as a key intermediate is able to accomplish the β-glycosylation in one step.

The 2β-chloro-3β-phenylthio sialylate **2a** can be expected to be condensed to the 2,6,6′-tri-*O*-pivaloylthiolactoside **3** to construct the Neu5Ac-α-(2 → 3)-Gal-β-(1 → 4)-Glc-β-SEt, which is glycosylated with an azidosphingosine derivative **4**, devised by Schmidt [21,23], by activation of the thioglycoside using a promotor to accomplish the GM_3 backbone structure. Finally, transformation of the azidosphingosine to the ceramide by reductive acylation of the azido group and deprotection involving radical desulfurization should give GM_3 (see Scheme 1).

*Preparation and α-stereoselective glycosylation of methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-5-deoxy-3-S-phenyl-3-thio-α-*D-erythro-L-gluco-*2-nonulopyranosyl)onate chloride* (**2a**).—Kuhn's 4,7,8,9-tetra-*O*-acetylneuraminate **5** [6] was treated with thionyl chloride in hot benzene in the presence of hexamethylphosphoric triamide (HMPA) to afford 2,3-dehydroneuraminate **6** [24] in an 81% yield.

Addition of freshly prepared phenylsulfenyl chloride (PhSCl) to **6** gave a mixture of

Table 1
Yields of products **2a** and **2b** with variations in conditions and solvents

Solvent	Reaction temp (°C)	Time (day)	Yield (%)	
			2a	**2b**
Toluene	80	3	46	5
CH_2Cl_2	30	2	77	15
CH_3CN	30	2	35	60
CH_3NO_2	30	2	30	64

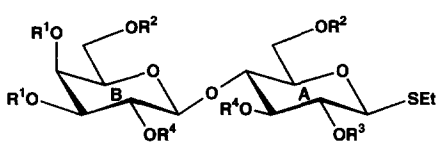
Table 2
Silver trifluoromethanesulfonate-promoted glycosylation of compounds **3**, **12**, and **13** with **2a**

Donor	Acceptor	D/A/P ratio	Product	Yield
2a	**3**	1/1.1/2.0	**16**	72%
2a	**12**	1/1.5/2.1	**14**	64%
2a	**13**	1/1.5/2.0	**15**	55%

3β- (**2a**) and 3α- (**2b**) adducts, with the anomeric ratio depending on the solvent (see Scheme 2). Solvent effects on production are summarized in Table 1. By using nonpolar solvents such as toluene or dichloromethane (CH_2Cl_2), the desired 2β-chloro-3β-phenylthio derivative **2a** was predominantly produced. PhSCl (2.3 equiv) was added to the solution of 2,3-dehydro derivative **6** in CH_2Cl_2, and the reaction was allowed to proceed at 30 °C in the dark for 2 days to give the 2β-chloro-3β-phenylthio derivative **2a** (77%), isolated as crystals, and a lesser amount of the 3α-phenylthio isomer **2b** (15%).

Glycosylation of **12**, **13**, and **3** with **2a**, promoted by silver trifluoromethanesulfonate (AgOTf), gave exclusively the α glycosyl products **14**, **15**, and **16**, respectively, in good yields (Table 2). Therefore, the phenylthio auxiliary in the 3β-position was concluded to act as an effective α-stereocontroller of the sialic acid donor.

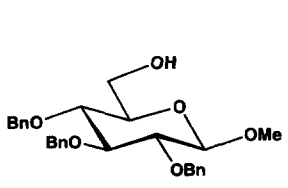
Preparation of the trisaccharide of GM_3.—In order to choose a protecting group for 2-OH on the thiolactoside **3**, we performed a preliminary glycosylation of octylalcohol or the azidosphingosine **4** with a number of acyl protecting thiolactosides, promoted with dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST) [25]. Using either the acetyl or benzoyl thiolactosides, the major products were the orthoesters and their resulting compounds, such as the 2-OH lactoside and the acylated lipid. However, use of the perpivalate for condensation of the azidosphingosine **4** gave β-glycolipid products, but the other acylate did not. Thus, a pivaloyl group was selected for protection of the 2-OH of the thiolactoside [26].



	R¹	R²	R³	R⁴
7	**Ac**	**Ac**	**Ac**	**Ac**
8	**H**	**H**	**H**	**H**
9	**isopropylidene**	**H**	**H**	**H**
10	**isopropylidene**	**Piv**	**H**	**H**
11	**isopropylidene**	**Piv**	**Piv**	**H**
3	**H**	**Piv**	**Piv**	**H**

The reactivity at the 3′-position of the nonreducing residue of a lactoside derivative is presumed to depend on the steric and electronic accessibility of the accepting hydroxy group [13]. Therefore, we chose ethyl 2,6,6′-tri-*O*-pivaloylthiolactoside (**3**) as a glycosyl acceptor [9,10,27].

Acid-catalyzed acetonide formation of ethyl thiolactoside **8** [28] with 2,2-dimethoxypropane afforded the desired 3′,4′-*O*-isopropylidene lactoside **9** in a 62% yield. Partial acylation of **9** with pivaloyl chloride (3 equiv) in the presence of 4-dimethylaminopyridine (DMAP, 0.2 equiv) in pyridine at 40 °C resulted in the 6,6′-di-*O*-pivaloylthiolactoside (**10**) in almost a 100% yield. Regioselective monopivaloylation at the 2-OH of **10** with pivaloyl chloride (1 equiv) added to a solution of **10** in CH_2Cl_2 at −78 °C in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 1 equiv) and DMAP (0.2 equiv) produced the desired 2,6,6′-tri-*O*-pivaloylthiolactoside **11** in a 88% yield, which showed a proton signal at δ 4.89 ($J_{1,2} = J_{2,3} = 9.5$ Hz, H-2 proton of the glucose residue, A-2). However, direct tripivaloylation of **9** with excess pivaloyl chloride gave rise to undesired pivalates as byproducts. The acetonide in **11** was removed by treatment with *p*-toluenesulfonic acid in methanol to give ethyl 2,6,6′-tri-*O*-pivaloylthiolactoside (**3**) in a 96% yield.



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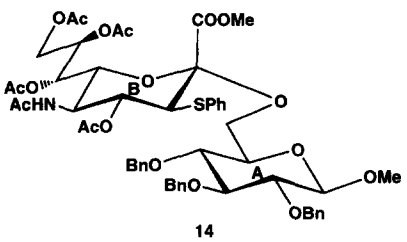

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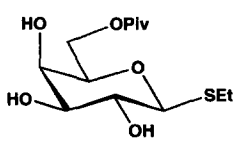

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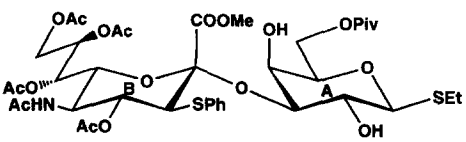

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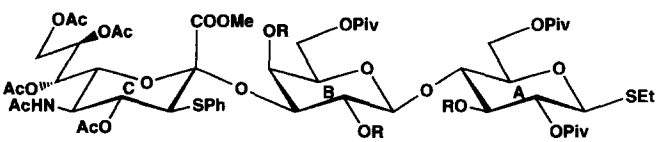
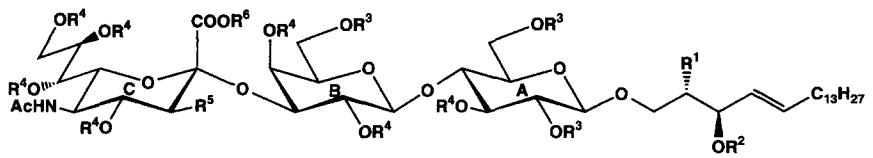


16 R = H
17 R = Ac

Glycosylation of **3** with the 2β-chloro-3β-phenylthio-neuraminate derivative **2a** (the molar ratio of **3** to **2a** was 1:0.7) in the presence of AgOTf and 3A molecular sieves in acetonitrile for 48 h at 60 °C gave the α-monosialyl lactoside **16**, exclusively, in a 72% yield. The anomeric configuration of the sialate in **16** was determined to be in α

according to Okamoto's rule [15], as the $|\delta C\text{-}9 - \delta C\text{-}9'|$ was 0.25 ppm, and $J_{7,8}$ was 9.0 Hz, which is characteristic of an α-glycosidically linked sialic acid. Acetylation of **16** for protection of the remaining hydroxyl groups gave the acetate **17** in a 94% yield. Also, the position of the sialylic linkage was determined to be at the 3′-OH position of **3** since the anomeric ^{13}C atom of the sialic acid residue correlated with the H-3 proton of the galactose residue (B-3) of the lactoside by HMBC.

