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# Synthesis of cerebroside, lactosyl ceramide, and ganglioside $GM_3$ analogs containing $\beta$-thioglycosidically linked ceramide*

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ABSTRACT

Coupling of the sodium salt of 2,3,4,6-tetra-*O*-acetyl-1-thio-$\beta$-D-glucopyranose, -$\beta$-D-galactopyranose, *O*-(2,3,4,6-tetra-*O*-acetyl-$\beta$-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-1-thio-$\beta$-D-glucopyranose, or *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-$\alpha$-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,3-di-*O*-acetyl-6-*O*-bezoyl-$\beta$-D-galactopyranosyl)-(1→4)-3-*O*-acetyl-2,6-di-*O*-benzoyl-1-thio-$\beta$-D-glucopyranose, which were prepared from the corresponding 1-*S*-acetates, **1**, **3**, **6**, and **9**, with (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-1-*O*-(*p*-tolylsulfonyl)-4-octadecene-1,3-diol (**12**) derived by tosylation of **11**, gave the corresponding $\beta$-thioglycosides **13**, **17**, **21**, and **25**, respectively in good yield. The $\beta$-thioglycosides obtained were converted, *via* selective reduction of the azide group, condensation with octadecanoic acid, and removal of the protecting groups, into the title compounds.

## INTRODUCTION

It is well known that glycolipids, the so-called cerebrosides, glycosphingolipids, and gangliosides, have biological roles[2–5] such as cell growth, differentiation, adhesion, oncogenis, and receptor functions for viruses and bacterial toxins. Recently, we have synthesized[6] several ganglioside analogs containing $\alpha$-thioglycosides of sialic acid, and have observed that these analogs are potent inhibitors[7] of sialidase activities of different subtypes of influenza viruses. Further modification of the glycolipid molecule, to place sulfur in the glycosidic linkage between the sugar and ceramide, should be carried out, not only for obtaining endoglycoceramidase[8] inhibitors, but also for elucidating the functions of the glycolipids at the molecular level. We describe here the synthesis of cerebrosides, lactosyl ceramide, and ganglioside $GM_3$ analogs, containing $\beta$-thioglycosidically linked ceramide.

## RESULTS AND DISCUSSION

The title thioglycolipids **1** and **3**, by potassium thioacetate treatment of the corresponding per-*O*-acetyl-$\alpha$-D-hexopyranosyl bromides, and **6** and **9** by treatment of the corresponding $\alpha$-trichloroacetimidates **5** (ref. 9) and **8** (ref. 10), respectively, with

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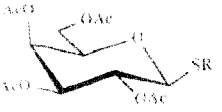
thioacetic acid in the presence of boron trifluoride etherate, were prepared in good yields as the required intermediates.

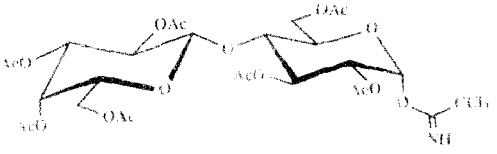
(2*S*,3*R*,4*E*)-2-Azido-3-*O*-benzoyl-1-*O*-(*p*-tolylsulfonyl)-4-octadecene-1,3-diol (**12**), derived by *p*-tolylsulfonylation of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[11] (**11**), was used as the glycosyl acceptor. The coupling products could be readily converted into the target compounds.

Treatment of the sodium salt **2**, freshly prepared from 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (**1**) by selective *S*-deacetylation with sodium methox-

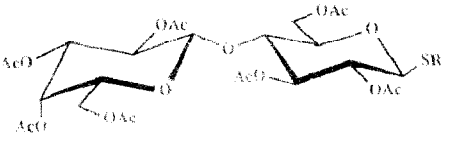
1 R = Ac
2 R = Na



3 R = Ac
4 R = Na



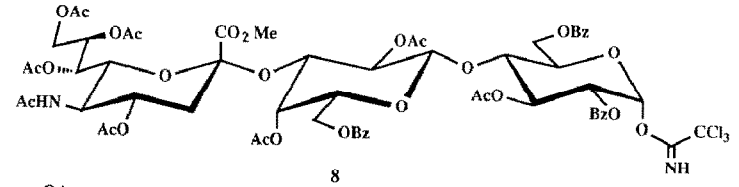
5



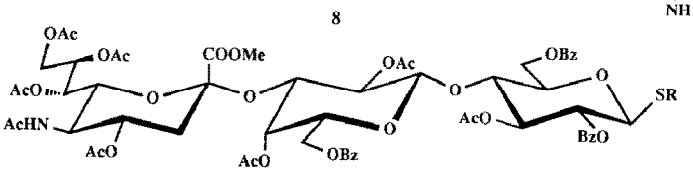
6 R = Ac
7 R = Na

ide, with compound **12** in *N*,*N*-dimethylformamide under nitrogen, afforded *S*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-(1→1)-(2*R*,3*R*,4*E*)-2-azido-3-benzoyloxy-4-octadecene-1-thiol (**13**) in 87% yield, after column chromatography. The structure of **13** was unambiguously proved by 270-*MHz* $^1$H-n.m.r. spectroscopy. The observed signals exhibited four sharp singlets, each integrating for three protons, which demonstrated the presence of four *O*-acetyl groups; H-1 resonated at δ 4.55 as a wide doublet ($J_{1,2}$ 10.1 Hz), indicating the β configuration of the glycosidic linkage. Other $^1$H-n.m.r. data are consistent with structure **13**. By essentially the same way as described for **13** condensation of **12** with the sodium salts **4**, **7**, and **10**, derived from the corresponding 1-*S*-acetyl derivatives **3**, **6**, and **9**, respectively, yielded the desired β-thioglycosides **17**, **21**, and **25** in

