Synthesis of the Thio-Linked Ganglioside GM_3 Epitope

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The synthesis of sulfur-linked GM_3 epitope **2** is based on acid-catalyzed and base-promoted *S*-glycosylation processes. As a precursor, 2-*O*-benzoyl-3-thiogalactoside **10** was required, and was obtained from 4,6-*O*-benzylidene-galactoside **3** in six high-yielding steps. Base-promoted *S*-glycosylation of **10** with neuraminic acid functionalized β-halogenose **11** in the presence of NaH as base and Kryptofix 21 as coactivator afforded α(2-3)-thio-linked disaccharide **13**, which was readily converted to α-halogenose **20**. Heptyl 1-thioglycoside **22** was obtained from *O*-galactosyl trichloroacetimidate **21** and heptylthiol via acid-catalyzed *S*-glycosylation. **22** was transformed into 2,3,6-tri-*O*-acylgalactoside **26** which, via the 4-*O*-triflate and treatment with potassium thioacetate, followed by selective removal of the *S*-acetyl group, furnished the 2,3,6-tri-*O*-acyl-4-thioglucoside **28**. Base-promoted *S*-glycosylation of **28** with halogenose **20** led to fully acylated target molecule **29**, which was quantitatively converted into **2**.

Ganglioside GM_3 (**1**, Scheme 1) is widely found in mammals; it is also found to be concentrated on the membranes of some tumor cells[1]. Several investigations have shown that the growth of tumor cells, transplanted into mice, is directly correlated to their GM_3 content[2]. It was also found that GM_3 inhibits the fibroblast growth factor (FGF)-dependent growth of baby hamster kidney cells and FGF itself[3].

Thioglycosides have proven to be much more stable to glycosidase action than glycosides[4], thus enzymatic hydrolysis is slowed down in the course of in vivo experiments. Therefore, we have initiated a program to synthesize sulfur-linked epitopes of glycoconjugates which additionally bear a spacer group, also attached via sulfur[5,6]. Thus, biological effects and conformational differences can be compared with the natural epitope[7].

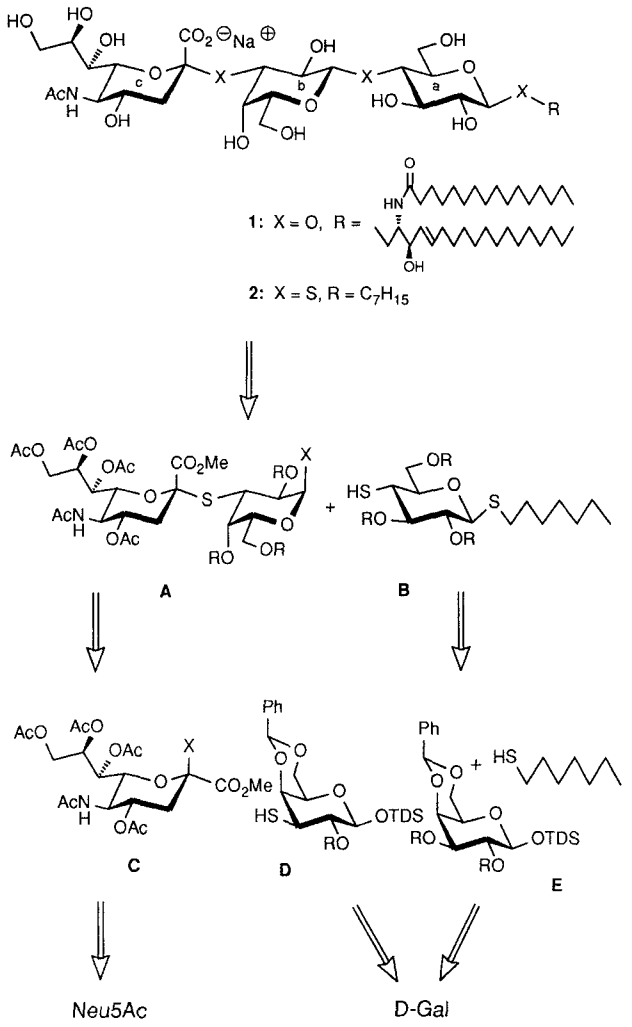
Ganglioside analogues of the *ganglio* series, in which glycosidic oxygens have been partially replaced by sulfur, have recently been synthesized[8]. These compounds exhibit interesting inhibition of influenza virus sialidases. In this paper we report the synthesis of the thio-linked GM_3 epitope **2**, which is fitted with a heptyl spacer, in which all glycosidic oxygens are replaced by sulfur. The synthetic strategy is outlined in the retrosynthetic analysis (Scheme 1). The thioglycoside bond formation is based on "base-promoted *S*-glycosylation" (**A** + **B** → **2**; **C** + **D** → **A**) and "acid-catalyzed *S*-glycosylation" (**E** + HS−C_7H_{15} → **B**). An important aspect in the course of the synthesis is the selection of permanent and temporary protective groups. Because hydrogenolytic debenzylation is generally not compatible with the presence of sulfur linkages, the regiocontrol is essentially based on different acyl groups (for instance, R in **A**, **B**, **C**, **D**, **E** = *O*-acetyl, *O*-chloroacetyl, *O*-benzoyl, *S*-acetyl, etc.) which can be regioselectively introduced or removed, and on the benzylidene group, which is employed for temporary protection via acid-catalyzed attachment and cleavage. Thiol groups at non-anomeric positions are generally introduced via an S_N2 reaction. However, as previously observed, the high density of functional groups in carbohydrates can lead to unexpected difficulties in this endeavour[5,6].

For the synthesis of building block **A**, a 3-thiogalactose of type **D** first had to be prepared. To this end, D-galactose was transformed into the known benzylidene derivative **3**[9] (Scheme 2). Treatment with monochloroacetyl chloride in the presence of pyridine resulted in regioselective 3-*O*-acylation affording compound **4** in high yield. Subsequent benzoylation with benzoyl cyanide in the presence of triethylamine gave the 2-*O*-benzoyl derivative **5** which could be selectively and quantitatively deprotected at the 3-position by treatment with hydrazinium acetate (N_2H_4 · HOAc) in DMF to give **6**. Various methods were investigated for the introduction of the mercapto group in the 3-position. For instance, treatment of **6** with trifluoromethanesulfonic anhydride (Tf_2O) in pyridine and then with tetrabutylammonium iodide (TBAI) furnished 3-iodo derivative **7**, reaction of which with potassium thioacetate (KSAc) in DMF at 110°C afforded a mixture of the desired 3-thiogalactose (**9**) and the undesired 3-thiogulose derivative. In an alternative approach, the configuration at 3-C of **6** was inverted via the 3-*O*-triflate, and treatment with tetrabutylammonium nitrite ($TBANO_2$)[10] afforded the gulose derivative **8**; subsequent 3-*O*-triflate formation and treatment with KSAc in DMF at 60°C (one-pot reaction) afforded the desired 3-acetylthiogalactoside **9** in high yield. Selective removal of the *S*-acetyl group was readily accomplished with N_2H_4 · HOAc affording compound **10**, representing **D**.

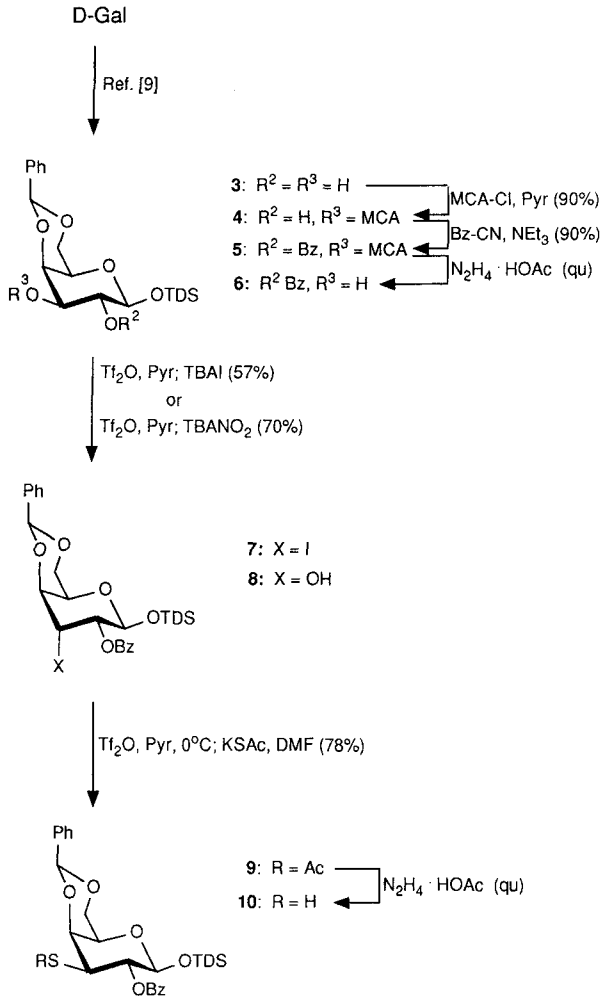
For the ligation of **10** to a neuraminic acid residue, the known β-halogenose **11**[11] was prepared (Scheme 3). Base-promoted *S*-glycosylation required extensive study in order

