**Synthesis and Intramolecular Glycosylation of Sialyl Mono-
esters of *o*-Xylylene Glycol. The Importance of Donor
Configuration and Nitrogen Protecting Groups on Cyclization
Yield and Selectivity; Isolation and Characterization of a *N*-
Sialyl Acetamide Indicative of Participation by Acetonitrile.**

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ABSTRACT: The synthesis and cyclization reactions, leading to spirocyclic medium ring-sized diolides, of *o*-(hydroxymethyl)xylylene monoesters of sialyl thioglycosides is described. Cyclization yields and stereoselectivities are found to vary as a function of the anomeric stereochemistry of the thioglycoside and of the N5 protecting group, and these effects are discussed in terms of the reaction mechanism. Cyclization in the presence of acetonitrile results in the isolation and characterization of a Ritter-type *N*-sialyl acetamide, which affords strong evidence for the participation of acetonitrile in the form of sialyl nitrilium ions.

Key Words: *N*-Glycosyl amide, Lactonization, Sialic Acid, Spirodiolide, Thioglycoside, Ritter Reaction

1. Introduction.

In continuation of our studies on the development of cyclization reactions for use as unimolecular clocks for estimating the molecularity of glycosylation reactions,¹⁻³ we report on the synthesis and cyclization of a series of *o*-(hydroxymethyl)benzyl (xylylene glycol monesters) of sialyl thioglycosides giving a series of spirocyclic eight-membered ring diolides. We report that the yield and stereoselectivity of these cyclizations is a function of the anomeric configuration of the initial thioglycoside and of the N5 protecting group. We also report on the isolation and characterization of an *N*-acetyl *N*-sialoside from a cyclization conducted in the presence of acetonitrile, which is strongly suggestive of participation by acetonitrile.

2. Results and Discussion.

In view of the importance of the sialic acid glycosides in biology and the considerable interest in their stereoselective synthesis,⁴⁻¹¹ a cation clock reaction for estimating the molecularity of sialylation reactions is desirable. Incompatibilities between our previous allylsilane clock reaction¹⁻² and the thioglycoside-based methods typically employed in sialylation reactions,⁶⁻¹¹ together with the absence of functionality at the 3-position, focused our attention on glycol mono-esters of the sialic acids and hence on intramolecular alcohols as nucleophiles in potential clock reactions. The predominance of the *trans*-configuration¹²⁻¹³ and the estimated 12 kcal.mol⁻¹ barrier to *cis-trans* isomerization¹⁴ of ester linkages suggested a 4-hydroxybutyl ester, leading to an eight-membered cyclic diolide,¹⁵⁻¹⁶ as the shortest alcohol-based system capable of

undergoing cyclization from the ground state of the ester. Unsaturation was then added to the tether in the form of an aromatic ring to minimize transannular interactions and accelerate the cyclization, leading to the choice of the 2-hydroxymethylbenzyl esters as first generation probes.

Cleavage of the methyl ester from the *N*-acetylneuraminate **1**¹⁷ with lithium iodide in pyridine at reflux¹⁸⁻²⁰ gave the corresponding acid **2** in 68% isolated yield. Coupling with benzene-1,2-dimethanol by means of dicyclohexylcarbodiimide and *N*-hydroxybenzotriazole then afforded the ester **3** in 70% yield (Scheme 1). The anomer **4**²¹ of **1** was similarly converted to the corresponding acid **5** in 70% yield by treatment with lithium iodide in pyridine at reflux. Alternatively, **4** was saponified giving, after reinstallation of the acetyl groups, a 73% yield of the acid **5** that was converted to the ester **6** in 35% yield (Scheme 1). Application of the saponification, reacylation protocol to **1** is less satisfactory owing to the formation of byproducts arising from lactonization in the course of the acetylation step. The considerable difference in yields on esterification of the diastereomeric acids **2** and **5** reflects the differing steric environments and the consequent lower reactivity of the axial acid. Application of the lithium iodide demethylation and DCC re-esterification protocol to the *N*-acetyl-oxazolidione¹⁷ and isothiocyanato¹¹ systems **7** and **10** then gave the esters **9** and **12**, via the acids **8** and **11**, in 53 and 43% overall yield, respectively (Scheme 1). In view of the relative inaccessibility of the equatorial thioglycoside **4**,²¹ no attempt was made to prepare, or study the cyclization of the α -anomers of either **9** or **12**.

Scheme 1. Synthesis of Sialic Acid Esters for Cyclization.

Activation of *N*-acetyl- β -thioglycoside **3** with *N*-iodosuccinimide and triflic acid in dichloromethane at -40°C in the presence of acid washed molecular sieves gave the anticipated diolides **13 α** and **13 β** in 58% combined yield and 1:2.4 α : β ratio favoring the anomer with the axial glycosidic bond (Scheme 2). Under the same conditions the anomeric system **6** afforded 76% combined yield of cyclized products with an α : β ratio of 1:5 (Scheme 2). Cyclization of the

N-acetyloxazolidinone-protected thioglycoside **9** under the same conditions yielded 42% of the diolides **14 α** and **14 β** in 1:0.4 ratio favoring the α -glycoside (Scheme 2). Finally, the isothiocyanate **12** gave 20% of the corresponding diolides **15 α** and **15 β** in 1:0.7 ratio favoring the α -glycoside (Scheme 2). Although not isolated and characterized owing to the multiple isomers possible, as demonstrated by mass spectrometric analysis of the crude reaction mixtures, all cyclization reactions exhibited competing intermolecular glycosylation processes resulting in the formation of dimeric species. These intermolecular processes, which do not arise from further reaction of the spirocyclic diolides under the reactions conditions as demonstrated by control experiments, were substantially more important for the *N*-acetyloxazolidinone **9** and especially the isothiocyanate **12** than for either of the simple acetamides **3** and **6**. While the reduced yields of diolides observed with donors **9** and **12** were reproducible, we do not have a satisfactory explanation for them at the present time.

Scheme 2. Cyclization Reactions.