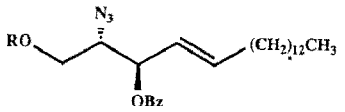
92, 91, and 41% yields. $^1$H-N.m.r. data for **17**, **21**, and **25** demonstrated them to be fully blocked glycosides; each H-1 signal from the newly formed $\beta$-glycosidic linkage appeared at $\delta$ 4.52 ($J_{1,2}$ 9.9 Hz), 4.55 ($J_{1,2}$ 10.1 Hz), and 4.80 ($J_{1,2}$ 9.5 Hz); other n.m.r. data are consistent with the structures assigned. Selective reduction[12,13] of the azide group in **13** with hydrogen sulfide in 5:1 pyridine–water gave the amine **14**, which, on condensation with octadecanoic acid using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) in dichloromethane, afforded the *S*-(per-*O*-acetyl-$\beta$-D-glucopyranosyl)-(1→1)-(2*R*,3*R*,4*E*)-3-benzoyloxy-2-octadecanamido-4-octadecene-1-thiol (**15**) in 75% yield. According to the same procedure described for **15**, selective reduction of the azide group in compounds **17**, **21**, and **25**, and subsequent condensation with octadecanoic acid yielded the corresponding desired products **19**, **23**, and **27**, respectively in high yields.




**8**



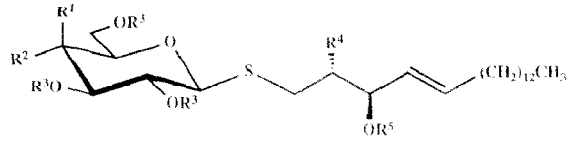

**9** R = Ac
**10** R = Na




**11** R = H
**12** R = Ts

Ts = p-tolylsulfonyl
Bz = benzoyl

Finally, *O*-deacylation of compounds **15**, **19**, and **23**, with sodium methoxide in methanol, yielded the target products **16**, **20**, and **24** respectively in good yields *O*-(5-Acetamido-3,5-dideoxy-D-*glycero*-$\alpha$-D-*galacto*-2-nonulopyranosylonic acid)-(2→3)-*O*-($\beta$-D-galactopyranosyl)-(1→4)-*S*-($\beta$-D-glucopyranosyl)-(1→1)-(2*R*,3*R*,4*E*)-3-hydroxy-2-octadecanamido-4-octadecene-1-thiol (**28**), a ganglioside $GM_3$ analog containing $\beta$-thioglycosidically linked ceramide, was obtained in good yield by *O*-deacylation of **27** with sodium methoxide and subsequent saponification of the methyl ester group.



13 $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$, $R^4 = N_3$, $R^5 = Bz$

14 $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$, $R^4 = NH_2$, $R^5 = Bz$

15 $R^1 = H$, $R^2 = OAc$, $R^3 = Ac$, $R^4 = NHCO(CH_2)_{16}CH_3$, $R^5 = Bz$

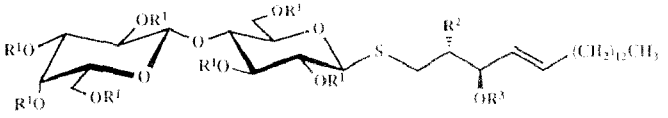
16 $R^1 = R^3 = R^5 = H$, $R^2 = OH$, $R^4 = NHCO(CH_2)_{16}CH_3$

17 $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$, $R^4 = N_3$, $R^5 = Bz$

18 $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$, $R^4 = NH_2$, $R^5 = Bz$

19 $R^1 = OAc$, $R^2 = H$, $R^3 = Ac$, $R^4 = NHCO(CH_2)_{16}CH_3$, $R^5 = Bz$

20 $R^1 = OH$, $R^2 = R^3 = R^5 = H$, $R^4 = NHCO(CH_2)_{16}CH_3$

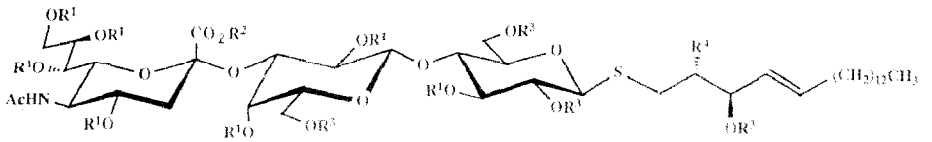


21 $R^1 = Ac$, $R^2 = N_3$, $R^3 = Bz$

22 $R^1 = Ac$, $R^2 = NH_2$, $R^3 = Bz$

23 $R^1 = Ac$, $R^2 = NHCO(CH_2)_{16}CH_3$, $R^3 = Bz$

24 $R^1 = R^3 = H$, $R^2 = NHCO(CH_2)_{16}CH_3$



25 $R^1 = Ac$, $R^2 = Me$, $R^3 = Bz$, $R^4 = N_3$

26 $R^1 = Ac$, $R^2 = Me$, $R^3 = Bz$, $R^4 = NH_2$

27 $R^1 = Ac$, $R^2 = Me$, $R^3 = Bz$, $R^4 = NHCO(CH_2)_{16}CH_3$

28 $R^1 = R^2 = R^3 = H$, $R^4 = NHCO(CH_2)_{16}CH_3$

## EXPERIMENTAL

*General methods.* — Melting points are uncorrected. Optical rotations were determined with a Union PM-201 polarimeter at 25°, and i.r. spectra were recorded with a Jasco A-100 spectrometer. $^1$H-N.m.r. spectra were recorded at 270 MHz with a Jeol JNM-GX270 spectrometer. Preparative chromatography was performed on silica gel (Wako Co.; 200 mesh) with the solvent systems specified. Concentrations and evaporations were conducted *in vacuo*.