  0947–3440/97/0505–0865 $ 17.50+.50/0

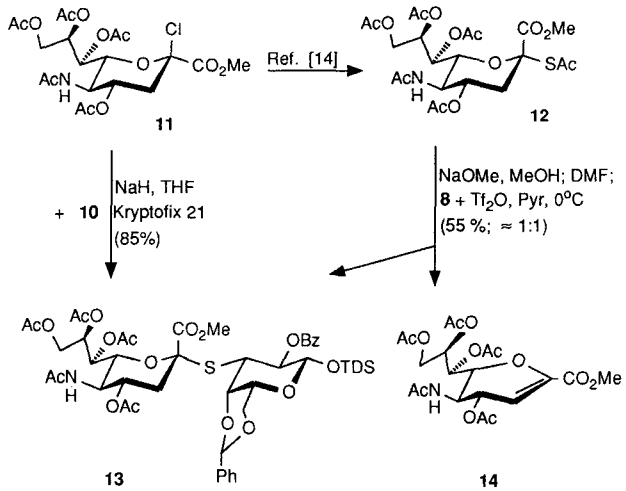
Scheme 1



Scheme 2



Scheme 3

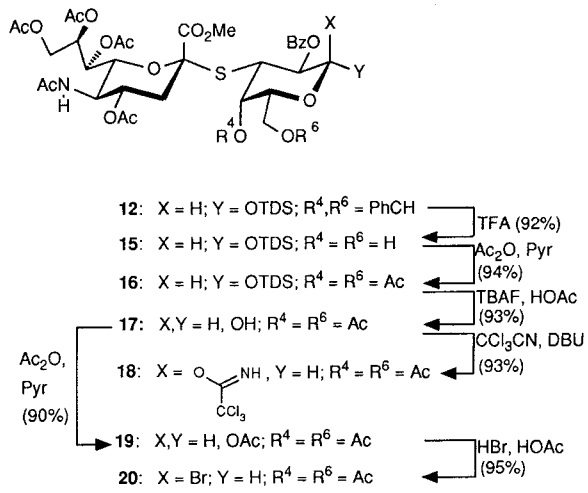


to find optimal conditions; very good yields of the *S*-α(2-3)-linked disaccharide **13** were obtained when the reaction was carried out with NaH as base and THF as solvent. For this process, Kryptofix 21[12], a good complexing agent for cations, was additionally required as coactivator. However, when **11**[11] was first transformed under phase transfer conditions[13] into the known 2-acetylthio derivative **12**[14], the *S*-acetyl group was removed in situ with NaOMe in MeOH at −40 °C, and in situ triflate activation of **8** was performed via the published procedure[14,15], anomeric *S*-alkylation afforded the known elimination product **14**[11a,c] in addition to **13**. The conditions for thioglycoside bond formation with **12** applied by von Itzstein et al.[15] led to elimination in **8**. The structural assignment of the Neu5Ac residue in **13** was based on the ^{1}H-NMR data which are in accordance with those typically observed for the α-configuration[11b]: $J_{7b,8b}$ = 9.9 Hz; δ (4b-H): 4.79; Δδ (9b-H − 9b′H) = 0.18.

For the transformation of disaccharide **13** into a glycosyl donor (corresponding to **A**), acid-catalyzed debenzylidenation was first performed, affording the 4,6-*O*-unprotected derivative **15** in high yield (Scheme 4). Treatment with acetic anhydride in pyridine (→ **16**) and then with tetrabutylammonium fluoride[16] in THF gave the 1-*O*-unprotected disaccharide **17**. Reaction with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base afforded α-trichloroacetimidate **18** in very high yield.

Alternatively, reaction of **17** with acetic anhydride in pyridine gave the fully acylated *S*-disaccharide **19** which, on treatment with HBr in acetic acid furnished α-halogenose **20**, again in high yield.

Scheme 4



Building block **B** was obtained via reaction of the known galactosyl donor **21**[17] and commercially available heptylthiol in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst (acid-catalyzed *S*-glycosylation) affording thioglycoside **22** in practically quantitative yield (Scheme 5). Removal of all acetyl groups under Zemplén conditions[18] (NaOMe, MeOH) (→ **23**), treatment with benzaldehyde dimethyl acetal in the presence of *p*-toluenesulfonic acid (*p*-TsOH) as catalyst, to furnish benzylidene intermediate **24**; *O*-acetylation (→ **25**), and regioselective 6-*O*-benzoylation with benzoyl cyanide in the presence of triethylamine, gave 4-*O*-unprotected *S*-galactoside **26** in very good overall yield. Introduction of the mercapto group at the 4-position was again a critical step. In situ formation of the 4-*O*-triflate from **26** by treatment with Tf_2O in the presence of pyridine, followed by reaction with KSAc in DMF, afforded the desired 4-acetylthioglucose derivative **27** in acceptable yield. Treatment with $N_2H_4 \cdot HOAc$ led again to selective removal of the *S*-acetyl group, thereby affording the 4-mercapto derivative **28**, representing **B**.

Base-promoted *S*-glycosylation of acceptor **28** with glycosyl donor **20** was readily performed by treatment with NaH in DMF at room temperature, furnishing the fully acylated target molecule **29** in very good yield (Scheme 6). On the other hand, acid-catalyzed *S*-glycosylation of **28** with glycosyl donor **18** was much less effective[6]. Removal of all the acyl groups from **29** under Zemplén conditions[18] and hydrolysis of the methyl ester moiety with potassium hydroxide led, after ion-exchange treatment and gel permeation chromatography, to target molecule **2**. The NMR data of **29** and **2** confirm the configurational assignments (**29**: 1a-H, $J_{1,2}$ = 10 Hz; 1b-H, $J_{1,2}$ = 9.6 Hz; 7c-H, $J_{7c,8c}$ = 10.2 Hz; **2**: 1a-H, $J_{1,2}$ = 10 Hz; 1b-H, $J_{1,2}$ = 8.9 Hz).

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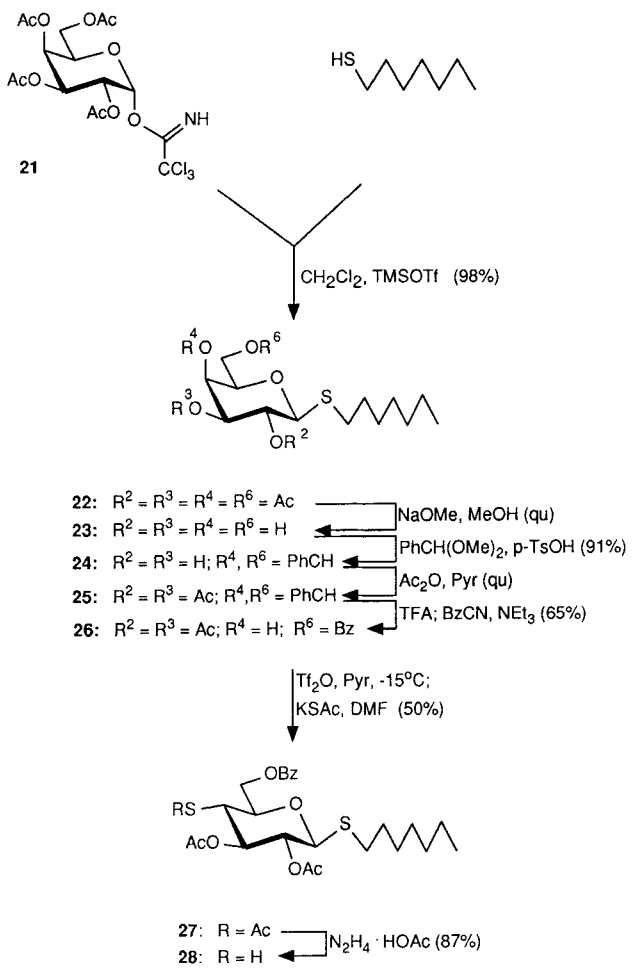
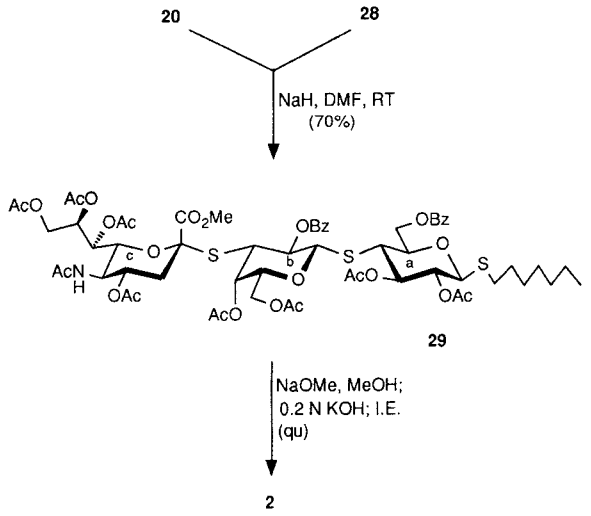
Scheme 5



Scheme 6



Experimental Section

Melting points: Uncorrected values. – ^1H NMR: Bruker AC 250 Cryospec and Bruker DRX 600. – Optical rotation: Perkin-Elmer polarimeter 241 MC; 1 dm cell. – Thin-layer chromatography

(TLC): DC-Plasikfolien Kieselgel F_{254} (Merck), detection by UV light (254 nm) or by spraying with 5% $(NH_4)_2MoO_4$ and 0.1% $Ce(SO_4)_2$ in 10% H_2SO_4 and heating to 120°C. – Flash chromatography: Silica gel (Baker, particle size 40 µm). – Medium pressure liquid chromatography (MPLC): Merck silica gel LiChroPreb Si 60 (particle size 15–25 mm). – FAB MS: Finnigan MAT 312 (170°C).

