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Influence of Protecting Groups on O- and C-Glycosylation with Neuraminy and Ulosonyl Dibutylphosphates.

Riku Ogasahara^{a,b,§}, Shuay Abdullayev^{a,c,§}, Vikram A Sarpe^{d,e}, Appi Reddy Mandhapati^a, David Crich^{a,d,e,f,*}

^a)Department of Chemistry, Wayne State University, 5101 Cass Avenue, Detroit, MI 48202, USA.

^b)Department of Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama, Kanagawa 223-8522, Japan.

^c)Department of Chemistry, Université Claude Bernard Lyon 1, Domaine Scientifique de la Doua, boulevard du 11 Novembre 1918, 69622 Villeurbanne Cedex, France.

^d)Department of Pharmaceutical and Biomedical Sciences, University of Georgia, 250 West Green Street, Athens, Georgia 30602, United States.

^e)Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, Georgia 30602, United States.

^f)Department of Chemistry, University of Georgia, 140 Cedar Street, Athens, Georgia 30602, United States.

Abstract

The adamantanyl thioglycosides of 5-isothiocyano and 5-azido 5-desamino-4,7,8,9-tetra-*O*-acetylneuraminic acid methyl ester were converted into the corresponding dibutyl phosphates, which proved to be excellent α -selective donors for *O*-sialidation with a range of typical acceptors, and good donors for reaction with allyltributylstannane, albeit without significant anomeric selectivity. In the KDN series the dibutylphosphate derived from a donor carrying a 4,5-cyclic carbonate protecting group afforded the corresponding *C*-glycoside with excellent α -selectivity on activation in the presence of allyltributylstannane, whereas the corresponding donor carrying acetate esters at the 4- and 5-positions was unselective. Overall, it is revealed that while the strongly electron-withdrawing isothiocyanato and azido groups are sufficient to promote highly α -selective *O*-sialidation, they are inadequate when faced with less reactive nucleophiles when mixtures of anomers are obtained.

Graphical Abstract

*Corresponding Author david.crich@uga.edu.

§:These authors made an equal contribution.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Keywords

Glycosyl phosphates; Sialidation; *C*-Glycosides; KDN *C*-Glycoside; Neuraminic acid

Introduction

Previously, we reported that the 1-adamantanyl thioglycosides of the 4,5-oxazolidinone and carbonate-protected derivatives **1** and **2** of *N*-acetylneuraminic (NeuAc) and ketodeoxynonulosonic acid (KDN), respectively, are excellent donors for the formation of the corresponding equatorial *O*-glycosides at low temperature in dichloromethane/acetonitrile mixtures at $-78\text{ }^{\circ}\text{C}$, in contrast to the corresponding peracetylated derivatives **3** and **4**.¹⁻² Comparable results were obtained by the Takahashi, De Meo and Xing laboratories with oxazolidinone-protected NeuAc derivatives, lacking the *N*-acetyl group.³⁻⁵ Wong and coworkers subsequently showed that the dibutylphosphates **5** corresponding to **1** were also superb donors for the formation of equatorial NeuAc glycosides at low temperature,⁶ while Xing and coworkers reported on the related ability of the sulfoxide **6**.⁷ Later, following up on a chance observation in the investigation of the *N*-acetyl oxazolidinthione **8**,⁸ we discovered that the isothiocyanate **7** also delivers the equatorial *O*-glycosides with excellent selectivity and yield at $-78\text{ }^{\circ}\text{C}$.⁹ Subsequently, we showed the azide **9** also serves as an efficient and selective donor for the glycosylation of primary, secondary and tertiary alcohols provided it is activated at $-78\text{ }^{\circ}\text{C}$.¹⁰ Finally, we reported the *N*-acetyloxazolidinone-protected sialyl phosphate **5** to furnish equatorial *C*- and *S*-glycosides with excellent selectivity when activated in the presence of suitable nucleophiles at low temperature.¹¹⁻¹²

Generalizing on this ensemble of results, we report here that the isothiocyanate and azide-protected phosphates **10** and **11**, while serving as selective donors for equatorial *O*-glycosylation afford mixtures of axial and equatorial *C*-glycosides on reaction with allyltributylstannane. We also report that cyclic carbonate-protected KDN phosphate **12** functions as an equatorially selective *C*-glycosyl donor, in contrast to the peracetyl analog **13**.

Results and Discussion

We began our investigation by conversion of the isothiocyanate and azide-protected NeuAc thioglycosides to the corresponding phosphates **10** and **11** by reaction with dibutylphosphoric acid, *N*-iodosuccinimide and triflic acid in dichloromethane at 0 °C (Scheme 1). The KDN thioglycosides **2** and **4** were converted into the corresponding dibutylphosphate **12** and **13** analogously, as previously described.¹³

A series of *O*-glycosylation reactions was then conducted with phosphates **10** and **11** in dichloromethane at –78 °C with activation by trimethylsilyl trifluoromethanesulfonate essentially as described by Wong for the *N*-acetyloxazolidinone-protected phosphate **5**.⁶ Each of these glycosylations was found to be highly α -selective as recorded in Table 1. The anomeric configuration of all products in this study was established by measurement of the $^3J_{C1,H3ax}$ heteronuclear coupling constants in the usual manner.^{14–18}

Having established that phosphates **10** and **11** afford outstanding equatorial selectivity in line with that reported for **5** and indeed for the thioglycosides **7** and **9**, we turned to the formation of *C*-glycosides using the potent¹⁹ allyltributylstannane as nucleophile (Table 2).

Activation of the 4,5-*O*-carbonate protected KDN donor **12** in the presence of allyltributyltin resulted in the formation of *C*-glycoside **24** as a single α -isomer. On the other hand, donors **10**, **11**, and **13** produced mixtures of anomers, albeit favoring the α -isomer, when coupled to allyltributylstannane under the standard conditions. The configuration of the both KDN α -*C*-glycosides **24a** and **25a** was established by the observation of a nuclear Overhauser correlation between the allylic protons and the axial hydrogen atom at H3 in the pyranoside ring, while that of the KDN β -*C*-glycoside was confirmed by an nOe interaction between the allylic hydrogens and the axial hydrogens at positions 4 and 6 of the pyranose ring. These assignments were further confirmed by the $^3J_{C1,H3ax}$ heteronuclear coupling constants from C1 to H3 axial of 8.3 and 8.0 Hz for the α -anomers **24a** and **25a**, respectively, and of 3.9 Hz for the β -anomer **25b**. These heteronuclear coupling constants are larger than those

typically seen for the sialyl *O*-glycosides^{14–18} but compare with the 8.8 and 2.0 Hz values for the anti and gauche $^3J_{C,H}$ coupling constant in the hydrocarbon propane computed from a Karplus relationship.²⁰ This trend in the magnitude of 3J coupling constants is consistent with the typical influence of electronegative substituents.^{20–21}

The anomeric configuration of the α -anomer of the isothiocyanate **26a** was established by chemical conversion to the known corresponding acetamide **30a**^{22–23} by treatment with thioacetic acid,^{24–26} while that of azide **28a** was similarly determined by exposure to trimethylphosphine and dipyridyl disulfide and acetic acid²⁷ followed by acetyl chloride (Scheme 2).