*O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-1-S-acetyl-1-thio-β-D-glucopyranose* (**6**). — To a solution of *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl trichloroacetimidate[9] (**5**, 90 mg, 0.12 mmol) in dry $CH_2Cl_2$ (3 mL) were added AcSH (0.01 mL) and $BF_3{\cdot}Et_2O$ (0.01 mL), and the mixture was stirred for 2 h at room temperature. The mixture was successively washed with M $Na_2CO_3$ and water, dried ($Na_2SO_4$), and concentrated to a syrup that was chromatographed on a column of silica gel (20 g) with 170:1 $CH_2Cl_2$–MeOH to give **6** (60 mg, 75%) as an amorphous mass; $[\alpha]_D$ 0° (*c* 1.2, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): δ 1.97, 2.02, 2.04, 2.05, 2.07, 2.11, 2.15 (7 s, 21 H, 7 $CH_3CO_2$), 2.38 (s, 3 H, $CH_3COS$), 4.47 (d, 1 H, $J_{1',2'}$ 8.1 Hz, H-1'), 4.95 (dd, 1 H, $J_{2',3'}$, 10.3, $J_{3',4'}$ 3.8 Hz, H-3'), 5.04 (t, 1 H, $J_{2,3} = J_{3,4} = 10.3$ Hz, H-3), 5.11 (dd, 1 H, H-2'), 5.23 (dd, 1 H, $J_{1,2}$ 6.6 Hz, H-2), 5.31 (d, 1 H, H-1), and 5.35 (d, 1 H, H-4').

*Anal.* Calc. for $C_{28}H_{38}O_{18}S$ (694.7): C, 48.41; H, 5.51. Found: C, 48.54; H, 5.63.

*O-(Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-O-(2,4-di-O-acetyl-6-O-benzoyl-β-D-galactopyranosyl)-(1→4)-3-O-acetyl-1-S-acetyl-2,6-di-O-benzoyl-1-thio-β-D-glucopyranose* (**9**). — To a solution of *O*-(methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-*glycero*-α-D-*galacto*-2-nonulopyranosylonate)-(2→3)-*O*-(2,4-di-*O*-acetyl-6-*O*-benzoyl-β-D-galactopyranosyl)-(1→4)-3-*O*-acetyl-2,6-di-*O*-benzoyl-α-D-glucopyranosyl trichloroacetimidate[10] (**8**, 100 mg, 71.5 μmol) in dry $CH_2Cl_2$ (5 mL) were added AcSH (0.01 mL) and $BF_3{\cdot}Et_2O$ (0.01 mL), and the mixture was stirred overnight at room temperature. A similar processing as that described for **6**, and column chromatography (silica gel, 50 g) using 90:1 $CH_2Cl_2$–MeOH as eluant gave **9** (85 mg, 91%) as an amorphous mass; $[\alpha]_D$ +0.5° (*c* 0.2, $CHCl_3$); $\nu_{max}$ 3400 (NH), 1750 and 1230 (ester), 1700 (*S*-acetyl), 1680 and 1550 (amide), and 720 $cm^{-1}$ (Ph); $^1$H-n.m.r. ($CDCl_3$): Neu5Ac unit δ 1.67 (t, 1 H, $J_{3a,3e} = J_{3a,4} = 12.5$ Hz, H-3*a*), 1.83 (s, 3 H, $CH_3CON$), 2.57 (dd, 1 H, $J_{3e,4}$ 4.6 Hz, H-3*e*), 3.60 (dd, 1 H, $J_{5,6}$ 10.7, $J_{6,7}$ 2.6 Hz, H-6), 3.71 (s, 3 H, $CH_3O$), 4.12 (m, 1 H, $J_{4,5}$ 9.9 Hz, H-5), 4.23 (dd, 1 H, $J_{8,9}$ 7.1, $J_{9,9'}$ 11.4 Hz, H-9), and 4.40 (dd, 1 H, $J_{8,9'}$ 3.7 Hz, H-9'); Gal unit δ 4.33 (d, 1 H, 8.0 Hz, H-1), 5.01 (dd, 1 H, $J_{2,3}$ 10.3, $J_{3,4}$ 3.3 Hz, H-3), and 5.39 (d, 1 H, H-4); Glc unit δ 2.22 (s, 3 H, $CH_3COS$), 5.32 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 5.45 (t, 1 H, $J_{3,4}$ 9.3 Hz, H-3); *O*-acyl groups δ 1.94, 2.00, 2.01 (2), 2.02, 2.11, and 2.21 (7 s, 21 H, 7 $CH_3CO_2$), 7.38–8.12 (m, 15 H, 3 Ph-*H*).

*Anal.* Calc. for $C_{61}H_{69}NO_{29}S$ (1312.2): C, 55.83; H, 5.30; N, 1.07. Found: C, 55.70; H, 5.21; N, 1.12.

*(2S,3R,4E)-2-Azido-3-O-benzoyl-1-O-(p-tolylsulfonyl)-4-octadecene-1,3-diol* (**12**). — To a solution of (2*S*,3*R*,4*E*)-2-azido-3-*O*-benzoyl-4-octadecene-1,3-diol[11] (**11**, 653 mg, 1.52 mmol) in $CHCl_3$ (30 mL) and $Et_3N$ (3 mL), cooled to 0°, was added *p*-toluenesulfonyl chloride (1.2 g), and the mixture was stirred for 24 h at room temperature, the progress of the reaction being monitored by t.l.c. Methanol (1 mL) was added to the mixture, which was stirred for 10 min and concentrated. The residue was chromatographed on a column of silica gel (50 g) with hexane–EtOAc to give **12** (815 mg, 92%) as a syrup; $[\alpha]_D$ −38° (*c* 1.2, $CHCl_3$); $\nu_{max}$ 2100 (azide), 1740 and 1220 (ester), and 720 $cm^{-1}$ (Ph); $^1$H-n.m.r. ($CDCl_3$): δ 0.87 (m, 3 H, $CH_3CH_2$), 1.24 (s, 22 H, 11 $CH_2$),

2.02 (m, 2 H, H-6,6'), 2.42 (s, 3 H, Ph-C$H_3$), 5.46 (dd, 1 H, $J_{3,4}$ 6.8, $J_{4,5}$ 14.3 Hz, H-4), 5.52 (dd, 1 H, $J_{2,3}$ 4.2 Hz, H-3), 5.88 (td, 1 H, $J_{5,6} = J_{5,6'}$ = 6.8 Hz, H-5), and 7.10–8.14 (m, 9 H, COPh-*H*, $CH_3$Ph-*H*).

