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Imposing the *trans*/*gauche* conformation on a sialic acid donor with a 5-*N*,7-*O*-oxazinanone group: effect on glycosylation stereoselectivity

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Abstract

A 5-*N*,7-*O*-oxazinanone derivative of a thiosialic acid ester has been synthesized and investigated for the effect of conformational restriction on glycosylation. The cyclic group is found to be powerfully disarming, but to have no beneficial effect on reaction stereoselectivity.

1. Introduction

Sialic acid residues such as *N*-acetylneuraminic acid (Neu5Ac), normally incorporated into complex glycolipids or glycoproteins at the terminal positions of the oligosaccharide chains, are involved in a wide range of biological processes.[1] In these complex oligosaccharides, *N*-acetylneuraminic acid is typically linked α-(2,3) or α-(2,6) to galactoside residues, or is polymerized in the form of α-(2,8) or α-(2,9) linkages. Several challenges are associated with sialylation reactions arising from a number of factors: (i) frequent low yields due to the sterically encumbered C2-position. (ii) H3 protons on ring C3 have the tendency to undergo 2,3-elimination during the coupling processes. (iii) The contra-thermodynamic equatorial nature of the glycosidic bond that necessitates the overriding of the anomeric effect. Many innovative methodologies and strategies including chemical, enzymatic, and chemoenzymatic synthesis have been developed for α-sialoside installation.[2] Recently, we directed our efforts to the α-sialylation field and have investigated sialoside donors **1**[3] based on the knowledge that fused structures in sugar donors have shown beneficial effects on either reactivities or selectivities in glycoslation reactions.[4] This is exemplified by compounds such as 4,6-*O*-benzylidene-protected mannosyl triflate **2** in β-mannosylation, the corresponding α-selective glucosyl triflate **2**,[5,6] the 2-*N*,3-*O*-carbamate fused glycosamine **4** as an α-selective glycosyl donor,[7–9] the 2,3-*O*-carbonate fused thioglycoside **5**, a β-selective glucosyl donor not dependent on neighboring participation group,[9] and the 3,4-*O*-carbonate fused rhamnopyranose **6**, as a β-selective donor.[10]

The Takahashi group also reported on the use of 5-*N*,4-*O*-oxazolidinone protected sialic acids, including donor **7** and acceptors **8** and **9** and achieved an elegant synthesis of α-(2→8)-oligosialosides by this method.[11] A similar study on the stereoselective synthesis of α-(2→3) and α-(2→6) linked galactosyl sialosides was reported by De Meo and Farris.[12] The 1-adamantanylthio sialoside **10** was developed later in this laboratory to address the poor selectivities encountered with donor **1** when coupling with secondary sugar acceptors. This improved donor could be activated by NIS/TfOH in nitrile solvents at −78 °C to afford coupled products with excellent α-selectivity in high yields.[13] Inspired by these beneficial cyclic structures in sugar chemistry, we became interested in exploring alternative cyclic protected donors and especially in the use of the 5-*N*,7-*O*-oxazinanone derivative **11**, which was designed to mimic a benzylidene acetal. We describe here the synthesis of donor **11** and its application in sialylation reactions under diphenyl sulfoxide (Ph_2SO) and triflic anhydride (Tf_2O) promotion conditions.