Total synthesis of GM_3.—The thioglycoside **17** was reacted with the azidosphingosine **4** by activation using DMTST or NIS-TfOH [29] as promotors to give the corresponding glycosylazidosphingosine **18** as a major product in yields of 62 and 46%, respectively. The anomeric proton of **18** appeared at δ 4.54 ppm ($J_{1,2}$ 8.0 Hz), indicating that the glycosylic linkage of **18** was β. Acyl-migrated saccharides were obtained as minor products, presumably produced via an orthoester intermediate. This direct condensation resulted in a short-step synthesis of these gangliosides.



	R^1	R^2	R^3	R^4	R^5	R^6
18	N_3	Bz	Piv	Ac	SPh	Me
19	NH_2	Bz	Piv	Ac	SPh	Me
20	$NHCOC_{17}H_{35}$	Bz	Piv	Ac	SPh	Me
21	$NHCOC_{17}H_{35}$	Bz	Piv	Ac	H	Me
1	$NHCOC_{17}H_{35}$	H	H	H	H	H

Transformation of the azide in **18** to the ceramide according to Schmidt's procedure [30] is a well-known and often applied procedure for synthesis of gangliosides [5,10,11]. However, reduction of the azide group in **18** to the corresponding amine **19** by treatment with H_2S in aqueous pyridine did not always progress to completion. Since the reproducibility of the reduction was poor, we applied the phosphine reduction–acylation method [31] for transformation to the ganglioside. The azide **18** was reduced with tri-*n*-butylphosphine (1.3 equiv) in the presence of octadecanoic acid (2 equiv) in CH_2Cl_2 at room temperature to afford the corresponding ceramide **20** and the corresponding sphingosine **19**, detected by the nihydrin test. To accomplish the transformation, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC) was added to the reaction mixture to give an 88% yield of the desired ceramide **20**.

Radical reduction of **20** using tri-*n*-butyltin hydride (n-Bu_3SnH) in the presence of azobisisobutyronitrile (AIBN) in toluene was carried out to selectively remove the

3β-phenylthio auxiliary and afforded the desired compound **21** in 70% yield without any damage to the olefinic group in the ceramide moiety.

Finally, *O*-deacylation of **21** with potassium *tert*-butoxide in methanol, with subsequent saponification of the sialate methyl ester group, yielded the ganglioside GM_3 **1** in quantitative yield. The ^1H NMR data of the synthetic **1** were consistent with previously reported data [32].

The work described above showed that the 3β-phenylthio group on the NANA donor and 2-*O*-pivaloylthioglycosides play an important role in ganglioside synthesis. Use of this simple methodology is a promising approach for synthesis of a series of α-sialyl gangliosides and their analogues.

3. Experimental

General methods.—Optical rotations were determined with a JASCO DIP-181 polarimeter at 25 °C, and IR spectra were recorded with a JASCO IR-700 spectrophotometer. ^1H NMR spectra were recorded at 500 MHz with a JEOL GX-500 in the Fourier-transform mode. Chemical shifts (δ) were expressed in parts per million from internal tetramethylsilane unless otherwise noted, and coupling constants (*J*) in Hz. Preparative column chromatography was performed on silica gel (Fuji Devison Co., BW-300) with the solvent systems specified. Evaporations were conducted in vacuo.

*Preparation of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,3,5-trideoxy-*D-glycero-D-galacto-*non-2-enopyranosonate* (**6**).—To a solution of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-2-nonulopyranosonate [6] (**5**; 13 g, 26 mmol) and hexamethylphosphoric triamide (HMPA; 7.3 mL, 42 mmol) in benzene (300 mL) was added thionyl chloride (2.4 mL, 33 mmol), and the mixture was stirred and refluxed at 80 °C for 7 h. After the reaction completed, the mixture was washed with satd aq $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel with 2:1 hexane–acetone to give 2,3-dehydro Neu5Ac **6** (10 g, 81%) as an amorphous mass. The ^1H NMR data were in agreement with those previously reported [19].

*Methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*S*-phenyl-3-thio-α-*D-erythro-L-gluco-*2-nonulopyranosyl)onate chloride* (**2a**) *and methyl (5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*S*-phenyl-3-thio-α-*D-erythro-L-manno-*2-nonulopyranosyl)onate chloride* (**2b**) [16].—To a solution of **6** (1.0 g, 2.1 mmol) in CH_2Cl_2 (9.0 mL) was added phenylsulfenyl chloride (PhSCl; 0.7 g, 4.8 mmol) under an argon atmosphere, and the mixture was left under darkness at 30 °C. After 2 days, the mixture was washed with satd aq $NaHCO_3$, water and brine, dried with Na_2SO_4, and concentrated. The residue was chromatographed on a column of silica gel with 3:3:1 hexane–EtOAc–acetone to give **2a** (1.0 g, 77%) as a white powder and **2b** (0.20 g, 15%) as an amorphous mass. Compounds **2a** and **2b** were respectively crystallized as white needles from hexane–EtOAc and toluene–acetone.

Compound **2a**: mp 131 °C; $[\alpha]_D$ −8.8° (*c* 0.40, $CHCl_3$); IR (KBr) 3398, 1750, 1665, 1539, 1438, 1370, 1219, 1124, 1034 cm^{-1}; UV λ_{max} 253 nm (ε 4800); ^1H NMR ($CDCl_3$): δ 1.87, 1.90, 2.05, 2.11, 2.12 (5 s, 15 H, 5 Ac), 3.82 (s, 3 H, MeO), 3.99 (dd,

1 H, $J_{8,9}$ 5.0, $J_{9,9'}$ 12.5 Hz, H-9), 4.00 (d, 1 H, $J_{3,4}$ 11.0 Hz, H-3), 4.27 (dd, 1 H, $J_{8,9'}$ 2.5, $J_{9,9'}$ 12.5 Hz, H-9'), 4.34 (q, 1 H, $J_{4,5} = J_{5,6} = J_{5,NH}$ = 10.0 Hz, H-5), 4.40 (dd, 1 H, $J_{5,6}$ 10.0, $J_{6,7}$ 2.0 Hz, H-6), 5.12 (ddd, 1 H, $J_{7,8}$ 8.0, $J_{8,9}$ 5.0, $J_{8,9'}$ 2.5 Hz, H-8), 5.36 (dd, 1 H, $J_{3,4}$ 11.0, $J_{4,5}$ 10.0 Hz, H-4), 5.43 (dd, 1 H, $J_{6,7}$ 2.0, $J_{7,8}$ 8.0 Hz, H-7), 5.43 (d, 1 H, $J_{5,NH}$ 10.0 Hz, NH), 7.2–7.5 (m, 5 H, Ph); FABMS (*m*-nitrobenzyl alcohol: NBA) *m/z* 618 and 620 $[M + H]^+$. Anal. Calcd for $C_{26}H_{32}ClNO_{12}S \cdot 1.5H_2O$ (645.14): C, 48.40; H, 5.48; N, 2.17. Found: C, 48.34; H, 5.20; N, 2.36.

Compound **2b**: mp 178 °C; $[\alpha]_D$ −21.4° (*c* 0.49, $CHCl_3$); IR (KBr) 3390, 1750, 1665, 1546, 1438, 1370, 1222, 1045, 748, 602 cm^{-1}; UV λ_{max} 254 nm (ϵ 5200); ^1H NMR ($CDCl_3$): δ 1.81, 1.95, 2.06, 2.07, 2.20 (5 s, 15 H, 5 Ac), 3.85 (s, 3 H, MeO), 4.16 (dd, 1 H, $J_{8,9}$ 6.0, $J_{9,9'}$ 12.5 Hz, H-9), 4.18 (d, 1 H, $J_{3,4}$ 4.0 Hz, H-3), 4.44 (dd, 1 H, J_{56} 11.0, $J_{6,7}$ 2.0 Hz, H-6), 4.49 (dd, 1 H, $J_{8,9'}$ 2.5, $J_{9,9'}$ 12.5 Hz, H-9'), 4.54 (dt, 1 H, $J_{4,5}$ 10.5, $J_{5,NH}$ 9.5 Hz, H-5), 5.27 (ddd, 1 H, $J_{7,8}$ 7.0, $J_{8,9}$ 6.0, $J_{8,9'}$ 2.5 Hz, H-8), 5.42 (dd, 1 H, $J_{6,7}$ 2.0, $J_{7,8}$ 7.0 Hz, H-7), 5.45 (d, 1 H, $J_{5,NH}$ 9.5 Hz, NH), 5.85 (dd, 1 H, $J_{3,4}$ 4.0, $J_{4,5}$ 10.5 Hz, H-4), 7.2–7.6 (m, 5 H, Ph); FABMS (*m*-nitrobenzyl alcohol) *m/z* 618 and 620 $[M + H]^+$. Anal. Calcd for $C_{26}H_{32}ClNO_{12}S$ (618.11): C, 50.52; H, 5.23; N, 2.27. Found: C, 50.28; H, 5.26; N, 2.30.