*Anal.* Calc. for $C_{32}H_{45}N_3O_8S$ (583.8): C, 65.83; H, 7.77; N, 7.20. Found: C, 65.99; H, 7.68; N, 7.16.

S-*(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-(1→1)-(2R,3R,4E)*-2-azido-3-benzoyloxy-4-octadecene-1-thiol (**13**). — To a stirred solution of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-β-D-glucopyranose (**1**, 400 mg, 0.98 mmol) in dry MeOH (4 mL) and $CHCl_3$ (0.5 mL), cooled to −20°, was added a solution of sodium metal (22.6 mg) in dry MeOH (1 mL). Stirring was continued for 5 min at −20°, and the mixture was concentrated to give **2** as an amorphous mass, which was used for the next reaction without purification. A solution of **2** (1.08 g, 2.78 mmol) and **12** (810 mg, 1.39 mmol) in dry *N,N*-dimethylformamide (DMF; 20 mL) was stirred for 24 h at 40° under $N_2$; the course of the reaction being monitored by t.l.c. Acetic anhydride (5 mL) and pyridine (10 mL) were added to the mixture, which was stirred overnight at room temperature, and concentrated. The residue was dissolved in $CH_2Cl_2$ (200 mL), and the solution was successively washed with 2M HCl, M $Na_2CO_3$, and water, and then dried ($Na_2SO_4$), and evaporated to a syrup that was chromatographed on a column of silica gel (100 g) with 6:1 hexane–EtOAc to afford **13** (940 mg, 87%) as an amorphous mass; $[\alpha]_D$ −64.5° (*c* 0.73, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): Glc unit δ 1.92, 2.01, 2.02, 2.05 (4 s, 12 H, 4 C$H_3$CO$_2$), 3.72 (m, 1 H, H-5), 4.12 (dd, 1 H, $J_{5,6}$ 2.2, $J_{6,6'}$ 12.5 Hz, H-6), 4.26 (dd, 1 H, $J_{5,6'}$ 4.8 Hz, H-6'), 4.55 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 5.06 (dd, 1 H, $J_{2,3}$ 9.9 Hz, H-2), 5.09 (broad t, 1 H, $J_{3,4}$ 9.3 Hz, H-3), and 5.24 (t, 1 H, $J_{4,5}$ 9.3 Hz, H-4); sphingosine unit δ 0.87 (t, 3 H, C$H_3$CH$_2$), 1.24 (s, 22 H, 11 C$H_2$), 2.61 (dd, 1 H, $J_{1,1'}$ 14.3, $J_{1,2}$ 9.0 Hz, H-1), 2.92 (dd, 1 H, $J_{1',2}$ 4.8 Hz, H-1'), 4.02 (m, 1 H, H-2), 5.55 (dd, 1 H, $J_{3,4}$ 8.1, $J_{4,5}$ 14.7 Hz, H-4), 5.63 (dd, 1 H, $J_{2,3}$ 5.0 Hz, H-3), 5.93 (td, 1 H, $J_{5,6} = J_{5,6'}$ = 6.8 Hz, H-5), and 7.43–8.09 (m, 5 H, Ph-*H*).

*Anal.* Calc. for $C_{50}H_{83}N_3O_{13}S$ (775.9): C, 60.37; H, 7.41; N, 5.42. Found: C, 60.33; H, 7.60; N, 5.29.

S-*(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-(1→1)-(2R,3R,4E)-3-benzoyloxy-2-octadecanamido-4-octadecene-1-thiol* (**15**). — Hydrogen sulfide was bubbled through a solution of **13** (756 mg, 0.97 mmol) in pyridine (25 mL) and water (5 mL) for 2 days while the solution was stirred at room temperature. The mixture was concentrated to give the amine **14**, which was used for the next reaction without purification. To a solution of **14** obtained as already described, in dry $CH_2Cl_2$ (30 mL), were added octadecanoic acid (540 mg, 1.9 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC; 500 mg, 2.6 mmol), and the mixture was stirred for 2 h at room temperature; the progress of the reaction being monitored by t.l.c. After completion of the reaction, $CH_2Cl_2$ (50 mL) was added to the mixture, and the solution was washed with water, dried ($Na_2SO_4$), and evaporated to a syrup that was chromatographed on a column of silica gel (20 g) with 4:1 hexane–EtOAc, to give compound **15** (739 mg, 72%) as an amorphous mass; $[\alpha]_D$ −50.5° (*c* 0.63, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): Glc unit δ 2.00, 2.01 (2), 2.02 (4 s, 12 H, 4 C$H_3$CO$_2$), 3.76 (m, 1 H, H-5), 4.14 (dd, 1 H, $J_{5,6}$

4.8, $J_{6,6'}$ 12.6 Hz, H-6), 4.22 (dd, 1 H, H-6'), 4.50 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 5.01 (t, 1 H, $J_{2,3}$ 9.9 Hz, H-2), 5.07 (t, 1 H, $J_{3,4}$ 9.9 Hz, H-3), and 5.22 (t, 1 H, $J_{4,5}$ 9.9 Hz, H-4); Cer unit $\delta$ 0.87 (t, 6 H, 2 C$H_3$CH$_2$), 1.24 (s, 50 H, 25 C$H_2$), 1.60 (m, 2 H, COCH$_2$C$H_2$), 2.85 (dd, 1 H, $J_{1,1'}$ 13.6, $J_{1,2}$ 7.7 Hz, H-1), 2.92 (dd, 1 H, $J_{1',2}$ 4.4 Hz, H-1'), 5.49 (dd, 1 H, $J_{3,4}$ 6.8, $J_{4,5}$ 15.4 Hz, H-4), 5.87 (td, 1 H, $J_{5,6} = J_{5,6'} = 7.0$ Hz, H-5), and 7.45–8.04 (m, 5 H, Ph-*H*).