The formation of *C*-glycoside **24** in high yield and excellent selectivity from donor **12** establishes that the 4,5-*O*-carbonate protecting group in the KDN series in every way mimics the 4,5-oxazolidinone in the NeuAc series. On the other hand, while the 5-desamino-5-isothiocyanato and 5-azido modifications of NeuAc **10** and **11** are sufficient to provide excellent α -selectivity in *O*-glycosylations, they afford only moderate selectivity in *C*-glycosylation with a competent nucleophile clearly demonstrating the superiority of the 4,5-oxazolidinone type protection. It remains possible that the 5-desamino-5-isothiocyanato and 5-azido modifications may yet prove suitable for use in α -selective *C*-glycosylations as and when chemistry is developed for the synthesis of comparable donors with less activated leaving groups.²⁸

Conclusion

Consistent with expectation, *O*-glycosylations with 5-deasmino 5-isothiocyanato and 5-azido NeuAc dibutylphosphates are highly α -selective. With respect to *C*-glycosylation these donors lacking cyclic protection were only moderately selective. On the other hand, the KDN 4,5-*O*-carbonate derivative afforded excellent equatorial selectivity for *C*-glycoside formation. Clearly, the presence of a strongly electron-withdrawing protecting group at the 5-position of the NeuAc and KDN series is insufficient to afford high equatorial selectivity with the less nucleophilic carbon nucleophile in the absence of additional conformational constraint.

Experimental Section

General Experimental Methods.

Commercially available starting materials were used without further purification. All solvents were dried according to standard methods. TLC was performed on precoated glass plates employing UV absorption and charring with ceric ammonium molybdate (CAM) stain for visualization. For column chromatography, silica gel 60, 230–400 mesh, 40–63 μ m was used. ^1H and ^{13}C NMR spectra were recorded on 400 and 600 MHz instruments at 300 K. Chemical shifts were referenced to residual solvent peaks. Stereochemical assignments of coupled sialosides are based on $^3J_{C1-H3ax}$ values. Specific rotations were measured using a digital polarimeter; values are given in 10^{-1} deg $\cdot$ cm 2 $\cdot$ g $^{-1}$. High resolution mass spectra were recorded with an electrospray source coupled to a time-of-flight mass analyzer.

Acid-Washed Molecular Sieves.

Molecular sieves (4 Å, 30 g) were soaked in 2 N HCl (80 mL) for 12 h. The mixture was concentrated under reduced pressure and then slurried with water (100 mL). The slurry was filtered and washed with water (200 mL). The resulting solid was dried at 254 °C for 24 h to give acid-washed molecular sieves (28 g), which were used directly for glycosylation.

Dibutyl [methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-isothiocyanato-D-glycero- α -D-galactono-2-ulopyranosyl)onate] phosphate (10):

A solution of thiosialoside **7**⁹ (300.0 mg, 0.47 mmol), dibutyl phosphoric acid (252.5 mg, 1.20 mmol), and activated 4 Å powdered molecular sieves (100.0 mg, 2.0 glmmol) in anhydrous CH₂Cl₂ (11.0 mL) was stirred for 1 h under Ar and then cooled to 0 °C followed by addition of NIS (154.8 mg, 0.69 mmol) and TfOH (12 μ L, 0.14 mmol). The reaction mixture was stirred at 0 °C for 5 h and then quenched with Hunig's base (0.7 mL, 4.7 mmol). The mixture was diluted with CH₂Cl₂ (5.0 mL), filtered through Celite, washed with 20% aqueous Na₂S₂O₃ solution, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with EtOAc: toluene (gradient elution 5% to 40%) affording the desired compound (243 mg, 76%) in a 3:2 ratio, as a brown oil, whose spectral data are consistent with the literature data.⁹ **Compound 10 α** : *R*_f = 0.71, 25% EtOAc in toluene; [α]_D²⁶ -22.4 (*c* 1.45, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 5.44 (dd, *J* = 9.2, 1.4 Hz, 1H), 5.23 (ddd, *J* = 9.1, 4.1, 2.4 Hz, 1H), 4.97 (ddd, *J* = 12.1, 9.9, 4.7 Hz, 1H), 4.29 (dd, *J* = 12.6, 2.4 Hz, 1H), 4.19 (dd, *J* = 10.6, 1.4 Hz, 1H), 4.15 (dd, *J* = 4.1 Hz, 1H), 4.09-4.03 (m, 1H), 4.03-3.96 (m, 3H), 3.80 (s, 3H), 3.63 (t, *J* = 10.3 Hz, 1H), 2.73 (dd, *J* = 13.0, 4.8 Hz, 1H), 2.29 (t, *J* = 12.6 Hz, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 1.61 (m, 4H), 1.36 (m, 4H), 0.89 (td, *J* = 7.4, 5.4 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 170.6, 169.5, 169.5, 169.4, 166.5, 140.7, 97.9 (d, *J*_{C-P} = 7.2 Hz), 77.3, 77.1, 76.8, 72.7, 70.0, 69.4, 68.9, 68.3, 68.04, 68.00, 67.90, 67.86, 67.2, 61.3, 56.8, 56.1, 53.3, 36.81, 36.78, 32.1, 32.03, 32.01, 31.98, 20.9, 20.8, 20.7, 20.6, 18.6, 18.5, 13.54, 13.51; ³¹P NMR (151 MHz, CDCl₃) δ -6.96; ESI-HRMS: *m/z* calcd. for C₂₇H₄₂NO₁₅PSNa [M+Na]⁺ 706.1911, found: 706.1893.

Compound 10 β :

*R*_f = 0.70, 25% EtOAc in toluene; [α]_D²⁶ -45.8 (*c* 0.95, CH₂Cl₂); ¹H NMR (600 MHz, CDCl₃) δ 5.50 (dd, *J* = 6.5, 1.8 Hz, 1H), 5.36 (ddd, *J* = 11.4, 9.9, 4.9 Hz, 1H), 5.23 (td, *J* = 6.1, 2.4 Hz, 1H), 4.43 (dd, *J* = 12.5, 2.5 Hz, 1H), 4.29 (dd, *J* = 10.6, 1.8 Hz, 1H), 4.23 (dd, *J* = 12.6, 5.7 Hz, 1H), 4.12-4.02 (m, 5H), 3.80 (s, 3H), 3.68 (t, *J* = 10.3 Hz, 1H), 2.72 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.15 (s, 3H), 2.10 (s, 3H), 2.08 (s, 3H), 2.03 (s, 3H), 1.90 (ddd, *J* = 11.4, 3.2 Hz, 1H), 1.64 (m, 4H), 1.38 (m, 4H), 0.92 (td, *J* = 7.4, 3.8 Hz, 6H); ¹³C NMR (151 MHz, CDCl₃) δ 170.6, 169.9, 169.4, 169.3, 165.6, 140.7, 98.9 (d, *J*_{C-P} = 5.3 Hz), 71.8, 69.8, 68.8, 68.5, 68.45, 68.40, 68.3, 61.8, 56.3, 53.3, 36.64, 36.61, 32.1, 32.06, 29.7, 20.9, 20.87, 20.76, 20.6, 18.6, 13.5 ³¹P NMR (151 MHz, CDCl₃) δ -6.17; ESI-HRMS: *m/z* calcd. For C₂₇H₄₂NO₁₅ PSNa [M+Na]⁺ 706.1911, found: 706.1887.

Dibutyl [methyl 4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-azido-*D*-glycero- α / β -*D*-galacto-non-2-ulopyranosyl)onate] phosphate (11).

A solution of thiosialoside donor **9** (443 mg, 0.71 mmol), dibutyl phosphate (250 μ L, 1.26 mmol) and pulverized activated 4Å AWMS (840 mg) in dry CH_2Cl_2 (12 mL) was stirred for 1 h and then cooled to 0 °C followed by with activation by NIS (262 mg, 0.85 mmol) and TfOH (30 μ L, 0.34 mmol). The reaction mixture was stirred at 0 °C for 5 h and then quenched with Hunig's base (0.7 mL). The mixture was diluted with CH_2Cl_2 (10.0 mL), filtered through Celite, washed with 20% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ solution, dried over Na_2SO_4 , and concentrated under reduced pressure. After chromatographic purification (gradient elution of toluene 5 % to 30 % in EtOAc; R_f = 0.55, 20% EtOAc in toluene; compound **11** (254 mg, 0.380 mmol, 54%) was obtained as a brown oil as a 3:2 mixture of isomers. ^1H NMR (400 MHz, CDCl_3) δ : The major isomer was characterized by the following signals: 5.54 (d, J = 6.3 Hz, 1H), 5.21 (td, J = 6.4, 2.4 Hz, 1H), 4.44 (dd, J = 12.5, 2.0 Hz, 1H); The minor isomer was characterized by the following signals: 5.49 (d, J = 9.0 Hz, 1H), 4.88 (td, J = 12.1, 4.8 Hz, 1H), 2.33 (t, J = 12.5 Hz, 1H); Common signals: 5.30 – 5.24 (m, 2H), 4.36 – 4.15 (m, 2H), 4.14 – 3.92 (m, 10H), 3.79 (s, 6H), 3.29 (dd, J = 11.9, 8.5 Hz, 2H), 2.75 (td, J = 13.5, 4.9 Hz, 2H), 2.16 (s, 6H), 2.09 (s, 3H), 2.08 (s, 6H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.88 (dd, J = 17.8, 7.2 Hz, 2H); 1.69 – 1.57 (m, 8H), 1.43 – 1.32 (m, 8H), 0.91 (m, 12H); ^{13}C NMR (100 MHz, CDCl_3) δ : 170.9, 170.3, 170.1, 169.9, 169.7, 166.97, 166.89, 166.1, 99.4 (d, $J_{\text{C-P}}$ = 6.01 Hz), 98.4 (d, $J_{\text{C-P}}$ = 7.14 Hz), 72.9, 72.1, 70.97, 70.3, 70.25, 68.76, 68.70, 68.6, 68.57, 67.7, 62.2, 61.8, 59.98, 59.8, 53.5, 53.5, 36.9, 36.9, 32.44, 32.41, 32.38, 32.35, 29.97, 21.2, 21.1, 21.06, 21.00, 18.9, 13.8; ^{31}P NMR (162 MHz, CDCl_3) δ : –6.33, –7.00; ESIHRMS calcd for $\text{C}_{26}\text{H}_{42}\text{N}_3\text{O}_{15}$ ($\text{M}+\text{Na}$) 690.2251, found 690.2228.

Dibutyl [methyl (7,8,9-tri-*O*-acetyl-4,5-*O*-carbonyl-3-deoxy-*D*-glycero- β -*D*-galacto-non-2-ulopyranosyl)onate] phosphate (12):

A solution of thiosialoside **2**² (58 mg, 0.09 mmol), dibutyl phosphoric acid (59 μ L, 0.29 mmol) and AW-MS300 (180 mg) in dry CH_2Cl_2 were stirred under argon for 1 h. The mixture was cooled to 0 °C, and NIS (23 mg, 0.1 mmol) and TfOH (0.7 μ L, 0.009 mmol in 50 μ L Et_2O) were added. The reaction was complete in 15 min and was quenched with Hunig's base (50 μ L). The molecular sieves were filtered off and reaction mixture was washed with sat. aqueous sodium thiosulfate and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a crude reaction mixture, which was purified by chromatography over silica gel eluting with 50% EtOAc in hexanes (R_f = 0.25, 20% EtOAc in toluene) to give phosphate **12** (48 mg, 78%), whose spectral data of the compound were consistent with the literature data.¹³ $[\alpha]_{\text{D}}^{23}$ –13.0 (c 1, CHCl_3). ^1H NMR (500 MHz, CDCl_3) δ : 5.47 (dd, J = 4.4, 2.8 Hz, 1H), 5.29 (dt, J = 4.4, 2.0 Hz, 1H), 4.68 (m, 1H), 4.40 (dd, J = 10, 2.5 Hz, 1H), 4.28 (dd, J = 10, 4.8 Hz, 1H), 4.12–4.05 (m, 5H), 3.85 (s, 3H), 2.91 (dd, J = 10, 3.2 Hz, 1H), 2.30 (dt, J = 10, 2.4 Hz, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 1.70–1.61 (m, 4H), 1.44–1.35 (m, 4H), 0.94 (t, J = 6 Hz, 1H) ^{13}C NMR (125 MHz, CDCl_3) δ : 171.8, 170.6, 169.5, 169.2, 167.2 (C-1, $^3J_{\text{C-H}}$ = 0 Hz), 152.9, 98.2 (d, $J_{\text{C-P}}$ = 6.3 Hz), 76.0, 73.9, 68.1, 68.0, 68.0, 67.9, 67.3, 61.2, 53.6, 53.5, 37.1, 37.1, 32.09, 32.06, 32.04, 32.0, 20.7, 20.7, 20.5, 18.6, 18.5, 13.5 ESIHRMS: m/z calcd. for $\text{C}_{25}\text{H}_{39}\text{NO}_{16}\text{PNa}$ [$\text{M} + \text{Na}$]⁺ 649.1873, found 649.1859.

Dibutyl [methyl (4,5,7,8,9-penta-O-acetyl-3-deoxy-D-glycero β -D-galacto-non-2-ulopyranosyl)onate] phosphate (13):

A solution of compound **4** (100 mg, 0.155 mmol), dibutyl phosphoric acid (92 L, 0.467 mmol) AW-MS300 (300 mg) in dry CH₂Cl₂ were stirred under argon for 1 h. The mixture was cooled to 0 °C, and NIS (36 mg, 0.163 mmol) and TfOH (1.2 μ L, 0.014 mmol in 50 μ L Et₂O) were added sequentially. The reaction was complete in 15 min and was quenched with Hunig's base (100 μ L). The molecular sieves were filtered off and reaction mixture was washed with sat. aqueous sodium thiosulfate and brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to give a crude reaction mixture, which was purified by chromatography over silica gel eluting with 50% EtOAc in toluene (*R*_f = 0.5, 1:1 EtOAc in toluene) to give phosphate **13** (77 mg, 72%), whose spectral data were consistent with the literature data.¹³ [α]_D²³ +63 (*c* 1, CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 5.43 (dd, *J* = 5.2, 2 Hz, 1H), 5.34 (dt, *J* = 11.2, 4.8 Hz, 1H), 5.29-5.26 (m, 1H), 4.95 (t, *J* = 10 Hz, 1H), 4.51 (dd, *J* = 13.2, 2 Hz, 1H), 4.45 (dd, *J* = 11.2, 2 Hz, 1H), 4.26-4.05 (m, 4H), 3.83 (s, 3H), 2.74 (dd, *J* = 13.2, 6.2 Hz, 1H), 2.10 (s, 3H), 2.07 (s, 3H), (s, 3H), 2.02 (s, 4H), 2.0 (s, 3H), 1.71-631.63 (m, 4H), 1.44-1.37 (m, 4H), 0.97 (dt, *J* = 7.2, Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 170.5, 170.0, 170.0, 169.8, 169.8, 165.8 (C-1, ³*J*_{C-H} = 0 Hz), 99.2 (d, *J*_{C-P} = 5.7 Hz), 77.2, 71.6, 70.5, 68.5, 68.4, 68.3, 68.3, 68.2, 67.2, 67.2, 62.2, 53.2, 36.8, 36.7, 3.1, 32.0, 20.8, 20.8, 20.7, 20.7, 20.6, 20.6, 18.6, 13.5. ESIHRMS: *m/z* calcd. for C₂₈H₄₅NO₁₇PNa [M + Na]⁺ 707.2292, found 707.2278.

General Procedure for O-glycosylation.

A mixture of donor (1 equiv), acceptor (1.2 equiv), and activated 4 Å acid-washed powdered molecular sieves (2 g/mmol of donor) in CH₂Cl₂ (0.1 molar) was stirred for 1 h at room temperature, was cooled to -78 °C, and treated with TMSOTf (1.6 equiv). The reaction mixture was stirred at -78 °C for 5 h and then quenched with triethylamine before it was diluted with CH₂Cl₂, filtered through Celite, washed with 20% aqueous Na₂S₂O₃, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with mixtures of EtOAc and hexane to afford the desired coupled products.

General Procedure for C-glycosylation.

A mixture of donor (1 equiv), allyltributylstannane (5.2 equiv), and activated 4 Å acid-washed powdered molecular sieves (2 g/mmol of donor) in CH₂Cl₂ (0.1 molar) was stirred for 1 h at room temperature, was cooled to -78 °C, and treated with TMSOTf (1.0 equiv). The reaction mixture was stirred at -78 °C for 5 h and then quenched with triethylamine. The mixture was diluted with CH₂Cl₂, filtered through Celite, washed with 20% aqueous Na₂S₂O₃, dried over Na₂SO₄, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with mixtures of EtOAc and hexane to afford the desired coupled products.

Methyl [methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-isothiocyanato-*D*-glycero- α -*D*-galacto-2-nonulopyranosyl)onate]-(2 $\rightarrow$ 6)-2,3,4-tri-*O*-benzyl- β -*D*-galactopyranoside (15):

Compound **15** was prepared according to the general *O*-glycosylation procedure using donor **10** (54.0 mg, 0.08 mmol) and acceptor **14** (43.0 mg, 0.09 mmol) in CH₂Cl₂ (1.0 mL) at -78 °C. After chromatographic purification (gradient elution of EtOAc and hexanes 3% to 30%; *R*_f = 0.46, 2:3 EtOAc in hexane) compound **15** (35.0 mg, 52%) was obtained as white foam with spectral data consistent with the literature data.⁹ [α]_D²³ -10.3 (*c* 1, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ : 7.35-7.22 (m, 15H), 5.45 (d, *J* = 9.2 Hz, 1H), 5.33 (m, 1H), 4.94 (d, *J* = 11.7 Hz, 1H), 4.92-4.89 (m, 1H), 4.87 (d, *J* = 11.0 Hz, 1H), 4.75-4.68 (m, 3H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.28-4.26 (m, 2H), 4.15 (dd, *J* = 12.8, 4.4 Hz, 1H), 4.01 (d, *J* = 10.6 Hz, 1H), 3.88- 3.85 (m, 1H), 3.82 (d, *J* = 2.6 Hz, 1H), 3.77 (t, *J* = 9.5 Hz, 1H), 3.63 (s, 3H), 3.58 (t, *J* = 10.3 Hz, 1H), 3.55 (s, 3H), 3.52-3.48 (m, 3H), 2.67 (dd, *J* = 13.2, 4.8 Hz, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 1.75 (t, *J* = 12.5 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ : 170.7, 169.6, 169.5, 169.4, 167.2, 140.2, 138.8, 138.5, 128.3, 128.2, 128.1, 128.0, 127.6, 127.5, 127.4, 127.3, 104.9, 98.5, 81.9, 79.5, 75.1, 74.2, 73.4, 72.9, 72.6, 71.8, 69.7, 67.9, 67.6, 63.0, 61.7, 57.0, 56.3, 52.9, 37.2, 20.9, 20.8, 20.7, 20.6; ESIHRMS calcd for C₄₇H₅₅O₁₇NSNa [M + Na]⁺ 960.3088, found 960.3089.

Methyl [methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-isothiocyanato-*D*-glycero- α -*D*-galacto-2-non-ulopyranosyl)onate]-(2 $\rightarrow$ 3)-2,6-di-*O*-benzyl- β -*D*-galactopyranoside (17):

Compound **17** was prepared according to the general *O*-glycosylation procedure using donor **10** (30 mg, 0.04 mmol) and acceptor **16** (19.7 mg, 0.05 mmol) in CH₂Cl₂ (0.7 mL) at -78 °C. After chromatographic purification (gradient elution of EtOAc /Hexanes 2% to 40%; *R*_f = 0.42, 1:1 EtOAc in hexane), compound **17** (16.0 mg, 43%) was obtained as a white foam, with spectral data consistent with the literature data.⁹ [α]_D²³ -11.9 (*c* 1.1, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ : 7.35-7.27 (m, 10H), 5.43 (d, *J* = 8.8 Hz, 1H), 5.38 (m, 1H), 4.91 (m, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 4.64 (d, *J* = 11.7 Hz, 1H), 4.58-4.56 (m, 1H), 4.32 (d, *J* = 7.7 Hz, 1H), 4.25 (dd, *J* = 2.2, 12.8 Hz, 1H), 4.04 (dd, *J* = 9.2, 4.7 Hz, 1H), 4.02 (d, *J* = 4.0 Hz, 1H), 3.97 (dd, *J* = 10.6, 1.5 Hz, 1H), 3.80 (s, 3H), 3.78 (d, *J* = 5.9 Hz, 1H), 3.75-3.71 (m, 2H), 3.59 (t, *J* = 5.9 Hz, 1H), 3.55 (m, 4H), 3.51-3.48 (m, 2H), 2.65 (dd, *J* = 4.8 Hz, 1H), 2.11 (s, 3H), 2.07 (s, 3H), 2.05 (s, 3H), 1.93 (s, 3H), 1.78 (t, *J* = 12.5 Hz, 1H); ¹³C NMR (151 MHz, CDCl₃) δ : 170.6, 169.8, 169.3, 169.2, 167.9 (³*J*_{C-H} = 7.5 Hz), 140.3, 138.9, 138.0, 128.36, 128.1, 127.7, 127.4, 104.6, 97.7, 77.3, 75.8, 74.8, 73.5, 72.6, 71.9, 69.7, 69.2, 68.2, 67.9, 67.6, 61.8, 56.9, 56.2, 53.2, 36.3, 29.5, 20.8, 20.7, 20.3; ESIHRMS calcd for C₄₀H₄₉O₁₇NSNa [M + Na]⁺ 870.2618, found 870.2619.

Methyl [methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-isothiocyanato-*D*-glycero- α -*D*-galacto-non-2-ulopyranosyl)onate]-(2 $\rightarrow$ 3)-2,4,6-tri-*O*-benzyl- β -*D*-galactopyranoside (19):

Compound **19** was prepared according to the general *O*-glycosylation procedure using donor **10** (32.5 mg, 0.5 mmol) and acceptor **18** (26.4 mg, 0.6 mmol) in CH₂Cl₂ (0.9 mL) at -78 °C. After chromatographic purification (gradient elution of EtOAc in hexanes 2% to 20%; *R*_f = 0.45, 2:3 EtOAc in hexane), compound **19** (16.0 mg, 55%) was obtained as a white foam, with spectral data consistent with the literature data.⁹ [α]_D²³ -23.0 (*c* 0.9, CHCl₃); ¹H NMR (600 MHz, CDCl₃) δ : 7.35-7.22 (m, 15H), 5.43-5.39 (m, 2H), 4.95 (dt, *J* = 10.3, 4.7

Hz, 1H), 4.84 (d, $J = 11.7$ Hz, 1H), 4.80 (d, $J = 11.4$ Hz, 1H), 4.64 (d, $J = 11.4$ Hz, 1H), 4.50 (d, $J = 11.7$ Hz, 1H), 4.44 (d, $J = 11.4$ Hz, 1H), 4.38 (d, $J = 11.7$ Hz, 1H), 4.30–4.26 (m, 2H), 3.99 (dd, $J = 12.8, 3.7$ Hz, 1H), 3.93 (dd, $J = 9.9, 2.9$ Hz, 1H), 3.85 (d, $J = 10.3$ Hz, 1H), 3.74 (s, 3H), 3.68 (d, $J = 2.6$ Hz, 1H), 3.67–3.57 (m, 3H), 3.54 (m, 4H), 3.50 (t, $J = 10.3$ Hz, 1H), 2.58 (dd, $J = 4.8, 13.6$ Hz, 1H), 2.13 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.90 (s, 3H), 1.85 (t, $J = 12.8$ Hz, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ : 170.6, 169.6, 169.3, 169.2, 167.5, 140.3, 139.0, 138.7, 137.9, 128.4, 128.1, 128.0, 127.8, 127.7, 127.6, 127.4, 127.2, 104.9, 98.77, 77.5, 76.3, 76.2, 74.8, 73.5, 73.0, 71.6, 69.9, 68.4, 68.0, 67.5, 61.5, 57.0, 56.3, 53.0, 35.5, 21.0, 20.8, 20.7, 20.3; ESIHRMS calcd for $\text{C}_{47}\text{H}_{55}\text{O}_{17}\text{NSNa}$ $[\text{M} + \text{Na}]^+$ 960.3088, found 960.3090.

Methyl [methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-isothiocyanato- α -D-glycero-D-galactono-2-ulopyranosyl)onate]-(2 $\rightarrow$ 9)-[(5-acetamido-2,4,7-tri-*O*-benzoyl-3,5-dideoxy- α -D-glycero-D-galactono-2-ulopyranosyl)onate] (21):

Compound **21** was prepared according to general *O*-glycosylation procedure using donor **10** (32.0 mg, 0.05 mmol) and acceptor **20** (35.7 mg, 0.06 mmol) in CH_2Cl_2 (1.0 mL) at -78°C . After chromatographic purification (gradient elution of EtOAc in Hexanes 5% to 70%; $R_f = 0.35$, 3:2 EtOAc in hexane) compound **21** (26.0 mg, 55%) was obtained as a white foam, with spectral data consistent with the literature data.⁹ $[\alpha]_{\text{D}}^{20} -10.6$ (c 0.5, CH_2Cl_2); ^1H NMR (600 MHz, CDCl_3) δ : 8.10 (dd, $J = 7.7, 3.7$ Hz, 4H), 7.95 (d, $J = 7.3$ Hz, 2H), 7.63 (t, $J = 7.3$ Hz, 1H), 7.57 (t, $J = 7.3$ Hz, 1H), 7.53–7.44 (m, 5H), 7.37 (t, $J = 7.7$ Hz, 2H), 5.73 (td, $J = 10.6, 4.7$ Hz, 1H), 5.60 (d, $J = 9.5$ Hz, 1H), 5.39 (m, 2H), 5.16 (m, 1H), 4.82 (td, $J = 9.9, 4.4$ Hz, 1H), 4.57 (dd, $J = 10.6, 1.5$ Hz, 1H), 4.26 (m, 2H), 4.10 (dd, $J = 12.5, 2.2$ Hz, 1H), 4.00 (dd, $J = 10.6, 1.5$ Hz, 1H), 3.92 (dd, $J = 12.8, 2.2$ Hz, 1H), 3.83 (s, 3H), 3.68 (m, 4H), 3.46 (m, 2H), 2.88 (dd, $J = 13.2, 5.1$ Hz, 1H), 2.49 (dd, $J = 13.2, 4.7$ Hz, 1H), 2.17 (t, $J = 11.4$ Hz, 1H), 2.09 (s, 3H), 2.07 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.84 (s, 3H), 1.57 (t, $J = 12.8$ Hz, 1H); ^{13}C NMR (151 MHz, CDCl_3) δ : 170.8, 170.1, 169.8, 169.5, 169.4, 169.3, 167.4, 166.3, 165.4, 164.6, 139.9, 134.0, 133.4, 133.1, 130.0, 130.0, 129.8, 129.2, 128.7, 128.8, 128.8, 98.54, 97.8, 71.9, 69.6, 69.5, 69.5, 68.3, 67.9, 67.8, 66.9, 61.7, 60.0, 56.2, 53.2, 52.9, 49.3, 37.1, 36.7, 29.6, 23.2, 21.0, 20.8, 20.4; ESIHRMS calcd for $\text{C}_{52}\text{H}_{56}\text{O}_{23}\text{N}_2\text{SNa}$ $[\text{M} + \text{Na}]^+$ 1131.2860, found 1131.2892.

Methyl [Methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-azido-D-glycero- α -D-galactono-2-ulopyranosyl)onate]-(2 $\rightarrow$ 6)-2,3,4-tri-*O*-benzyl- β -D-galactopyranoside (22).¹⁰

Compound **22** was prepared according to the general *O*-glycosylation procedure using donor **11** (100 mg, 0.15 mmol) and acceptor **14** (83.5 mg, 0.18 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 5 h, the reaction mixture was allowed to warm to -60°C over 1.5 h before quenching with triethylamine (50 μL). After chromatographic purification on silica gel (gradient elution of EtOAc in hexanes 10 to 40%, $R_f = 0.45$, 45% EtOAc: hexanes), compound **22** (109 mg, 79%) was obtained as a white foam, with spectral data consistent with the literature data.¹⁰ $[\alpha]_{\text{D}}^{21} -10.0$ (c 1.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.39 – 7.20 (m, 15H), 5.49 (dd, $J = 9.0, 1.6$ Hz, 1H), 5.35 (ddd, $J = 9.1, 4.4, 2.4$ Hz, 1H), 4.95 (d, $J = 11.4$ Hz, 1H), 4.88 (d, $J = 10.9$ Hz, 1H), 4.82 (ddd, $J = 11.9, 9.7, 4.9$ Hz, 1H), 4.78 – 4.68 (m, 3H), 4.66 (t, $J = 11.5$ Hz, 1H), 4.33 – 4.26 (m, 2H), 4.18 (dd, $J = 12.6, 4.4$ Hz, 1H), 3.89 (dd, $J = 8.5, 5.3$ Hz, 1H), 3.85 (d, $J = 2.9$ Hz, 1H), 3.82 – 3.76 (m, 2H), 3.62 (s, 3H), 3.56 (s,

3H), 3.55 – 3.44 (m, 3H), 3.23 (dd, $J = 10.7, 9.7$ Hz, 1H), 2.71 (dd, $J = 12.8, 4.9$ Hz, 1H), 2.15 (s, 3H), 2.13 (s, 3H), 2.11 (s, 3H), 2.05 (s, 3H), 1.76 (t, $J = 12.4$ Hz, 1H). ^{13}C NMR (101 MHz, CDCl_3) δ 170.7, 169.8, 169.7, 169.6, 167.4, 138.8, 138.5, 128.3, 128.3, 128.1, 128.1, 127.7, 127.5, 127.4, 127.3, 104.9, 98.4, 82.0, 79.5, 75.1, 74.3, 73.3, 72.9, 72.6, 71.6, 71.1, 68.0, 67.8, 62.9, 61.8, 59.9, 57.1, 52.9, 37.3, 21.0, 20.9, 20.7, 1.0.; ESI-HRMS $\text{C}_{46}\text{H}_{55}\text{N}_3\text{NaO}_{17}$ $[\text{M} + \text{Na}]^+$ m/z 944.3429, found 944.3420.

Methyl [Methyl (4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-5-azido-*D*-glycero- α -*D*-galactono-2-ulopyranosyl)onate]-(2 $\rightarrow$ 3)-2,4,6-tri-*O*-benzyl- β -*D*-galactopyranoside (23).

Compound **23** was prepared according to the *O*-general glycosylation procedure using donor **11** (100 mg, 0.15 mmol) and acceptor **18** (83.5 mg, 0.18 mmol) in CH_2Cl_2 (1.5 mL). After stirring for 5 h, the reaction mixture was allowed to warm to -40°C , over 1.5 h before quenching with triethylamine (50 μL). After chromatographic purification on silica gel (gradient elution of EtOAc in hexanes 10 to 40%, $R_f = 0.5$, 40% EtOAc: hexanes), compound **23** (98 mg, 71%) was obtained as a white foam, with spectral data consistent with the literature data.¹⁰ $[\alpha]_{\text{D}}^{21} -17.8$ (c 1.0, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ 7.53 – 6.93 (m, 15H), 5.47 (dd, $J = 9.4, 1.2$ Hz, 1H), 5.39 (td, $J = 9.4, 2.4$ Hz, 1H), 4.95 – 4.88 (m, 2H), 4.80 (d, $J = 11.2$ Hz, 1H), 4.65 (d, $J = 11.2$ Hz, 1H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.42 (d, $J = 11.5$ Hz, 1H), 4.39 (d, $J = 11.6$ Hz, 1H), 4.32 (dd, $J = 4.8, 2.6$ Hz, 1H), 4.30 (d, $J = 2.1$ Hz, 1H), 4.01 (d, $J = 4.2$ Hz, 1H), 3.99 (d, $J = 4.2$ Hz, 1H), 3.96 – 3.94 (m, 2H), 3.72 (s, 3H), 3.62–3.59 (m, 4H), 3.53 (s, 3H), 3.50 (d, $J = 3.9$ Hz, 1H), 3.14 (t, $J = 10.2$ Hz, 1H), 2.63 (dd, $J = 13.4, 4.8$ Hz, 1H), 2.10 (s, 3H), 2.04 (s, 3H), 2.00 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (151 MHz, CDCl_3) δ 170.5, 169.5, 169.4, 167.6, 139.1, 138.8, 138.0, 128.3, 128.1, 128.0, 127.8, 127.7, 127.7, 127.4, 127.1, 104.9, 98.8, 77.5, 76.3, 76.2, 74.9, 74.8, 73.5, 73.1, 71.4, 71.2, 68.5, 68.2, 67.7, 61.6, 59.8, 57.1, 52.9, 41.7, 35.9, 35.4, 29.4, 28.5, 21.0, 20.8, 20.7, 20.4; ESI-HRMS $\text{C}_{46}\text{H}_{55}\text{N}_3\text{NaO}_{17}$ $[\text{M} + \text{Na}]^+$ m/z 944.3429, found 944.3435.

Methyl 2-*C*-allyl-7,8,9-tri-*O*-acetyl-4,5-*O*-carbonyl-3-deoxy-2,6-anhydro-*D*-glycero- α -*D*-galactono-2-ulopyranoside (24).

Compounds **24** was prepared according to the general *C*-glycosylation procedure using donor **12** (40 mg, 0.06 mmol), allyltributylstannane (106 μL , 0.32 mmol), AW 4Å MS (80 mg), and TMSOTf (12 μL , 0.06 mmol). After being stirred at the -78°C for 5 h, the reaction mixture was quenched with triethylamine (100 μL) at -40°C . Purification of the residue by flash chromatography (25% ethyl acetate in hexanes, $R_f = 0.3$, 40% EtOAc: hexanes) afforded compound **24** (22 mg, 74%) as a colorless oil. $[\alpha]_{\text{D}}^{24} +11.5$ (c 0.2, CHCl_3), ^1H NMR (600 MHz, CDCl_3) δ 5.75 – 5.67 (m, 1H), 5.43 (dd, $J = 7.7, 2.8$ Hz, 1H), 5.38 – 5.33 (m, 1H), 5.16 – 5.07 (m, 2H), 4.39 – 4.31 (m, 2H, H-6), 4.19 (dd, $J = 12.6, 5.1$ Hz, 1H), 4.12 (ddd, $J = 12.7, 10.9, 3.9$ Hz, 1H), 3.84 (dd, $J = 9.9$ Hz, 1H), 3.73 (s, 3H), 2.83 (dd, $J = 12.1, 3.9$ Hz, 1H), 2.56 – 2.46 (m, 2H), 2.13 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.05 – 2.02 (m, 1H)., ^{13}C NMR (151 MHz, CDCl_3) δ 171.1, 170.7, 169.9, 169.1, 153.2, 130.6, 120.0, 81.3, 78.5, 77.4, 72.9, 68.3, 68.1, 61.7, 52.8, 36.4, 21.0, 20.7, 20.6., ESIHRMS Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}_{12}\text{Na}$ $[\text{M} + \text{Na}]^+$, 481.1322; found 481.1333

Methyl 2-*C*-allyl-4,5,7,8,9-penta-*O*-acetyl-2,6-anhydro-3-deoxy-*D*-glycero- α/β -*D*-galactononate (25 α /25 β).

Compounds **25 α /25 β** were prepared according to the general *C*-glycosylation procedure from donor **13** (34 mg, 0.05 mmol), allyltributylstannane (80 μ L, 0.26 mmol), acid washed 4Å MS (70 mg) in dry DCM (0.5 mL), and TMSOTf (10 μ L, 0.05 mmol). After being stirred at the same temperature for 5 h the reaction mixture was quenched with triethylamine (100 μ L). The residue was purified by flash chromatography (gradient elution of EtOAc 10% to 300% in hexane) to obtain compound **25 α** (14 mg, 52%) and **25 β** (7 mg, 26%) as colorless oils. **Compound 25 α** : *R*_f = 0.24, 30% EtOAc: hexanes; $[\alpha]^{24}_{\text{D}} -13.6$ (*c* 0.5, CHCl₃), ¹H NMR (600 MHz, CDCl₃) δ 5.78 – 5.69 (m, 1H), 5.39 (ddd, *J* = 8.1, 5.4, 2.5 Hz, 1H), 5.33 (dd, *J* = 7.9, 2.2 Hz, 1H), 5.16 – 5.01 (m, 2H), 4.91 (ddd, *J* = 12.0, 9.5, 4.9 Hz, 1H), 4.79 (app. t, *J* = 9.9 Hz, 1H), 4.36 (dd, *J* = 12.5, 2.5 Hz, 1H), 4.16 (dd, *J* = 12.5, 5.3 Hz, 1H), 4.07 (dd, *J* = 10.2, 2.2 Hz, 1H), 3.74 (s, 3H), 2.56 (dd, *J* = 13.1, 4.9 Hz, 1H), 2.46 (d, *J* = 7.3 Hz, 2H), 2.14 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.00 (s, 6H), 1.74 (app. t, *J* = 12.5 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 171.2, 170.7, 170.1, 170.01, 169.99, 169.9, 131.1, 119.3, 80.2, 72.0, 70.3, 68.8, 68.3, 67.1, 62.1, 52.3, 44.0, 36.7, 21.1, 20.9, 20.74, 20.69, 20.6., ESIHRMS Calcd. for C₂₃H₃₂O₁₃Na [M + Na]⁺, 539.1741; found 539.1761

Compound 25 β :

*R*_f = 0.25, 30% EtOAc: hexanes; $[\alpha]^{24}_{\text{D}} +9.5$ (*c* 0.2, CHCl₃), ¹H NMR (600 MHz, CDCl₃) δ 5.66 – 5.53 (m, 1H), 5.35 (dd, *J* = 4.5, 2.3 Hz, 1H), 5.23 – 5.11 (m, 4H), 4.84 (app. t, *J* = 9.8 Hz, 1H), 4.69 (dd, *J* = 12.4, 2.4 Hz, 1H), 4.19 – 4.11 (m, 1H), 3.98 (dd, *J* = 2.4 Hz, 1H), 3.73 (s, 3H), 2.76 (dd, *J* = 14.8, 7.6 Hz, 1H), 2.62 (dd, *J* = 14.6, 6.7 Hz, 1H), 2.36 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.09 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.90 (dd, *J* = 13.5, 11.5 Hz, 1H). ¹³C NMR (151 MHz, CDCl₃) δ 171.1, 170.5, 170.3, 170.2, 170.1, 169.8, 130.6, 119.7, 79.1, 71.6, 70.7, 69.6, 68.2, 68.0, 62.3, 52.5, 36.6, 35.2, 21.0, 20.9, 20.74, 20.65, 20.6., ESIHRMS Calcd. for C₂₃H₃₂O₁₃Na [M + Na]⁺, 539.1741; found 539.1738

Methyl 2-*C*-allyl-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-5-isothiocyanato-*D*-glycero- α/β -*D*-galactononate (26 α /26 β).

Compounds **26 α /26 β** were prepared according to the general *C*-glycosylation procedure from donor **10** (162 mg, 0.24 mmol), allyltributylstannane (400 μ L, 1.30 mmol) in CH₂Cl₂ (2 mL). Purification on a silica cartridge by HPLC (gradient elution of EtOAc 10% to 50% in hexane), gave **26 α** (50mg, 10 mmol, 41%), **26 β** (23 mg, 0.04 mmol, 19%) along with elimination product **27** (22 mg, 0.05 mmol, 19%). **Compound 26 α** : *R*_f = 0.46, 25% EtOAc in toluene; Yellowish-brown oil, $[\alpha]^{21}_{\text{D}} -40.0$ (*c* 0.03, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ : 5.75 (ddt, *J* = 17.3, 10.2, 7.2 Hz, 1H), 5.45 (dd, *J* = 8.5, 1.6 Hz, 1H), 5.36 (ddd, *J* = 8.5, 4.5, 2.4 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 5.05 (dd, *J* = 17.1, 1.6 Hz, 1H), 4.93 (ddd, *J* = 11.8, 10.0, 4.7 Hz, 1H), 4.35 (dd, *J* = 2.3 Hz, 1H), 4.20 (dd, *J* = 12.6, 4.5 Hz, 1H), 3.98 (dd, *J* = 10.5, 1.6 Hz, 1H), 3.74 (s, 3H), 3.5 (t, *J* = 10.2 Hz, 1H), 2.58 (dd, *J* = 13.1, 4.7 Hz, 1H), 2.43 (d, *J* = 7.1 Hz, 2H), 2.15 (br s, 6H), 2.11 (s, 3H), 2.07 (s, 3H), 1.56 (t, *J* = 12.9 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ : 169.9, 169.1, 168.8, 168.6, 138.6, 129.9, 118.7, 79.2, 71.4, 69.8, 67.6, 67.2, 60.9, 56.1, 51.7, 43.0, 35.8, 20.2, 20.1, 19.96, 19.8; ESIHRMS calcd for C₂₂H₂₉NO₁₁S [M+Na] 538.1359, found 538.1353.

Compound 26 β :

R_f = 0.46, 25% EtOAc in toluene; Yellowish-brown oil $[\alpha]^{21}_D$ -23.2 (c 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 5.53 – 5.60 (m, 1 H), 5.47 (dd, J = 5.7, 1.7 Hz, 1 H), 5.25 (td, J = 5.8, 2.3 Hz, 1 H), 5.22 – 5.12 (m, 3 H), 4.58 (dd, J = 12.5, 2.3 Hz, 1 H), 4.19 (dd, J = 12.6, 6.0 Hz, 1 H), 3.83 (dd, J = 10.3, 1.8 Hz, 1 H), 3.74 (s, 3 H), 3.60 (t, J = 10.1 Hz, 1 H), 2.68 (ddd, J = 43.1, 14.8, 7.0 Hz, 1 H), 2.40 (dd, J = 13.5, 4.8 Hz, 1 H), 2.17 (s, 3 H), 2.12 (s, 3 H), 2.09 (s, 3 H), 2.06 (s, 3 H), 1.76 (dd, J = 13.3, 11.8, 2 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 171.1, 171.0, 170.4, 170.2, 169.9, 140.6, 130.5, 120.3, 79.6, 71.3, 71.0, 70.4, 69.3, 62.3, 57.3, 52.9, 36.6, 35.4, 21.4, 21.3, 21.1, 21.0; ESIHRMS calcd for $\text{C}_{22}\text{H}_{29}\text{NO}_{11}\text{S}$ $[\text{M} + \text{Na}]^+$ 538.1359, found 538.1344.

Methyl 5-isothiocyanato-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-D-glycero-D-galacto-non-2-enonate (27).

$[\alpha]^{21}_D$ 15.2 (c 0.5, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 5.97 (d, J = 2.6 Hz, 1H), 5.65 (dd, J = 7.8, 2.5 Hz, 1H), 5.58 (dd, J = 6.2, 2.5 Hz, 1H), 5.36 (td, J = 6.0, 3.1 Hz, 1H), 4.51 (dd, J = 12.5, 2.7 Hz, 1H), 4.25 (dd, J = 9.8, 2.4 Hz, 1H), 4.18 (dd, J = 5.6 Hz, 1H), 4.04 (dd, J = 9.5, 8.2 Hz, 1H), 3.80 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ : 169.8, 169.1, 168.8, 168.4, 160.2, 144.1, 140.7, 106.3, 74.7, 68.7, 68.6, 66.9, 60.8, 53.4, 51.9, 28.9, 20.0, 19.9, 19.7; ESIHRMS calcd for $\text{C}_{19}\text{H}_{23}\text{NO}_{11}\text{S}$ $[\text{M} + \text{Na}]^+$ 496.0890, found 496.0880.

Methyl 2-C-allyl-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-5-azido-D-glycero- α/β -D-galacto-nononate (28 α /28 β).

Compounds **28 α /28 β** were prepared according to the general *C*-glycosylation procedure from donor **11** (85 mg, 0.13 mmol) and allyltributylstannane (210 μL , 0.68 mmol) in CH_2Cl_2 (2.5 mL). Purification on a silica cartridge by HPLC (gradient elution of EtOAc 10% to 50% in hexane), gave **28 α** (28 mg, 0.06 mmol, 44%), **28 β** (14.5 mg, 0.03 mmol, 23%) along with elimination byproduct **29** (5.5 mg, 0.01 mmol, 9%) as yellow-brownish oils. **Compound 28 α** . R_f = 0.51, 25% EtOAc in toluene; $[\alpha]^{21}_D$ = -32.0 (c 0.03, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 5.75 – 5.68 (m, 1H), 5.48 (dd, J = 8.4, 1.5 Hz, 1 H), 5.36 (dd, J = 6.5, 4.1 Hz, 1 H), 5.10 (d, J = 9.5 Hz, 1H) (d, J = 17.1 Hz, 1H), 4.83 (dt, J = 11.9, 5.8 Hz, 1 H), 4.37 (dd, J = 12.6, 2.2 Hz, 1 H), 4.22 (dd, J = 12.6, 4.6 Hz, 1 H), 3.72 (s, 3 H), 3.15 (t, J = 10.1 Hz, 1 H), 2.59 (dd, J = 12.8, Hz, 1 H), 2.43 (d, J = 6.4 Hz, 2 H), 2.17 (s, 3 H), 2.13 (s, 3 H), 2.10 (s, 3 H), 2.06 (s, 3 H), 1.57 (t, J = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 171.3, 171.0, 170.1, 169.9, 169.8, 119.5, 80.1, 72.1, 68.8, 68.5, 62.1, 60.6, 52.5, 44.1, 36.7, 21.2, 21.1, 21.0, 20.9; ESIHRMS calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_{11}$ $[\text{M} + \text{Na}]^+$ 522.1700, found 522.1695.

Compound 28 β .

R_f = 0.56, 25% EtOAc in toluene; $[\alpha]^{21}_D$ = -86.6 (c 0.03, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ : 5.62 – 5.56 (m, 1H), 5.49 (dd, J = 5.7, 1.5 Hz, 1H), 5.21 (td, J = 5.9, 2.2 Hz, 1H), 5.14 – 5.07 (m, 3H), 4.59 (dd, J = 12.6, 2.2 Hz, 1H), 4.18 (dd, J = 12.6, 6.0 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, J = 10.5, 1.5 Hz, 1H), 3.20 (t, J = 10.1 Hz, 1H), 2.67 (dd, J = 14.7, 7.1 Hz, 1H), 2.57 (dd, J = 14.7, 6.9 Hz, 1H), 2.39 (dd, J = 13.3, 4.9 Hz, 1H), 2.16 (s, 3H), 2.08 (s,

3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.74 (t, $J = 12.6$ Hz, 1H); ^{13}C NMR (150 MHz, CDCl_3) δ : 171.0, 170.4, 170.3, 170.2, 130.8, 120.1, 79.5, 71.6, 71.2, 71.0, 69.5, 62.4, 60.8, 36.7, 35.3, 21.4, 21.3, 21.1, 21.1; ESIHRMS calcd for $\text{C}_{21}\text{H}_{29}\text{N}_3\text{O}_{11}$ $[\text{M} + \text{Na}]^+$ 522.1700, found 522.1718.

Methyl 4,7,8,9-tetra-O-acetyl-2,6-anhydro-5-azido-3,5-dideoxy-D-glycero-D-galacto-non-2-enonate (29).

$[\alpha]_D^{21}$ 43.8 (c 2.0, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ : 5.94 (s, 1H), 5.56 (dd, $J = 17.4$, 6.7 Hz, 2H), 5.34 (s, 1H), 4.53 (d, $J = 12.5$ Hz, 1H), 4.18 (dd, $J = 12.5$, 5.4 Hz, 1H), 4.04 (d, $J = 10.4$ Hz, 1H), 3.77 (s, 3H), 3.65 (t, $J = 9.1$ Hz, 1H), 2.16 (s, 3H), 2.12 (s, 3H), 2.05 (br s, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ : 170.7, 170.2, 169.8, 169.6, 161.4, 145.0, 107.4, 75.4, 70.4, 69.96, 68.1, 61.9, 57.3, 52.7, 20.98, 20.96, 20.86, 20.7; ESIHRMS calcd for $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_{11}$ $[\text{M} + \text{Na}]$ 480.1230, found 480.1232.

Methyl 2-C-allyl-4,7,8,9-tetra-O-acetyl-2,6-anhydro-3,5-dideoxy-5-N-acetamido-D-glycero- α -D-galacto-nononate (30).

From Isothiocyanate 26a.—To a solution of **26a** (22 mg, 43 μmol) in dry THF (150 μL) were added thioacetic acid (8 μL , 112 μmol), potassium *tert*-butoxide (2 mg, 18 μmol) and 18-crown-6 (4 mg, 15 μmol). The mixture was stirred for 4 h at 70 $^\circ\text{C}$. The reaction mixture diluted with EtOAc (1 mL) and washed with saturated aq. NaHCO_3 , and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. After chromatographic purification (gradient elution of hexane 10% to 50% in EtOAc, $R_f = 0.55$, 50% EtOAc in hexanes) compound **30** (15 mg, 29 μmol , 68%) was obtained as a brown oil, with spectral data consistent with the literature.^{9,22} $[\alpha]_D^{21}$ -27.5 (c 0.04, CHCl_3); ^1H NMR (600 MHz, CDCl_3) δ : 5.74 (ddt, $J = 17.2$, 10.1, 7.2 Hz, 1H), 5.38 – 5.27 (m, 2H), 5.12 (d, $J = 9.5$ Hz, 1H), 5.08 (dd, $J = 4.6$, 1.5 Hz, 1H), 5.03 (d, $J = 1.3$ Hz, 1H), 4.83 (ddd, $J = 11.9$, 9.7, 4.6 Hz, 1H), 4.40 (dd, $J = 12.4$, 2.4 Hz, 1H), 4.14 – 4.08 (m, 1H), 4.02 (d, $J = 10.0$ Hz, 1H), 3.99 (d, $J = 1.9$ Hz, 1H), 3.73 (s, 3H), 2.58 – 2.42 (m, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.87 (s, 3H), 1.79 (t, $J = 12.5$ Hz, 1H); ESIHRMS calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_{12}$ $[\text{M} + \text{Na}]^+$ 538.1900, found 538.1890.

From azide 28a.—To a solution of **28a** (27 mg, 54 μmol) in dry toluene (150 μL) were added 1M trimethylphosphine in toluene (160 μL , 160 μmol), 2,2'-dipyridyl disulfide (2.6 mg, 12 μmol) and acetic acid (5 μL , 83 μmol) at 0 $^\circ\text{C}$. The reaction mixture was stirred for 6 h before acetyl chloride (50 μL , 700 μmol) was added. The reaction mixture diluted with EtOAc (1 mL) and washed with saturated aq. NaHCO_3 , and brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. After chromatographic purification (gradient elution of EtOAc/hexane 10% to 50%), compound **30** (5 mg, 10 μmol , 18%) was obtained as a brown oil with physical characteristics consistent with those of the above sample.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Neuraminic acid dibutylphosphates with C5-NCS and C5-N₃ groups offer excellent α -selectivity for *O*-glycosylation
- Neuraminic acid dibutylphosphates with C5-NCS and C5-N₃ groups are not selective for *C*-glycosylation with allyltributylstannane
- KDN dibutylphosphates with a 4,5-carbonyl group offer highly α selective *C*-glycosylation with allyltributylstannane
- Peracetyl-KDN dibutylphosphates generate mixture of *C*-glycosides with allyltributylstannane acceptor

Scheme 1.
Preparation of Ulosonic Acid Dibutylphosphates.

Scheme 2. Chemical Correlation of **26α** and **28α** with Acetamide **30**.

Table 1.

O-Glycosylation Reactions.^a

	Donor	Acceptor	Product % yield, ^b α:β ratio
1			15, 52%, α-only
2	10		17, 43%, α-only
3	10		19, 55%, α-only
4	10		21, 55%, α-only
5 ^c			22, 79%, α-only
6 ^c	11		23, 71%, α-only

^aExcess TMSOTf (1.6 equiv) was used to drive the reaction to completion as the longer reaction times needed with catalytic TMSOTf resulted in formation of the glycal.

^bThe modest yields of the reaction are due to competing elimination to the glycal.

^cReaction was quenched at -60 °C.

Table 2.

C-Glycosylation Reactions with Allyltributylstannane.

	Donor	Product % yield, α : β ratio	
1 ^a	12	24 , 74%, α -only	
2	13	25 , 52% α , + 26% β	
3	10	26 , 41% α + 19% β	27 , 19%
4	11	28 , 44% α + 23% β	29 , 9%

^aReaction was quenched at -40°C .