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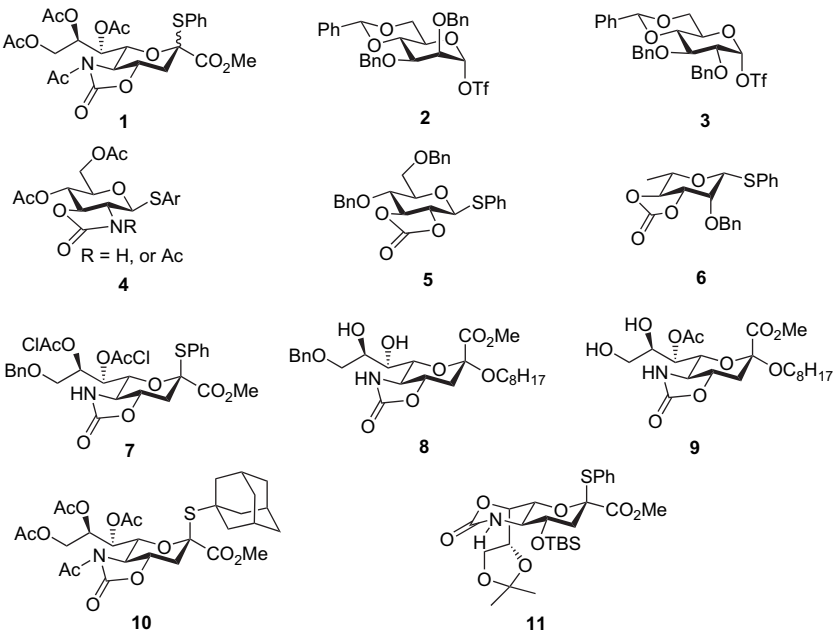
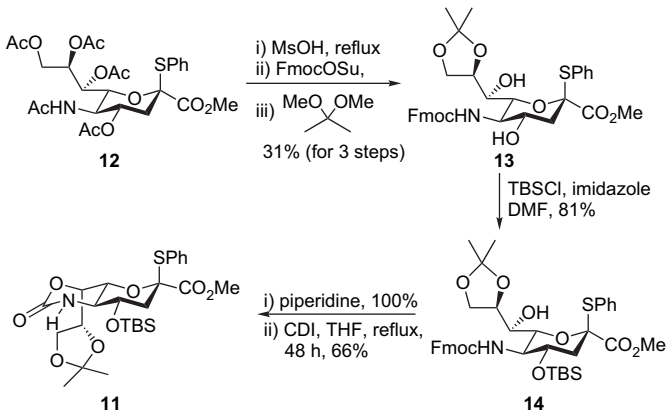


2. Results and discussion

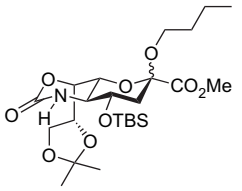
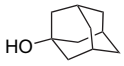
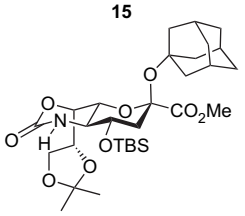
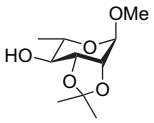
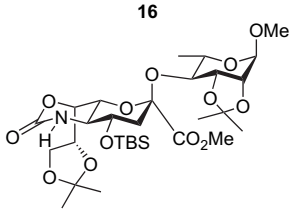
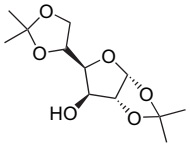
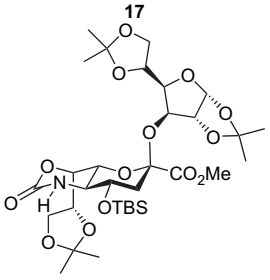
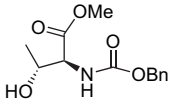
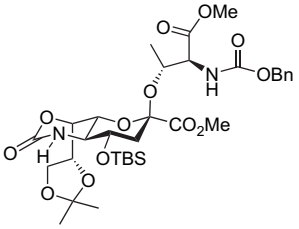
The preparation of donor **11** started from the known thioglycoside **12**,[14] from which hydrolytic removal of acetyl group followed by selective acylation of the amine group with FmocOSu gave the intermediate carbamate. Further treatment with 2,2-dimethoxypropane in the presence of catalytic *p*-toluenesulfonic acid afforded thioglycoside **13** in 31% overall yield for the three steps.[15] Treatment of **13** with TBSCl in DMF smoothly furnished TBS ether **14** in 81% yield.[16] The silyl ether protecting group was selected over the more common acyl group to avoid the extra disarming property of the ester function.[17] Removal of the Fmoc group with piperidine followed by 4-*N*,7-*O*-oxazinanone ring formation with 1,1′-carbonyldiimidazole in THF at reflux delivered the sialoside donor **11** in 66% overall yield (Scheme 1).[18] Establishment of the oxazinanone moiety in donor **11** was confirmed by chemical shift (δ 151.4–151.7) of the carbamate carbon, which was distinct from that of the alternative five-membered oxazolidinone expected to resonate around δ 160.0.[11,4] Of note in the final transformation is that the employment of 4-nitrophenyl chloroformate, a classical carbamate ring closure reagent,[3,7,11] was ineffective, providing **11** in only 30% yield, along with a significant amount of an unidentified byproduct.