*Anal.* Calc. for $C_{57}H_{93}NO_{12}S$ (1016.4): C, 67.35; H, 9.22; N, 1.38. Found: C, 67.33; H, 9.28; N, 1.44.

S-(*β*-D-*Glucopyranosyl*)-(*1→1*)-(*2*R,*3*R,*4*E)-*3-hydroxy-2-octadecanamido-4-octadecene-1-thiol* (**16**). — To a solution of **15** (102 mg, 0.1 mmol) in dry MeOH (10 mL) was added NaOMe (10 mg). The mixture was stirred overnight at room temperature and then made neutral with Amberlite IR-120 ($H^+$) resin. The resin was filtered off, and washed with MeOH. The filtrate and washings were combined and concentrated to a syrup. The residue was chromatographed on a column of Sephadex LH-20 (80 g) with 1:1 $CHCl_3$–MeOH, to give compound **16** (68 mg, 91%) as an amorphous mass; $[\alpha]_D$ −34.0° (*c* 0.2, $Me_2SO$); $^1$H-n.m.r. ($Me_2SO$-$d_6$): Glc unit $\delta$ 4.26 (d, 1 H, $J_{1,2}$ 9.3 Hz, H-1); Cer unit $\delta$ 0.87 (t, 6 H, 2 C$H_3$CH$_2$), 1.25 (m, 50 H, 25 C$H_2$), 1.28 (m, 2 H, COCH$_2$C$H_2$), 2.70 (dd, 1 H, $J_{1,1'}$ 13.9, $J_{1,2}$ 8.4 Hz, H-1), 2.98 (dd, 1 H, $J_{1',2}$ 4.4 Hz, H-1'), 5.40 (dd, 1 H, $J_{3,4}$ 6.6, $J_{4,5}$ 15.6 Hz, H-4), and 5.60 (td, 1 H, $J_{5,6} = J_{5,6'} = 6.8$ Hz, H-5).

*Anal.* Calc. for $C_{42}H_{81}NO_7S$ (744.1): C, 67.79; H, 10.97; N, 1.88. Found: C, 67.61; H, 11.03; N, 1.92.

S-(*2,3,4,6-Tetra*-O-*acetyl-β*-D-*galactopyranosyl*)-(*1→1*)-(*2*R,*3*R,*4E*)-*2-azido-3-benzoyloxy-4-octadecene-1-thiol* (**17**). — To a solution of 2,3,4,6-tetra-*O*-acetyl-1-*S*-acetyl-1-thio-*β*-D-galactopyranose (**3**, 400 mg, 0.98 mmol) in dry MeOH (4 mL), cooled to −20°, was added, with stirring, a solution of sodium metal (22.6 mg) in dry MeOH (1 mL). The mixture was stirred for 5 min at −20°, and concentrated to the crude **4** which was used for the next reaction without purification. A solution of **4** (1.0 g, 2.59 mmol) and compound **12** (760 mg, 1.32 mmol) in dry DMF (20 mL) was stirred for 24 h at 40° under $N_2$. Acetic anhydride (5 mL) and pyridine (10 mL) were added, and the mixture was stirred overnight at room temperature and concentrated to a syrup which was dissolved in $CH_2Cl_2$ (200 mL). The solution was successively washed with 2M HCl, M $Na_2CO_3$, and water, then dried ($Na_2SO_4$), and evaporated. The residue was chromatographed on a column of silica gel (50 g) with 6:1 hexane–EtOAc to give **17** (920 mg, 92%) as an amorphous mass; $[\alpha]_D$ −50.5° (*c* 0.63, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): Gal unit $\delta$ 1.98, 1.99, 2.07, 2.16 (4 s, 12 H, 4 C$H_3$CO$_2$), 3.94 (t, 1 H, $J_{5,6} = J_{5,6'} = 6.8$ Hz, H-5), 4.52 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 5.06 (dd, 1 H, $J_{2,3}$ 9.9, $J_{3,4}$ 3.3 Hz, H-3), 5.27 (t, 1 H, H-2), and 5.44 (broad d, 1 H, H-4); sphingosine unit $\delta$ 0.87 (t, 3 H, C$H_3$CH$_2$), 1.24 (s, 22 H, 11 C$H_2$), 2.63 (dd, 1 H, $J_{1,1'}$ 14.3, $J_{1,2}$ 8.8 Hz, H-1), 2.95 (dd, 1 H, $J_{1',2}$ 5.1 Hz, H-1'), 4.04 (m, 1 H, H-2), 5.56 (dd, 1 H, $J_{3,4}$ 8.2, $J_{4,5}$ 14.5 Hz, H-4), 5.63 (dd, 1 H, $J_{2,3}$ 3.8 Hz, H-3), 5.96 (td, 1 H, $J_{5,6} = J_{5,6'} = 6.8$ Hz, H-5), and 7.43–8.08 (m, 5 H, Ph-*H*).

*Anal.* Calc. for $C_{39}H_{57}N_3O_{11}S$ (775.9): C, 60.37; H, 7.41; N, 5.42. Found: C, 63.51; H, 7.52; N, 5.38.

S-(*2,3,4,6-Tetra*-O-*acetyl-β*-D-*galactopyranosyl*)-(*1→1*)-(*2*R,*3*R,*4*E)-*3-benzoyloxy-2-octadecanamido-4-octadecene-1-thiol* (**19**). — Selective reduction of the azide