Thexyldimethylsilyl 4,6-O-Benzylidene-3-O-chloroacetyl-β-D-galactopyranoside (**4**): To a solution of compound **3**[9] (500 mg, 1.22 mmol) in dry acetonitrile (20 ml), were added pyridine (111 µl, 1.33 mmol) and chloroacetyl chloride (105 µl, 1.28 mmol) at −15°C. After stirring for 1 h, the mixture was concentrated in vacuo. Flash chromatography (toluene/ethyl acetate, 30:1 → 10:1) gave **4** (535 mg, 90%) as a colorless foam. – TLC (toluene/ethyl acetate, 30:1): R_f = 0.11, $[\alpha]_D$ = +67.1 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.20 (s, 3H, SiMe), 0.23 (s, 3H, SiMe), 0.88, 0.89, 0.90, 0.92 (4 s, 12H, CH_3), 1.61–1.72 (m, 1H, CH), 2.17 (d, $J_{2,OH}$ = 2.2 Hz, 1H, OH), 3.49–3.51 (m, 1H, 5-H), 3.94 (ddd, $J_{2,OH}$ = 2.2, $J_{1,2}$ = 7.4, $J_{2,3}$ = 10.2 Hz, 1H, 2-H), 4.06 (dd, $J_{5,6}$ = 1.8, $J_{6,6'}$ = 12.4 Hz, 1H, 6-H), 4.11, 4.18 (2 d, J_{gem} = 15.2 Hz, 2H, CH_2Cl), 4.28 (dd, $J_{5,6'}$ = 1.5, $J_{6,6'}$ = 12.4 Hz, 1H, 6′-H), 4.40 (dd, $J_{3,4}$ = 3.7, $J_{4,5}$ < 1 Hz, 1H, 4-H), 4.62 (d, $J_{1,2}$ = 7.4 Hz, 1H, 1-H), 4.91 (dd, $J_{2,3}$ = 10.2, $J_{3,4}$ = 3.7 Hz, 1H, 3-H), 5.49 (s, 1H, C*H*Ph), 7.19–7.51 (m, 5H, Ph). – $C_{23}H_{35}ClO_7Si$ (487.07): calcd. C 56.72, H 7.24; found C 56.86, H 7.23.

Thexyldimethylsilyl 2-O-Benzoyl-4,6-O-benzylidene-3-O-chloroacetyl-β-D-galactopyranoside (**5**): To a solution of **4** (260 mg, 534 µmol) in dry acetonitrile (8 ml), were added benzoyl cyanide (150 mg, 1.14 mmol) and triethylamine (10 µl, 71.8 µmol). After stirring for 24 h at room temp., methanol (1 ml) was added and the reaction mixture was stirred for a further 30 min. Evaporation in vacuo and flash chromatography (toluene/ethyl acetate, 30:1 → 20:1) gave **5** (284 mg, 90%) as a colorless foam. – TLC (toluene/ethyl acetate, 30:1): R_f = 0.22, $[\alpha]_D$ = +58.6 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.07, 0.17 (2 s, 6H, SiMe), 0.69, 0.70, 0.71, 0.72 (4 s, 12H, CH_3), 1.43–1.54 (m, 1H, CH), 3.55–3.56 (m, 1H, 5-H), 3.92, 4.02 (2 d, J_{gem} = 15.3 Hz, 2H, CH_2Cl), 4.08 (dd, $J_{5,6}$ = 1.8, $J_{6,6'}$ = 12.3 Hz, 1H, 6-H), 4.31 (dd, $J_{5,6'}$ = 1.4, $J_{6,6'}$ = 12.3 Hz, 1H, 6′-H), 4.44 (dd, $J_{3,4}$ = 3.7, $J_{4,5}$ = 0.8 Hz, 1H, 4-H), 4.90 (d, $J_{1,2}$ = 7.6 Hz, 1H, 1-H), 5.16 (dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 3.7 Hz, 1H, 3-H), 5.51 (s, 1H, C*H*Ph), 5.60 (dd, $J_{1,2}$ = 7.6, $J_{2,3}$ = 10.4 Hz, 1H, 2-H), 7.24–7.58 (m, 8H, Ph), 7.95–7.99 (m, 2H, Ph). – $C_{30}H_{39}ClO_8Si$ (591.17): calcd. C 60.95, H 6.65; found C 61.03, H 6.61.

Thexyldimethylsilyl 2-O-Benzoyl-4,6-O-benzylidene-β-D-galactopyranoside (**6**): Hydrazinium acetate (47 mg, 507 µmol) was added to a solution of compound **5** (200 mg, 338 µmol) in dry dimethyl formamide (10 ml). The mixture was stirred for 45 min, then diluted with ethyl acetate (40 ml), washed with a satd. NaCl solution (4 × 10 ml) and dried ($MgSO_4$). The residue was purified by flash chromatography (toluene/acetone, 10:1) to give compound **6** (174 mg, quant.) as a colorless foam. – TLC (toluene/acetone, 10:1): R_f = 0.23, $[\alpha]_D$ = +2.2 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.10, 0.18 (2 s, 6H, SiMe), 0.70, 0.71, 0.73 (4 s, 12H, CH_3), 1.45–1.56 (m, 1H, CH), 2.54 (d, $J_{3,OH}$ = 11.2 Hz, 1H, OH), 3.50–3.51 (m, 1H, 5-H), 3.84 (ddd, $J_{3,OH}$ = 11.2, $J_{2,3}$ = 10, $J_{3,4}$ = 3.8 Hz, 1H, 3-H), 4.08 (dd, $J_{5,6}$ = 1.9, $J_{6,6'}$ = 12.3 Hz, 1H, 6-H), 4.23 (dd, $J_{3,4}$ = 3.8, $J_{4,5}$ = 0.9 Hz, 1H, 4-H), 4.30 (dd, $J_{5,6'}$ = 1.4, $J_{6,6'}$ = 12.3 Hz, 1H, 6′-H), 4.85 (d, $J_{1,2}$ = 7.6 Hz, 1H, 1-H), 5.29 (dd, $J_{1,2}$ = 7.6, $J_{2,3}$ = 10 Hz, 1H, 2-H), 5.56 (s, 1H, C*H*Ph), 7.35–7.57 (m, 8H, Ph), 8.01–8.05 (m, 2H, Ph). – $C_{28}H_{38}O_7Si$ (514.69): calcd. C 65.34, H 7.44; found C 65.27, H 7.48.

Thexyldimethylsilyl 2-O-Benzoyl-4,6-O-benzylidene-3-iodo-β-D-gulopyranoside (**7**): A solution of compound **6** (300 mg, 583 µmol) in dry dichloromethane (10 ml) and pyridine (86 µl) was treated at −17°C with trifluoromethanesulfonic anhydride (163 µl, 968 µmol) and stirred for 30 min at −17°C. The reaction mixture was diluted with dichloromethane (15 ml) and washed with satd. aqueous $NaHCO_3$ solution (2 × 10 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was redissolved in dry toluene (10 ml) and treated with tetrabutylammonium iodide (431 mg, 1.17 mmol). After stirring for 3 h at 60°C, the solvent was evaporated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 7:1) gave **7** (218 mg, 60%) as a pale-yellow syrup. – TLC (toluene/ethyl acetate, 30:1): R_f = 0.55, $[\alpha]_D$ = +3.4 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.13, 0.19 (2 s, 6H, SiMe), 0.71, 0.72, 0.73, 0.74 (4 s, 12H, CH_3), 1.49–1.55 (m, 1H, CH), 4.07 (dd, $J_{5,6}$ = 1.8, $J_{6,6'}$ = 12.4 Hz, 1H, 6-H), 4.23 (m, 1H, 5-H), 4.32 (dd, $J_{5,6'}$ = 1.3, $J_{6,6'}$ = 12.4 Hz, 1H, 6′-H), 4.38 (dd, $J_{3,4}$ = 2.7, $J_{4,5}$ < 1 Hz, 1H, 4-H), 4.60 (dd, $J_{1,2}$ = 7.4, $J_{2,3}$ = 4.2 Hz, 1H, 2-H), 4.80 (dd, $J_{2,3}$ = 4.2, $J_{3,4}$ = 2.7 Hz, 1H, 3-H), 5.26 (d, $J_{1,2}$ = 7.4 Hz, 1H, 1-H), 5.50 (s, 1H, C*H*Ph), 7.35–7.56 (m, 8H, PH), 8.04–8.08 (m, 2H, Ph). – The crude product **7** was used for the next step without further purification.