*Ethyl 2,3,4,6-tetra-*O*-acetyl-β-*D*-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-acetyl-1-thio-β-*D*-glucopyranoside* (**7**) *[28].*—To a solution of β-lactose peracetate [2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1 → 4)-1,2,3,6-tetra-*O*-acetyl-β-D-glucopyranose] (2.0 g, 2.9 mmol) in CH_2Cl_2 (10 mL) was added ethanethiol (0.25 mL, 3.3 mmol) and 47% boron trifluoride etherate (1.0 mL, 3.3 mmol), and the mixture was stirred for 1.5 h at room temperature. The solution was washed successively with 5% aq $NaHCO_3$ and brine, and dried with Na_2SO_4. After treatment with active charcoal, the solvent was evaporated and the residue was chromatographed on a column of silica gel with 1:1 EtOAc–hexane to give **7** (1.8 g, 90%) as an amorphous mass: mp 72–74 °C, $[\alpha]_D$ −1.4° (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.26 (t, 3 H, CH_3CH_2S), 1.96, 2.04(2), 2.05, 2.06, 2.11, 2.15, (7 s, 21 H, 7 Ac), 2.66 (m, 2 H, CH_3CH_2S), 3.62 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 5.5, $J_{5,6'}$ 2.0 Hz, A-5), 3.78 (t, 1 H, $J_{3,4} = J_{4,5}$ = 10.0 Hz, A-4), 3.84 (t, 1 H, $J_{5,6} = J_{5,6'}$ = 6.0 Hz, B-5), 4.08 (dd, 1 H, $J_{5,6}$ 6.0, $J_{6,6'}$ 11.5 Hz, B-6), 4.09 (dd, 1 H, $J_{5,6}$ 5.5, $J_{6,6'}$ 12.5 Hz, A-6), 4.13 (dd, 1 H, $J_{5,6'}$ 6.0, $J_{6,6'}$ 11.5 Hz, B-6'), 4.47 (dd, 1 H, $J_{5,6'}$ 2.0, $J_{6,6'}$ 12.5 Hz, A-6'), 4.48 (d, 1 H, $J_{1,2}$ 8.0 Hz, B-1), 4.48 (d, 1 H, $J_{1,2}$ 10.0 Hz, A-1), 4.93 (t, 1 H, $J_{1,2} = J_{2,3}$ = 10.0 Hz, A-2), 4.95 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 4.0 Hz, B-3), 5.11 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.0 Hz, B-2), 5.21 (t, 1 H, $J_{2,3} = J_{3,4}$ = 10.0 Hz, A-3), 5.35 (d, 1 H, $J_{3,4}$ 4.0 Hz, B-4). Anal. Calcd for $C_{28}H_{40}O_{17}S \cdot 0.5H_2O$ (689.76): C, 48.75; H, 6.00. Found: C, 48.80; H, 5.94.

*Ethyl β-*D*-galactopyranosyl-(1 → 4)-1-thio-β-*D*-glucopyranoside* (**8**) *[28].*—To a solution of ethyl per-*O*-acetyl-1-thiolactoside **7** (1.6 g, 2.3 mmol) in MeOH (60 mL) was added *t*-BuOK (150 mg, 1.3 mmol), and the mixture was stirred for 6 h at room temperature, and then neutralized with Dowex 50W × 8 (H^+). Water was added to the mixture for dissolving white precipitate, and this mixture was filtered and washed with MeOH. The filtrate and washings were combined and concentrated. Crystallization of the residue was conducted from water–EtOH and gave **8** (850 mg, 94%) as a white powder; mp 189–192 °C, $[\alpha]_D$ −27.4° (*c* 0.50, CH_3OH); ^1H NMR (D_2O): δ 1.16 (t, 3 H, *J* 7.2 Hz, CH_3CH_2S), 2.65 (m, 2 H, CH_3CH_2S), 3.26 (t, 1 H, $J_{1,2} = J_{2,3}$ = 9.8 Hz,

A-2), 3.43 (t, 1 H, $J_{1,2} = J_{2,3} = 8.4$ Hz, B-2), 3.61 (m, 1 H, B-6), 3.81 (d, 1 H, J 3.0 Hz, B-4), 3.85 (dd, 1 H, $J_{5,6'}$ 2.0, $J_{6,6'}$ 12.6 Hz, A-6′), 4.34 (d, 1 H, $J_{1,2}$ 8.4 Hz, B-1), 4.45 (d, 1 H, $J_{1,2}$ 9.8 Hz, A-1). Anal. Calcd for $C_{14}H_{26}O_{10}S \cdot 0.5H_2O$ (395.48): C, 42.52; H, 6.90. Found: C, 42.66; H, 6.77.

*Ethyl 3,4-*O*-isopropylidene-β-*D*-galactopyranosyl-(1 → 4)-1-thio-β-*D*-glucopyranoside* (**9**).—To a solution of **8** (3.1 g, 8.0 mmol) in *N*,*N*-dimethylformamide (31 mL) and acetone (65 mL) was added 2,2-dimethoxypropane (1.7 mL) and sulfuric acid (0.09 mL), and the mixture was stirred for 20 h at 60 °C. The mixture was neutralized with anhyd Na_2CO_3 and concentrated under reduced pressure. Column chromatography (8:1, CH_2Cl_2–CH_3OH) of the residue on silica gel (200 g) gave **9** (2.1 g, 62%) as an amorphous mass: mp 206–207 °C, $[\alpha]_D$ −1.0° (*c* 0.20, CH_3OH); ^{1}H NMR (CD_3OD): δ 1.28 (t, 3 H, J 7.5 Hz, CH_3CH$_2$S), 1.32, 1.47 (2 s, 6 H, (CH_3)$_2$C), 2.65–2.80 (m, 2 H, CH$_3$CH_2S), 3.26 (t, 1 H, $J_{1,2} = J_{2,3} = 9.5$ Hz, A-2), 3.39 (ddd, 1 H, $J_{4,5}$ 9.5, $J_{5,6}$ 4.0, $J_{5,6'}$ 2.5 Hz, A-5), 3.44 (t, 1 H, $J_{1,2} = J_{2,3} = 8.0$ Hz, B-2), 3.50 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, A-3), 3.56 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, A-4), 3.72–3.81 (m, 3 H, A-6, B-6, B-6′), 3.86 (dd, 1 H, $J_{5,6'}$ 2.5, $J_{6,6'}$ 12.0 Hz, A-6′), 3.92 (ddd, 1 H, $J_{4,5}$ 2.0, $J_{5,6}$ 4.5, $J_{5,6'}$ 8.0 Hz, B-5), 4.04 (dd, 1 H, $J_{2,3}$ 8.0, $J_{3,4}$ 5.5 Hz, B-3), 4.18 (dd, 1 H, $J_{3,4}$ 5.5, $J_{4,5}$ 2.0 Hz, B-4), 4.35 (d, 1 H, $J_{1,2}$ 8.0 Hz, B-1), 4.37 (d, 1 H, $J_{1,2}$ 9.5 Hz, A-1). Anal. Calcd for $C_{17}H_{30}O_{10}S \cdot 0.8H_2O$ (440.96): C, 46.30; H, 7.24. Found: C, 45.98; H, 6.92.