Stereochemical assignment of the diolides **13α** and **13β** was achieved by a variation on the ³J_{C,H} heteronuclear coupling method²²⁻²⁵ typically applied to the sialic acid glycosides. Thus, the α-anomer exhibited a ³J_{C,H} coupling of 6.5 Hz between the axial hydrogen at C3 and the carboxyl carbon, while the β-anomer displayed a ³J_{C,H} of 0 Hz. Comparable ³J_{C,H} heteronuclear coupling constants were recorded in the *N*-acetyloxazolidone series and the configuration of the lactone **14α** was confirmed crystallographically (CCDC 149904). The configuration of the two

isothiocyanates **15a** and **15b** was established by chemical conversion to the acetamides **13a** and **13b** by reaction with thioacetic acid.^{11,26-31} The X-ray crystal structure of **14a** also revealed the *cis*-conformation about the lactone carboxyl bond indicating this to be the more stable conformation consistent with Huisgen's original work¹⁶ on the conformation of medium ring lactones.

The changes in anomeric selectivity of the cyclization reactions according to configuration (Scheme 2, donors **3** and **6**) and protecting group system (Scheme 2, donors **3**, **9** and **12**) are instructive. The two anomers **3** and **6** of the acetamide-protected donors both exhibit selectivity for the formation of the axial glycoside **13b** but to differing extents, indicating that a significant proportion of the products formed does not involve a fully equilibrated common intermediate, ie, a glycosyl oxocarbenium ion. We deduce that a significant fraction of the products formed with inversion of configuration at the anomeric center arise from the direct S_N2-like displacement of the activated thioglycoside by the intramolecular nucleophile (Scheme 3). Thus, activation of the axial thioglycoside **3** with the *N*-iodosuccinimide/triflic acid combination³² is expected to lead first to the iodosulfonium ion **16**, which then undergoes S_N2-like displacement by the intramolecular alcohol through a transition state **17** leading to the diolide **13a** (Scheme 3). Similarly, the anomeric donor **6** undergoes activation to the iodonium ion **18** and then S_N2-like substitution via transition state **19** to the epimeric diolide **13b** (Scheme 3). In drawing transition states **17** and **19**, we make no assumption about the synchronicity of C-S bond cleavage and C-O bond formation, the degree to which the transition states are “exploded”, nor of the conformation of the ester group relative to the pyranose ring oxygen. We draw the ester linkage in the preferred *trans*-conformation consistent with our design principles, assuming relaxation to the

cis-lactone, observed crystallographically in **14a**, subsequent to the cyclization. Consideration of the relative stereoselectivities observed in the cyclization of the anomers **3** and **6** suggests that the cyclization of **6** via **18** and **19** is more facile than that of **3** via **16** and **17**, consistent with transition state **19** benefitting from the anomeric effect.

Scheme 3. S_N2-like Pathways for Cyclization with Inversion.

The less than perfect selectivity observed in the cyclizations of **3** and **6** requires the convolution of S_N2-like mechanisms with other pathways for the formation of **13a** and **13β**. Possibilities for such competing pathways include the collapse of the activated thioglycosides **16** and **18** to oxocarbenium-type intermediates, most likely stabilized in the form of glycosyl triflates,³³⁻³⁵ and equilibrated glycosyl disulfonium ions such as suggested by Ellervik and coworkers in the activation of sialyl thioglycosides by interhalogen compounds and silver triflate.³⁶

Turning to the influence of protecting groups on cyclization selectivity, comparison of the three axial thioglycosides **3**, **9**, and **12** (Scheme 2), reveals that the *N*-acetyloxazolidinone **9** and the isothiocyanate **12** are significantly more equatorially selective than the simple acetamide **3**. These observations are consistent with intermolecular glycosylations conducted with the corresponding methyl esters in which the *N*-acetyloxazolidinone^{8,17} and isothiocyanate systems¹¹ are among the most equatorially selective of sialyl donors described to date. Accordingly, we attribute the higher equatorial selectivity observed with **9** and **12** to the stabilization of S_N2-like transition states for cyclization akin to **17** with respect to the corresponding oxocarbenium ion by the more electron-withdrawing *N*-acetyl oxazolidinone³⁷ and isothiocyanate groups.¹¹

We next turned our attention to reactions conducted in the presence of acetonitrile. Indeed, since its introduction to the sialidation field at the end of the 1980s³⁸⁻⁴⁰ acetonitrile, either alone or in admixture with other solvents, is by far the most widespread medium for the conduct of sialic acid glycosylations.^{6,41} This predominance of acetonitrile as a solvent in sialidation reactions arises from the enhanced equatorial selectivities it occasions, which is most commonly attributed to the trapping of the sialyl oxocarbenium ion in the form of β -sialyl nitrilium ions, with an axial nitrilium group, which are subsequently displaced by the incoming nucleophile in an S_N2-like manner. This rationale follows that advanced for the formation of equatorial glycosides from simple perbenzyl protected glycopyranosyl donors when reactions are conducted in acetonitrile.⁴²⁻⁴³ However, unlike the case of the simple α -glucopyranosyl nitrilium ions for which ample evidence exists from inter- and intramolecular trapping experiments,⁴⁴⁻⁴⁹ and NMR spectroscopic investigations,⁵⁰⁻⁵¹ unequivocal evidence for the existence of the sialyl nitrilium ions has yet to be provided.

In the event, activation of **6** with *N*-iodosuccinimide and triflic acid in a 7/3 dichloromethane:acetonitrile mixture at -40 °C, with monitoring by UPLC/ESIMS revealed the formation of the β -anomer **13 β** of the anticipated diolide and two new peaks both with *m/z* 643, which we attribute to the sodiated molecular ions of the cyclic imidates **20** (Scheme 4). The observation of two isomers of **20** may be due to the formation of two anomers as indicated in Scheme 4, but we cannot rule out the possibility of a two isomers with a common anomeric configuration but differing in configuration of the imidate linkage. Quenching at -40 °C followed by work-up and extensive chromatographic purification enabled the isolation of the β -anomer of **13** in 40% yield, and an impure sample of one isomer of **20** in approximately 6% yield. Attempted further purification of **20** resulted in the isolation and characterization of the amide **21** in 4% overall yield (Scheme 4). Amide **21** was isolated as a single axial isomer, whose configuration is assigned on the basis of the 3J heteronuclear coupling constant of 0 Hz between the carboxyl carbon and the axial H3. The preferential formation of the β -diolide **13 β** in the presence of acetonitrile is best interpreted in terms of lactonization by direct cyclization on the activated thioglycoside **18**, consistent with Schemes 2 and 3, taking place in competition with glycosyl nitrilium ion formation. The glycosyl nitrilium ion is trapped intramolecularly leading to **20** and thus to **21** and so does not result in the formation of the α -diolide.