Thexyldimethylsilyl 2-O-Benzoyl-4,6-O-benzylidene-β-D-gulopyranoside (**8**): A solution of compound **6** (2.63 g, 5.1 mmol) in dry dichloromethane (40 ml) and pyridine (730 µl) was treated at −17°C with trifluoromethanesulfonic anhydride (1.38 ml, 8.2 mmol) and stirred for 30 min at −17°C. The reaction mixture was then diluted with dichloromethane (40 ml) and washed with satd. aqueous $NaHCO_3$ solution (2 × 20 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was redissolved in acetonitrile (40 ml) and treated with tetrabutylammonium nitrite (4 g, 13.9 mmol). After stirring for 24 h at room temp., the solvent was evaporated in vacuo, the residue was redissolved in ethyl acetate (100 ml), washed with water (3 × 20 ml) and dried ($MgSO_4$). Evaporation of the solvent and purification of the residue by flash chromatography (toluene/acetone, 50:1 → 10:1) gave **8** (1.84 g, 70%) as a colorless foam. – TLC (toluene/acetone, 10:1): R_f = 0.33, $[\alpha]_D$ = −30.9 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.12, 0.18 (2 s, 6H, SiMe), 0.70, 0.71, 0.72, 0.73 (4 s, 12H, CH_3), 1.45–1.56 (m, 1H, CH), 2.25 (d, $J_{3,OH}$ = 2.3 Hz, 1H, OH), 3.84–3.85 (m, 1H, 5-H), 4.04–4.09 (m, 2H, 4-H, 6-H), 4.26–4.32 (m, 2H, 3-H, 6′-H), 5.29–5.31 (m, 2H, 1-H, 2-H), 5.54 (s, 1H, C*H*Ph), 7.33–7.60 (m, 8H, Ph), 8.01–8.05 (m, 2H, Ph). – $C_{28}H_{38}O_7Si$ (514.69): calcd. C 65.34, H 7.44; found C 65.46, H 7.75.

Thexyldimethylsilyl 3-S-Acetyl-2-O-benzoyl-4,6-O-benzylidene-3-thio-β-D-galactopyranoside (**9**): A solution of compound **8** (14.8 g, 28.8 mmol) in dry dichloromethane (200 ml) and pyridine (2.4 ml) was treated at 0°C with trifluoromethanesulfonic anhydride (9.5 ml, 58 mmol), stirred for 30 min at 0°C and for 2 h at room temp. The reaction mixture was diluted with dichloromethane (200 ml) and washed with satd. aqueous $NaHCO_3$ solution (50 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was redissolved in dry dimethyl formamide (100 ml) and treated for 4 h with potassium thioacetate (10 g, 87.56 mmol) at 60°C. The reaction mixture was concentrated in vacuo, redissolved in ethyl acetate (250 ml), washed with water (4 × 50 ml) and the solvent was evaporated in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 8:1 → 6:1) of the residue afforded **9** (12.87 g, 78%) as a colorless foam. – TLC (toluene/acetone, 30:1): R_f = 0.40, $[\alpha]_D$ = +29.8 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.05, 0.15 (2 s, 6H, SiMe), 0.66, 0.67, 0.68,

0.69 (4 s, 12H, CH_3), 1.44–1.54 (m, 1H, CH), 2.18 (s, 3H, $COCH_3$), 3.65–3.66 (m, 1H, 5-H), 4.03–4.10 (m, 2H, 4-H, 6-H), 4.19 (dd, $J_{2,3}$ = 11.4, $J_{3,4}$ = 3.3 Hz, 1H, 3-H), 4.28 (dd, $J_{5,6'}$ = 1.4, $J_{6,6'}$ = 12.4 Hz, 1H, 6'-H), 4.94 (d, $J_{1,2}$ = 7.4 Hz, 1H, 1-H), 5.38 (dd, $J_{1,2}$ = 7.4, $J_{2,3}$ = 11.4 Hz, 1H, 2-H), 5.52 (s, 1H, C*H*Ph), 7.35–7.54 (m, 8H, Ph), 7.94–7.97 (m, 2H, Ph). – $C_{30}H_{40}O_7SSi$ (572.79): calcd. C 62.91, H 7.04; found C 63.05, H 7.06.

Thexyldimethylsilyl 2-O-Benzoyl-4,6-benzylidene-3-thio-β-D-galactopyranoside (**10**): Hydrazinium acetate (2.4 g, 26.2 mmol) was added to a solution of compound **9** (10 g, 17.46 mmol) in dry dimethyl formamide (150 ml). After stirring for 30 min at room temp., the mixture was diluted with ethyl acetate (200 ml) and a satd. NaCl solution (70 ml) was added. The organic layer was washed with water (4 × 70 ml) and dried ($MgSO_4$). The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 6:1) to give compound **10** (9.26 g, quant.) as a colorless foam. – TLC (petroleum ether/ethyl acetate, 6:1): R_f = 0.25, $[\alpha]_D$ = +37.4 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.07, 0.16 (2 s, 6H, SiMe), 0.68, 0.69, 0.70, 0.71 (4 s, 12H, CH_3), 1.46–1.54 (m, 1H, CH), 2.18 (d, $J_{3,SH}$ = 11 Hz, 1H, SH), 3.07 (ddd, $J_{3,SH}$ = 11, $J_{2,3}$ = 11.1, $J_{3,4}$ = 3.2 Hz, 1H, 3-H), 3.56–3.57 (m, 1H, 5-H), 4.04–4.12 (m, 2H, 4-H, 6-H), 4.28 (dd, $J_{5,6'}$ = 1.3, $J_{6,6'}$ = 12.3 Hz, 1H, 6'-H), 4.82 (d, $J_{1,2}$ = 7.5 Hz, 1H, 1-H), 5.26 (dd, $J_{1,2}$ = 7.5, $J_{2,3}$ = 11.1 Hz, 1H, 2-H), 5.56 (s, 1H, C*H*Ph), 7.35–7.57 (m, 8H, Ph), 8.01–8.05 (m, 2H, Ph). – $C_{28}H_{38}O_6SSi$ (530.76): calcd. C 63.36, H 7.22; found C 63.78, H 7.36.

Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-2-S-acetyl-3,5-dideoxy-2-thio-D-glycero-α-D-galacto-2-nonulopyranosonate (**12**): Compound **12** can be prepared as previously described[14] or as follows: Tetrabutylammonium hydrogensulfate (5.68 g, 16.72 mmol) and potassium thioacetate (2.29 g, 20.06 mmol) were added to a solution of compound **11**[11] (8.51 g, 16.71 mmol) in ethyl acetate (85 ml) and aqueous sodium carbonate (1 M, 85 ml). After stirring for 45 min at room temp., the mixture was diluted with ethyl acetate (500 ml). The organic layer was separated and successively washed with a satd. aqueous $NaHCO_3$ solution (200 ml), water (200 ml), and a satd. NaCl solution (200 ml). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Crystallization from ethyl acetate/petroleum ether gave compound **13** (6.6 g, 72%) as colorless crystals. The physical properties found for **13** are in full accordance with those described in ref.[14].

Thexyldimethylsilyl 2-O-Benzoyl-4,6-O-benzylidene-3-S-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-3-thio-β-D-galactopyranoside (**13**) *and Methyl 5-Acetamido-4,7,8,9-tetra-O-acetyl-2,3,5-trideoxy-D-glycero-D-galacto-non-2-enonate* (**14**): a) *From* **8** *and* **12**: To a stirred solution of compound **12** (190 mg, 345 μmol) in dry methanol (6 ml) at −40 °C, was added a solution of sodium methoxide (2 ml) [prepared from sodium metal (7.55 mg, 329 μmol) and dry methanol (2 ml)]. The mixture was stirred for 20 min at −40 °C and then concentrated in vacuo. To the residue, redissolved in dry dimethyl formamide (1.5 ml), was added a solution of compound **8** which carried a 3-*O*-trifluoromethanesulfonyl group [prepared from **8** (355 mg, 690 μmol), see synthesis of **9**]. After stirring for 45 h at room temp., the mixture was diluted with ethyl acetate (30 ml) and satd. aqueous NH_4Cl solution (10 ml). The organic layer was washed with water (4 × 10 ml), dried ($MgSO_4$), and concentrated in vacuo. Medium pressure chromatography (dichloromethane/methanol, 30:1) of the residue gave **13** (103 mg, 30%) as an amorphous mass, together with the known compound **14** (41 mg, 25%), also as an amorphous mass.

b) *From* **10** *and* **11**: Sodium hydride (106 mg, 4.4 mmol) was added to a solution of compound **10** (2.16 g, 4.08 mmol) in dry tetrahydrofuran (60 ml). The suspension was stirred under an inert atmosphere until hydrogen evolution had ceased. 1,7,10-Trioxa-4,13-diazacyclopentadecane (890 mg, 816 μmol) was then added, followed dropwise by a solution of compound **11** (1.6 g, 3.14 mmol) in dry tetrahydrofuran (20 ml). After stirring for 30 min at room temp., the mixture was diluted with dichloromethane (150 ml) washed with a half satd. aqueous NaCl solution (3 × 50 ml), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (dichloromethane/methanol, 90:1 → 60:1) of the residue afforded **13** (3.48 g, 85%) as a colorless, amorphous mass. – **13**: TLC (toluene/acetone, 4:3): R_f = 0.43, $[\alpha]_D$ = +57.8 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.07, 0.15 (2 s, 6H, SiMe), 0.65, 0.66, 0.67, 0.68 (4 s, 12H, CH_3), 1.39–1.51 (m, 1H, CH), 1.71, 1.82 (2 s, 6H, $COCH_3$), 1.88 (dd, $J_{3b,3'b}$ = 12.8, $J_{3b,4}$ = 12.8 Hz, 1H, 3b-H), 1.95, 2.06, 2.19 (3 s, 9H, $COCH_3$), 2.54 (dd, $J_{3b,3'b}$ = 12.8, $J_{3'b,4b}$ = 4.6 Hz, 1H, 3'b-H), 3.68–3.73 (m, 3H, 4a-H, 5a-H, 6b-H), 3.74 (s, 3H, OCH_3), 3.75–3.85 (m, 2H, 3a-H, 5b-H), 4.03 (dd, $J_{5a,6a}$ < 1, $J_{6a,6'a}$ = 12.6 Hz, 1H, 6a-H), 4.13 (dd, $J_{8b,9b}$ = 5.6, $J_{9b,9'b}$ = 12.5 Hz, 1H, 9b-H), 4.24 (dd, $J_{5a,6'a}$ < 1, $J_{6a,6'a}$ = 12.6 Hz, 1H, 6'a-H), 4.31 (dd, $J_{8b,9'b}$ = 2.4, $J_{9b,9'b}$ = 12.5 Hz, 1H, 9'b-H), 4.79 (ddd, $J_{3b,4b}$ = 12.8, $J_{3'b,4b}$ = 4.6, $J_{4b,5b}$ = 10.2 Hz, 1H, 4b-H), 5.02 (d, $J_{NH,5b}$ = 9.9 Hz, 1H, NH), 5.14–5.24 (m, 3H, 7b-H, 1a-, 2a-H), 5.44 (s, 1H, C*H*Ph), 5.62 (ddd, $J_{7b,8b}$ = 9.9, $J_{8b,9'b}$ = 2.4, $J_{8b,9b}$ = 5.6 Hz, 1H, 8b-H), 7.30–7.56 (m, 8H, Ph), 8.08–8.11 (m, 2H, Ph). – $C_{48}H_{65}NO_{18}SSi$ (1004.19): calcd. C 57.41, H 6.52, N 1.39; found C 57.02, H 6.35, N 1.60. – **14**: The physical properties found for **14** are in full accordance with those described previously[11b].