*Ethyl 3,4-*O*-isopropylidene-6-*O*-pivaloyl-β-*D*-galactopyranosyl-(1 → 4)-6-*O*-pivaloyl-1-thio-β-*D*-glucopyranoside* (**10**).—To a solution of **9** (2.1 g, 4.9 mmol) and 4-dimethylaminopyridine (105 mg, 0.86 mmol) in pyridine (65 mL) was added pivaloyl chloride (1.9 mL, 15 mmol), and the mixture was stirred for 24 h at 40 °C. The mixture was concentrated under reduced pressure and dissolved in EtOAc. The solution was washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel, with 2:1 hexane–acetone to give **10** (2.9 g, 99%) as a white crystal: mp 196–197 °C, $[\alpha]_D$ +33.5° (*c* 0.20, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.20, 1.22 (2 s, 18 H, 2 Piv), 1.32 (t, 3 H, J 7.7 Hz, CH_3CH$_2$S), 1.35, 1.53 (2 s, 6 H, (CH_3)$_2$C), 2.61 (d, 1 H, $J_{2,OH}$ 1.5 Hz, A-2OH), 2.74 (m, 2 H, CH$_3$CH_2S), 3.30 (dd, 1 H, $J_{3,4}$ 8.8, $J_{4,5}$ 9.9 Hz, A-4), 3.41 (ddd, 1 H, $J_{1,2}$ 9.9, $J_{2,3}$ 8.8, $J_{2,OH}$ 1.5 Hz, A-2), 3.47 (d, 1 H, $J_{2,OH}$ 3.3 Hz, B-2OH), 3.51 (ddd, 1 H, $J_{4,5}$ 9.9, $J_{5,6}$ 6.0, $J_{5,6'}$ 1.4 Hz, A-5), 3.61 (dt, 1 H, $J_{2,3} = J_{3,4} = 8.8$, $J_{3,OH}$ 1.0 Hz, A-3), 3.64 (dt, 1 H, $J_{1,2} = J_{2,3} = 7.7$, $J_{2,OH}$ 3.3 Hz, B-2), 4.06–4.12 (m, 3 H, A-6, B-3, B-5), 4.15 (dd, 1 H, $J_{3,4}$ 2.2, $J_{4,5}$ 5.5 Hz, B-4), 4.23 (d, 1 H, $J_{1,2}$ 8.4 Hz, B-1), 4.25 (dd, 1 H, $J_{5,6}$ 7.8, $J_{6,6'}$ 12.1 Hz, B-6), 4.26 (d, 1 H, $J_{3,OH}$ 1.0 Hz, A-3OH), 4.39 (d, 1 H, $J_{1,2}$ 9.9 Hz, A-1), 4.45 (dd, 1 H, $J_{5,6'}$ 3.7, $J_{6,6'}$ 12.1 Hz, B-6′), 4.64 (dd, 1 H, $J_{5,6'}$ 1.4, $J_{6,6'}$ 12.0 Hz, A-6′). Anal. Calcd for $C_{27}H_{46}O_{12}S$ (594.80): C, 54.52; H, 7.81. Found: C, 54.37; H, 7.83.

*Ethyl 3,4-*O*-isopropylidene-6-*O*-pivaloyl-β-*D*-galactopyranosyl-(1 → 4)-2,6-di-*O*-pivaloyl-1-thio-β-*D*-glucopyranoside* (**11**).—To a stirred solution of **10** (1.0 g, 1.7 mmol) and 4-dimethylaminopyridine (40 mg, 0.33 mmol) in dry CH_2Cl_2 (50 mL), cooled to −78 °C, was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.27 mL, 1.8 mmol), and the mixture was stirred for 15 min at −78 °C. Pivaloyl chloride (0.23 mL, 1.9 mmol) was added dropwise to the mixture, and the mixture was stirred for 2.5 h at −78 °C. MeOH (1 mL) was added to the mixture, and the solution was successively

washed with satd aq $NaHCO_3$, water and brine, dried (Na_2SO_4), and then evaporated. The residue was chromatographed on a column of silica gel (40 g) with 5:1 hexane–acetone, to give **11** (1.0 g, 88%) as an amorphous mass: mp 128–129 °C, $[\alpha]_D$ +31.5° (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.1–1.3 (m, 30 H, 3 Piv, CH_3CH_2S), 1.34, 1.52 (2 s, 6 H, $(CH_3)_2C$), 2.67 (m, 2 H, CH_3CH_2S), 3.36 (dd, 1 H, $J_{3,4}$ 9.5, $J_{4,5}$ 10.0 Hz, A-4), 3.45 (br, 1 H, OH), 3.51 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 5.5, $J_{5,6'}$ 1.5 Hz, A-5), 3.62 (t, 1 H, $J_{1,2} = J_{2,3} = 8.0$ Hz, B-2), 3.73 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, A-3), 4.07–4.14 (m, 4 H, A-6, B-3, B-4, B-5), 4.21 (br, 1 H, OH), 4.23 (d, 1 H, $J_{1,2}$ 8.0 Hz, B-1), 4.24 (dd, 1 H, $J_{5,6}$ 9.0, $J_{6,6'}$ 12.0 Hz, B-6), 4.43 (dd, 1 H, $J_{5,6'}$ 3.0, $J_{6,6'}$ 12.0 Hz, B-6'), 4.43 (d, 1 H, $J_{1,2}$ 9.5 Hz, A-1), 4.66 (dd, 1 H, $J_{5,6'}$ 1.5, $J_{6,6'}$ 12.6 Hz, A-6'), 4.89 (t, 1 H, $J_{1,2} = J_{2,3} = 9.5$ Hz, A-2). Anal. Calcd for $C_{32}H_{54}O_{13}S$ (678.93): C, 56.61; H, 8.03. Found: C, 56.39; H, 7.95.

*Ethyl 6-*O*-pivaloyl-β-*D*-galactopyranosyl-(1 → 4)-2,6-di-*O*-pivaloyl-1-thio-β-*D*-glucopyranoside* (**3**).—To a solution of **11** (1.0 g, 1.5 mmol) in MeOH (100 mL) was added *p*-toluenesulfonic acid monohydrate (60 mg, 0.32 mmol), and the mixture was stirred for 1.5 h at 50 °C. To the mixture was added satd aq $NaHCO_3$, and the mixture was extracted by CH_2Cl_2. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The residue was chromatographed on a column of silica gel (60 g) with 5:1 hexane–acetone, to give **3** (0.9 g, 96%) as an amorphous mass: mp 90–91 °C, $[\alpha]_D$ +12.5° (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.10–1.33 (m, 30 H, 3 Piv, CH_3CH_2S), 2.67 (m, 2 H, CH_3CH_2S), 3.40 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, A-4), 3.54 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 5.5, $J_{5,6'}$ 1.5 Hz, A-5), 3.61 (dd, 1 H, $J_{2,3}$ 8.5, $J_{3,4}$ 4.0 Hz, B-3), 3.74 (dd, 1 H, $J_{1,2}$ 7.5, $J_{2,3}$ 8.5 Hz, B-2), 3.74 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 9.0 Hz, A-3), 3.78 (dd, 1 H, $J_{5,6}$ 8.0, $J_{5,6'}$ 4.5 Hz, B-5), 3.91 (d, 1 H, $J_{3,4}$ 4.0 Hz, B-4), 4.16 (dd, 1 H, $J_{5,6}$ 5.5, $J_{6,6'}$ 12.0 Hz, A-6), 4.24 (dd, 1 H, $J_{5,6}$ 8.0, $J_{6,6'}$ 12.0 Hz, B-6), 4.28 (d, 1 H, $J_{1,2}$ 7.5 Hz, B-1), 4.41 (dd, 1 H, $J_{5,6'}$ 4.5, $J_{6,6'}$ 12.0 Hz, B-6'), 4.44 (d, 1 H, $J_{1,2}$ 10.0 Hz, A-1), 4.64 (dd, 1 H, $J_{5,6}$ 1.5, $J_{6,6'}$ 12.0 Hz, A-6'), 4.88 (t, 1 H, $J_{1,2} = J_{2,3} = 10.0$ Hz, A-2). Anal. Calcd for $C_{29}H_{50}O_{13}S \cdot 0.3H_2O$ (644.27): C, 54.06; H, 7.93. Found: C, 53.96; H, 7.77.