Scheme 4. Formation and Isolation of Ritter Product from Reaction in the Presence of Acetonitrile

3. Conclusion

Activation of the thioglycoside in the sialyl donors **3**, **6**, **9**, and **12** in dichloromethane solution results in the formation of spirocyclic medium-sized diolides. The yield of these cyclizations varies substantially as a function of the N5 protecting group such that with the 5-isothiocyanto system the competing intermolecular glycosylation is the main process; the predominance of the intermolecular reaction prevents the use of the *o*-xylylene esters as probes in clock reactions. Nevertheless, the dependence of cyclization stereoselectivity on the anomeric configuration and on the N5 protecting group is informative and points to direct attack on the activated thioglycoside as a significant reaction pathway. Conducting the cyclization in the presence of acetonitrile leads to the isolation of a Ritter product that is strongly suggestive of participation by the acetonitrile.

4. Experimental Section

4.1. General

All extracts were dried over sodium sulfate, filtered, and evaporated under reduced pressure at 35 °C unless otherwise stated. LiI was dried under reduced pressure at 90 °C for 23 h. Anhydrous CH₂Cl₂ and CH₃CN were dried over 4 Å and 3 Å molecular sieves respectively for use in glycosylation reactions. Flash chromatographic purifications were carried out over silica gel unless otherwise stated. HPLC purifications were performed on Varian prep star HPLC using an Agilent DYNAMAX SI-column (5 µm, 21.4 x 250 mm) at ambient temperature with a flow rate of 21.5 mL/min. ¹H and ¹³C NMR spectra were recorded in CDCl₃ solution unless otherwise stated with 400, 500, or 600 MHz instruments. ESIHRMS were recorded using a Waters LCT Premier Xe TOF mass spectrometer. Specific rotations were recorded in CH₂Cl₂ or CHCl₃ solution at room temperature. UHPLC analysis was performed with a BEH C18 1.7 µm (2.1 × 100 mm) column equipped with LC-MS and TUV (205 nm) detector. Commercial AW-MS 300 were used for all glycosylation reactions.

4.2. **1-Adamantanyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero-β-D-galacto-non-2-ulopyranosidonic acid (2).**

A mixture of **1**¹⁷ (1.00 g, 1.56 mmol) and anhydrous pyridine (14.2 mL) was added to anhydrous LiI (0.75 g, 5.58 mmol) under an argon atmosphere. The reaction mixture was heated to reflux for 3.5 h before it was cooled to room temperature and concentrated under reduced pressure. The

residue was dissolved in CH_2Cl_2 , and the organic layer was washed with 1N HCl and brine, dried and evaporated to dryness. The crude residue was purified by chromatography over neutral alumina, eluting with ethyl acetate/glacial acetic acid 20:1 to 10:1, to obtain the carboxylic acid **2** (0.51 g, 68%). $[\alpha]_{\text{D}}^{\text{RT}} = -51.6$ (c 2.7, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3) δ 5.55 (d, $J = 10.3$ Hz, 1H), 5.42 – 5.39 (m, 1H), 5.36 (dt, $J = 11.4, 4.4$ Hz, 1H), 5.25 – 5.21 (m, 1H), 4.72 (d, $J = 11.2$ Hz, 1H), 4.49 (dd, $J = 10.6, 2.7$ Hz, 1H), 4.13 (dd, $J = 12.5, 8.1$ Hz, 1H), 4.10 (q, $J = 10.6$ Hz, 1H), 2.60 (dd, $J = 13.7, 4.5$ Hz, 1H), 2.12 – 2.07 (m, 7H), 2.02 (s, 3H), 2.02 (s, 3H), 2.01 – 1.94 (m, 9H), 1.88 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.7, 171.2, 171.1, 170.8, 170.7, 170.3, 85.5, 72.9, 72.2, 69.3, 68.8, 63.4, 51.1, 49.6, 43.7, 39.6, 36.0, 30.0, 23.2, 21.5, 21.0, 20.9, 20.8. ESIHRMS Calcd for $\text{C}_{29}\text{H}_{40}\text{NO}_{12}\text{S}$ $[\text{M} - \text{H}]^-$, 626.2271; found, 626.2279.

4.3. 2-Hydroxymethylbenzyl (1-adamantanyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero- β -D-galacto-non-2-ulopyranosid)onate (3).

A solution of *N,N'*-dicyclohexylcarbodiimide (0.10 g, 0.47 mmol) in anhydrous CH_2Cl_2 (0.3 mL) was added to a mixture of **2** (0.18 g, 0.29 mmol), 1,2-benzenedimethanol (0.16 g, 1.17 mmol) and hydroxybenzotriazole (0.08 g, 0.59 mmol) in anhydrous CH_2Cl_2 (0.4 mL) at 0 $^\circ\text{C}$. The reaction mixture was stirred for 5 min then warmed to room temperature and stirring for 48 h under an argon atmosphere. The reaction mixture was then filtered through Celite, and the organic layer was diluted with CH_2Cl_2 before washing with sat. NaHCO_3 , water, and brine. The organic layer was evaporated to dryness and purified by silica gel chromatography, eluting with hexane/ethyl acetate 3:1 to 3:2, to give **3** (0.15 g, 70 %). $[\alpha]_{\text{D}}^{\text{RT}} = -51.0$ (c 1.1, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3) δ 7.46 (d, $J = 7.3$ Hz, 1H), 7.42 (d, $J = 7.5$ Hz, 1H), 7.38 – 7.35 (m, 1H), 7.31 – 7.28 (m, 1H), 5.45 – 5.43 (m, 1H), 5.43 – 5.34 (m, 3H), 5.29 (dt, $J = 10.5, 4.5$ Hz,

1H), 5.18 – 5.15 (m, 1H), 4.87 (dd, $J = 12.3, 1.6$ Hz, 1H), 4.80 (s, 2H), 4.50 (dd, $J = 10.5, 2.6$ Hz, 1H), 4.28 (dd, $J = 12.3, 8.7$ Hz, 1H), 4.05 (q, $J = 10.4$ Hz, 1H), 2.56 (br s, 1H), 2.49 (dd, $J = 13.7, 4.7$ Hz, 1H), 2.12 (s, 3H), 2.06 (s, 3H), 1.99 (s, 7H), 1.90 (s, 3H), 1.85 (s, 2H), 1.84 – 1.74 (m, 7H), 1.63 – 1.53 (m, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.3, 171.0, 170.7, 170.4, 170.3, 169.2, 140.2, 132.8, 130.8, 129.4, 129.3, 128.1, 86.4, 73.7, 73.0, 69.4, 69.0, 65.9, 63.2, 62.9, 51.0, 49.8, 43.6, 39.9, 35.9, 29.9, 23.3, 21.2, 21.0, 20.9, 20.8; ESIHRMS Calcd for $\text{C}_{37}\text{H}_{49}\text{NO}_{13}\text{SNa}$ $[\text{M} + \text{Na}]^+$, 770.2822; found, 770.2830.