Scheme 1. Synthesis of sialoside donor **11**.

With access to the 4-*N*,7-*O*-oxazinanone donor **11** established, we next investigated its coupling to a range of acceptors. To our surprise, promotion systems such as NIS/TfOH, which were adopted for activation of the 4-*N*,3-*O*-oxalidinone protected donors **1**, **7**, and **10** were ineffective toward donor **11** with the starting material recovered completely in repeated experiments. The BSP/TTBP/Tf_2O[6,19] promotion system, developed in this laboratory for glycosylation of thioglycoside donors also failed to activate **11**. Accordingly we turned our attention to the more potent activation system Ph_2SO/Tf_2O, initially developed by Gin and co-workers[20] for dehydrative glycosylation and later extended by van Boom and co-workers to the glycosylation of thioglycosides,[21] and applied to thiosialoside activation in this laboratory.[22] Fortunately, following our previous protocol, treatment of sialoside donor **11** with Ph_2SO (3 equiv)/Tf_2O (1.2 equiv) in the presence of the hindered non-nucleophilic base 2,4,6-tri-*tert*-butylpyrimidine (TTBP) followed by subsequent addition of 1-butanol smoothly gave the coupled product **15** in excellent yield and moderate selectivity (Table 1, entry 1). Coupling to the tertiary alcohol 1-admantanol and to the protected secondary alcohol threonine favored the β-sialosides (Table 1, entries 2 and 5), and similar results were obtained in the case of secondary carbohydrate acceptors (Table 1, entries 3 and 4). The anomeric stereochemistry of all coupling products was assigned based on the $^3J_{C1,H\text{-}3ax}$ coupling constants.[23] While it is not clear whether the β-selectivity observed in the majority of these couplings is the result of the presence of the oxazinanone ring, or of the enforced use of the diphenyl sulfoxide activation system, as was the case with donor **1**,[3] it is clear that the cyclic protecting group is highly disarming. Thus, the failure to activate **11** by the NIS or BSP methods stands

Table 1
Ph_2SO/Tf_2O promoted coupling of donor **1**

	Acceptor	Coupled product	% Yield[a] (α/β ratio[b])
1	BuOH	 **15**	85 (1.4:1)
2		 **16**	93 (β only)
3		 **17**	81 (β only)
4		 **18**	63 (β only)
5		 **19**	80 (β only)

[a] Isolated yields after chromatography.
[b] Determined by ^1H NMR analysis on the crude reaction mixture, the anomeric stereochemistry is assigned based on the $^3J_{C1,H\text{-}3ax}$ coupling constant.

in contrast to the activation of **1** and other ester protected thiosialosides by these systems, and signals the importance of the conformational restriction imposed on **11** by the fused ring. We suggest that the disarming effect of the oxazinanone ring is due to the superposition of the most electron-withdrawing t_g conformation of the C6–C7 bond with the presence of electron-withdrawing carbonyl group. This conformational effect on reactivity is closely related to that determined by Bols to be at the heart of the benzylidene effect in donors such as **2** and **3**.[24]

Hydrolysis of the oxazinanones was realized with the use of lithium hydroxide in hot aqueous ethanol (Scheme 2). The use of either sodium methoxide in methanol or sodium hydroxide in aqueous THF at room temperature was found to complicate the reaction, affording undesired byproducts or more complex mixtures.[3,7]

3. Conclusion

The 5-*N*,7-*O*-oxazinanone group is powerfully disarming in sialic acid donors owing to the combination of its innate electron-withdrawing effect and the imposition of the t_g conformation on the C6–C7 bond.