*Methyl (methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*S*-phenyl-3-thio-*D*-erythro-β-*L*-gluco-2-nonulopyranosylonate)-(2 → 6)-2,3,4-tri-*O*-benzyl-β-*D*-glucopyranoside* (**14**).—To a solution of **2a** (50 mg, 0.081 mmol) and methyl 2,3,4-tri-*O*-benzyl-β-D-glucopyranoside (**12**; 56 mg, 0.12 mmol) in dry MeCN (0.50 mL) was added 3A molecular sieves (MS-3A, 100 mg) and disodium hydrogenphosphate (Na_2HPO_4; 100 mg). To the mixture was added, with stirring, silver trifluoromethanesulfonate (AgOTf; 43 mg, 0.17 mmol) in MeCN (0.30 mL), and the stirring was continued under darkness for 3 days at room temperature, 1 day at 40 °C and then 1 day at 55 °C. The solids were filtered off and washed thoroughly with EtOAc. The filtrate and washings were combined, and the solution was successively washed with 5% aq $Na_2S_2O_3$, 5% aq $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated to a syrup that was chromatographed on a column of silica gel (20 g), with 2:1 hexane–acetone, to give **14** (54 mg, 64%) as an amorphous mass: mp 85–87 °C, $[\alpha]_D$ −2.8° (*c* 0.18, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.89, 1.92, 1.96, 1.97, 1.98, (5 s, 15 H, 5 Ac), 3.25 (d, 1 H, $J_{3,4}$ 11.1 Hz, B-3), 3.33 (t, 1 H, $J_{3,4} = J_{4,5} = 9.0$ Hz, A-4), 3.36 (dd, 1 H, $J_{1,2}$ 7.5, $J_{2,3}$ 8.8 Hz, A-2), 3.43 (ddd, 1 H, $J_{4,5}$ 9.0, $J_{5,6}$ 5.0, $J_{5,6'}$ 1.9 Hz, A-5), 3.49 (s, 3 H, MeO), 3.59 (t, 1

H, $J_{2,3} = J_{3,4} = 9.0$ Hz, A-3), 3.78 (s, 3 H, MeO), 3.94 (dd, 1 H, $J_{8,9}$ 5.6, $J_{9,9'}$ 12.5 Hz, B-9), 4.04 (dd, 1 H, $J_{5,6}$ 5.0, $J_{6,6'}$ 10.6 Hz, A-6), 4.15 (dd, 1 H, $J_{5,6'}$ 1.9, $J_{6,6'}$ 10.6 Hz, A-6′), 4.19 (dd, 1 H, $J_{8,9'}$ 2.5, $J_{9,9'}$ 12.5 Hz, B-9′), 4.21 (d, 1 H, $J_{1,2}$ 7.5 Hz, A-1), 4.21 (m, 1 H, B-5), 4.34 (dd, 1 H, $J_{5,6}$ 11.3, $J_{6,7}$ 2.3 Hz, B-6), 4.61 (d, 1 H, J 10.0 Hz, CH_2Ph), 4.66 (d, 1 H, J 10.0 Hz, CH_2Ph), 4.73 (d, 1 H, J 11.3 Hz, CH_2Ph), 4.78 (d, 1 H, J 11.3 Hz, CH_2Ph), 4.90 (d, 1 H, J 11.3 Hz, CH_2Ph), 4.91 (d, 1 H, J 11.3 Hz, CH_2Ph), 5.27–5.32 (m, 2 H, B-4, B-7), 5.33 (ddd, 1 H, $J_{7,8}$ 8.8, $J_{8,9}$ 5.6, $J_{8,9'}$ 2.5 Hz, B-8), 5.47 (d, 1 H, $J_{5,NH}$ 10.0 Hz, NH), 7.1–7.5 (m, 20 H, 4 Ph); FABMS (*m*-nitrobenzylalcohol) *m/z* 1045.9 $[M + H]^+$. Anal. Calcd for $C_{54}H_{63}O_{18}NS \cdot 3\ H_2O$ (1100.3): C, 58.94; H, 6.33; N, 1.27. Found: C, 58.54; H, 5.93; N, 1.62.

Ethyl (methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-5-deoxy-3*-S-*phenyl-3-thio*-D-erythro-β-L-gluco-*2-nonulopyranosylonate)-(2 → 3)-6*-O-*pivaloyl-1-thio-β*-D-*galactopyranoside* (**15**).—To a solution of **2a** (100 mg, 0.16 mmol) and ethyl 6-*O*-pivaloyl-1-thio-β-D-galactopyranoside (**13**; 75 mg, 0.24 mmol) in dry MeCN (1.0 mL) was added MS-3A (200 mg) and Na_2HPO_4 (200 mg). AgOTf (82 mg, 0.32 mmol) in MeCN (1.0 mL) was added with stirring, and the stirring was continued under darkness for 1 day at room temperature, successively 1 day at 40 °C, 1 day at 55 °C, and then 1 day at 70 °C. The solids were filtered off and washed thoroughly with EtOAc. The filtrate and washings were combined, and the solution was successively washed with 5% aq $Na_2S_2O_3$, 5% aq $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated to a syrup that was chromatographed on a column of silica gel (52 g), with 2:1 toluene–acetone, to give **15** (78 mg, 55%) as an amorphous mass: mp 89–90 °C, $[\alpha]_D$ +30.0° (*c* 0.19, $CHCl_3$); IR (KBr, cm^{-1}), 3518, 3494, 3382, 2962, 1747, 1668, 1550, 1439, 1370, 1221, 1154, 1034; ^1H NMR ($CDCl_3$): δ 1.21, (s, 9 H, Piv), 1.30 (t, 3 H, J 8.0 Hz, CH_3CH$_2$S), 1.92, 2.04, 2.06, 2.07, 2.14 (5 s, 15 H, 5 Ac), 2.73 (m, 2 H, CH$_3$CH_2S), 2.83 (br, 1 H, A-2OH), 3.48 (d, 1 H, $J_{3,4}$ 11.3 Hz, B-3), 3.52 (br. t, 1 H, J 10.0 Hz, A-2), 3.66 (br. t, 1 H, J 6.3 Hz, A-5), 3.91 (s, 3 H, MeO), 4.05 (dd, 1 H, $J_{8,9}$ 5.6, $J_{9,9'}$ 12.5 Hz, B-9), 4.09 (br, 1 H, A-4), 4.16 (dd, 1 H, $J_{2,3}$ 8.8, $J_{3,4}$ 3.1 Hz, A-3), 4.19 (dd, 1 H, $J_{8,9'}$ 3.1, $J_{9,9'}$ 12.5 Hz, B-9′), 4.21 (q, 1 H, $J_{4,5} = J_{5,6} = J_{5,NH} = 10.0$ Hz, B-5), 4.26–4.28 (m, 2 H, A-6, A-6′), 4.35 (dd, 1 H, $J_{5,6}$ 10.0, $J_{6,7}$ 1.9 Hz, B-6), 4.38 (d, 1 H, $J_{1,2}$ 10.0 Hz, A-1), 5.27 (dd, 1 H, $J_{6,7}$ 1.9, $J_{7,8}$ 8.8 Hz, B-7), 5.34 (ddd, 1 H, $J_{7,8}$ 8.8, $J_{8,9}$ 5.6, $J_{8,9'}$ 3.1 Hz, B-8), 5.38 (dd, 1 H, $J_{3,4}$ 11.3, $J_{4,5}$ 10.0 Hz, B-4), 5.42 (d, 1 H, $J_{5,NH}$ 10.0 Hz, NH), 7.2–7.6 (m, 5 H, Ph); FABMS (*m*-nitrobenzyl alcohol) *m/z* 890.1 $[M + H]^+$. Anal. Calcd for $C_{39}H_{55}O_{18}NS_2 \cdot H_2O$ (908.11): C, 51.58; H, 6.34; N, 1.54. Found: C, 51.46; H, 5.99; N, 1.89.

Ethyl (methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-5-deoxy-3*-S-*phenyl-3-thio*-D-erythro-β-L-gluco-*2-nonulopyranosylonate)-(2 → 3)-6-pivaloyl-β*-D-*galactopyranosyl-(1 → 4)-2,6-di*-O-*pivaloyl-1-thio-β*-D-*glucopyranoside* (**16**).—To a solution of **2a** (88 mg, 0.14 mmol) and tripivaloyl lactoside **3** (100 mg, 0.16 mmol) in dry MeCN (0.5 mL) was added MS-3A (140 mg), and the mixture was stirred 1 h at room temperature. AgOTf was added with stirring, (73 mg, 0.28 mmol), and the stirring was continued under darkness for 14 h at 40 °C, 1 day at 60 °C, and 1 day at 70 °C. The solids were filtered off and washed thoroughly with EtOAc. The filtrate and washings were combined, and the solution was successively washed with satd aq $Na_2S_2O_3$, satd aq $NaHCO_3$, water and brine, dried (Na_2SO_4), and concentrated to a syrup that was