4.4. 1-Adamantanyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid (**5**).

4.4.1. A mixture of **4**^{17,21} (0.10 g, 0.16 mmol) and anhydrous pyridine (1.4 mL) was added to anhydrous LiI (0.07 g, 0.56 mmol) under an argon atmosphere. The reaction mixture was heated to reflux for 4 h under an argon atmosphere before it was cooled to room temperature and concentrated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 , and the organic layer was washed with 1N HCl, brine, and anhydrous Na_2SO_4 before drying over Na_2SO_4 and evaporation to dryness. The crude residue was then purified by chromatography over neutral alumina (eluting with ethyl acetate/glacial acetic acid 20:1 to 10:1) to give the carboxylic acid **5** (0.07 g, 70%).

4.4.2. A solution of **4**^{17,21} (0.98 g, 1.52 mmol), methanol (9.8 mL) and 1N NaOH (19.5 mL) was stirred for 24 h, then co-evaporated with ethanol ($\times 2$) and toluene ($\times 3$). The crude residue was dissolved in pyridine (8.9 mL), treated with acetic anhydride (10.3 mL) at 0 $^\circ\text{C}$, and stirred overnight at room temperature. The reaction mixture was then treated with methanol (15.0 mL) at 0 $^\circ\text{C}$ and stirred at room temperature for 30 min. After concentration, the crude residue was

purified by chromatography over using neutral alumina, eluting with ethyl acetate/acetic acid 20:1 to 10:1, to afford **5** (0.94 g, 73%). $[\alpha]_{\text{D}}^{\text{RT}} = + 20.3$ (c 2.6, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 6.36 (s, 1H), 5.31 (s, 2H), 4.86 (dt, $J = 11.1, 4.4$ Hz, 1H), 4.38 (d, $J = 12.0$ Hz, 1H), 4.21 – 4.16 (m, 2H), 4.05 (q, $J = 10.4$ Hz, 1H), 2.71 (dd, $J = 12.6, 4.2$ Hz, 1H), 2.15 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H), 2.02 – 1.96 (m, 13H), 1.88 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.8, 171.7, 171.3, 170.71, 170.67, 170.4, 84.4, 74.4, 70.6, 70.1, 68.2, 62.1, 51.1, 48.7, 43.5, 39.8, 35.9, 29.8, 22.8, 21.1, 21.0, 20.82, 20.76; ESIHRMS Calcd for $\text{C}_{29}\text{H}_{41}\text{NO}_{12}\text{SNa}$ $[\text{M} + \text{Na}]^+$, 650.2247; found, 650.2247.

4.5. 2-Hydroxymethylbenzyl (1-adamantanyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-glycero- α -D-galacto-non-2-ulopyranosid)onate (6).

Compound **6** was prepared by the same procedure as compound **3** from acid **5** (0.50 g, 0.80 mmol), 1,2-benzenedimethanol (0.44 g, 3.19 mmol), hydroxybenzotriazole (0.22 g, 1.6 mmol) and *N,N'*-dicyclohexylcarbodiimide (0.26 g, 1.27 mmol) in anhydrous CH_2Cl_2 (2.0 mL). After chromatographic purification (gradient elution with hexanes/acetone 3:1 to 3:2), **6** (0.21 g, 35 %) was obtained. $[\alpha]_{\text{D}}^{\text{RT}} = - 4.3$ (c 1.2, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3) δ 7.46 (d, $J = 7.4$ Hz, 1H), 7.41 – 7.35 (m, 2H), 7.30 (t, $J = 7.3$ Hz, 1H), 5.42 (d, $J = 11.9$ Hz, 2H), 5.28 (dd, $J = 8.6, 1.6$ Hz, 1H), 5.26 – 5.22 (m, 1H), 5.19 (d, $J = 12.1$ Hz, 1H), 5.16 (d, $J = 9.9$ Hz, 1H), 4.79 (d, $J = 12.8$ Hz, 1H), 4.75 (d, $J = 12.8$ Hz, 1H), 4.73 (dt, $J = 11.4, 4.4$ Hz, 1H), 4.32 (dd, $J = 12.5, 2.4$ Hz, 1H), 4.12 (dd, $J = 12.5, 4.5$ Hz, 1H), 4.06 (dd, $J = 10.8, 1.5$ Hz, 1H), 3.94 (q, $J = 10.3$ Hz, 1H), 2.67 (dd, $J = 12.8, 4.6$ Hz, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 2.01 (s, 3H), 1.98 (s, 3H), 1.99–1.91 (m, 7H), 1.86 (s, 3H), 1.89 – 1.79 (m, 3H), 1.62 (s, 6H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.3, 170.8, 170.3, 170.2, 170.1, 169.3, 140.3, 132.6, 131.3, 129.6, 129.2, 128.2, 84.8, 74.1,

69.8, 69.5, 67.5, 66.0, 63.1, 62.0, 51.6, 49.4, 43.7, 40.1, 36.1, 30.1, 23.4, 21.3, 21.1, 21.0, 20.9; ESIHRMS Calcd for C₃₇H₄₉NO₁₃SNa [M + Na]⁺, 770.2822; found, 770.2792.

4.6. 2-Hydroxymethylbenzyl (1-adamantanyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-2-thio-*D*-glycero- β -*D*-galacto-non-2-ulopyranosid)onate (9).