Thexyldimethylsilyl 2-O-Benzoyl-3-S-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-3-thio-β-D-galactopyranoside (**15**): Compound **13** (2.04 g, 2.03 mmol) was dissolved in dichloromethane (80 ml) and aqueous trifluoroacetic acid (50%, 16 ml). After stirring for 4 h at room temp., the mixture was diluted with dichloromethane (50 ml), washed with satd. aqueous $NaHCO_3$ solution (2 × 40 ml), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography (dichloromethane/methanol, 30:1 → 20:1) to give **15** (1.73 g, 92%) as an amorphous mass. – TLC (toluene/acetone, 4:3): R_f = 0.21, $[\alpha]_D$ = +19.2 (*c* = 0.5, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.05, 0.13 (2 s, 6H, SiMe), 0.64, 0.65, 0.66, 0.67 (4 s, 12H, CH_3), 1.39–1.47 (m, 1H, CH), 1.70, 1.81, 1.96, 2.04, 2.18 (5 s, 15H, $COCH_3$), 2.56 (dd, $J_{3b,3'b}$ = 12.8, $J_{3'b,4b}$ = 4.6 Hz, 1H, 3'b-H), 3.54 (d, *J* = 2.6 Hz, 1H, OH), 3.64–3.93 (m, 10H, 3a-, 4a-, 5a-, 6a-, 6'a-, 5b-, 6b-H, OCH_3), 4.06 (dd, $J_{8b,9b}$ = 6.1 Hz, $J_{9b,9'b}$ = 12.4 Hz, 1H, 9b-H), 4.31 (dd, $J_{8b,9'b}$ = 2.4, $J_{9b,9'b}$ = 12.5 Hz, 1H, 9'b-H), 4.75 (ddd, $J_{3'b,4b}$ = 4.6, $J_{3b,4b}$ = 11.8, $J_{4b,5b}$ = 10.1 Hz, 1H, 4b-H), 5.02 (d, $J_{NH,5b}$ = 9.9 Hz, 1H, NH), 5.06–5.19 (m, 3H, 1a-, 2a-, 7b-H), 5.58 (ddd, $J_{7b,8b}$ = 9.7, $J_{8b,9'b}$ = 2.4, $J_{8b,9b}$ = 6.1 Hz, 1H, 8b-H), 7.40–7.56 (m, 3H, Ph), 8.07–8.11 (m, 2H, Ph). – $C_{41}H_{61}NO_{18}SSi \cdot 0.5\ H_2O$ (925.09): calcd. C 53.23, H 6.75, N 1.51; found C 53.27, H 6.51, N 1.83.

Thexyldimethylsilyl 4,6-Di-O-acetyl-2-O-benzoyl-3-S-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-3-thio-β-D-galactopyranoside (**16**): Compound **15** (1.55 g, 1.68 mmol) was stirred in pyridine/acetic anhydride (1:1, 50 ml) at room temp. for 18 h. Concentration of the mixture in vacuo and purification of the residue by flash chromatography (toluene/acetone, 3:1) gave **16** (1.58 g, 94%) as an amorphous mass. – TLC (toluene/acetone, 3:1): R_f = 0.16, $[\alpha]_D$ = +40.6 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.05, 0.12 (2 s, 6H, SiMe), 0.66, 0.67, 0.68, 0.69 (4 s, 12H, CH_3), 1.39–1.47 (m, 1H, CH), 1.68 (s, 3H, $COCH_3$), 1.80 (dd, $J_{3b,3'b}$ =

12.7, $J_{3b,4b}$ = 10.7 Hz, 1H, 3b-H), 1.81, 1.94, 2.04, 2.05, 2.12, 2.22 (6 s, 18H, $COCH_3$), 2.54 (dd, $J_{3b,3'b}$ = 12.7, $J_{3'b,4b}$ = 4.6 Hz, 1H, 3'b-H), 3.65 (dd, $J_{5b,6b}$ = 10.5, $J_{6b,7b}$ = 2.2 Hz, 1H, 6b-H), 3.81 (dd, $J_{2a,3a}$ = 11.8, $J_{3a,4a}$ = 3.2 Hz, 1H, 3a-H), 3.83 (s, 3H, OCH_3), 3.86 (ddd, $J_{4b,5b}$ = 10.2, $J_{5b,6b}$ = 10.5, $J_{5b,NH}$ = 10.1 Hz, 1H, 5b-H), 4.01 (dd, $J_{5a,6a}$ = 7.4, $J_{6a,6'a}$ = 11.3 Hz, 1H, 6a-H), 4.05 (dd, $J_{5a,6'a}$ = 5.5, $J_{6a,6'a}$ = 11.3 Hz, 1H, 6'a-H), 4.10 (dd, $J_{8b,9b}$ = 5.7, $J_{9b,9'b}$ = 12.5 Hz, 1H, 9b-H), 4.13 (m, 1H, 5a-H), 4.32 (dd, $J_{8b,9'b}$ = 2.3, $J_{9b,9'b}$ = 12.5 Hz, 1H, 9'b-H), 4.77 (ddd, $J_{3a,4b}$ = 10.7, $J_{3e,4b}$ = 4.6, $J_{4b,5b}$ = 10.2 Hz, 1H, 4b-H), 4.92 (dd, $J_{3a,4a}$ = 3.2, $J_{4a,5a}$ < 1 Hz, 1H, 4a-H), 5.00 (d, $J_{NH,5b}$ = 10.1 Hz, 1H, NH), 5.02 (dd, $J_{1a,2a}$ = 7.4, $J_{2a,3a}$ = 11.8 Hz, 1H, 2a-H), 5.19 (d, $J_{1a,2a}$ = 7.4 Hz, 1H, 1a-H), 5.20 (dd, $J_{6b,7b}$ = 2.2, $J_{7b,8b}$ = 10.2 Hz, 1H, 7b-H), 5.62 (ddd, $J_{7b,8b}$ = 10.2, $J_{8b,9'b}$ = 2.3, $J_{8b,9b}$ = 5.7 Hz, 1H, 8b-H), 7.40–7.56 (m, 3H, Ph), 8.06–8.10 (m, 2H, Ph). – $C_{45}H_{65}NO_{20}SSi$ (1000.16): calcd. C 54.08, H 6.55, N 1.40; found C 54.27, H 6.82, N 1.74.

4,6-Di-O-acetyl-2-O-benzoyl-3-S-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-3-thio-α/β-D-galactopyranose (**17**): Compound **16** (1.28 g, 1.28 mmol) was dissolved in dry tetrahydrofuran (20 ml). Acetic acid (73 µl, 1.28 mmol) and then a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran (1.5 ml, 1.5 mmol) were added at 0°C. The mixture was slowly warmed to room temp. and stirred for 30 min. After the addition of diethyl ether (50 ml), the organic layer was washed with brine (3 × 15 ml), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (toluene/acetone, 2:1) gave compound **17** (1.02 g, 93%) in the ratio α:β = 5:95 as a colorless foam. – TLC (toluene/acetone, 2:1): R_f = 0.16, $[\alpha]_D$ = +67.8 (*c* = 0.5, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.82–2.21 (m, 22H, 3b-H, $COCH_3$), 2.58 (dd, $J_{3b,3'b}$ = 12.6, $J_{3'b,4b}$ = 4.5 Hz, 1H, 3'b-H), 3.55 (d, $J_{1a,OH}$ = 7.7 Hz, 1H, OH), 3.68 (dd, $J_{6b,7b}$ = 2.4, $J_{5b,6b}$ = 10.5 Hz, 1H, 6b-H), 3.85 (s, 3H, OCH_3), 3.92–4.30 (m, 7H, 3a-, 5a-, 6a-, 6'a-, 5b-, 9b-, 9'b-H), 4.80 (ddd, $J_{3b,4b}$ = 11.6, $J_{3'b,4b}$ = 4.5, $J_{4b,5b}$ = 10.5 Hz, 1H, 4b-H), 4.93 (dd, $J_{1a,2a}$ = 7.7, $J_{2a,3a}$ = 11.9 Hz, 1H, 2a-H), 4.99 (m, 1H, 4a-H), 5.04 (d, $J_{NH,5b}$ = 10.2 Hz, 1H, NH), 5.19 (dd, $J_{1a,2a}$ = $J_{1a,OH}$ = 7.7 Hz, 1H, 1a-H), 5.30 (dd, $J_{6b,7b}$ = 2.4, $J_{7b,8b}$ = 10.1 Hz, 1H, 7b-H), 5.61 (ddd, $J_{7b,8b}$ = 10.1, $J_{8b,9'b}$ = 2.5, $J_{8b,9b}$ = 5 Hz, 1H, 8b-H), 7.44–7.58 (m, 3H, Ph), 8.13–8.17 (m, 2H, Ph). – $C_{37}H_{47}NO_{20}S$ (857.84): calcd. C 51.81, H 5.52, N 1.63; found C 52.17, H 5.59, N 2.10.