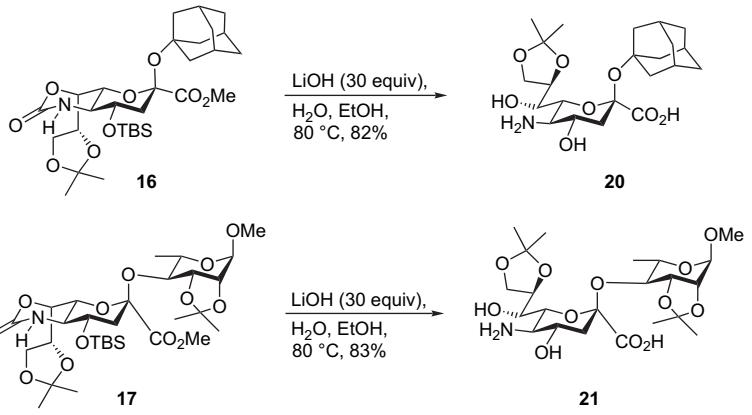
4. Experimental section

4.1. General methods

^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, with chemical shifts reported downfield from tetramethylsilane. All solvents were dried by standard procedures. Commercial reagents were used without purification. Air and/or moisture-sensitive reactions were carried out under an atmosphere of argon or nitrogen using oven-dried glassware. High-resolution mass spectra were recorded with electrospray ionization.

4.2. Methyl [phenyl 3,5-dideoxy-8,9-isopropylidene-5-(9-fluorenylmethoxycarbonylamino)-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside]onate (*13*)

A mixture of methyl (phenyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycerol-β-D-galacto-non-2-ulopyranoside)onate **12** (2.0 g, 2.9 mmol) and methanesulfonic acid (1.4 mL, 23.2 mmol) in MeOH (30 mL) was heated at 60 °C for 24 h. The reaction mixture was then cooled down to room temperature and concentrated under vacuum, affording a residue, which was redissolved in acetonitrile (20 mL) and water (3 mL) followed by neutralization with triethylamine until the pH was 7–8. 9-Fluorenylmethyl succinimidyl carbonate (1.2 g, 3.5 mmol) was added to the above solution at room temperature. After being stirred for 3 h, the solvent was removed under vacuum to give a residue, which was diluted with ethyl acetate (100 mL). The organic layer was washed with 0.5 M HCl solution, aq $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated. The crude residue was used for the next step without purification. To a stirred solution of the residue in DMF (8 mL) was added *p*-toluenesulfonic acid monohydrate (0.1 g, 0.5 mmol) followed by 2,2-dimethoxypropane (3 mL, 8.4 mmol). The resulting reaction mixture was stirred at room temperature for 30 min, and then diluted with ethyl acetate (100 mL). The organic layer was washed twice with water, aq $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 1:1) to give the title compound **13** (0.52 g, 0.9 mmol, 31%). $[\alpha]_D^{14}$ −190.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J=7.5 Hz, 2H), 7.52–7.58 (m, 4H), 7.27–7.40 (m, 7H), 5.05 (d, J=7.5 Hz, 1H), 4.41–4.51 (m, 2H), 4.30 (d, J=10.5 Hz, 1H), 4.20 (t, J=6.5 Hz, 1H), 4.13 (t, J=7.5 Hz, 1H), 4.03–4.08 (m, 1H),



Scheme 2. Hydrolysis of oxazinanone groups in compounds **16** and **17**.

3.94–4.01 (m, 2H), 3.74 (q, J=9.0 Hz, 1H), 3.65 (br s, 2H), 3.43 (s, 3H), 3.00 (br s, 1H), 2.78 (dd, J=4.5, 13.5 Hz, 1H), 2.08 (dd, J=11.5, 13.5 Hz, 1H), 1.95 (br s, 1H), 1.41 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 157.6, 143.7, 143.5, 141.3, 136.2, 127.7, 129.6, 128.7, 127.8, 127.2, 125.0, 120.1, 109.0, 90.2, 74.6, 72.8, 70.4, 67.7, 67.2, 67.1, 54.6, 52.4, 47.1, 41.1, 26.9, 25.5; ESIHRMS calcd for $C_{34}H_{37}NO_9SNa$ $[M+Na]^+$: 658.2082, found 658.2083.