A mixture of **7**¹⁷ (0.60 g, 0.96 mmol) and anhydrous pyridine (8.7 mL) was added to LiI (0.46 g, 3.43 mmol) under an argon atmosphere, and the mixture heated to reflux at 135 °C for 3.5 h under argon. After cooling to room temperature and drying under reduced pressure, the residue was dissolved in CH₂Cl₂, and the organic layer was washed with 1N HCl and brine before evaporation to dryness. A solution of *N,N'*-dicyclohexylcarbodiimide (0.32 g, 1.53 mmol) in anhydrous CH₂Cl₂ (1.0 mL) was added to a stirred solution of the resulting residue, 1,2-benzenedimethanol (0.53 g, 3.83 mmol) and hydroxybenzotriazole (0.26 g, 1.92 mmol) in anhydrous CH₂Cl₂ (1.4 mL) at 0 °C. The mixture was stirred for 5 min before warming to room temperature and stirring for another 36 h under an argon atmosphere. The crude product was obtained by following the same workup as described for compound **3**, and was purified by silica gel chromatography, eluting with hexane/ethyl acetate 3:1 to 1:1, to afford **9** (0.37 g, 53%). $[\alpha]_D^{RT} = -39.6$ (*c* 3.1, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.47 (d, *J* = 7.1 Hz, 1H), 7.42 (d, *J* = 7.4 Hz, 1H), 7.40 – 7.35 (m, 1H), 7.33 – 7.27 (m, 1H), 5.71 – 5.68 (m, *J* = 3.5 Hz, 1H), 5.43 (d, *J* = 12.1 Hz, 1H), 5.34 (d, *J* = 12.1 Hz, 1H), 5.27 – 5.21 (m, 1H), 4.79 (s, 2H), 4.75 – 4.66 (m, 2H), 4.60 (dd, *J* = 12.2, 2.3 Hz, 1H), 4.12 (dd, *J* = 12.2, 7.6 Hz, 1H), 3.67 (dd, *J* = 11.3, 9.3 Hz, 1H), 2.77 (dd, *J* = 12.9, 3.6 Hz, 1H), 2.62 (br s, 1H), 2.48 (s, 3H), 2.22 (t, *J* = 12.9 Hz, 1H), 2.10 (s, 3H), 2.03 (s, 3H), 2.00 (s, 3H), 1.92 (br s, 3H), 1.87 – 1.72 (m, 6H), 1.65 – 1.53 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 170.8, 170.7, 169.7, 168.8, 153.7, 140.2, 132.5, 130.8, 129.4,

129.2, 127.9, 85.8, 75.1, 74.3, 72.7, 71.7, 66.0, 63.0, 62.8, 60.3, 51.4, 43.6, 38.2, 35.8, 29.8, 24.7, 21.2, 20.7, 20.6. ESIHRMS Calcd for $C_{36}H_{45}NO_{13}SNa$ $[M + Na]^+$, 754.2509; found, 754.2491.

4.7. 2-Hydroxymethylbenzyl (1-adamantanyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-isothiocyanato-2-thio-D-glycero- β -D-galacto-non-2-ulopyranosid)onate (12).

A solution of **10**^{11,52} (0.24 g, 0.38 mmol) in anhydrous pyridine (3.4 mL) was added to anhydrous LiI (0.18 g, 1.36 mmol) under an inert atmosphere, and the mixture heated to reflux for 2 h before cooling to room temperature and concentration to dryness. The resultant residue was dissolved in CH_2Cl_2 , and the organic layer was washed with 1N HCl and brine before evaporation to dryness. A stirred solution of the residue, 1,2-benzenedimethanol (0.21 g, 1.51 mmol) and hydroxybenzotriazole (0.10 g, 0.76 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was treated with a solution of *N,N'*-dicyclohexylcarbodiimide (0.12 g, 0.61 mmol) in anhydrous CH_2Cl_2 (0.4 mL) at 0 °C and stirred for 5 min before warming up to room temperature and stirring for 48 h. The reaction mixture was worked up as described for compound **3**, and the resultant residue was purified by silica gel chromatography, eluting with toluene/acetone 5:1, and then by preparative HPLC, eluting by hexanes/ethyl acetate 9:1 to 4:6 over 50 min, to give **12** (0.12 g, 43%). $[\alpha]_D^{RT} = -90.5$ (*c* 1.01, CH_2Cl_2); 1H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.3 Hz, 1H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.36 (dt, *J* = 7.5, 3.7 Hz, 1H), 7.30 (dt, *J* = 7.5, 3.8 Hz, 1H), 5.46 (dd, *J* = 4.7, 2.4 Hz, 1H), 5.43 – 5.31 (m, 3H), 5.28 – 5.23 (m, 1H), 4.77 (s, 2H), 4.60 (dd, *J* = 12.5, 2.2 Hz, 1H), 4.48 (dd, *J* = 10.3, 2.4 Hz, 1H), 4.27 (dd, *J* = 12.5, 6.8 Hz, 1H), 3.65 (t, *J* = 10.1 Hz, 1H), 2.60 (dd, *J* = 13.8, 4.7 Hz, 1H), 2.45 (br s, 1H), 2.13 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.90 (s, 4H), 1.86 – 1.70 (m, 6H), 1.63– 1.51 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.4, 169.7, 169.5, 169.0, 140.3, 139.6, 132.6, 130.8, 129.5, 129.3, 128.1, 86.1, 71.3, 71.1, 69.8,

69.6, 66.0, 63.0, 62.4, 57.4, 51.2, 43.5, 39.3, 35.9, 29.9, 21.2, 21.1, 20.9, 20.7; ESIHRMS Calcd for $C_{36}H_{45}NO_{12}S_2Na$ $[M + Na]^+$, 770.2281; found, 770.2263.

4.8. General Procedure for cyclization reactions.

A solution of substrate (0.008 M) in anhydrous CH_2Cl_2 was stirred under argon at room temperature with freshly activated AW-300 molecular sieves (100 mg/mL) for 30 min and then at $-40\ ^\circ C$ for another 30 min. *N*-Iodosuccinimide (2.4 equiv) and TfOH (1 equiv) were then added respectively and the reaction mixture stirred for 2 h before Et_3N (~1.5 equiv) was added. The reaction mixture was diluted with CH_2Cl_2 , filtered through Celite, washed with saturated aqueous $NaHCO_3$, saturated aqueous $Na_2S_2O_3$, brine, and finally concentrated to dryness. The crude residue was purified by silica gel column chromatography to obtain mixtures of cyclized products from which the pure anomers were obtained by preparative HPLC.