O-(Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-S-4,6-di-O-acetyl-2-O-benzoyl-3-thio-α,β-D-galactopyranosyl-trichloroacetimidate (**18**): To a solution of **17** (291 mg, 332 µmol) in dry dichloromethane (10 ml) were added trichloroacetonitrile (2 ml, 19.95 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (2 drops). After 1 h the mixture was concentrated in vacuo. Flash chromatography (toluene/acetone, 2:1) of the residue furnished **18** (309 mg, 93%) in the ratio α:β = 1:2 as an amorphous mass. – TLC (toluene/acetone, 2:1): R_f = 0.28, $[\alpha]_D$ = +48.8 (*c* = 0.5, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.63–2.25 (several s, 42H, 14 $COCH_3$ α/β), 2.56 (dd, $J_{3b,3'b}$ = 4.5, $J_{3'b,4b}$ = 12.6 Hz, 1H, 3'b-H), 6.37 (d, $J_{1a,2a}$ = 8 Hz, 1H, 1a-Hβ), 6.67 (d, $J_{1a,2a}$ = 4 Hz, 1H, 1a-Hα), 8.55 (s, 1H, NH), 8.62 (s, 1H, NH). – $C_{39}H_{47}Cl_3N_2O_{20}S$ (1002.23): calcd. C 46.74, H 4.73, N 2.80; found C 46.45, H 5.06, N 2.54.

1,4,6-Tri-O-acetyl-2-O-benzoyl-3-S-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-3-thio-α/β-D-galactopyranose (**19**): Compound **17** (269 mg, 314 µmol) was stirred in pyridine/acetic anhydride (1:1, 8 ml) at room temp. for 18 h. Concentration of the mixture in vacuo and purification of the residue by flash chromatography (toluene/acetone, 3:1) gave **19** (254 mg, 90%) in the ratio α:β = 5:95 as an amorphous mass. – **19β**: TLC (toluene/acetone, 2:1): R_f = 0.22, $[\alpha]_D$ = +73 (*c* = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.65–2.23 (m, 25H, 3b-H, $COCH_3$), 2.55 (dd, $J_{3b,3'b}$ = 12.6, $J_{3'b,4b}$ = 4.6 Hz, 1H, 3'b-H), 3.62 (dd, $J_{5b,6b}$ = 10.7, $J_{6b,7b}$ = 2.3 Hz, 1H, 6b-H), 3.85 (s, 3H, OCH_3), 3.81–4.13 (m, 5H, 3a-, 6a-, 6'a-, 5b-, 9b-H), 4.32 (dd, $J_{8b,9'b}$ = 2.2, $J_{9b,9'b}$ = 12.4 Hz, 1H, 9'b-H), 4.40 (m, 1H, 5a-H), 4.76 (ddd, $J_{3b,4b}$ = 11.5, $J_{3'b,4b}$ = 4.6, $J_{4b,5b}$ = 10.4 Hz, 1H, 4b-H), 4.95–5.00 (m, 2H, NH, 4a-H), 5.14–5.28 (m, 2H, 7b-H, 2a-H), 5.62 (ddd, $J_{7b,8b}$ = 10.1, $J_{8b,9'b}$ = 2.2, $J_{8b,9b}$ = 6.2 Hz, 1H, 8b-H), 6.26 (d, $J_{1a,2a}$ = 8.1 Hz, 1H, 1a-H), 7.43–7.60 (m, 3H, Ph), 8.06–8.10 (m, 2H, Ph). – $C_{39}H_{49}NO_{21}S$ (899.88): calcd. C 52.05, H 5.49, N 1.56; found C 51.74, H 5.52, N 1.88.

4,6-Di-O-acetyl-2-O-benzoyl-3-S-(methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-3-thio-α-D-galactopyranosyl Bromide (**20**): HBr in acetic acid (33%, 1.26 ml) was added to a cold solution of **19** (87 mg, 96.7 µmol) in dichloromethane (3.6 ml). After stirring for 5 h at 0°C, the reaction mixture was diluted with dichloromethane (20 ml) and water (4 ml). The organic layer was successively washed with an ice-cold satd. aqueous $NaHCO_3$ solution (2 × 5 ml) and water (2 × 5 ml), dried ($MgSO_4$), and concentrated in vacuo to give crude **20** (84.6 mg, 95%) as a colorless powder. The crude product was used for the next step without further purification. – TLC (toluene/acetone, 3:2): R_f = 0.35, $[\alpha]_D$ = +34.5 (*c* = 1.0 in chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.88 (s, 3H, $COCH_3$), 1.97, 2.02, 2.03, 2.07, 2.11, 2.18 (6 s, 18H, $COCH_3$), 2.58 (dd, $J_{3'b,3b}$ = 12.8, $J_{3'b,4b}$ = 4.6 Hz, 1H, 3'b-H), 3.78 (dd, $J_{5b,6b}$ = 10.8, $J_{6b,7b}$ = 2 Hz, 1H, 6b-H), 3.82 (s, 3H, OCH_3), 4.01 (m, 4H, 3a-, 5a-, 6'a-, 9'b-H), 4.27 (dd, $J_{5a,6a}$ = 2.8, $J_{6a,6'a}$ = 12.6 Hz, 1H, 6a-H), 4.44 (dd, $J_{8b,9b}$ = 2.9, $J_{9b,9'b}$ = 12.1 Hz, 1H, 9b-H), 4.76–4.87 (m, 1H, 4b-H), 5.04 (dd, $J_{1a,2a}$ = 3.9, $J_{2a,3a}$ = 12.1 Hz, 1H, 2a-H), 5.11 (d, $J_{NH,5b}$ = 10.1 Hz, 1H, NH), 5.24–5.26 (m, 1H, 4a-H), 5.38 (dd, $J_{6b,7b}$ = 2, $J_{7b,8b}$ = 9.9 Hz, 1H, 7b-H), 5.68 (ddd, $J_{7b,8b}$ = 9.9, $J_{8b,9b}$ = 2.9, $J_{8b,9'b}$ = 6.7 Hz, 1H, 8b-H), 6.74 (d, $J_{1a,2a}$ = 3.9 Hz, 1H, 1a-H), 7.48–7.65 (m, 3H, Ph), 8.14–8.17 (m, 2H, Ph). – FAB MS (matrix: 3-nitrobenzyl alcohol): *m/z* (%) = 944 (45) [MNa^+], 922 (5) [MH^+], 474 (18) [$C_{20}H_{28}NO_{12}^+$], 414 (96) [$C_{18}H_{24}NO_{10}^+$].

Heptyl 2,3,4,6-Tetra-O-acetyl-1-thio-β-D-galactopyranoside (**22**): A solution of **21**[17] (29.85 g, 60.85 mmol) and heptylthiol (20 ml, 130 mmol) in dry dichloromethane (80 ml) was treated at room temp. with a 0.1 M solution of trimethylsilyl trifluoromethanesulfonate in dichloromethane (6 ml, 600 µmol). After stirring for 10 min, the reaction mixture was neutralized with triethylamine and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 3:1 → 5:2) to give **22** (27.5 g, 98%) as a colorless oil. – TLC (petroleum ether/ethyl acetate, 5:2): R_f = 0.31, $[\alpha]_D$ = −14.7 (*c* = 1.0 in chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (dd, *J* = 6.8 Hz, 3H, CH_2CH_3), 1.24–1.37 (m, 8H, CH_2), 1.52–1.61 (m, 2H, SCH_2CH_2), 1.96, 2.01, 2.04, 2.13 (4 s, 12H, $COCH_3$), 2.62–2.70 (m, 2H, SCH_2), 3.90 (ddd, $J_{4,5}$ = 1, $J_{5,6}$ = 6.6, $J_{5,6'}$ = 7.6 Hz, 1H, 5-H), 4.04–4.18 (m, 2H, 6-H, 6'-H), 4.44 (d, $J_{1,2}$ = 9.9 Hz, 1H, 1-H), 5.01 (dd, $J_{2,3}$ = 10, $J_{3,4}$ = 3.4 Hz, 1H, 3-H), 5.20 (dd, $J_{1,2}$ = 9.9, $J_{2,3}$ = 10 Hz, 1H, 2-H), 5.40 (dd, $J_{3,4}$ = 3.4, $J_{4,5}$ = 1 Hz, 1H, 4-H). – $C_{21}H_{34}O_9S$ (462.56): calcd. C 54.53, H 7.41; found C 54.42, H 7.42.

Heptyl 1-Thio-β-D-galactopyranoside (**23**): To a solution of compound **22** (27.5 g, 59.4 mmol) in dry methanol was added a 1 M

solution of sodium methoxide in methanol (6 ml, 6 mmol). The resulting mixture was stirred for 45 min at room temp. and then neutralized with Amberlite IR 120 (H^+) resin. The solvent was evaporated to give compound **23** (17.65 g, quant.) as a colorless powder. – TLC (dichloromethane/methanol, 10:1): R_f = 0.14, $[\alpha]_D$ = +20.6 (c = 1.0, methanol). – ^{1}H NMR (250 MHz, CD_3OD): δ = 0.90 (dd, J = 6.8 Hz, 3H, CH_3), 1.30–1.44 (m, 8H, CH_2), 1.58–1.67 (m, 2H, CH_2), 2.66–2.78 (m, 2H, SCH_2), 3.42–3.57 (m, 3H, 2-, 3-, 5-H), 3.64–3.77 (m, 2H, 6-, 6′-H), 3.88 (dd, $J_{3,4}$ = 3.2, $J_{4,5}$ = 1 Hz, 4-H), 4.29 (d, $J_{1,2}$ = 9.3 Hz, 1H, 1-H). – $C_{13}H_{26}O_5S$ (294.41): calcd. C 53.04, H 8.90; found C 53.42, H 8.95.

Heptyl 4,6-O-Benzylidene-1-thio-β-D-galactopyranoside (**24**): To a stirred solution of compound **23** (17.5 g, 59.44 mmol) in dry acetonitrile (350 ml), were added benzaldehyde dimethyl acetal (13.4 ml, 89.2 mmol) and *p*-toluenesulfonic acid (350 mg). After stirring for 1 h at room temp., the reaction mixture was neutralized with triethylamine and concentrated in vacuo. The residue was dissolved in ethyl acetate (200 ml) and precipitated through addition of petroleum ether (400 ml) to give compound **24** (20.69 g, 91%) as an amorphous mass. – TLC (petroleum ether/ethyl acetate, 1:2): R_f = 0.17, $[\alpha]_D$ = –63.2 (c = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.86 (dd, J = 6.8 Hz, 3H, CH_3), 1.25–1.38 (m, 8H, CH_2), 1.63–1.67 (m, 2H, CH_2), 2.57–2.76 (m, 4H, SCH_2, OH), 3.49–3.51 (m, 1H, 5-H), 3.62–3.71 (m, 1H, 3-H), 3.78 (dd, $J_{1,2}$ = $J_{2,3}$ = 9.3 Hz, 1H, 2-H), 4.01 (dd, $J_{5,6'}$ = 1.8, $J_{6,6'}$ = 12.5 Hz, 1H, 6′-H), 4.23 (dd, $J_{3,4}$ = 3.6, $J_{4,5}$ = 1.1 Hz, 1H, 4-H), 4.30 (d, $J_{1,2}$ = 9.3 Hz, 1H, 1-H), 4.33 (dd, $J_{5,6}$ = 1.5, $J_{6,6'}$ = 12.5 Hz, 1H, 6-H), 5.52 (s, 1H, C*H*Ph), 7.34–7.48 (m, 5H, Ph). – $C_{20}H_{30}O_5S$ (382.52): calcd. C 62.80, H 7.91; found C 62.57, H 7.91.

Heptyl 2,3-Di-O-acetyl-4,6-O-benzylidene-1-thio-β-D-galactopyranoside (**25**): Compound **24** (929 mg, 2.43 mmol) was stirred in pyridine/acetic anhydride (1:1, 16 ml) at room temp. for 16 h. Concentration of the mixture in vacuo and purification of the residue by flash chromatography (toluene/acetone, 25:1) gave **25** (1.13 g, quant.) as a colorless oil. – TLC (toluene/acetone, 25:1): R_f = 0.23, $[\alpha]_D$ = +2.8 (c = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84 (dd, J = 6.8 Hz, 3H, CH_3), 1.23–1.27 (m, 8H, CH_2), 1.55–1.72 (m, 2H, CH_2), 2.04, 2.06 (2 s, 6H, $COCH_3$), 3.54 (m, 1H, 5-H), 3.99 (dd, $J_{5,6'}$ = 1.7, $J_{6,6'}$ = 12.5 Hz, 1H, 6′-H), 4.32 (dd, $J_{5,6}$ = 1.5, $J_{6,6'}$ = 12.5 Hz, 1H, 6-H), 4.39 (dd, $J_{3,4}$ = 3.5, $J_{4,5}$ < 1 Hz, 1H, 4-H), 4.43 (d, $J_{1,2}$ = 9.8 Hz, 1H, 1-H), 4.95 (dd, $J_{2,3}$ = 10, $J_{3,4}$ = 3.5 Hz, 1H, 3-H), 5.45 (dd, $J_{1,2}$ = 9.8, $J_{2,3}$ = 10 Hz, 1H, 2-H), 5.47 (s, 1H, C*H*Ph), 7.34–7.50 (m, 5H, Ph). – $C_{24}H_{34}O_7S$ (466.59): calcd. C 61.78, H 7.34; found C 61.67, H 7.39.

Heptyl 2,3-Di-O-acetyl-6-O-benzoyl-1-thio-β-D-galactopyranoside (**26**): Compound **25** (460 mg, 988 μmol) was dissolved in dichloromethane (10 ml) and aqueous trifluoroacetic acid (50%, 2 ml). After stirring for 3 h at room temp., the mixture was diluted with dichloromethane (20 ml), washed with satd. aqueous $NaHCO_3$ solution (3 × 10 ml), dried ($MgSO_4$), and concentrated in vacuo. The residue was redissolved in dry acetonitrile/triethylamine (5:1, 10 ml) and cooled to –40 °C. To this solution was added benzoyl cyanide (144 mg, 1.1 mmol). After stirring for 30 min at –40 °C, methanol (0.5 ml) was added and the reaction mixture was allowed to warm to room temp. Flash chromatography (toluene/acetone, 13:1) afforded **26** (310 mg, 65%) as a colorless powder. – TLC (toluene/acetone, 8:1): R_f = 0.22, $[\alpha]_D$ = –7.3 (c = 0.5, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.85 (dd, J = 6.7 Hz, 3H, CH_3), 1.18–1.33 (m, 8H, CH_2), 1.53–1.59 (m, 2H, CH_2), 2.04, 2.08 (2 s, 6H, $COCH_3$), 2.39 (d, $J_{4,OH}$ = 4.9 Hz, 1H, OH), 2.62–2.71 (m, 2H, SCH_2), 3.90 (ddd, $J_{4,5}$ < 1, $J_{5,6}$ = $J_{5,6'}$ = 6.5 Hz, 1H, 5-H), 4.12 (ddd, $J_{4,OH}$ = 4.9, $J_{3,4}$ = 3.2, $J_{4,5}$ < 1 Hz, 1H, 4-H), 4.44–4.51 (m, 2H, 1-, 6′-H), 4.60 (dd, $J_{5,6}$ = 6.5, $J_{6,6'}$ = 11.5 Hz, 1H, 6-H), 5.00 (dd, $J_{2,3}$ = 9.9, $J_{3,4}$ = 3.2 Hz, 1H, 3-H), 5.30 (dd, $J_{1,2}$ = $J_{2,3}$ = 9.9 Hz, 1H, 2-H), 7.39–7.56 (m, 3H, Ph), 7.99–8.03 (m, 2H, Ph). – $C_{24}H_{34}O_8S$ (482.59): calcd. C 59.73, H 7.10; found C 59.97, H 7.07.

Heptyl 2,3-Di-O-acetyl-4-S-acetyl-6-O-benzoyl-1,4-dithio-β-D-glucopyranoside (**27**): A solution of compound **26** (244 mg, 505.6 μmol) in dry dichloromethane (10 ml) and pyridine (82 μl) was treated at –17 °C with trifluoromethanesulfonic acid (133 μl, 809 μmol), stirred for 30 min at –17 °C and for 30 min at 0 °C. The reaction mixture was then diluted with dichloromethane (20 ml) and washed with satd. aqueous $NaHCO_3$ solution (2 × 10 ml). The organic layer was dried ($MgSO_4$), filtered, and the solvent was evaporated in vacuo. The residue was redissolved in dry dimethyl formamide (7 ml) and treated for 10 min with potassium thioacetate (114 mg, 1 mmol) at room temp. The reaction mixture was concentrated in vacuo, redissolved in dichloromethane (30 ml), washed with water (3 × 10 ml) and the solvent was evaporated in vacuo. Flash chromatography (petroleum ether/ethyl acetate, 5:1) of the residue gave **27** (137 mg, 50%) as a colorless syrup. – TLC (toluene/acetone, 15:1): R_f = 0.43, $[\alpha]_D$ = –20.6 (c = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.82 (dd, J = 6.4 Hz, 3H, CH_3), 1.16–1.26 (m, 8H, CH_2), 1.41–1.56 (m, 2H, CH_2), 2.00, 2.03 (2 s, 6H, $COCH_3$), 2.30 (s, 3H, $COCH_3$), 2.55–2.67 (m, 2H, SCH_2), 3.74 (dd, $J_{3,4}$ = $J_{4,5}$ = 11 Hz, 1H, 4-H), 3.97 (ddd, $J_{5,6}$ = 2.2, $J_{5,6'}$ = 5.4, $J_{4,5}$ = 11 Hz, 1H, 5-H), 4.42 (dd, $J_{5,6'}$ = 5.4, $J_{6,6}$ = 12.2 Hz, 1H, 6′-H), 4.52 (d, $J_{1,2}$ = 10 Hz, 1H, 1-H), 4.59 (dd, $J_{5,6}$ = 2.2, $J_{6,6'}$ = 12.2 Hz, 1H, 6-H), 5.00 (dd, $J_{1,2}$ = 10, $J_{2,3}$ = 9.1 Hz, 1H, 2-H), 5.27 (dd, $J_{2,3}$ = 9.1, $J_{3,4}$ = 11 Hz, 1H, 3-H), 7.40–7.59 (m, 3H, Ph), 8.01–8.06 (m, 2H, Ph). – $C_{26}H_{36}O_8S_2$ (540.70): calcd. C 57.76, H 6.71; found C 57.73, H 6.76.

Heptyl 2,3-Di-O-acetyl-6-O-benzoyl-1,4-dithio-β-D-glucopyranoside (**28**): Hydrazinium acetate (30 mg, 323 μmol) was added to a solution of compound **27** (116.4 mg, 215 μmol) in dry dimethyl formamide (5 ml). After stirring for 20 min at room temp., the mixture was diluted with ethyl acetate (30 ml) and a satd. aqueous NaCl solution (7 ml) was added. The organic layer was washed with water (4 × 10 ml) and dried ($MgSO_4$). The residue was purified by flash chromatography (toluene/acetone, 40:1) to give compound **28** (94 mg, 87%) as a colorless oil. – TLC (toluene/acetone, 30:1): R_f = 0.26, $[\alpha]_D$ = +3.7 (c = 1.0, chloroform). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.83 (dd, J = 6.8 Hz, 3H, CH_3), 1.16–1.26 (m, 8H, CH_2), 1.51–1.58 (m, 3H, SH, CH_2), 2.04, 2.09 (2 s, 6H, $COCH_3$), 2.56–2.66 (m, 2H, SCH_2), 2.99 (ddd, $J_{4,SH}$ = 9.5, $J_{3,4}$ = 10.3, $J_{4,5}$ = 10.6 Hz, 1H, 4-H), 3.69 (ddd, $J_{5,6}$ = 2.2, $J_{5,6'}$ = 4.9, $J_{4,5}$ = 10.6 Hz, 1H, 5-H), 4.51 (d, $J_{1,2}$ = 9.6 Hz, 1H, 1-H), 4.63 (dd, $J_{5,6'}$ = 4.9, $J_{6,6'}$ = 12.1 Hz, 1H, 6′-H), 4.76 (dd, $J_{5,6}$ = 2.2, $J_{6,6'}$ = 12.1 Hz, 1H, 6-H), 4.93 (dd, $J_{1,2}$ = 9.6, $J_{2,3}$ = 9.1 Hz, 1H, 2-H), 5.03 (dd, $J_{2,3}$ = 9.1, $J_{3,4}$ = 10.3 Hz, 1H, 3-H), 7.40–7.57 (m, 3H, Ph), 8.00–8.04 (m, 2H, Ph). – $C_{24}H_{34}O_7S_2$ (498.66): calcd. C 57.81, H 6.87; found C 57.61, H 7.01.

Heptyl (Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-S-(4,6-di-O-acetyl-2-O-benzoyl-3-thio-β-D-galactopyranosyl)-(1→4)-S-2,3-di-O-acetyl-6-O-benzoyl-1,4-dithio-β-D-glucopyranoside (**29**): Sodium hydride (3.95 mg, 164 μmol) was added to a solution of **28** (86.3 mg, 173 μmol) in dry dimethyl formamide (3 ml) at room temp. The solution was stirred under argon until hydrogen evolution had ceased. A solution of crude **20** (88 mg, 96 μmol) in dry dimethyl formamide (3 ml) was added dropwise and the mixture was stirred for 30 min at room temp. The solution was diluted with

ethyl acetate (30 ml) and water (10 ml), washed with brine (3 × 10 ml), dried ($MgSO_4$) and concentrated in vacuo. Flash chromatography (toluene/acetone, 3:1) of the residue gave **29** (90 mg, 70%) as an amorphous mass. – TLC (toluene/acetone, 3:1): R_f = 0.20, $[\alpha]_D$ = −4.1 (*c* = 0.3, chloroform). – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.81 (dd, *J* = 6.4 Hz, 3H, CH_3), 1.15–1.23 (m, 8H, CH_2), 1.41–1.53 (m, 2H, CH_2), 1.76 (dd, $J_{3c,3'c}$ = 12.4, $J_{3c,4c}$ = 12.1 Hz, 1H, 3c-H), 1.83 (s, 3H, $COCH_3$), 1.92, 1.94, 1.99, 2.06, 2.07, 2.08, 2.10, 2.18 (8 s, 24H, $COCH_3$), 2.48–2.68 (m, 3H, 3'c-H, SCH_2), 3.07 (dd, $J_{3a,4a}$ = 10.9, $J_{4a,5a}$ = 11 Hz, 1H, 4a-H), 3.74 (dd, $J_{5c,6c}$ = 10.7, $J_{6c,7c}$ = 2.5 Hz, 1H, 6c-H), 3.85 (s, 3H, OCH_3), 3.88–4.01 (m, 4H, 5a-, 3b-, 6'b-, 5c-H), 4.10 (dd, $J_{5b,6b}$ = 4.8, $J_{6b,6'b}$ = 11.5 Hz, 1H, 6b-H), 4.26–4.29 (m, 2H, 5b-, 9'c-H), 4.37 (dd, $J_{8c,9c}$ = 2.2, $J_{9c,9'c}$ = 13.1 Hz, 1H, 9c-H), 4.46 (d, $J_{1a,2a}$ = 10 Hz, 1H, 1a-H), 4.76 (dd, $J_{5a,6'a}$ = 4.3, $J_{6a,6'a}$ = 12 Hz, 1H, 6'a-H), 4.79–4.83 (m, 2H, 6a-, 4c-H), 4.93 (dd, $J_{1a,2a}$ = 10, $J_{2a,3a}$ = 9.2 Hz, 1H, 2a-H), 5.01–5.08 (m, 3H, NH, 2b-, 4b-H), 5.29 (dd, $J_{2a,3a}$ = 9.2, $J_{3a,4a}$ = 10.9 Hz, 1H, 3a-H), 5.35 (d, $J_{1b,2b}$ = 9.6 Hz, 1H, 1b-H), 5.44 (dd, $J_{6c,7c}$ = 2.5, $J_{7c,8c}$ = 10.2 Hz, 1H, 7c-H), 5.69–5.73 (m, 1H, 8c-H), 7.38–7.56 (m, 6H, Ph), 7.96–8.15 (m, 4H, Ph). – $C_{61}H_{79}NO_{26}S_3$ (1338.48): calcd. C 54.74, H 5.95, N 1.05; found C 54.94, H 6.01, N 1.84.

Heptyl (Sodium 5-acetamido-3,5-dideoxy-D-glycero-α-D-galacto-2-nonulopyranosylonate)-(2→3)-S-(3-thio-β-D-galactopyranosyl)-(1→4)-S-1,4-dithio-β-D-glucopyranoside (**2**): To a solution of compound **29** (50 mg, 37 μmol) in dry methanol (6 ml), was added a solution of sodium methoxide in methanol (1 M, 2 ml) and the mixture was stirred for 24 h at room temp. An aqueous solution of potassium hydroxide (0.2 M, 2 ml) was then added and the mixture was stirred for a further 20 h at room temp. before being neutralized with Amberlite IR 120 (H^+) resin and filtered. The solvent was evaporated and the residue was chromatographed on a column of Sephadex LH-20 (chloroform/methanol, 1:1) to give **2** (27 mg, 99%) as a colorless powder. – TLC (chloroform/methanol/water, 5:4:1): R_f = 0.4, $[\alpha]_D$ = −88.1 (*c* = 0.3, methanol). – ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.69 (d, *J* = 6.9 Hz, 3H, CH_3), 1.10–1.29 (m, 8H, CH_2), 1.44–1.47 (m, 2H, CH_2), 1.65 (dd, $J_{3c,3'c}$ = $J_{3c,4c}$ = 12.2 Hz, 1H, 3c-H), 1.86 (s, 3H, $COCH_3$), 2.53–2.67 (m, 3H, 3'c-H, SCH_2), 2.75 (dd, $J_{3a,4a}$ = $J_{4a,5a}$ = 10.7 Hz, 1H, 4a-H), 3.16–3.92 (m, 19H, 2a-, 3a-, 5a-, 6a-, 6'a-, 2b-, 3b-, 4b-, 5b-, 6b-, 6'b-, 4c-, 5c-H, NH, 6c-, 7c-, 8c-, 9c-, 9'c-H), 4.36 (d, $J_{1a,2a}$ = 10 Hz, 1H, 1a-H), 4.54 (d, $J_{1b,2b}$ = 8.9 Hz, 1H, 1b-H). – $C_{30}H_{52}NaNO_{16}S_3 \cdot 2.5\ H_2O$ (846.86): calcd. C 42.54, H 6.78, N 1.65; found C 42.64, H 6.55, N 1.94.

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