*4.3. Methyl [phenyl 3,5-dideoxy-8,9-isopropylidene-5-(9-fluorenylmethoxycarbonylamino)-4-O-tert-butyldimethylsilyl-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside]onate (**14**)*

A mixture of compound **13** (0.34 g, 0.54 mmol), *tert*-butyldimethylsilyl chloride (0.12 g, 0.80 mmol) and imidazole (0.72 g, 1.08 mmol) in dry DMF (1 mL) was stirred at room temperature for 20 h, and then diluted with ethyl acetate (50 mL). The organic layer was washed twice with water, aq $NaHCO_3$, brine, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 2:1) to give title compound **14** (0.33 g, 0.44 mmol, 81%). $[\alpha]_D^{20}$ −99.5 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J=7.5 Hz, 2H), 7.56–7.61 (m, 4H), 7.26–7.42 (m, 7H), 4.81 (d, J=7.5 Hz, 1H), 4.51–4.55 (m, 1H), 4.42–4.46 (m, 2H), 4.39 (d, J=10.5 Hz, 1H), 4.13–4.21 (m, 3H), 4.07 (dd, J=5.5, 8.5 Hz, 1H), 3.96 (t, J=9.0 Hz, 1H), 3.77 (t, J=7.0 Hz, 1H), 3.60–3.67 (m, 2H), 3.43 (s, 3H), 2.68 (dd, J=4.5, 13.5 Hz, 1H), 2.06 (dd, J=11.5, 13.5 Hz, 1H), 1.45 (s, 3H), 1.43 (s, 3H), 0.86 (s, 9H), 0.10 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 157.3, 143.8, 143.7, 141.4, 136.2, 129.9, 129.6, 128.7, 127.8, 127.2, 127.1, 125.0, 124.9, 120.1, 108.8, 90.3, 74.9, 72.9, 70.3, 67.8, 67.2, 66.9, 54.9, 52.4, 47.2, 42.1, 26.9, 25.7, 25.6, 17.9, −4.3, −4.7; ESIHRMS calcd for $C_{40}H_{51}NO_9SiSNa$ $[M+Na]^+$: 772.2946, found 772.2934.

*4.4. Methyl [phenyl 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-2-thio-D-glycero-β-D-galacto-non-2-ulopyranoside]onate (**11**)*

To a stirred solution of compound **14** (0.4 g, 0.53 mmol) in dry DMF (4 mL) was added piperidine (0.8 mL, 7.7 mmol) at room temperature, the resulting reaction mixture was stirred at room temperature for 1 h, and then diluted with ethyl acetate (50 mL). The organic layer was washed twice with water, dried over anhydrous Na_2SO_4, and concentrated to afford the residue. Purification by a short silica gel column (hexane/ethyl acetate, 1:1) give amino alcohol intermediate (0.28 g, 0.53 mmol), which was dissolved in dry THF (15 mL), followed by addition of 1,1′-carbonyldiimidazole (0.19 g, 1.2 mmol). The resulting reaction mixture was heated at reflux for 48 h, then cooled down to room temperature and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 3:1) to afford donor **11** (0.19 g, 0.35 mmol, 66%) as a white solid. Mp 163–164 °C; $[\alpha]_D^{16}$ −63.8 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31–7.38 (m, 5H), 5.26 (s, 1H), 4.76 (dd, J=6.0, 10.5 Hz, 1H), 4.53 (t, J=5.0 Hz, 1H), 4.45 (q, J=6.0 Hz, 1H), 4.01–4.05 (m, 2H), 3.56 (s, 3H), 3.31 (t, J=10.5 Hz, 1H), 2.57 (dd, J=4.5, 14.0 Hz, 1H), 1.99 (dd, J=11.0, 14.0 Hz, 1H), 1.37 (s, 3H), 1.34 (s, 3H), 0.91 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0, 151.5, 135.3, 129.7, 129.3, 129.1, 109.7, 90.0, 75.0, 69.8, 66.1, 65.4, 55.1, 52.6, 40.2, 26.4, 25.7, 25.6, 17.9, −4.1, −4.6; ESIHRMS calcd for $C_{26}H_{39}NO_8SiSNa$ $[M+Na]^+$: 576.2058, found 576.2050.

*4.5. General procedure for sialylation with donor **11***

A solution of donor **11** (50 mg, 0.09 mmol, 1 equiv), diphenyl sulfoxide (55 mg, 0.27 mmol, 3 equiv), TTBP (45 mg, 0.18 mmol, 2 equiv), and activated 4 Å molecular sieves in anhydrous CH_2Cl_2 (2 mL) was stirred at room temperature for 1 h under an argon atmosphere, and then cooled down to −78 °C, followed by addition of Tf_2O (18 μL, 0.11 mmol, 1.2 equiv). After 15 min, a solution of the acceptor (0.18 mmol, 2 equiv) in CH_2Cl_2 (1 mL) was added. The reaction mixture was stirred at −78 °C for 30 min, and then warmed up to 0 °C slowly over 1 h, and quenched with aq $NaHCO_3$, diluted with CH_2Cl_2 (20 mL), and filtered through Celite. The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by chromatography on silica gel to afford the sialosides, eluting with toluene/ethyl acetate or toluene/acetone systems.