4.8.1. 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid spirolactone (**13 α**) and 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- β -D-galacto-non-2-ulopyranosidonic acid spirolactone (**13 β**).

4.8.1.1. **From 3.** According to the general procedure for cyclization, compounds **13 α** and **13 β** were prepared using peracetylated thioglycoside donor **3** (0.051 g, 0.068 mmol), freshly activated AW-300 molecular sieves (0.880 g), anhydrous CH_2Cl_2 (8.4 mL), *N*-iodosuccinimide (0.036 g, 0.162 mmol) and TfOH (5.9 μ L, 0.066 mmol). The crude residue was purified using silica gel column chromatography (gradient elution with toluene/2-propanol 14:1 to 6:1) to give **13 α** and **13 β** (0.022 g, 58%) as a mixture (1:2.4, α : β) of anomers.

4.8.1.2. *From 6.* The cyclization reaction was carried using the general procedure for cyclization using donor **6** (0.013 g, 0.017 mmol), AW-300 molecular sieves (0.221 g), anhydrous CH₂Cl₂ (2.1 mL), *N*-iodosuccinimide (0.009 g, 0.040 mmol) and TfOH (1.5 μ L, 0.017 mmol) to afford **13 α** and **13 β** (0.008 g, 76%) as a mixture (1:5, α : β) of anomers.

4.8.1.3. *Purification.* The combined mixtures of products from the cyclization of **3** and **6** was separated by preparative HPLC, gradient elution with hexanes/ethyl acetate 1:1 to 1:4 over 30 min, to obtain pure **13 α** and **13 β** . UHPLC was used to analyze the pure samples of **13 α** and **13 β** (UHPLC method, flow rate: 0.35 mL/min; Initial: CH₃CN 30% in H₂O; 10.5 min: CH₃CN 30% in H₂O; 15.0 min: CH₃CN 100%; t_R (min): **13 β** = 7.18, **13 α** = 5.90).

4.8.1.4. **2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid spirolactone (13 α).**

$[\alpha]^{RT}_D = +39.4$ (c 1.1, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.34 (t, J = 7.4 Hz, 1H), 7.29 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 7.4 Hz, 1H), 7.14 (d, J = 7.2 Hz, 1H), 6.12 (d, J = 10.0 Hz, 1H), 6.04 (d, J = 13.0 Hz, 1H), 5.51 (ddd, J = 8.4, 5.5, 2.6 Hz, 1H), 5.34 (dd, J = 9.2, 2.0 Hz, 1H), 5.23 (d, J = 15.1 Hz, 1H), 5.11 (td, J = 11.8, 4.7 Hz, 1H), 4.98 (d, J = 13.1 Hz, 1H), 4.86 (d, J = 15.2 Hz, 1H), 4.62 (d, J = 10.5 Hz, 1H), 4.26 (dd, J = 12.5, 2.5 Hz, 1H), 4.21 (q, J = 10.4 Hz, 1H), 4.09 (dd, J = 12.5, 5.6 Hz, 1H), 2.70 (dd, J = 13.0, 4.7 Hz, 1H), 2.16 (s, 3H), 2.13 (s, 3H), 2.08 (t, J = 12.8 Hz, 1H), 2.02 (s, 6H), 1.87 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.2 (³ $J_{C1,H3ax}$ = 6.5 Hz), 170.8, 170.7, 170.5, 170.2, 169.9, 134.8, 133.9, 129.5, 129.3, 128.8, 128.4, 99.3, 73.7, 71.9, 69.0, 68.8, 68.2, 67.1, 62.6, 49.2, 37.2, 23.1, 21.2, 21.04, 21.02, 20.9; ESIHRMS Calcd for C₂₇H₃₃NO₁₃Na [M + Na]⁺, 602.1850; found, 602.1824.

4.8.1.5. 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- β -D-galacto-non-2-ulopyranosidonic acid spirolactone (13 β).

$[\alpha]_D^{RT} = -32.2$ (c 1.5, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3) δ 7.30 – 7.25 (m, 2H), 7.19 (d, $J = 8.1$ Hz, 1H), 7.12 (d, $J = 6.6$ Hz, 1H), 5.66 (d, $J = 13.5$ Hz, 1H), 5.60 (d, $J = 9.3$ Hz, 1H), 5.43 (d, $J = 4.7$ Hz, 1H), 5.40 (d, $J = 13.4$ Hz, 1H), 5.34 – 5.24 (m, 2H), 4.81 (dd, $J = 12.4, 2.3$ Hz, 1H), 4.46 (d, $J = 13.4$ Hz, 1H), 4.16 – 4.05 (m, 3H), 2.35 (dd, $J = 13.3, 4.9$ Hz, 1H), 2.14 (s, 3H), 2.04 – 2.02 (m, 4H), 2.00 (s, 3H), 1.99 (s, 3H), 1.86 (s, 3H); ^{13}C NMR (150 MHz, CDCl_3) δ 171.2, 170.70, 170.67, 170.4, 170.3, 168.1 ($^3J_{\text{C1,H3ax}} = 0.0$ Hz), 135.9, 133.0, 132.1, 128.9, 128.8, 128.1, 97.7, 71.6, 69.4, 69.0, 68.2, 67.1, 62.2, 49.6, 36.0, 23.3, 21.1, 21.0, 20.9; ESIHRMS Calcd for $\text{C}_{27}\text{H}_{33}\text{NO}_{13}\text{Na}$ $[\text{M} + \text{Na}]^+$, 602.1850; found, 602.1846.

4.8.2. 2-Hydroxymethylbenzyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid spirolactone (14 α) and 2-Hydroxymethylbenzyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero- β -D-galacto-non-2-ulopyranosidonic acid spirolactone (14 β).

The general procedure for cyclization was used to synthesize a mixture of **14 α** and **14 β** from **9** (0.044 g, 0.060 mmol), AW-300 molecular sieves (0.781 g), anhydrous CH_2Cl_2 (7.5 mL), *N*-iodosuccinimide (0.032 g, 0.141 mmol) and TfOH (5.2 μL , 0.059 mmol). After silica gel chromatography using hexanes/ethyl acetate as eluent, products **14 α** and **14 β** (0.014 g, 42%) were obtained as a mixture (1:0.4, α : β) of anomers.

4.8.2.1. 2-Hydroxymethylbenzyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid spirolactone (14 α).