group in **17** (920 mg, 1.2 mmol) with $H_2S$, and subsequent condensation of the amine **18** with octadecanoic acid (660 mg, 2.32 mmol) using WSC (667 mg, 3.47 mmol), as described for **15**, gave compound **19** (1.03 g, 85.5%) as an amorphous mass: $[\alpha]_D$ −12.2° (*c* 1.0, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): Gal unit $\delta$ 1.98, 1.99, 2.03, 2.12 (4 s, 12 H, 4 $CH_3CO_2$), 3.96 (t, 1 H, $J_{5,6} = J_{5,6'}$ = 6.9 Hz, H-5), 4.07 (dd, 1 H, $J_{6,6'}$ 11.4 Hz, H-6), 4.14 (dd, 1 H, H-6'), 4.48 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 5.04 (dd, 1 H, $J_{2,3}$ 9.9, $J_{3,4}$ 3.3 Hz, H-3), 5.22 (t, 1 H, H-2), and 5.44 (d, 1 H, H-4); Cer unit $\delta$ 0.87 (t, 6 H, 2 $CH_3CH_2$), 1.25 (s, 50 H, 25 $CH_2$), 1.61 (m, 2 H, $COCH_2CH_2$), 2.88 (dd, 1 H, $J_{1,1'}$ 13.7, $J_{1,2}$ 7.9 Hz, H-1), 3.08 (dd, 1 H, $J_{1',2}$ 4.6 Hz, H-1'), 5.49 (dd, 1 H, $J_{3,4}$ 7.1, $J_{4,5}$ 15.8 Hz, H-4), 5.60 (t, 1 H, H-4), 5.87 (td, 1 H, $J_{5,6} = J_{5,6'}$ = 6.6 Hz, H-5), and 7.42-8.06 (m, 5 H, Ph-*H*).

*Anal.* Calc. for $C_{57}H_{103}NO_{12}S$ (1016.4): C, 67.35; H, 9.22; N, 1.38. Found: C, 67.21; H, 9.34; N, 1.24.

S-(*β*-D-*Galactopyranosyl*)-(1→1)-(2R,3R,4E)-*3-hydroxy-2-octadecanamido-4-octadecene-1-thiol* (**20**). — *O*-Deacylation of **19** (510 mg, 0.5 mmol), as described for **16**, gave **20** in quantitative yield; $[\alpha]_D$ −30° (*c* 0.4, $Me_2SO$); $^1$H-n.m.r. ($Me_2SO$-$d_6$): Gal unit $\delta$ 3.28 (dd, 1 H, $J_{2,3}$ 9.2, $J_{3,4}$ 3.1 Hz, H-3), 3.72 (broad d, 1 H, H-4), and 4.19 (d, 1 H, $J_{1,2}$ 8.9 Hz, H-1); Cer unit $\delta$ 0.86 (t, 6 H, 2 $CH_3CH_2$), 1.25 (s, 50 H, 25 $CH_2$), 1.47 (m, 2 H, $COCH_2CH_2$), 2.70 (dd, 1 H, $J_{1,1'}$ 13.7, $J_{1,2}$ 8.4 Hz, H-1), 2.92 (dd, 1 H, $J_{1',2}$ 3.9 Hz, H-1'), 5.38 (dd, 1 H, $J_{3,4}$ 6.1, $J_{4,5}$ 15.0 Hz, H-5), and 5.56 (td, 1 H, $J_{5,6} = J_{5,6'}$ = 6.8 Hz, H-5).

*Anal.* Calc. for $C_{42}H_{83}NO_7S$ (744.1): C, 67.79; H, 10.97; N, 1.88. Found: C, 67.54; H, 11.09; N, 1.87.

O-(*2,3,4,6-Tetra*-O-*acetyl*-*β*-D-*galactopyranosyl*)-(1→4)-S-(*2,3,6-tri*-O-*acetyl*-*β*-D-*glucopyranosyl*)-(1→1)-(2R,3R,4E)-*2-azido-3-benzoyloxy-4-octadecene-1-thiol* (**21**). — Condensation of **7**, derived from **6** (200 mg, 0.29 mmol) by treatment with NaOMe in MeOH, with **12** (85 mg, 0.15 mmol) as described for **13**, afforded compound **21** (145 mg, 91%) as an amorphous mass; $[\alpha]_D$ −42.2° (*c* 2.2, $CHCl_3$); $\nu_{max}$ 2130 (azide), 1760 and 1230 (ester), and 720 cm$^{-1}$ (Ph); $^1$H-n.m.r. ($CDCl_3$): Gal unit $\delta$ 3.89 (t, 1 H, $J_{5,6} = J_{5,6'}$ = 7.3 Hz, H-5), 4.48 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.96 (dd, 1 H, $J_{2,3}$ 10.2, $J_{3,4}$ 2.9 Hz, H-3), 5.11 (dd, 1 H, H-2), and 5.35 (broad d, 1 H, H-4); Glc unit $\delta$ 3.64 (m, 1 H, H-5), 3.80 (t, 1 H, $J_{3,4} = J_{4,5}$ = 9.2 Hz, H-4), 4.55 (d, 1 H, $J_{1,2}$ 10.1 Hz, H-1), 4.98 (t, 1 H, $J_{2,3}$ 9.2 Hz, H-3), and 5.22 (t, 1 H, H-2); sphingosine unit $\delta$ 0.88 (t, 3 H, $CH_3CH_2$), 1.24 (s, 22 H, 11 $CH_2$), 2.60 (dd, 1 H, $J_{1,1'}$ 14.5, $J_{1,2}$ 8.6 Hz, H-1), 2.83 (dd, 1 H, $J_{1',2}$ 5.5 Hz, H-1'), 5.60 (dd, 1 H, $J_{3,4}$ 8.3, $J_{4,5}$ 15.0 Hz, H-4), 5.67 (dd, 1 H, $J_{2,3}$ 3.5 Hz, H-3), 5.96 (td, 1 H, $J_{5,6} = J_{5,6'}$ = 6.6 Hz, H-5), and 7.43–8.08 (m, 5 H, Ph-*H*); *O*-acetyl groups $\delta$ 1.94, 1.96, 2.03, 2.06 (2), 2.07, 2.09 (7 s, 21 H, 7 $CH_3CO_2$).

*Anal.* Calc. for $C_{51}H_{73}N_3O_{19}S$ (1064.2): C, 57.56; H, 6.91; N, 3.95. Found: C, 57.41; H, 7.09; N, 3.80.