chromatographed on a column of silica gel (45 g), with 3:1 toluene–acetone, to give **16** (123 mg, 72%) as an amorphous mass: mp 109–110 °C, $[\alpha]_D$ +16.8° (*c* 0.40, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.14–1.27 (m, 30 H, 3 Piv, CH_3CH$_2$S), 1.93, 2.02, 2.06, 2.09, 2.12 (5 s, 15 H, 5 Ac), 2.57–2.77 (m, 2 H, CH$_3$CH_2S), 3.21 (d, 1 H, $J_{2,OH}$ 1.0 Hz, B-2OH), 3.44 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, A-4), 3.47 (d, 1 H, $J_{3,4}$ 11.0 Hz, C-3), 3.51 (dt, 1 H, $J_{1,2} = J_{2,3} = 7.5$, $J_{2,OH}$ 1.0 Hz, B-2), 3.60 (ddd, 1 H, $J_{5,6}$ 2.0, $J_{5,6'}$ 7.0, $J_{4,5}$ 9.5 Hz, A-5), 3.70 (t, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, A-3), 3.72 (ddd, 1 H, $J_{4,5}$ 3.0, $J_{5,6}$ 4.0, $J_{5,6'}$ 8.0 Hz, B-5), 3.91 (s, 3 H, MeO), 4.02 (dd, 1 H, $J_{8,9}$ 7.0, $J_{9,9'}$ 12.5 Hz, C-9), 4.07 (br, 1 H, B-4), 4.10 (dd, 1 H, $J_{2,3}$ 7.5, $J_{3,4}$ 3.0 Hz, B-3), 4.11 (dd, 1 H, $J_{5,6}$ 7.0, $J_{6,6'}$ 12.0 Hz, A-6), 4.18 (dd, 1 H, $J_{5,6}$ 8.6, $J_{6,6'}$ 12.0 Hz, B-6), 4.21 (dt, 1 H, $J_{4,5}$ 11.0, $J_{5,6} = J_{5,NH} =$ 10.0 Hz, C-5), 4.27 (dd, 1 H, $J_{9,9'}$ 12.5 Hz, C-9′), 4.29 (s, 1 H, OH), 4.30 (d, 1 H, $J_{1,2}$ 7.5 Hz, B-1), 4.32 (dd, 1 H, $J_{5,6'}$ 4.0, $J_{6,6'}$ 12.0 Hz, B-6′), 4.41 (dd, 1 H, $J_{5,6}$ 10.0, $J_{6,7}$ 1.5 Hz, C-6), 4.42 (d, 1 H, $J_{1,2}$ 9.5 Hz, A-1), 4.66 (dd, 1 H, $J_{5,6'}$ 2.0, $J_{6,6'}$ 12.0 Hz, A-6′), 4.87 (t, 1 H, $J_{1,2} = J_{2,3} = 9.5$ Hz, A-2), 5.23 (dd, 1 H, $J_{6,7}$ 1.5, $J_{7,8}$ 9.0 Hz, C-7), 5.33 (ddd, 1 H, $J_{7,8}$ 9.0, $J_{8,9}$ 7.0, $J_{8,9'}$ 2.5 Hz, C-8), 5.36 (t, 1 H, $J_{3,4} = J_{4,5} = 11.0$ Hz, C-4), 5.39 (d, 1 H, $J_{5,NH}$ 10.0 Hz, NH), 7.13–7.25 (m, 5 H, Ph). Anal. Calcd for $C_{55}H_{81}NO_{25}S_2 \cdot H_2O$ (1238.5): C, 53.33; H, 6.77; N, 1.13. Found: C, 53.30; H, 6.68; N, 1.36.

Ethyl (methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-5-deoxy-3*-S-*phenyl-3-thio*-D-erythro-*β*-L-gluco-*2-nonulopyranosylonate)-(2 → 3)-2,4-di*-O-*acetyl-6*-O-*pivaloyl-β*-D-*galactopyranosyl-(1 → 4)-3*-O-*acetyl-2,6-di*-O-*pivaloyl-1-thio-β*-D-*glucopyranoside* (**17**).—To a solution of **16** (1.26 g, 1.03 mmol) was added Ac_2O (20 mL) and pyridine (40 mL), and the mixture was stirred for 22 h at 50 °C. When the reaction was finished, the mixture was concentrated under reduced pressure. The residue was purified directly by column chromatography (2:1 hexane–acetone) on silica gel (20 g) to give trisaccharide **17** (1.31 g, 94%) as an amorphous mass: mp 128–130 °C, $[\alpha]_D$ +30.1° (c 0.76, $CHCl_3$); ν 3452 (NH), 1749 and 1222 (ester), 1691 (amide); ^{1}H NMR ($CDCl_3$): δ 1.1–1.3 (m, 30 H, 3 Piv, CH_3CH$_2$S), 1.82, 1.86, 1.93, 2.03, 2.04, 2.06, 2.13, 2.18 (8 s, 24 H, 8 Ac), 2.57–2.76 (m, 2 H, CH$_3$CH_2S), 3.05 (d, 1 H, $J_{3,4}$ 12.0 Hz, C-3), 3.57 (dd, 1 H, $J_{5,6}$ 10.5, $J_{6,7}$ 3.0 Hz, C-6), 3.67 (ddd, 1 H, $J_{4,5}$ 10.0, $J_{5,6}$ 6.5, $J_{5,6'}$ 2.0 Hz, A-5), 3.78 (t, 1 H, $J_{3,4} = J_{4,5} = 10.0$ Hz, A-4), 3.90 (dd, 1 H, $J_{5,6}$ 6.5, $J_{5,6'}$ 7.5 Hz, B-5), 3.91 (s, 3 H, MeO), 3.97 (dd, 1 H, $J_{5,6}$ 6.5, $J_{6,6'}$ 10.5 Hz, B-6), 4.00 (dt, 1 H, $J_{4,5} = J_{5,NH} =$ 10.0, $J_{5,6}$ 10.5 Hz, C-5), 4.05 (dd, 1 H, $J_{8,9}$ 4.5, $J_{9,9'}$ 12.5 Hz, C-9), 4.09 (dd, 1 H, $J_{5,6}$ 6.5, $J_{6,6'}$ 12.0 Hz, A-6), 4.16 (dd, 1 H, $J_{5,6'}$ 6.5, $J_{6,6'}$ 10.5 Hz, B-6′), 4.40 (dd, 1 H, $J_{8,9'}$ 3.0, $J_{9,9'}$ 12.5 Hz, C-9′), 4.52 (d, 1 H, $J_{1,2}$ 10.0 Hz, A-1), 4.63 (dd, 1 H, $J_{5,6'}$ 2.0, $J_{6,6'}$ 12.0 Hz, A-6′), 4.66 (d, 1 H, $J_{1,2}$ 7.5 Hz, B-1), 4.84 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 3.5 Hz, B-3), 4.93 (t, 1 H, $J_{1,2} = J_{2,3} = 10.0$ Hz, A-2), 5.10 (dd, 1 H, $J_{1,2}$ 7.5, $J_{2,3}$ 10.0 Hz, B-2), 5.22 (dd, 1 H, $J_{3,4}$ 12.0, $J_{4,5}$ 10.0 Hz, C-4), 5.23 (d, 1 H, $J_{5,NH}$ 10.0 Hz, NH), 5.26 (d, 1 H, $J_{3,4}$ 3.5 Hz, B-4), 5.27 (t, 1 H, $J_{2,3} = J_{3,4} = 10.0$ Hz, A-3), 5.39 (dd, 1 H, $J_{6,7}$ 3.0, $J_{7,8}$ 9.0 Hz, C-7), 5.48 (ddd, 1 H, $J_{7,8}$ 9.0, $J_{8,9}$ 4.5, $J_{8,9'}$ 3.0 Hz, C-8), 7.2–7.5 (m, 5 H, Ph). Anal. Calcd for $C_{61}H_{87}NO_{28}S_2$ (1346.6): C, 54.40; H, 6.53; N, 1.04. Found: C, 54.39; H, 6.66; N, 1.16.

(Methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-5-deoxy-3*-S-*phenyl-3-thio*-D-erythro-*β*-L-gluco-*2-nonulopyranosylonate)-(2 → 3)-2,4-di*-O-*acetyl-6*-O-*pivaloyl-β*-D-*galactopyranosyl-(1 → 4)-3*-O-*acetyl-2,6-di*-O-*pivaloyl-β*-D-*glucopyranosyl-(1 → 1)-(2*S*,3*R*,4*E*)-2-*

azido-3-O-benzoyl-4-octadecene-1,3-diol (**18**).—To a solution of **17** (115 mg, 85 μmol) and (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol [20,23] (**4**; 96 mg, 0.22 mmol) in dry CH_2Cl_2 (12 mL) was added MS-3A (100 mg), and the mixture was stirred overnight at room temperature. To the suspension was added a mixture (180 mg; 50% DMTST by weight) of DMTST (4.1 equiv relative to the donor) and MS-3A, and the mixture was stirred for 22 h at room temperature. The solids were filtered off and washed thoroughly with CH_2Cl_2, and the combined filtrate and washings were concentrated. Column chromatography (4:1 toluene–acetone) of the residue on silica gel (10 g) gave a glycosyl azidosphingosine **18** (90 mg, 62%) as an amorphous solid: mp 84–85 °C, $[\alpha]_D$ +23.3° (*c* 0.52, $CHCl_3$); *ν* 3340 (NH), 2927 and 2850 (Me, CH_2), 2106 (N_3), 1750 and 1220 (ester), 1640 and 1541 (amide), 773 and 714 (Ph); ^{1}H NMR ($CDCl_3$): lactose unit δ 3.66 (ddd, 1 H, $J_{4,5}$ 9.6, $J_{5,6}$ 6.4, $J_{5,6'}$ 1.6 Hz, A-5), 3.82 (t, 1 H, $J_{3,4} = J_{4,5} = 9.6$ Hz, A-4), 3.91 (dd, 1 H, $J_{5,6}$ 8.8, $J_{5,6'}$ 6.4 Hz, B-5), 3.98 (dd, 1 H, $J_{5,6}$ 8.8, $J_{6,6'}$ 11.2 Hz, B-6), 4.09 (dd, 1 H, $J_{5,6}$ 6.4, $J_{6,6'}$ 12.0 Hz, A-6), 4.15 (dd, 1 H, $J_{5,6'}$ 6.4, $J_{6,6'}$ 11.2 Hz, B-6′), 4.54 (d, 1 H, $J_{1,2}$ 8.0 Hz, A-1), 4.62 (dd, 1 H, $J_{5,6'}$ 1.6, $J_{6,6'}$ 12.0 Hz, A-6′), 4.67 (d, 1 H, $J_{1,2}$ 8.0 Hz, B-1), 4.84 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 4.0 Hz, B-3), 4.92 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 9.6 Hz, A-2), 5.10 (dd, 1 H, $J_{1,2}$ 8.0, $J_{2,3}$ 10.4 Hz, B-2), 5.25 (t, 1 H, $J_{2,3} = J_{3,4} = 9.6$ Hz, A-3), 5.25 (d, 1 H, $J_{3,4}$ 4.0 Hz, B-4); Neu5Ac unit δ 3.04 (d, 1 H, $J_{3,4}$ 11.2 Hz, C-3), 3.57 (dd, 1 H, $J_{5,6}$ 11.2, $J_{6,7}$ 2.4 Hz, C-6), 3.91 (s, 3 H, MeO), 4.02 (ddd, 1 H, $J_{4,5}$ 6.4, $J_{5,NH}$ 2.4, $J_{5,6}$ 11.2 Hz, C-5), 4.03 (dd, 1 H, $J_{8,9}$ 4.8, $J_{9,9'}$ 12.8 Hz, C-9), 4.38 (dd, 1 H, $J_{8,9'}$ 2.4, $J_{9,9'}$ 12.8 Hz, C-9′), 5.20 (dd, 1 H, $J_{3,4}$ 11.2, $J_{4,5}$ 6.4 Hz, C-4), 5.24 (d, 1 H, $J_{5,NH}$ 2.4 Hz, NH), 5.39 (dd, 1 H, $J_{6,7}$ 2.4, $J_{7,8}$ 9.6 Hz, C-7), 5.50 (ddd, 1 H, $J_{7,8}$ 9.6, $J_{8,9}$ 4.8, $J_{8,9'}$ 2.4 Hz, C-8); sphingosine unit δ 0.88 (t, 3 H, *Me*CH_2), 1.2–1.4 (br, 24 H, 11 C*H*$_2$, H-6, H-6′), 3.58 (dd, 1 H, $J_{1,1'}$ 10.4, $J_{1,2}$ 5.6 Hz, H-1), 3.81 (dd, 1 H, $J_{1,1'}$ 10.4, $J_{1',2}$ 7.2 Hz, H-1′), 3.91 (ddd, 1 H, $J_{1,2}$ 5.6, $J_{1',2}$ 7.2, $J_{2,3}$ 4.0 Hz, H-2), 5.52 (dd, 1 H, $J_{3,4}$ 8.0, $J_{4,5}$ 15.2 Hz, H-4), 5.56 (dd, 1 H, $J_{2,3}$ 4.0, $J_{3,4}$ 8.0 Hz, H-3), 5.90 (dt, 1 H, $J_{4,5}$ 15.2 Hz, H-5); phenyl groups 7.2–8.1 (m, 10 H, 2 Ph); *O*-acetyl groups δ 1.82, 1.85, 1.94, 2.03, 2.04, 2.06, 2.12, 2.19 (8 s, 24 H, 8 Ac); *O*-pivaloyl groups δ 1.18(2), 1.21 (3 s, 27 H, 3 Piv). Anal. Calcd for $C_{84}H_{120}N_4O_{31}S \cdot H_2O$ (1732.2): C, 58.24; H, 7.11; N, 3.24. Found: C, 58.33; H, 7.01; N, 3.24.

*(Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-5-deoxy-3-*S*-phenyl-3-thio-*D-erythro-*β*-L-gluco-2-nonulopyranosonate)-(2 → 3)-2,4-di-*O*-acetyl-6-*O*-pivaloyl-*β*-D-galactopyranosyl-(1 → 4)-3-*O*-acetyl-2,6-di-*O*-pivaloyl-*β*-D-glucopyranosyl-(1 → 1)-(2*S*,3*R*,4*E*)-3-*O*-benzoyl-2-octadecanamido-4-octadecene-1,3-diol* (**20**).—To a solution of **18** (100 mg, 58.3 μmol) and octadecanoic acid (35 mg, 123 μmol) in CH_2Cl_2 (7.5 mL) was added tri-*n*-butylphosphine (19 μL, 76.3 μmol), and the solution was stirred for 6 h at room temperature, the course of the reaction being monitored by TLC. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (WSC, 30 mg) was added to the solution, and the mixture was stirred for 12 h at room temperature. After completion of the reaction, the solution was washed with 0.1 N NaOH and water, dried (Na_2SO_4), and concentrated to a syrup that was chromatographed (2:1 hexane–acetone) on a column of silica gel (10 g), to give a protecting ganglioside GM_3 **20** (100 mg, 88%) as an amorphous mass: mp 83–84 °C, $[\alpha]_D$ +25.2° (*c* 0.33, $CHCl_3$); *ν* 3327 (NH), 2925 and 2855 (Me, CH_2), 1752 and 1225 (ester), 1664 and 1541 (amide), 750 and 714 (Ph); ^{1}H

NMR ($CDCl_3$): lactose unit δ 3.60 (m, 1 H, A-5), 3.78 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, A-4), 3.95–4.05 (m, 3 H, A-6, B-5, B-6), 4.15 (dd, 1 H, $J_{5,6'}$ 6.4, $J_{6,6'}$ 10.7 Hz, B-6'), 4.47 (d, 1 H, $J_{1,2}$ 8.1 Hz, A-1), 4.54 (dd, 1 H, $J_{5,6'}$ 1.7, $J_{6,6'}$ 11.5 Hz, A-6'), 4.64 (d, 1 H, $J_{1,2}$ 8.3 Hz, B-1), 4.82 (dd, 1 H, $J_{2,3}$ 10.0, $J_{3,4}$ 3.9 Hz, B-3), 4.86 (dd, 1 H, $J_{1,2}$ 8.1, $J_{2,3}$ 9.8 Hz, A-2), 5.09 (dd, 1 H, $J_{1,2}$ 8.3, $J_{2,3}$ 10.0 Hz, B-2), 5.19–5.26 (m, 2 H, A-3, B-4); Neu5Ac unit δ 3.04 (d, 1 H, $J_{3,4}$ 11.3 Hz, C-3), 3.57 (dd, 1 H, $J_{5,6}$ 11.0, $J_{6,7}$ 2.7 Hz, C-6), 3.90 (s, 3 H, MeO), 3.95–4.05 (m, 2 H, C-5, C-9), 4.38 (dd, 1 H, $J_{8,9'}$ 2.7, $J_{9,9'}$ 13.0 Hz, C-9'), 5.19–5.26 (m, 2 H, C-4, NH), 5.40 (dd, 1 H, $J_{6,7}$ 2.7, $J_{7,8}$ 9.3 Hz, C-7), 5.49 (ddd, 1 H, $J_{7,8}$ 9.3, $J_{8,9}$ 4.9, $J_{8,9'}$ 2.7 Hz, C-8); ceramide unit δ 0.88 (t, 6 H, J 6.4 Hz, $MeCH_2$(2)), 1.20–1.65 (m, 52 H, 11 CH_2, 15 CH_2), 1.97–2.20 (m, 4 H, $COCH_2$, H-6, H-6'), 3.60 (dd, 1 H, $J_{1,1'}$ 10.0, $J_{1,2}$ 3.9 Hz, H-1), 3.89 (m, 1 H, H-1'), 4.45 (ddd, 1 H, $J_{1,2}$ 3.9, $J_{1',2}$ 13.2, $J_{2,3}$ 7.1 Hz, H-2), 5.46 (dd, 1 H, $J_{3,4}$ 7.1, $J_{4,5}$ 15.6 Hz, H-4), 5.54 (t, 1 H, $J_{2,3} = J_{3,4} = 7.1$ Hz, H-3), 5.75 (d, 1 H, $J_{2,NH}$ 9.3 Hz, NH), 5.85 (dt, 1 H, $J_{4,5}$ 15.6, $J_{5,6}$ 6.4 Hz, H-5); phenyl groups 7.21–8.02 (m, 10 H, 2 Ph); *O*-acetyl groups δ 1.82, 1.85, 1.93, 2.02, 2.04, 2.06, 2.13, 2.17 (8 s, 24 H, 8 Ac); *O*-pivaloyl groups δ 1.13, 1.15, 1.22 (3 s, 27 H, 3 Piv). Anal. Calcd for $C_{102}H_{156}N_2O_{32}S$ (1954.7): C, 62.67; H, 8.06; N, 1.43. Found: C, 62.40; H, 8.11; N, 1.58.