After preparative HPLC of the mixture of cyclized anomers (eluting with hexanes/ethyl acetate 7:3 to 1:1 over 40 min), an analytical sample of **14 α** was obtained. Recrystallization from

CH₂Cl₂/Hexanes (3:7) gave crystals of **14a** suitable for X-ray analysis. Mp 208 °C; $[\alpha]_{\text{D}}^{\text{RT}} = +63.4$ (*c* 1.4, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.28 (m, 2H), 7.23 (d, *J* = 7.2 Hz, 1H), 7.17 (d, *J* = 6.9 Hz, 1H), 5.96 (d, *J* = 13.0 Hz, 1H), 5.61 (dd, *J* = 8.6, 1.6 Hz, 1H), 5.53 – 5.48 (m, 1H), 5.32 (d, *J* = 14.8 Hz, 1H), 5.14 (d, *J* = 13.0 Hz, 1H), 4.84 (d, *J* = 14.8 Hz, 1H), 4.78 (dd, *J* = 9.4, 1.6 Hz, 1H), 4.42 (dd, *J* = 12.3, 2.9 Hz, 1H), 4.29 (ddd, *J* = 13.4, 11.3, 3.7 Hz, 1H), 4.08 (dd, *J* = 12.3, 6.8 Hz, 1H), 3.80 (t, *J* = 10.3 Hz, 1H), 2.89 (dd, *J* = 12.3, 3.8 Hz, 1H), 2.51 (s, 3H), 2.19 – 2.17 (m, 4H), 2.09 (s, 3H), 2.03 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.2, 170.8, 170.4 (³*J*_{C1,H3ax} = 5.5 Hz), 170.2, 170.1, 153.7, 134.1, 134.1, 130.1, 129.4, 128.9, 128.6, 99.1, 76.3, 74.4, 71.6, 71.4, 69.4, 68.9, 63.3, 59.0, 35.4, 24.8, 21.17, 21.15, 20.9; ESIHRMS Calcd for C₂₆H₂₉NO₁₃Na [M + Na]⁺, 586.1537; found, 586.1535.

4.8.2.2. 2-Hydroxymethylbenzyl 5-acetamido-7,8,9-tri-*O*-acetyl-5-*N*,4-*O*-carbonyl-3,5-dideoxy-*D*-glycero-β-*D*-galacto-non-2-ulopyranosidonic acid spirolactone (14β**).**

After preparative HPLC of the mixture of cyclized anomers (eluting with hexanes/ethyl acetate 7:3 to 1:1 over 40 min), an analytical sample of **14β** was obtained. $[\alpha]_{\text{D}}^{\text{RT}} = -5.9$ (*c* 0.4, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.36 – 7.29 (m, 2H), 7.27 – 7.24 (m, 1H), 7.17 (d, *J* = 7.1 Hz, 1H), 5.69 – 5.64 (m, 2H), 5.52 (d, *J* = 13.0 Hz, 1H), 5.40 (ddd, *J* = 7.4, 4.5, 2.8 Hz, 1H), 5.36 (d, *J* = 13.6 Hz, 1H), 4.69 (dd, *J* = 12.3, 2.6 Hz, 1H), 4.59 (td, *J* = 12.4, 3.7 Hz, 1H), 4.53 (dd, *J* = 9.4, 1.4 Hz, 1H), 4.49 (d, *J* = 13.0 Hz, 1H), 4.11 (dd, *J* = 12.2, 7.6 Hz, 1H), 3.72 (dd, *J* = 11.1, 9.6 Hz, 1H), 2.59 (dd, *J* = 12.5, 3.8 Hz, 1H), 2.51 (s, 3H), 2.24 (t, *J* = 12.6 Hz, 1H), 2.15 (s, 3H), 2.11 (s, 3H), 2.02 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 172.3, 171.0, 170.7, 170.1, 167.9 (³*J*_{C1,H3ax} = 0.0 Hz), 153.9, 136.3, 133.2, 132.5, 129.3, 128.8, 127.8, 97.0, 75.2, 74.5, 72.9, 71.7, 69.2, 67.6, 62.8, 59.6, 34.9, 24.8, 21.2, 21.0, 20.9; ESIHRMS Calcd for C₂₆H₂₉NO₁₃Na [M + Na]⁺, 586.1537; found, 586.1530.

4.8.3. 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid spirolactone (15 α) and 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- β -D-galacto-non-2-ulopyranosidonic acid spirolactone (15 β).

Cyclization of compound **12** was conducted by the general procedure for cyclization using sialyl donor **12** (0.031 g, 0.041 mmol), AW-300 molecular sieves (0.540 g), anhydrous CH₂Cl₂ (5.2 mL), *N*-iodosuccinimide (0.022 g, 0.097 mmol) and TfOH (3.6 μ L, 0.041 mmol), and afforded a mixture of **15 α** and **15 β** (0.04 g, 20 %, 1:0.4, α : β).

4.8.3.1. 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- α -D-galacto-non-2-ulopyranosidonic acid spirolactone (15 α).

Preparative HPLC of the mixture of cyclized anomers (eluting with hexanes/ethyl acetate 9:1 to 7:3 over 50 min) afforded an analytical sample of **15 α** . $[\alpha]_D^{RT} = +13.3$ (*c* 0.06, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.32 – 7.29 (m, 2H), 7.22 (dd, *J* = 5.4, 3.5 Hz, 1H), 7.15 (dd, *J* = 5.3, 3.5 Hz, 1H), 5.77 (d, *J* = 13.2 Hz, 1H), 5.53 (dd, *J* = 9.5, 1.4 Hz, 1H), 5.48 (ddd, *J* = 9.5, 4.2, 2.3 Hz, 1H), 5.37 (d, *J* = 14.2 Hz, 1H), 5.21 (d, *J* = 13.1 Hz, 1H), 5.15 (ddd, *J* = 11.9, 10.0, 4.9 Hz, 1H), 4.69 (d, *J* = 14.2 Hz, 1H), 4.34 (dd, *J* = 12.6, 2.3 Hz, 1H), 4.21 (dd, *J* = 12.6, 4.2 Hz, 1H), 4.15 (dd, *J* = 10.5, 1.4 Hz, 1H), 3.64 (t, *J* = 10.2 Hz, 1H), 2.68 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.21 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 1.77 (t, *J* = 12.5 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 170.9, 170.0, 170.0, 169.5, 140.7, 135.1, 133.4, 131.5, 129.1, 128.9, 128.4, 98.3, 72.2, 70.4, 69.8, 68.8, 67.9, 67.6, 61.8, 56.6, 36.2, 21.2, 21.1, 20.9, 20.9; ESIHRMS Calcd for C₂₆H₂₉NO₁₂SNa [M + Na]⁺, 602.1308; found, 602.1306.