*4.6. Methyl [2-butyl 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-D-glycerol-β-D-galacto-non-2-ulopyranoside]onate (**15β**) and methyl [2-butyl 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-D-glycerol-α-D-galacto-non-2-ulopyranoside]onate (**15α**)*

Compound **15β**: $[\alpha]_D^9$ 36.3 (*c* 0.25, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 4.60 (t, *J*=5.5 Hz, 1H), 4.46 (m, 1H), 4.05–4.14 (m, 2H), 3.93 (dd, *J*=5.5, 10.5 Hz, 1H), 3.84 (s, 3H), 3.73–3.77 (m, 1H), 3.49–3.52 (m, 1H), 3.32–3.40 (m, 2H), 2.62 (dd, *J*=4.5, 13.0 Hz, 1H), 1.76 (dd, *J*=11.5, 13.0 Hz, 1H), 1.47–1.54 (m, 2H), 1.44 (s, 3H), 1.25–1.39 (m, 2H), 1.37 (s, 3H), 0.83–0.92 (m, 3H), 0.88 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 ($^3J_{C1,H\text{-}3ax}$=0 Hz), 151.4, 110.0, 100.1, 75.7, 74.7, 70.3, 67.9, 66.1, 64.4, 54.4, 52.8, 40.2, 31.6, 26.4, 25.7, 25.6, 19.1, 17.9, 13.8, −4.2, −4.7; ESIHRMS calcd for $C_{24}H_{44}NO_9Si$ $[M+H]^+$: 518.2780, found 517.2779. Compound **15α**: $[\alpha]_D^9$ 27.6 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (s, 1H), 4.58 (dd, *J*=4.5, 5.5 Hz, 1H), 4.50–4.53 (m, 1H), 4.07–4.14 (m, 2H), 3.98 (dd, *J*=6.0, 10.5 Hz, 1H), 3.88–3.93 (m, 1H), 3.79 (s, 3H), 3.43–3.47 (m, 1H), 3.30–3.34 (m, 2H), 2.30 (dd, *J*=4.5, 13.0 Hz, 1H), 1.66 (dd, *J*=11.0, 13.0 Hz, 1H), 1.54–1.59 (m, 2H), 1.46 (s, 3H), 1.38 (s, 3H), 1.33–1.41 (m, 2H), 0.93 (t, *J*=7.5 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9 ($^3J_{C1,H\text{-}3ax}$=6.25 Hz), 151.7, 109.7, 99.8, 75.4, 75.1, 69.4, 65.41, 65.37, 63.8, 54.9, 52.7, 40.3, 31.5, 26.3, 26.1, 25.7, 19.3, 17.9, 13.9, −4.1, −4.6; ESIHRMS calcd for $C_{24}H_{44}NO_9Si$ $[M+H]^+$: 518.2780, found 517.2773.

*4.7. Methyl [2-(1-adamantanyl) 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-D-glycerol-β-D-galacto-non-2-ulopyranoside]onate (**16**)*

$[\alpha]_D^{16}$ 15.1 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (s, 1H), 4.57–4.59 (m, 1H), 4.50–4.54 (m, 1H), 4.22 (dd, *J*=5.5, 10.5 Hz, 1H), 4.12–4.15 (m, 1H), 4.06–4.09 (m, 1H), 3.90 (dt, 4.5, 10.0 Hz, 1H), 3.77 (s, 3H), 3.18 (t, *J*=10.0 Hz, 1H), 2.31 (dd, *J*=4.5, 13.0 Hz, 1H), 2.10 (br s, 3H), 1.78–1.85 (m, 6H), 1.54–1.61 (m, 6H), 1.43–1.48 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 0.88 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 ($^3J_{C1,H\text{-}3ax}$=2.5 Hz), 151.7, 109.5, 98.2, 78.3, 75.3, 75.1, 69.7, 65.3, 65.1, 55.0, 52.6, 43.2, 42.9, 36.0, 30.9, 26.4, 25.7, 17.9, −4.1, −4.6; ESIHRMS calcd for $C_{30}H_{50}NO_9Si$ $[M+H]^+$: 596.3249, found 596.3233.