(Methyl 5-acetamido-4,7,8,9-tetra-O-*acetyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosonate)-(2 → 3)-2,4-di*-O-*acetyl-6*-O-*pivaloyl-β*-D-*galactopyranosyl-(1 → 4)-3*-O-*acetyl-2,6-di*-O-*pivaloyl-β*-D-*glucopyranosyl-(1 → 1)-(2S,3R,4E)-3*-O-*benzoyl-2-octadecanamido-4-octadecene-1,3-diol* (**21**).—To a solution of **20** (50 mg, 26 μmol) and α,α'-azobisisobutyronitrile (AIBN; 55 mg, 0.33 mmol) in toluene (10 mL) was added tri-*n*-butyltin hydride (0.10 mL, 0.37 mmol), and the solution was refluxed for 3 h at 110 °C. After completion of the reaction, the solution was concentrated. Column chromatography (3:1 hexane–acetone) of the residue on silica gel (10 g) gave **21** (34 mg, 70%) as an amorphous mass: mp 73–74 °C, $[\alpha]_D$ +11.7° (*c* 0.12, $CHCl_3$); ^1H NMR ($CDCl_3$): lactose unit δ 3.57–3.62 (m, 1 H, A-5), 3.76 (t, 1 H, $J_{3,4} = J_{4,5} = 9.3$ Hz, A-4), 3.83 (m, 1 H, B-5), 3.89 (dd, 1 H, $J_{5,6}$ 8.3, $J_{6,6'}$ 10.8 Hz, B-6), 3.93 (dd, 1 H, $J_{5,6}$ 6.4, $J_{6,6'}$ 12.2 Hz, A-6), 4.11 (dd, 1 H, $J_{5,6'}$ 5.9, $J_{6,6'}$ 10.8 Hz, B-6'), 4.44 (d, 1 H, $J_{1,2}$ 7.8 Hz, A-1), 4.51 (dd, 1 H, $J_{5,6'}$ 1.5, $J_{6,6'}$ 11.7 Hz, B-6'), 4.57 (dd, 1 H, $J_{2,3}$ 10.3, $J_{3,4}$ 3.4 Hz, B-3), 4.64 (d, 1 H, $J_{1,2}$ 8.3 Hz, B-1), 4.84 (dd, 1 H, $J_{1,2}$ 7.8, $J_{2,3}$ 9.3 Hz, A-2), 4.88–4.95 (m, 2 H, B-2, B-4), 5.22 (t, 1 H, $J_{2,3} = J_{3,4} = 9.3$ Hz, A-3); Neu5Ac unit δ 1.66 (t, 1 H, $J_{3,3'} = J_{3,4} = 12.7$ Hz, C-3), 2.57 (dd, 1 H, $J_{3,3'}$ 12.7, $J_{3',4}$ 4.4 Hz, C-3'), 3.57–3.62 (m, 1 H, C-6), 3.83 (s, 3 H, MeO), 4.01–4.06 (m, 2 H, C-5, C-9), 4.32 (dd, 1 H, $J_{8,9'}$ 2.9, $J_{9,9'}$ 12.7 Hz, C-9'), 4.88–4.95 (m, 1 H, C-4), 5.03 (d, 1 H, $J_{5,NH}$ 10.3 Hz, NH), 5.40 (dd, 1 H, $J_{6,7}$ 3.0, $J_{7,8}$ 9.8 Hz, C-7), 5.56 (ddd, 1 H, $J_{7,8}$ 9.8, $J_{8,9}$ 5.0, $J_{8,9'}$ 2.9 Hz, C-8); ceramide unit δ 0.88 (t, 6 H, J 5.9 Hz, $MeCH_2$(2)), 1.2–1.4 (br, 52 H, 11 CH_2, 15 CH_2), 1.97–2.20 (m, 4 H, $COCH_2$, H-6, H-6'), 3.57–3.62 (m, 1 H, H-1), 4.01–4.06 (m, 1 H, H-1'), 4.44 (m, 1 H, H-2), 5.45 (dd, 1 H, $J_{3,4}$ 7.8, $J_{4,5}$ 15.6 Hz, H-4), 5.53 (t, 1 H, $J_{2,3} = J_{3,4} = 7.8$ Hz, H-3), 5.74 (d, 1 H, $J_{2,NH}$ 9.3 Hz, NH), 5.85 (dt, 1 H, $J_{4,5}$ 15.6, $J_{5,6} = J_{5,6'} = 7.4$ Hz, H-5); *O*-acyl groups δ 1.11, 1.14, 1.20 (3 s, 27 H, 3 Piv), 1.85, 2.00, 2.02, 2.06, 2.07, 2.09, 2.14, 2.21 (8 s, 24 H, 8 Ac), 7.4–8.0 (m, 5 H, Bz). Anal. Calcd for $C_{96}H_{151}N_2O_{32} \cdot 0.8H_2O$ (1859.9): C, 61.99; H, 8.29; N, 1.51. Found: C, 62.01; H, 8.32; N, 1.72.

5-Acetamido-3,5-dideoxy-D-glycero-α-D-galacto-*2-nonulopyranosylonic acid-(2 → 3)-*

β-D-*galactopyranosyl-(1 → 4)-β*-D-*glucopyranosyl-(1 → 1)-(2S,3R,4E)-2-octadecanamido-4-octadecene-1,3-diol* (GM_3, **1**).—To a solution of **21** (28 mg, 15.2 μmol) in MeOH (1.0 mL) was added *t*-BuOK (10 mg), and the mixture was stirred for 3 h at room temperature, the course of the reaction being monitored by TLC. Water was added and the mixture was stirred for 24 h at room temperature, then treated with Dowex 50W × 8 (H^+) resin to neutralize the base. The resin was filtered off and washed with MeOH, and the combined filtrate and washings were concentrated. Column chromatography (MeOH) of the residue on Sephadex LH-20 gave **1** (GM_3, 18 mg, quantitative) as an amorphous mass: $[\alpha]_D$ +2.0° (*c* 0.1, 1:1 $CHCl_3$–MeOH); ^1H NMR (6:1 CD_3OD–D_2O): lactose unit δ 4.36 (d, 1 H, $J_{1,2}$ 8.0 Hz, A-1), 4.48 (d, 1 H, $J_{1,2}$ 7.5 Hz, B-1); Neu5Ac unit δ 2.04 (s, 3 H, AcN), 2.85 (dd, $J_{3e,3a}$ 13.0, $J_{3e,4}$ 4.0 Hz, 1 H, C-3e); ceramide unit δ 0.90 (t, 3 H, *J* 6.8 Hz, $MeCH_2$), 0.94 (t, 3 H, *J* 7.3 Hz, $MeCH_2$), 2.20 (t, 2 H, *J* 6.7 Hz, $COCH_2$), 4.22 (dd, 1 H, $J_{1,1'}$ 10.3, $J_{1,2}$ 4.0 Hz, H-1), 5.44 (dd, 1 H, $J_{3,4}$ 7.5, $J_{4,5}$ 16.0 Hz, H-4), 5.71 (dt, 1 H, $J_{5,6} = J_{5,6'} = 7.0$ Hz, H-5). HRMS Calcd for $C_{59}H_{108}N_2O_{21}$: $[M + Na]^+$ 1203.7342. Found: 1203.7355.

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