4.8.3.2. 2-Hydroxymethylbenzyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-D-glycero- β -D-galacto-non-2-ulopyranosidonic acid spirolactone (15 β).

Preparative HPLC of the mixture of cyclized anomers (eluting with hexanes/ethyl acetate 9:1 to 7:3 over 50 min) afforded an analytical sample of **15 β** . $[\alpha]_D^{RT} = -40.0$ (*c* 0.03, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.31 (dd, *J* = 5.6, 3.3 Hz, 1H), 7.23 – 7.21 (m, 1H), 7.16 – 7.14 (m, 1H), 5.65 (d, *J* = 13.7 Hz, 1H), 5.56 (d, *J* = 7.3 Hz, 1H), 5.41 – 5.34 (m, 3H), 5.30 (d, *J* = 13.4 Hz, 1H), 4.58 (dd, *J* = 12.7, 2.4 Hz, 1H), 4.47 (d, *J* = 13.5 Hz, 1H), 4.17 (dd, *J* = 12.7, 5.3 Hz, 1H), 4.08 (dd, *J* = 10.5, 1.4 Hz, 1H), 3.65 (t, *J* = 10.2 Hz, 1H), 2.48 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.19 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.05 (s, 3H), 1.89 (t, *J* = 12.5 Hz, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 170.8, 170.2, 169.9, 169.7, 167.8, 140.6, 135.6, 132.9, 132.0, 129.1, 129.0, 128.2, 97.8, 70.4, 70.4, 69.9, 69.8, 69.7, 68.2, 68.2, 68.0, 67.4, 61.7, 56.8, 35.5, 21.13, 21.11, 20.94, 20.87. ESIHRMS Calcd for C₂₆H₂₉NO₁₂SNa [M + Na]⁺, 602.1308; found, 602.1307.

4.8.4. Conversion of **15 α** to **13 α** .

To a stirred solution of lactone **15 α** (0.002 g, 0.003 mmol), 18-crown-6 (0.0001 g, 0.0003 mmol) and thioacetic acid (0.0003 g, 0.004 mmol) in anhydrous THF (0.03 mL), potassium *tert*-butoxide (0.0001 g, 0.001 mmol) was added under an argon atmosphere. The reaction mixture was stirred at 60 °C for 4 h, then cooled to room temperature, diluted with ethyl acetate, washed with 1N HCl, saturated aqueous NaHCO₃, brine, and concentrated to dryness. UHPLC analysis revealed the product to be identical to **13 α** .

4.8.5. Conversion of **15 β** to **13 β** .

To a stirred solution of lactone **15 β** (0.002 g, 0.003 mmol), 18-crown-6 (0.0001 g, 0.0003 mmol) and thioacetic acid (0.0003 g, 0.004 mmol) in anhydrous THF (0.03 mL), potassium *tert*-butoxide (0.0001 g, 0.001 mmol) was added under an argon atmosphere. The reaction mixture was stirred at 60 °C for 4 h, then cooled to room temperature, diluted with ethyl acetate, washed

with 1N HCl, saturated aqueous NaHCO₃, brine, and concentrated to dryness. UHPLC analysis revealed the product to be identical to **13β**.

4.8.6. 2-Hydroxymethylbenzyl (Acetyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-amino-D-glycero-β-D-galacto-non-2-ulopyranosid)onate (20).

A solution of **6** (0.057 g, 0.076 mmol) in anhydrous CH₃CN/CH₂Cl₂ (3:7, 9.8 mL) was stirred at room temperature with AW300 molecular sieves (1.022 g) for 30 min before being cooled to -40 °C and stirred for another 30 min. *N*-Iodosuccinimide (0.048 g, 0.180 mmol) and TfOH (6.7 μL, 0.075 mmol) were added and reaction mixture was stirred at -40 °C under argon for 4.5 h before triethylamine (17.0 μL) was added. The reaction mixture was diluted with CH₂Cl₂, filtered through Celite, washed with saturated aqueous NaHCO₃, saturated Na₂S₂O₃, brine, and concentrated to dryness. The residue was purified by silica gel chromatography, eluting with hexanes/ethyl acetate 1:1 to 1:8 followed by toluene/ethanol 6:1 containing 1 % triethylamine, to afford **13β** (0.015 g, 40 %) and **20** (0.002 g, 4%). $[\alpha]_D^{RT} = -12.0$ (*c* 0.2, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 7.47 (d, *J* = 7.2 Hz, 1H), 7.39 – 7.35 (m, 2H), 7.32 – 7.28 (m, 1H), 5.75 (d, *J* = 9.0 Hz, 1H), 5.45 (td, *J* = 10.9, 5.1 Hz, 1H), 5.36 (d, *J* = 12.2 Hz, 1H), 5.29 (d, *J* = 12.3 Hz, 1H), 5.27– 5.24 (m, 2H), 5.16 – 5.12 (m, 1H), 4.75 (s, 2H), 4.53 (dd, *J* = 12.4, 2.3 Hz, 1H), 4.14 – 4.07 (m, 2H), 3.76 (q, *J* = 9.9 Hz, 1H), 2.71 (dd, *J* = 13.5, 5.0 Hz, 1H), 2.10 (s, 3H), 2.07– 2.03 (m, 4H), 2.02 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.89 (s, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 171.4, 171.14, 171.08, 171.0, 170.8, 170.7, 168.1 (³*J*_{Cl,H3ax} = 0.0 Hz), 140.4, 132.9, 130.4, 129.4, 129.4, 128.0, 84.2, 71.8, 70.9, 68.9, 68.5, 66.7, 62.8, 62.6, 50.7, 35.8, 23.4, 23.3, 21.2, 21.0, 20.9; ESIHRMS Calcd for C₂₉H₃₈N₂O₁₄Na [M + Na]⁺, 661.2221; found, 661.2209.

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Supplementary Material. Supplementary data to this article can be found online at ...

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Graphical Abstract: