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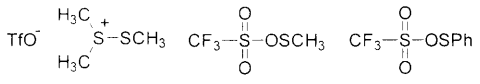
Abstract

Reaction of the methyl ester of 2-chloro-3-*S*-phenyl-3-thiosialic acid (**4**) with sodium thiomethoxide in acetonitrile at 0 °C affords the methyl ester of 2-*S*-methyl-3-*S*-phenyl-2,3-dithio-α-sialic acid (**6a**) in quantitative yield. Sialylation of tetrahydropyran-2-methanol (**7**) and 2-(trimethylsilyl)ethyl 2,2′,3,6,6′-penta-*O*-benzyl-α-lactoside (**8**) with **6a** in the presence of phenylsulfenyl triflate (PST) as promotor in CH_3CN at −40 °C gives α-sialosides **9** and **10** in good yield and excellent stereoselectivity. No β-sialosides are formed in either case. Acetylation of product **10**, and the subsequent reductive removal of the 3-thiophenyl group using Ph_3SnH, affords **12** — protected GM3 trisaccharide — in 82% yield after two steps. Sialylation of acceptor **8** with chloride **4** using silver triflate as promotor afforded **10** in 48% yield after two days at −15 °C in THF. A possible mechanism of sialylation with **6a** that involves intermediate α- and β-nitrilium ions is discussed. © 1997 Elsevier Science Ltd.

Keywords: Stereoselective α-sialylation; Thioglycoside; Phenylsulfenyl triflate; Sialyl glycoside

1. Introduction

This paper describes an effective preparation of α-sialyl glycosides using 2-*S*-methyl-3-*S*-phenyl-2,3-dithiosialic acid as the ultimate donor of the sialyl group and phenylsulfenyl triflate (PST) as promotor. Practical and stereocontrolled chemical syntheses of sialyl glycosides are of particular interest for the preparation of analogs of sialosides. Donors based on the 2-halogeno sialic acid group give poor yield and stereoselectivity [1]. Stereoselectivity can be increased with thioglycosides and xanthates of sialic acid, when these compounds are activated with equimolar amounts of thiophilic reagents in nitrile solvents at low temperature [2]. Dimethyl(methylthio)sulfonium triflate (DMTST) [3], methylsulfenyl triflate (MST) [4], and phenylsulfenyl triflate (PST) [5] — the reagent that we have introduced recently as a convenient substitute for MST — are the most effective activators.



Although the α-sialoside is the major stereoisomer formed in nitrile solvents, as much as 30% of the undesired β-product has been reported in some cases [6]. As we have shown previously [5], the amount of

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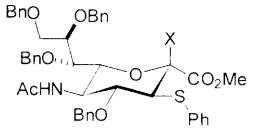
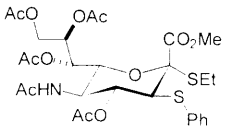
the β-product increases with more reactive acceptors such as primary or allylic alcohols. The 2-halogeno and 2-thio sialic acid-derived donors (without a substituent in the 3-position) undergo substantial elimination to sialyl glycal; an excess of these donors (they are expensive and relatively difficult to prepare) is required in order to obtain reasonable yields.

Sialyl donors **1** and **2** that have an auxiliary 3-SPh group have recently been introduced by Ogawa [7] and Magnusson [8]. Donor **1b** was used by Nicolaou [9] in the total chemical synthesis of sialyl Lewis X.



1a: X = Cl
1b: X = Br



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Donors **1** and **2** give in most cases α-sialosides and do not undergo undesired elimination to sialyl glycal. The syntheses of donors of type **1**, however, require approximately six steps starting from sialyl glycal; when activated with mercury or silver salts, these donors give α-sialosides in only moderate yield [7,9]. Donor **2** was prepared in three steps from sialyl glycal and gave sialosides in a good yield when activated with MST in acetonitrile [8]. The major drawback of this method is that MST and the reagents used for its preparation are unstable and toxic. MST also gives by-products that are *O*-alkylated.