O-(*2,3,4,6-Tetra*-O-*acetyl*-*β*-D-*galactopyranosyl*)-(1→4)-S-(*2,3,6-tri*-O-*acetyl*-*β*-D-*glucopyranosyl*)-(1→1)-(2R,3R,4E)-*3-benzoyloxy-2-octadecanamido-4-octadecene-1-thiol* (**23**). — Selective reduction of the azide group in **21** (245 mg, 0.23 mmol) with $H_2S$, and subsequent coupling of the amine **22** with octadecanoic acid (150 mg, 0.52 mmol), as described for **15**, gave compound **23** (271 mg, 90%) as an amorphous mass; $\nu_{max}$ 3400 (NH), 1750 and 1230 (ester), 1660 and 1530 (amide), and 710 cm$^{-1}$ (Ph);

$^1$H-n.m.r. ($CDCl_3$): Gal unit $\delta$ 3.86 (t, 1 H, $J_{5,6} = J_{5,6'} = 7.2$ Hz, H-5), 4.52 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.96 (dd, 1 H, $J_{2,3}$ 10.4, $J_{3,4}$ 3.3 Hz, H-3), 5.11 (dd, 1 H, H-2), and 5.35 (broad d, 1 H, H-4); Glc unit $\delta$ 3.67 (m, 1 H, H-5), 3.78 (t, 1 H, $J_{3,4} = J_{4,5} = 9.7$ Hz, H-4), 4.48 (d, 1 H, $J_{1,2}$ 9.2 Hz, H-1), 4.92 (t, 1 H, $J_{2,3}$ 9.7 Hz, H-3), and 5.20 (t, 1 H, H-2); Cer unit $\delta$ 0.88 (t, 6 H, 2 $CH_3CH_2$), 1.26 (s, 50 H, 25 $CH_2$), 1.61 (m, 2 H, $COCH_2CH_2$), 2.86 (dd, 1 H, $J_{1,1'}$ 13.7, $J_{1,2}$ 7.3 Hz, H-1), 3.00 (dd, 1 H, $J_{1',2}$ 5.0 Hz, H-1'), 5.48 (dd, 1 H, $J_{3,4}$ 7.2, $J_{4,5}$ 15.2 Hz, H-4), 5.88 (td, 1 H, $J_{5,6} = J_{5,6'} = 6.8$ Hz, H-5), 5.89 (d, 1 H, NH), 7.43–8.05 (m, 5 H, Ph-*H*); *O*-acetyl groups $\delta$ 1.97, 2.01, 2.03, 2.05, 2.06, 2.11, 2.16 (7 s, 21 H, 7 $CH_3CO_2$).

*Anal.* Calc. for $C_{69}H_{109}NO_{20}S$ (1304.6): C, 63.52; H, 8.42; N, 1.07. Found: C, 63.40; H, 8.51; N, 0.99.

O-(*β*-D-*Galactopyranosyl*)-(*1→4*)-S-(*β*-D-*glucopyranosyl*)-(*1→1*)-(*2*R,*3*R,*4*E)-*3-hydroxy-2-octadecanamido-4-octadecene-1-thiol* (**24**). — *O*-Deacylation of **23** (124 mg, 95 $\mu$mol), as described for the preparation of **16**, gave **24** (81 mg, 94%) as an amorphous mass; $[\alpha]_D$ +10.2° (*c*, 0.8, $Me_2SO$); $^1$H-n.m.r. ($Me_2SO$-$d_6$): Gal unit $\delta$ 4.23 (d, 1 H, $J_{1,2}$ 7.3 Hz, H-1); Glc unit $\delta$ 4.29 (d, 1 H, $J_{1,2}$ 9.7 Hz, H-1); Cer unit $\delta$ 0.86 (t, 6 H, 2 $CH_3CH_2$), 1.25 (s, 50 H, 25 $CH_2$), 1.48 (m, 2 H, $COCH_2CH_2$), 2.67 (dd, 1 H, $J_{1,1'}$ 13.4, $J_{1,2}$ 8.8 Hz, H-1), 3.00 (dd, 1 H, H-1'), 5.38 (dd, 1 H, $J_{3,4}$ 15.5 Hz, H-4), and 5.88 (td, 1 H, $J_{5,6} = J_{5,6'} = 6.4$ Hz, H-5).

*Anal.* Calc. for $C_{48}H_{91}NO_{12}S$ (906.3): C, 63.61; H, 10.12; N, 1.55. Found: C, 63.59; H, 10.30; N, 1.48.

O-(*Methyl 5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosylonate*)-(*2→3*)-O-(*2,4-di*-O-*acetyl-6*-O-*benzoyl-β*-D-*galactopyranosyl*)-(*1→4*)-S-(*3*-O-*acetyl-2,6-di*-O-*benzoyl-β*-D-*galactopyranosyl*)-(*1→1*)-(*2*R,*3*R,*4*E)-*2-azido-3-benzoyloxy-4-octadecene-1-thiol* (**25**). — Condensation of compound **10** (29.3 mg, 22.6 $\mu$mol), derived from **9**, with **12** (26 mg, 45.6 $\mu$mol), as described for **13**, afforded compound **25** (15.5 mg, 41%) as an amorphous mass; $[\alpha]_D$ +0.2° (*c* 0.5, $CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): Neu5Ac unit $\delta$ 1.84 (s, 3 H, $CH_3CON$), 2.57 (dd, 1 H, $J_{3a,3e}$ 12.6, $J_{3e,4}$ 4.6 Hz, H-3e), 3.59 (dd, 1 H, $J_{5,6}$ 10.4, $J_{6,7}$ 2.4 Hz, H-6), and 3.71 (s, 3 H, $CH_3O$); Gal unit $\delta$ 4.74 (d, 1 H, $J_{1,2}$ 9.9 Hz, H-1), 5.36 (dd, 1 H, $J_{2,3}$ 8.4, $J_{3,4}$ 2.7 Hz, H-3), and 5.47 (broad d, 1 H, H-4); Glc unit $\delta$ 4.80 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1), 5.25 (t, 1 H, $J_{2,3} = J_{3,4} = 9.3$ Hz, H-3); sphingosine unit $\delta$ 0.88 (t, 3 H, $CH_3CH_2$), 1.21 (s, 22 H, 11 $CH_2$), 2.64 (dd, 1 H, $J_{1,1'}$ 13.9, $J_{1,2}$ 8.4 Hz, H-1), 2.86 (dd, 1 H, $J_{1',2}$ 5.3 Hz, H-1'), and 5.85 (td, 1 H, $J_{4,5}$ 13.4, $J_{5,6} = J_{5,6'} = 6.8$ Hz, H-5); *O*-acyl groups $\delta$ 1.98, 2.00 (2), 2.01 (2), 2.11, 2.20 (7 s, 21 H, 7 $CH_3CO_2$), 7.31–8.05 (m, 20 H, 4 Ph-*H*).