*4.8. Methyl O-[methyl 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-D-glycerol-β-D-galacto-non-2-ulopyranosylonate]-(2→4)-2,3-isopropylidene-α-L-rhamnopyranoside (**17**)*

$[\alpha]_D^{20}$ 1.2 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.23 (s, 1H), 4.80 (s, 1H), 4.52 (br s, 2H), 4.21–4.23 (m, 2H), 3.98–4.04 (m, 3H), 3.76–3.80 (m, 2H), 3.73 (s, 3H), 3.51 (t, *J*=10.0 Hz, 1H), 3.38–3.44 (m, 1H), 3.35 (s, 3H), 2.32 (dd, *J*=4.5, 13.5 Hz, 1H), 1.60 (dd, *J*=11.0, 13.5 Hz, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.38 (s, 3H), 1.29 (d, *J*=6.0 Hz, 3H), 1.26 (s, 3H), 0.88 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 ($^3J_{C1,H\text{-}3ax}$=1.25 Hz), 151.6, 109.9, 109.2, 99.2, 97.9, 76.0, 75.5, 75.0, 74.9, 69.3, 66.3, 65.5, 63.9, 54.9, 54.5, 52.4, 41.6, 28.1, 26.4, 26.3, 25.8, 25.7, 18.4, 17.9, −4.1, −4.7; ESIHRMS calcd for $C_{30}H_{52}NO_{13}Si$ $[M+H]^+$: 662.3202, found 662.3199.

*4.9. 3-O-[Methyl 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-D-glycerol-β-D-galacto-non-2-ulopyranosylonate]-(2→3)-1,2:5,6-di-isopropylidene-α-D-glucofuranose (**18**)*

$[\alpha]_D^{18}$ 8.9 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.82 (d, *J*=3.5 Hz, 1H), 5.21 (s, 1H), 4.73 (dd, *J*=5.5 Hz, 1H), 4.47–4.52 (m, 2H), 4.43 (d, *J*=3.5 Hz, 1H), 4.25 (d, *J*=4.0 Hz, 1H), 4.02–4.23 (m, 6H), 3.82–3.89 (m, 1H), 3.82 (s, 3H), 3.29 (t, *J*=10.0 Hz, 1H), 2.44 (dd, *J*=4.5, 14.0 Hz, 1H), 1.71 (dd, *J*=11.0, 13.5 Hz, 1H), 1.47 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.21 (s, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1 ($^3J_{C1,H\text{-}3ax}$=3.75 Hz), 151.5, 111.8, 110.1, 109.7, 104.7, 98.5, 82.7, 81.1, 75.5, 75.10, 75.05, 71.4, 69.6, 68.0, 65.5, 65.0, 54.5, 52.8, 40.4, 26.7, 26.4, 26.1, 25.7, 25.6, 24.8, 17.9, −4.0, −4.6; ESIHRMS calcd for $C_{32}H_{54}NO_{14}Si$ $[M+H]^+$: 704.3308, found 704.3312.

*4.10. N-Benzoyl-O-[methyl 5-amino-5-N,7-O-carbonyl-3,5-dideoxy-8,9-isopropylidene-4-O-tert-butyldimethylsilyl-D-glycerol-β-D-galacto-non-2-ulopyranosylonate]-L-threonine methyl ester (**19**)*

$[\alpha]_D^9$ 17.0 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.39 (m, 5H), 5.48 (d, *J*=9.0 Hz, 1H), 5.22 (s, 1H), 5.13 (d, *J*=1.5 Hz, 2H), 4.64 (t, *J*=5.0 Hz, 1H), 4.49–4.52 (m, 1H), 4.41 (dd, *J*=2.0, 9.5 Hz, 1H), 4.34–4.38 (m, 1H), 4.14–4.17 (m, 1H), 4.07 (dd, *J*=6.5, 8.0 Hz, 1H), 3.88 (dd, *J*=6.0, 10.5 Hz, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.69–3.73 (m, 1H), 3.34 (t, *J*=10.0 Hz, 1H), 2.29 (dd, *J*=4.5, 13.0 Hz, 1H), 1.56 (dd, *J*=11.0, 13.5 Hz, 1H), 1.45 (s, 3H), 1.37 (s, 3H), 1.12 (d, *J*=6.0 Hz, 3H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 ($^3J_{C1,H\text{-}3ax}$= 2.5 Hz), 168.5, 156.4, 151.5, 136.0, 128.6, 128.4, 128.3, 109.8, 98.1, 78.1, 76.4, 75.2, 74.9, 70.1, 69.3, 67.5, 66.4, 65.4, 58.8, 54.4, 52.9, 52.6, 40.9, 26.3, 25.71, 25.66, 17.9, 16.0, −4.2, −4.7; ESIHRMS calcd for $C_{33}H_{51}N_2O_{13}Si$ $[M+H]^+$: 711.3155, found 711.3147.

*4.11. 2-(1-Adamantanyl) 5-amino-3,5-dideoxy-D-glycerol-β-D-galacto-non-2-ulopyranosidic acid (**20**)*

To a stirred solution of compound **16** (28 mg, 0.05 mmol) in ethanol (2 mL) and water (2 mL) was added LiOH (34 mg, 1.5 mmol) at room temperature. The reaction mixture was then heated at 80 °C for 3 h, and cooled down to room temperature followed by removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl

acetate/isopropanol/water, 9:4:2) to give title compound **20** (17 mg, 82%). $[\alpha]_D^{19}$ −19.0 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 4.35 (br s, 1H), 4.00–4.17 (m, 4H), 3.45 (d, *J*=8.0 Hz, 1H), 3.03 (t, *J*=8.0 Hz, 1H), 2.45 (d, *J*=11.0 Hz, 1H), 1.99–2.14 (m, 9H), 1.58–1.67 (m, 6H), 1.39 (s, 3H), 1.31 (s, 3H), 1.31–1.39 (m, 1H); ^{13}C NMR (125 MHz, MeOD) δ 176.3, 109.3, 99.0, 76.4, 73.5, 70.9, 69.9, 67.6, 65.5, 53.5, 43.7, 42.4, 35.9, 31.2, 25.9, 24.1; ESIHRMS calcd for $C_{22}H_{36}NO_8$ $[M+H]^+$: 442.2435, found 442.2421.

*4.12. Methyl O-(5-amino-dideoxy-D-glycerol-β-D-galacto-non-2-ulopyranosylonate)-(2→4)-2,3-isopropylidene-α-L-rhamnopyranoside (**21**)*

To a stirred solution of compound **18** (30 mg, 0.05 mmol) in ethanol (2 mL) and water (2 mL) was added LiOH (33 mg, 1.5 mmol) at room temperature. The reaction mixture was then heated at 80 °C for 3 h, and cooled down to room temperature followed by removal of the solvent under reduced pressure. The residue was purified by chromatography on silica gel (ethyl acetate/isopropanol/water, 9:4:2) to give title compound **21** (19 mg, 83%). $[\alpha]_D^{19}$ −61.3 (*c* 1.0, MeOH); ^{1}H NMR (500 MHz, MeOD) δ 4.65 (s, 1H), 4.53 (br s, 1H), 4.36 (br s, 1H), 4.16 (br s, 1H), 3.85–4.02 (m, 6H), 3.46 (d, *J*=8.5 Hz, 1H), 3.37 (s, 3H), 3.05 (t, *J*=9.0 Hz, 1H), 2.48 (d, *J*=12.5 Hz, 1H), 1.95 (s, 1H), 1.55 (t, *J*=12.0 Hz, 1H), 1.47 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz, MeOD) δ 174.1, 109.6, 108.5, 100.1, 98.5, 76.7, 75.3, 73.7, 72.9, 70.7, 70.6, 67.5, 67.0, 65.6, 54.2, 53.2, 42.4, 26.7, 26.0, 24.9, 24.3, 17.2; ESIHRMS calcd for $C_{22}H_{37}NO_{12}Na$ $[M+Na]^+$: 530.2208, found 530.2197.

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