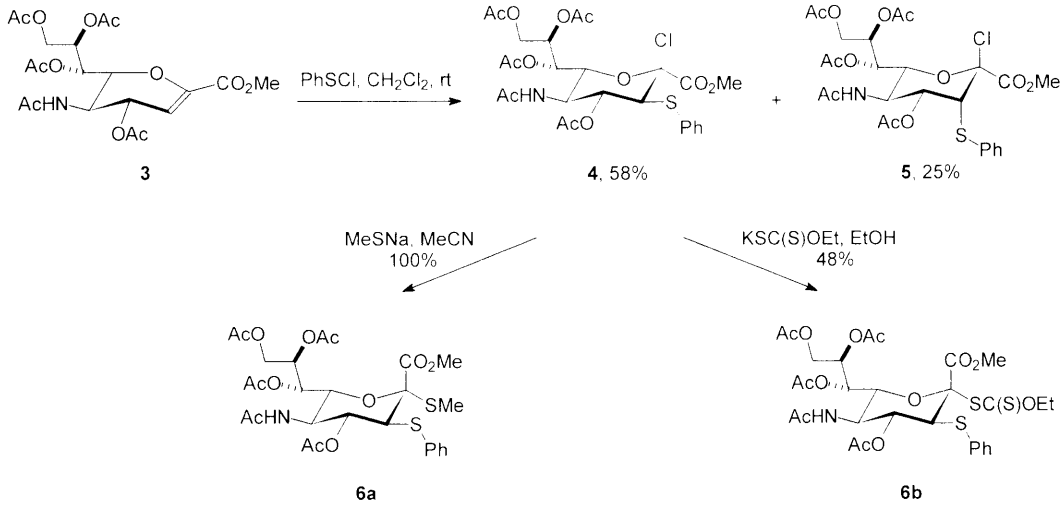
In this paper we show that α-sialyl donors of type **2** can be conveniently prepared in two steps starting from sialyl glycal **3**, and when activated with PST, they give α-sialosides in good yield. A possible mechanism of the reaction is also discussed.

2. Results and discussion

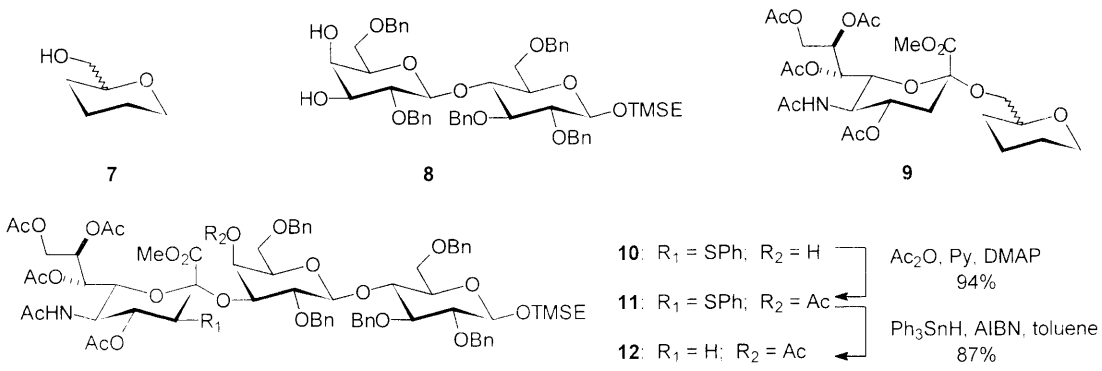
Preparation of sialyl donors and studies on sialylation.—Sialyl glycal **3**, on reaction with phenylsulfenyl chloride in dichloromethane at ambient temperature, gave a diastereomeric mixture of chlorides **4** and **5** in molar ratio 2.3:1 as described by Kondo [10] (Scheme 1). This mixture was separated by column chromatography. The ratio of diastereomers did not change when the reaction was carried out at 0 °C.

The most successful procedure for the synthesis of sialyl donor involved the reaction of chloride **4** with sodium thiomethoxide in acetonitrile at 0 °C. Thioglycoside **6a** was obtained in quantitative yield. In contrast, the reaction of **4** with *O*-ethyl *S*-potassium dithiocarbonate required 3 days in EtOH at 50 °C; the xanthate **6b** was isolated in only 48% yield, and it was contaminated by a number of unidentified by-products. When acetonitrile was used as a solvent in this reaction, a complex mixture of products was formed.

We studied sialylation of acceptors **7** and **8** with donor **6a** in CH_3CN at −40 °C using PST as promotor and di-*tert*-butylpyridine (DTBP) as proton scavenger (Scheme 2). We used racemic alcohol **7** as a model for preparation of the NeuAc-2,6-Gal linkage, a component that often occurs in gangliosides. Compound **9** was obtained as a 1:1 diastereomeric mixture



Scheme 1.

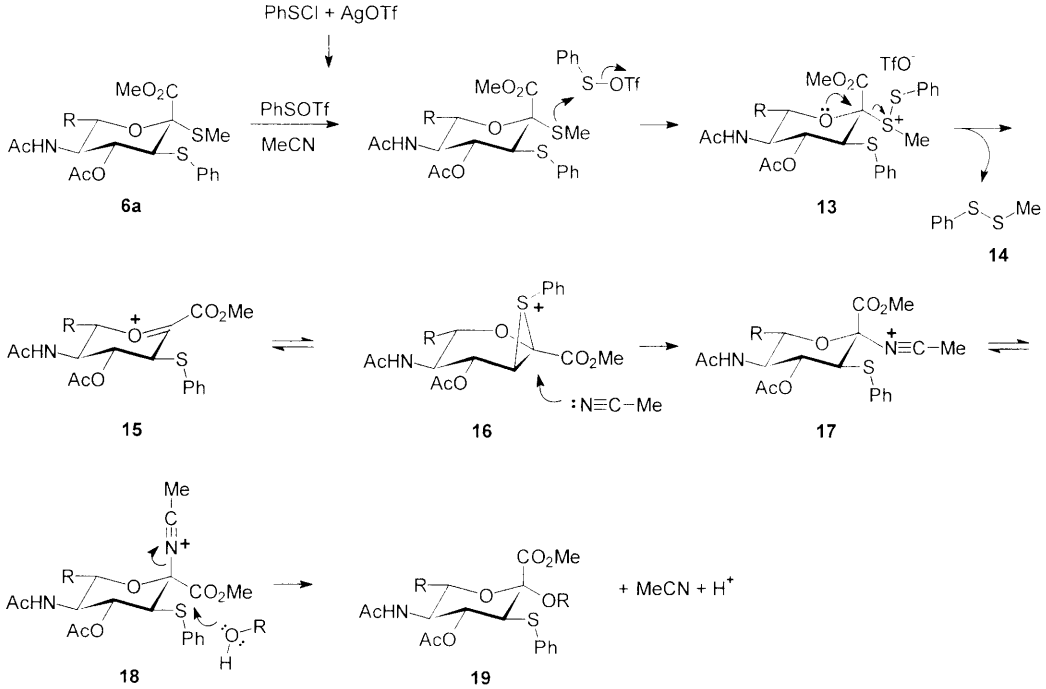


Scheme 2.

in 80% yield. Sialylation of acceptor **8** occurred selectively at the equatorial 3′-OH, rather than the axial 4′-OH, and generated the α-product **10** in 83% yield. No β-sialosides were detected in either case. The only compounds in the product mixture were the unreacted acceptor (used in excess) and a small amount of the unreacted donor **6a**. Acetylation of **10**, and the subsequent reductive removal of the 3-*S*-phenyl group using Ph_3SnH, afforded **12** — protected GM_3 trisaccharide — in 82% yield after two steps.

We also examined several less-successful alternative conditions for sialylation of acceptor **8** with chloride **4** using silver triflate as promotor. Product **10** was obtained in 48% yield after two days at −15 °C in THF as a solvent. No reaction occurred at −30 °C. Increasing the temperature to −5 °C resulted in lower yield of **10** and more by-products. THF was the best among the solvents tried (CH_2Cl_2, CCl_4, and CH_3CN).

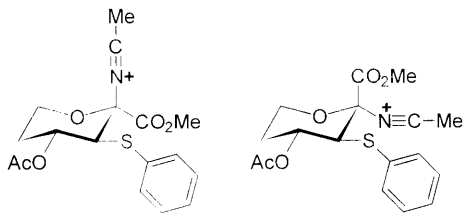
We identified the site of sialylation in the product **10** based on observation of a downfield shift of the C-4′ proton of its acetylation product **11**. We determined the stereochemistry of the glycosidic linkage in products **6a** and **10** to be α by the measurement of the long-range $^{13}C-^{1}H$ coupling constants ($J_{^{13}C(C-1)-^{1}H(H-3,axial)}$ 7.4 Hz for **6a**; $J_{^{13}C(C-1)-^{1}H(H-3,axial)}$ 6.2 Hz for **10**) of the sialic acid residue. This assignment was based on the observation by Hori [11] that α-sialosides show



Scheme 3.

$J_{^{13}C(C-1)-^{1}H(H-3,axial)}$ in the range 5.8–7.5 Hz, whereas the corresponding β-compounds have $J_{^{13}C(C-1)-^{1}H(H-3,axial)}$ in the range 1.0–1.7 Hz.

Mechanism of the reaction.—We speculate that in the first step, donor **6a** reacts with PST to give the oxonium ion **15** via the formation of the intermediate **13** and methyl phenyl disulfide (**14**) (Scheme 3). The presence of **14** in the reaction was identified by mass spectrometry. The oxonium ion **15** would be in equilibrium with the episulfonium ion **16.** According to our semiempirical MO calculations (PM3 [1] method [12]), ions **15** and **16** have approximately the same thermodynamic stability. In the second stage of the reaction, the reaction of ions **15** or **16** with acetonitrile could give the nitrilium ion **17**, which, according to PM3 calculations of enthalpies of model ions **20** and **21**, is 2.50 kcal/mol more stable than **18**.



20 21

We suggest that the nitrilium ion **17** is formed first. Attack of the acceptor ROH on the ion **17** is hindered by protons at C-4, C-6, and the CO_2Me group. We assume that the ion **17** is in the equilibrium with the more reactive **18**. In the final step the acceptor ROH reacts with the ion **18** to give the α-product **19**.

3. Conclusions

The reaction of 2-*S*-methyl-3-*S*-phenyl-2,3-dithio-α-sialic acid donor **6a** with primary and secondary glycosyl acceptors in the presence of PST in CH_3CN at low temperature affords α-sialosides in good yield, excellent stereoselectivity, and high purity. No undesired β-sialosides are formed during this reaction. The donor **6a** is prepared in two steps from sialic acid glycal; this fact makes this method of preparation of 3-*S*-phenyl-2,3-dithiosialic acid donors more convenient than others currently available. Unlike the commonly used 2-halogeno and 2-thio donors, donor **6a** does not undergo the elimination to sialyl glycal during sialylation; good yields of α-sialosides are obtained using less than equimolecular amounts of the donor. In comparison with other promotors, PST is non-toxic and does not give by-products that are *O*-alkylated. It is prepared from the stable phenylsulfenyl chloride. Sialosides prepared using this methods contain the 3-thiophenyl group, which is removed in high yield using Ph_3SnH.

4. Experimental

General.—Anhydrous reagents and solvents were prepared according to literature procedures [13]. *N*-Acetylneuraminic acid was obtained from extraction of the edible Chinese swiftlet's nest [14]. Sialic acid glycal **3** was prepared as described by Magnusson [8]. Phenylsulfenyl chloride was prepared by the reaction of phenyl thioacetate with SO_2Cl_2 [15]. It was stable at 4 °C under N_2 for at least 1 year. 2-(Trimethylsilyl)ethyl 2,6-di-*O*-benzyl-β-D-galactopyranosyl-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**8**) was prepared in total 26% yield from lactose (six steps [16]). *O*-Ethyl *S*-potassium dithiocarbonate was recrystallized before use from EtOH. The proton chemical shifts for all compounds were assigned using ^{1}H homonuclear decoupling experiments. [2]

Methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2-chloro-2,3,5-trideoxy-3-S-phenyl-3-thio-D-erythro-β-L-gluco-2-nonulopyranosonate (**4**) *and methyl 5-acetamido-4,7,8,9-tetra-O-acetyl-2-chloro-2,3,5-trideoxy-3-S-phenyl-2-thio-D-erythro-β-L-manno-2-nonulopyranosonate* (**5**). —Compounds **4** (20% of acetone in $CHCl_3$, R_f 0.30) and **5** (20% of acetone in $CHCl_3$, R_f 0.28) were prepared as described [10]. The ^{1}H NMR data were in agreement with those reported.

Methyl [5-acetamido-4,7,8,9-tetra-O-acetyl-2,3,5-trideoxy-2-S-methyl-3-S-phenyl-2,3-dithio-D-erythro-α-L-gluco-2-nonulopyranosid]onate (**6a**).—To a stirred suspension of MeSNa (46 mg, 0.66 mmol) in dried-over molecular sieves 4 Å MeCN (5 mL) cooled to 0 °C was added chloride **4** (272 mg, 0.44 mmol). The mixture was stirred at 0 °C for 3 h, after which the TLC (20% of acetone in $CHCl_3$, R_f 0.27) indicated the reaction was complete. The reaction mixture was dild with a suspension of silica gel (1 g) in EtOAc (5 mL), filtered through a short silica gel column (2 × 5

[1] PM3 was used from within MOPAC 6.0 [QCPE 455].

[2] Copies of NMR spectra of all new compounds described in this report are available on request from the authors.

cm), eluted with EtOAc, and concd in vacuo to give compound **6a** (276 mg, 100%) as a foam; $[\alpha]_D^{23}$ +91.8° (*c* 1.16, $CHCl_3$): ^1H NMR (500 MHz, $CDCl_3$): δ 1.83 (s, 3 H, SCH_3), 1.92 (s, 3 H), 2.00 (s, 3 H), 2.09 (s, 3 H), 2.12 (s, 3 H), 2.18 (s, 3 H), 3.39 (d, *J* 11.18 Hz, 1 H, *H*-3), 3.79 (dd, *J* 2.05, 11.20 Hz, 1 H, *H*-6), 3.86 (s, 3 H, CO_2CH_3), 4.07 (dd, *J* 5.17, 12.56 Hz, 1 H, *H*-9a), 4.10 (q, *J* 10.09 Hz, 1 H, *H*-5), 4.29 (dd, *J* 2.54, 12.49 Hz, 1 H, *H*-9b), 5.20 (t, *J* 10.60 Hz, 1 H, *H*-4), 5.27(dd, *J* 2.16, 7.66 Hz, 1 H, *H*-7), 5.30 (ddd, *J* 2.60, 5.38, 7.97 Hz, 1 H, *H*-8), 5.45 (d, *J* 10.08 Hz, 1 H, N*H*), 7.20–7.31 (m, 2 H), 7.50–7.54 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.10, 20.60, 20.68, 20.73, 21.07, 23.08, 50.36, 52.97, 58.85, 62.04, 67.35, 69.08, 73.63, 74.29, 86.78, 127.51, 129.04, 131.69, 136.94, 167.27 (C-1, $J^{13}_{C(C-1)-^1H(H-3,axial)}$ 7.40 Hz), 169.93, 170.05, 170.14, 170.57, 170.82; HRMS (FAB) calcd for $C_{32}H_{35}NO_{12}S_2Na$ [M + Na]: 652.1498; found: 652.1497.

Methyl [5-acetamido-4,7,8,9-tetra-O-*acetyl-2,3,5-trideoxy-2*-S-*ethylcarbonodithioyl-3*-S-*phenyl-2,3-dithio*-D-erythro-α-L-gluco-*2-nonulopyranosid]onate* (**6b**).—A mixture of chloride **4** (50 mg, 0.08 mmol) and *O*-ethyl *S*-potassium dithiocarbonate (26 mg, 0.16 mmol) in absolute EtOH (3 mL) was stirred at 50 °C for 3 days. The reaction mixture was dild with $CHCl_3$ (20 mL), washed with H_2O (2 × 5 mL), satd $NaHCO_3$ (5 mL), and brine (5 mL). After drying ($MgSO_4$) and concn in vacuo the residue was chromatographed (20% of acetone in $CHCl_3$, R_f 0.25) to afford **6b** (27 mg, 48%) as a yellow foam. ^1H NMR (500 MHz, $CDCl_3$): δ 1.37 (t, *J* 7.12, 3 H, OCH_2CH_3), 1.86 (s, 3 H), 1.98 (s, 3 H), 2.01 (s, 3 H), 2.06 (s, 3 H), 2.07 (s, 3 H), 3.86 (s, 3 H, CO_2CH_3), 3.90 (d, *J* 10.70, 1 H, *H*-3), 4.10 (dd, *J* 6.15, 12.39 Hz, 1 H, *H*-9a), 4.25 (q, *J* 10.50 Hz, 1 H, *H*-5), 4.28 (dd, *J* 2.41, 12.39 Hz, 1 H, *H*-9b), 4.38 (dd, *J* 1.80, 10.98 Hz, *H*-6), 4.42 (dd, *J* 7.11, 10.63 Hz, 1 H, OCH_2CH_3), 5.23 (dt, *J* 2.40, 6.22 Hz, 1 H, *H*-8), 5.26 (dd, *J* 2.00, 6.37 Hz, *H*-7), 5.35 (t, *J* 10.38 Hz, *H*-4), 5.38 (d, *J* 9.63 Hz, N*H*), 7.20–7.56 (m, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.53, 20.62, 20.70, 20.72, 20.75, 20.79, 23.12, 28.33, 49.72, 53.45, 56.18, 62.01, 67.72, 70.08, 70.13, 73.39, 74.97, 77.20, 93.06, 129.18, 132.51, 135.25, 166.92, 169.87, 169.98, 170.04, 170.50, 170.82, 207.26; HRMS (FAB) calcd for $C_{29}H_{37}NO_{13}S_3Na$ [M + Na]: 726.1325; found: 726.1301.

2-(Trimethylsilyl)ethyl 2,3,6-tri-O-*benzyl-4*-O-*[2,6-di*-O-*benzyl-3*-O-*[methyl [5-acetamido-4,7,8,9-tetra*-O-*acetyl-3*-S-*phenyl-3-thio-3,5-dideoxy*-D-erythro-α-L-gluco-*2-nonulopyranosyl]onate]-β*-D-*galactopyranosyl]-β*-D-*glucopyranoside* (**10**).—Toluene (2 × 5 mL) was evaporated from the mixture of **6a** (79 mg, 0.13 mmol) and **8** (150 mg, 0.17 mmol). The mixture was dissolved in CH_3CN (3 mL). DTBP (52 μL, 0.20 mmol) and dried and crushed molecular sieves 4 Å (0.5 g) were added. The mixture was stirred at rt for 0.5 h, then AgOTf (51 mg, 0.20 mmol) was added and stirring was continued in the dark for an additional 1 h. After cooling to −40 °C, PhSCl (23 μL, 0.19 mmol) was added and the mixture was stirred at −40 °C for 1 h. Diisopropylamine (50 μL, 0.35 mmol) was added, the mixture was stirred for 0.5 h, and a suspension of silica gel (1.0 g) in EtOAc (10 mL) was added to the cold reaction mixture. After filtration and concn in vacuo, the reaction mixture was chromatographed eluting with 10% of acetone in $CHCl_3$ → 15% acetone in $CHCl_3$ to give compound **10** (158 mg, 83%); $[\alpha]_D^{23}$ +18.8° (*c* 0.60, $CHCl_3$): ^1H NMR (500 MHz, C_6D_6): δ −0.26 [s, 9 H, $CH_2Si(CH_3)_3$], 0.99 [m, 2 H, $CH_2Si(CH_3)_3$], 1.54 (s, 3 H), 1.64 (s, 3 H), 1.71 (s, 3 H), 1.86 (s, 3 H), 1.90 (s, 3 H), 2.85 (bs, 1 H, 4-O*H*), 3.43 (m, 1 H, *H*-5), 3.44 (s, 3 H, CO_2CH_3), 3.58 (t, *J* 8.92 Hz, 1 H, *H*-2), 3.61 (d, *J* 11.29 Hz, 1 H, *H*-3″), 3.61 (m, 1 H, $OCH_2CH_2Si(CH_3)_3$), 3.69 (dd, *J* 5.55, 9.55 Hz, 1 H, *H*-6a′), 3.75 (t, *J* 9.10 Hz, 2 H, *H*-3), 3.77 (t, *J* 9.53 Hz, 1 H, *H*-2′), 3.88 (m, 1 H, *H*-5′), 3.89 (bs, 1 H, *H*-4′), 3.95 (dd, *J* 4.33, 10.95 Hz, 1 H, *H*-6a), 3.99 (dd, *J* 7.20, 9.55 Hz, 1 H, *H*-6b′), 4.10 (dt, *J* 7.00, 9.50 Hz, 1 H, $OCH_2CH_2Si(CH_3)_3$), 4.16 (dd, *J* 6.37, 12.52 Hz, 1 H, *H*-9a″), 4.22 (dd, *J* 2.31, 10.85 Hz, 1 H, *H*-6″), 4.22–4.34 (m, 4 H, *H*-6b, *H*-4, N*H* CH_2Ph), 4.43 (d, *J* 7.55 Hz, 1 H, *H*-1), 4.44 (d, *J* 11.98 Hz, 1 H), 4.56 (d, *J* 11.89 Hz, 1 H), 4.63 (d, *J* 11.25 Hz, 1 H), 4.65 (m, 2 H, *H*-5″, *H*-9″), 4.69 (d, *J* 12.55 Hz, 1 H), 4.73 (dd, *J* 3.24, 9.44 Hz, 1 H, *H*-3′), 4.86 (d, *J* 11.57 Hz, 1 H), 4.90 (d, *J* 12.58 Hz, 1 H), 4.92 (d, *J* 7.89 Hz, 1 H, *H*-1′), 4.96 (d, *J* 10.95 Hz, 1 H), 5.07 (d, *J* 11.47 Hz, 1 H), 5.30 (d, *J* 10.94 Hz, 1 H), 5.42 (dd, *J* 2.30, 7.69 Hz, 1 H, *H*-7″), 5.46 (t, *J* 10.77 Hz, 1 H, *H*-4″), 5.72 (dt, *J* 2.50, 7.80 Hz, 1 H, *H*-8″), 6.86–6.93 (m, 3 H), 7.05–7.30 (m, 15 H), 7.38 (m, 4 H), 7.43 (d, *J* 7.59 Hz, 2 H), 7.45 (d, *J* 7.53 Hz, 2 H), 7.54 (d, *J* 7.41 Hz, 2 H), 7.66 (d, *J* 7.42 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.42, 18.46, 20.58, 20.68, 20.92, 23.15, 49.94, 52.90, 57.68, 62.04, 67.14, 67.26, 68.50, 68.69, 68.90, 72.39, 72.44, 72.82, 72.95, 73.23, 74.40, 74.88, 75.19, 75.23, 76.23, 77.20, 78.09, 82.03, 82.75, 100.08, 102.47, 103.01, 127.15, 127.30, 127.37, 127.47, 127.59, 128.01, 128.11, 128.19, 128.23,

128.26, 129.05, 131.98, 135.36, 138.55, 138.80, 139.04, 139.15, 167.84 (C-1, $J^{13}_{C(C-1)-^1H(H-3,axial)}$ 6.20 Hz), 169.56, 169.89, 170.21, 170.44, 170.85; MS (FAB) calcd for $C_{78}H_{94}NO_{23}SSiNa$ [M + Na]: 1496; found: 1496.

*Methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-*O*-(methyl-1-tetrahydropyranyl)-3-*S*-phenyl-3-thio-*D*-erythro-α-*L*-gluco-2-nonulopyranosid]onate* (**9**).—Compound **9** (16.7 mg, 80% yield) was prepared from **6a** (20 mg, 0.030 mmol), **7** (6 μL, 0.045 mmol), AgOTf (12 mg, 0.045 mmol), and PhSCl (5 μL, 0.045 mmol) in MeCN (1.5 mL) as described above for preparation of compound **10**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (m, 1 H), 1.38–1.52 (m, 4 H), 1.73–1.82 (m, 1 H), 1.86 (s, 3 H), 1.99 (s, 3 H), 2.00 (s, 3 H), 2.01 (s, 3 H), 2.04 (s, 3 H), 2.08 (s, 3 H), 2.09 (s, 3 H), 3.32 (d, *J* 11.18 Hz, 1 H, *H*-3), 3.32 (d, *J* 11.18 Hz, 1 H, *H*-3), 3.34–3.41 (m, 2 H), 3.34–3.41 (m, 2 H), 3.60 and 3.63 (two dd, *J* 2.08, 11.11 Hz, 1 H, *H*-6), 3.71 (dd, *J* 5.23, 12.46 Hz, 1 H, *H*-9a), 3.83 (s, 3 H, CO_2CH_3), 3.95 (m, 1 H), 4.01 and 4.04 (two dd, *J* 2.39, 12.46 Hz, 1 H, *H*-9b), 4.15–4.27 (m, 3 H, *H*-5, OCH_2), 5.22–5.34 (m, 4 H, *H*-4, *H*-7, *H*-8, N*H*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.68, 20.72, 20.77, 20.87, 23.16, 25.100, 26.07, 28.14, 28.42, 49.82, 52.34, 57.48, 57.63, 62.33, 67.25, 67.84, 67.94, 68.29, 68.47, 68.79, 68.86, 72.13, 72.18, 72.88, 76.50, 76.69, 77.00, 77.32, 100.96, 101.11, 127.57, 128.81, 132.58, 132.67, 135.35, 168.35, 169.45, 170.04, 170.13, 170.51, 171.03, 173.65, 175.23; HRMS (FAB) calcd for $C_{32}H_{43}NO_{14}SNa$ [M + Na]: 720.2302; found: 720.2276.

*2-(Trimethylsilyl)ethyl 4-*O*-[4-*O*-acetyl-2,6-di-*O*-benzyl-3-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-3-*S*-phenyl-3-thio-*D*-erythro-α-*L*-gluco-2-nonulopyranosyl]onate]-β-*D*-galactopyranosyl]-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**11**).—To a soln of **10** (151 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) cooled to 0 °C was added DMAP (one crystal), pyridine (2 mL), and Ac_2O (1 mL). The resulting mixture was stirred overnight at rt, concd in vacuo, and chromatographed (20% of acetone in $CHCl_3$, R_f 0.41) to give **11** (146 mg, 94%). A signal *H*-4′ in ^{1}H NMR (500 MHz, C_6D_6) was detected at δ 5.84 (d, *J* 4.06 Hz). MS (FAB) calcd for $C_{80}H_{97}NO_{24}SSiNa$ [M + Na]: 1538; found: 1538.

*2-(Trimethylsilyl)ethyl 4-*O*-[4-*O*-acetyl-2,6-di-*O*-benzyl-3-*O*-[methyl [5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-*D*-erythro-α-*L*-gluco-2-nonulopyranosyl]onate]-β-*D*-galactopyranosyl]-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**12**).—To a stirred soln of **11** (140 mg, 0.092 mmol) and azoisobutyronitrile (4 mg, 0.024 mmol) in toluene (6 mL) was added a soln of triphenyltin hydride (150 mg, 0.427 mmol) in toluene (1 mL) under nitrogen. After refluxing for 10 h, the mixture was cooled to rt and applied directly on a silica gel column. Elution (20% acetonitrile in toluene → 33% acetonitrile in toluene, gradient) gave the recovered starting material **11** (15 mg, 11%) and the product **12** (113 mg, 87%); $[\alpha]_D^{23}$ −7.2° (*c* 0.85, $CHCl_3$); R_f 0.25 in 33% acetonitrile in toluene; ^{1}H NMR (500 MHz, C_6D_6): δ −0.29 (s, 9 H, $SiMe_3$), 0.98 (m, 2 H, CH_2SiMe_3), 1.59 (s, 3 H), 1.60 (s, 3 H), 1.74 (s, 3 H), 1.76 (s, 3 H), 1.81 (s, 3 H), 2.00 (t, *J* 12.70 Hz, 1 H, *H*-3ax″), 2.09 (s, 3 H), 2.84 (dd, *J* 4.68, 12.71 Hz, 1 H, *H*-3eq″), 3.38–3.47 (m, 3 H, *H*-5, *H*-5′, *H*-6a′), 3.57–3.63 (m, 3 H, *H*-2, *H*-6″, $OCH_2CH_2SiMe_3$), 3.74 (t, *J* 9.04, 1 H, *H*-3), 3.79 (s, 3 H, CO_2CH_3), 3.83 (dd, *J* 7.88, 9.46 Hz, 1 H, *H*-2′), 3.92 (d, *J* 10.45, 1 H), 3.96 (dd, *J* 1.60, 10.94 Hz, 1 H, *H*-6a), 4.00 (dd, *J* 4.24, 10.94 Hz, 1 H, *H*-6b), 4.06–4.12 (m, 2 H, $OCH_2CH_2SiMe_3$, *H*-6b′), 4.28 (dd, *J* 5.30, 12.55 Hz, 1 H, *H*-9a″), 4.36–4.43 (m, 4 H, CH_2Ph, *H*-5″, *H*-1, *H*-4), 4.60 (bd, *J* 11.70 Hz, 2 H, CH_2Ph, *H*-9b″), 4.77 (d, *J* 12.03 Hz, 1 H), 4.83 (d, *J* 11.67 Hz, 1 H), 4.87 (d, *J* 12.57 Hz, 1 H), 4.90 (dt, *J* 4.53, 11.86 Hz, 1 H, *H*-4″), 4.94–4.98 (m, 2 H, *H*-3′), 5.06 (bd, *J* 12.00 Hz, 1 H, two CH_2Ph), 5.17 (d, *J* 7.60 Hz, 1 H, *H*-1′), 5.33 (d, *J* 10.88 Hz, 1 H), 5.43 (dd, *J* 2.64, 8.68 Hz, 1 H, *H*-7″), 5.48 (d, *J* 3.28 Hz, 1 H, *H*-4′), 5.96 (ddd, *J* 2.63, 5.20, 8.25 Hz, 1 H, *H*-8″), 7.00–7.65 (m, 25 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ −1.45, 18.43, 20.37, 20.69, 20.75, 21.21, 23.13, 37.52, 49.10, 53.02, 62.02, 66.99, 67.24, 67.53, 68.45, 68.60, 68.90, 69.48, 71.31, 72.13, 72.75, 73.09, 73.80, 74.82, 74.92, 74.95, 76.62, 76.69, 77.00, 77.32, 79.42, 81.98, 82.82, 97.26, 102.04, 102.92, 126.95, 127.04, 127.15, 127.27, 127.38, 127.43, 127.58, 127.70, 127.90, 127.99, 128.06, 128.14, 128.18, 138.13, 138.65, 138.72, 139.26, 139.36, 167.82, 169.84, 169.91, 170.27, 170.49, 170.75; MS (FAB) calcd for $C_{74}H_{93}NO_{24}SiNa$ [M + Na]: 1430; found: 1430.

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References

[1] Y. Ito, J.J. Gaudino, and J.C. Paulson, *Pure Appl. Chem.*, 65 (1993) 753–762; M.P. DeNinno, *Synthesis*, (1991) 583–593.

[2] W. Birberg and H. Lönn, *Tetrahedron Lett.*, 32 (1991) 7453–7456; H. Lönn and K. Stenvall, *Tetrahedron Lett.*, 33 (1992) 115–116; A. Hasegawa, H. Ohki, T. Nagahama, H. Ishida, and M. Kiso, *Carbohydr. Res.*, 212 (1991) 277–281; S. Sabesan, S. Neira, F. Davidson, J. Duus, and K. Bock, *J. Am. Chem. Soc.*, 116 (1994) 1653–1654; A. Hasegawa, T. Nagahama, H. Ohki, and M. Kiso, *J. Carbohydr. Chem.*, (1992) 699–714.

[3] P. Fügedi and P. Garegg, *Carbohydr. Res.*, 149 (1986) C9–C12; Kavenscroft, R.M.G. Roberts, and J.G. Tillett, *J. Chem. Soc., Perkin Trans. 2*, 2 (1982) 1569–1572.

[4] F. Dasgupta and P. Garegg, *Carbohydr. Res.*, 177 (1988) C13–C17.

[5] V. Martichonok and G.M. Whitesides, *J. Org. Chem.*, 61 (1996) 1702–1706.

[6] B. Liebe and H. Kunz, *Tetrahedron Lett.*, 35 (1994) 8777–8778; A. Marra and P. Sinaÿ, *Carbohydr. Res.*, 195 (1990) 303–308.

[7] Y. Ito and T. Ogawa, *Tetrahedron*, 46 (1990) 89–102.

[8] T. Ercegovic and G. Magnusson, *J. Chem. Soc., Chem. Comm.*, (1994) 831–832; T. Ercegovic and G. Magnusson, *J. Org. Chem.*, 60 (1995) 3378–3384.

[9] K.C. Nicolaou, C. W. Hummel, and Y. Iwabuchi, *J. Am. Chem. Soc.*, 114 (1992) 3126–3128.

[10] T. Kondo, H. Abe, and T. Goto, *Chem. Lett.*, (1988) 1657–1660; T. Tomoo, T. Kondo, H. Abe, S. Tsukamoto, M. Isobe, and T. Goto, *Carbohydr. Res.*, 214 (1996) 207–222.

[11] H. Hori, T. Nakajima, Y. Nishida, H. Ohrui, and H. Meguro, *Tetrahedron Lett.*, 29 (1988) 6317–6320.

[12] J.J.P. Stewart, *J. Comput. Chem.*, 10 (1989) 209–220; J.J.P. Stewart, *J. Comput. Chem.*, 10 (1989) 221–264.

[13] D.D. Perin, W.L.F. Armarego, and D.R. Perrin, *Purification of Laboratory Chemicals*, Pergamon, New York, 1980.

[14] R. Roy and C.A. Laferriere, *Can. J. Chem.*, 68 (1990) 2045–2054.

[15] S. Thea and G. Cevasco, *Tetrahedron Lett.*, 29 (1988) 2865–2866.

[16] K. Jansson, S. Ahlfors, T. Frejd, J. Kihlberg, G. Magnusson, J. Dahmen, G. Noori, and K. Stenvall, *J. Org. Chem.*, 53 (1988) 5629–5647.