*Anal.* Calc. for $C_{84}H_{104}N_4O_{30}S$ (1681.8): C, 59.99; H, 6.23; N, 3.33. Found: C, 59.81; H, 6.40; N, 3.29.

O-(*Methyl 5-acetamido-4,7,8,9-tetra*-O-*acetyl-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosylonate*)-(*2→3*)-O-(*2,4-di*-O-*acetyl-6*-O-*benzoyl-β*-D-*galactopyranosyl*)-(*1→4*)-S-(*3*-O-*acetyl-2,6-di*-O-*benzoyl-β*-D-*glucopyranosyl*)-(*1→1*)-(*2*R,*3*R,*4*E)-*3-benzoyloxy-2-octadecanamido-4-octadecene-1-thiol* (**27**). — The azide group in **25** (15.5 mg, 9.2 $\mu$mol) was converted into the amine **26** as described for **15**, which was then condensed with octadecanoic acid (5 mg, 17.5 $\mu$mol) in the presence of WSC (3.5 mg), to give **27** (12.2 mg, 68.2%) as an amorphous mass; $[\alpha]_D$ +31.1° (*c* 0.58,

$CHCl_3$); $^1$H-n.m.r. ($CDCl_3$): Neu5Ac unit $\delta$ 1.84 (s, 3 H, $CH_3CON$), 2.57 (dd, 1 H, $J_{3a,3e}$ 12.8, $J_{3e,4}$ 5.0 Hz, H-3*e*), 3.58 (dd, 1 H, $J_{5,6}$ 10.7, $J_{6,7}$ 2.8 Hz, H-6), and 3.70 (s, 3 H, $CH_3O$); Gal unit $\delta$ 4.67 (d, 1 H, $J_{1,2}$ 9.5 Hz, H-1); Glc unit $\delta$ 5.21 (t, 1 H, $J_{2,3} = J_{3,4}$ = 9.9 Hz, H-3); Cer unit $\delta$ 0.88 (t, 6 H, 2 $CH_3CH_2$), 1.26 (s, 50 H, 25 $CH_2$), 1.60 (m, 2 H, $COCH_2CH2$), 2.89–3.03 (m, 2 H, H-1,1'), and 5.75 (td, 1 H, $J_{4,5}$ 13.2, $J_{5,6} = J_{5,6'}$ = 6.6 Hz, H-5); *O*-acyl groups $\delta$ 1.97, 2.00 (2), 2.01 (2), 2.20 (2) (7 s, 21 H, 7 $CH_3CO_2$), 7.36–8.05 (m, 20 H, 4 Ph-*H*).

*Anal.* Calc. for $C_{102}H_{140}N_2O_{31}S$ (1922.2): C, 63.73; H, 7.34; N, 1.46. Found: C, 63.50; H, 7.38; N, 1.44.

O-*(5-Acetamido-3,5-dideoxy*-D-glycero-α-D-galacto-*2-nonulopyranosylonic acid)*-*(2→3)*-O-*(β*-D-*galactopyranosyl)*-*(1→4)*-S-*(β*-D-*glucopyranosyl)*-*(1→1)*-*(2*R,*3*R,*4*E)-*3-hydroxy-2-octadecanamido-4-octadecene-1-thiol* (**28**). — To a solution of **27** (10 mg, 5.2 μmol) in dry MeOH (1 mL) was added NaOMe (5 mg), and the mixture was stirred overnight at room temperature. After completion of the reaction, water (0.1 mL) was added to the mixture, and this was stirred for 1 h, and treated with Amberlite IR-120 ($H^+$) resin to remove the base. The solution was concentrated, and the residue was chromatographed on a column of Sephadex LH-20 (20 g) with 1:1 $CHCl_3$–MeOH, to give **28** (4.8 mg, 77%) as an amorphous mass; $[\alpha]_D$ −21.8° (*c* 0.2, $CHCl_3$); $^1$H-n.m.r. (1:1 $CDCl_3$–$CD_3OD$): Neu5Ac unit $\delta$ 2.04 (s, 3 H, $CH_3CON$), 2.80 (dd, 1 H, $J_{3a,3e}$ 11.0, $J_{3e,4}$ 4.4 Hz, H-3e); Gal unit $\delta$ 4.12 (d, 1 H, $J_{1,2}$ 6.8 Hz, H-1); Glc unit $\delta$ 5.34 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1); Cer unit $\delta$ 0.89 (t, 6 H, 2 $CH_3CH_2$), 1.27 (s, 50 H, 25 $CH_2$), 1.60 (m, 2 H, $COCH_2CH_2$), 3.00 (dd, 1 H, $J_{1,1'}$ 14.1, $J_{1,2}$ 4.8 Hz, H-1'), 5.43 (dd, 1 H, $J_{3,4}$ 7.0, $J_{4,5}$ 15.0 Hz, H-4), and 5.73 (td, 1 H, $J_{5,6} = J_{5,6'}$ = 7.3 Hz, H-5).

*Anal.* Calc. for $C_{90}H_{168}N_2O_{20}S$ (1197.5): C, 59.17; H, 9.09; N, 2.34. Found: C, 59.00; H, 9.21; N, 2.39.

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