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FULL PAPER

A General Method for the Divergent Synthesis of C-9 Functionalised Sialic Acid Derivatives

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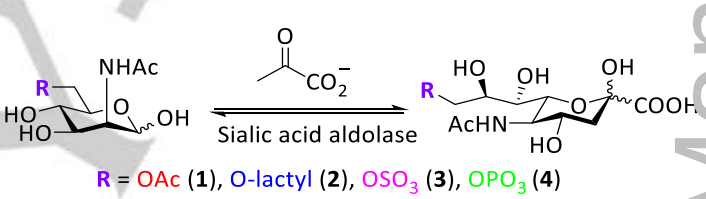
Abstract: Sialic acids, a ubiquitous family of sugars shown to be involved in numerous biologically important processes, exhibit remarkable structural diversity in nature. Access to these derivatives by chemical and enzymatic means is a major bottle neck in understanding the role played by each particular modification. As part of a program to study such roles and determine the substrate specificity of novel sialic acid aldolases, a general and robust synthetic protocol was devised to gain access to all naturally occurring C-9 functionalised *N*-acetylneuraminic acid derivatives including esters. These derivatives were synthesised in 11 linear steps from a common advanced intermediate, which allowed for divergent modification at the C-9 position. Four substitutions were installed in this study: O-acetyl, O-lactyl, O-SO_3, O-PO_3. This synthetic pathway includes both an effective way to benzylate neuraminic acid derivatives, as well as a working methodology towards unnatural β-linked neuraminic acid glycosides.

Introduction

Sialic acids are a family of nonulosonic acids that occur as terminal glycans in a large variety of glycoproteins and glycolipids.[1] Due to their peripheral location, in conjunction with their negative charge at physiological pH, sialic acids have regulatory and protective properties through their interactions with carbohydrate binding proteins.[2] This implicates them in numerous biologically important processes such as cellular recognition, adhesion and signalling phenomena.[3],[4] *N*-acetylneuraminic acid (Neu5Ac), the most abundant form of sialic acid found in mammalian cells, also exhibits remarkable structural diversity, with more than 50 different derivatives identified in nature.[5],[6] These structural variations can occur as a variety of *O*-substitutions (acetylation, lactylation, sulfation & methylation) at C-4,C-7,C-8 and C-9, or as *N*-substitutions at C-5. With a notable exception to the highly studied acetylated C-9 Neu5Ac derivatives,[7] the exact biological significance of the remaining derivatives is poorly understood; mostly due to limited access to these compounds. As the modification at the C-9 position of Neu5Ac has been shown to modulate a range of biological processes,[4] a robust and reliable protocol to functionalise the C-9 position of Neu5Ac is described in this report.

Originally in our research group, the corresponding C-6 functionalised *N*-acetylmannosamine (ManNAc) biosynthetic precursors were prepared as part of a program to study the substrate specificity of novel sialic acid aldolases isolated by biological collaborators. Sialic acid aldolases (also referred to as *N*-acetylneuraminate lyases) are a group of enzymes that catalyse the reversible aldol condensation of appropriately modified ManNAc precursors and pyruvate to generate the corresponding neuraminic acid derivatives (**Scheme 1**)[8],[9] Subsequently, we discovered there was a need for an efficient synthetic protocol to access these important class of sialic acid derivatives.



R = OAc (**1**), O-lactyl (**2**), OSO_3 (**3**), OPO_3 (**4**)

Scheme 1: Chemoenzymatic synthesis of C-9 functionalised Neu5Ac derivatives

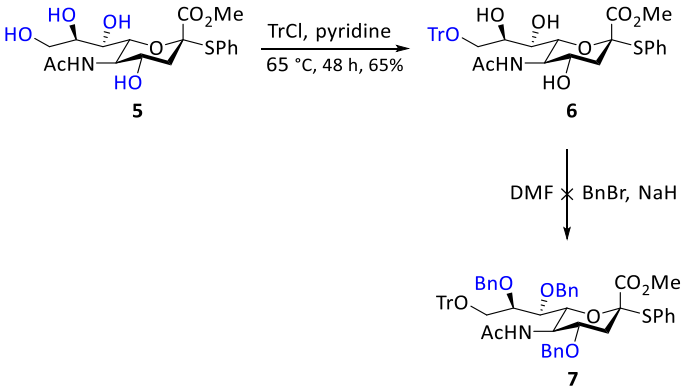
Although there are a few chemoenzymatic & chemical syntheses of C-9 analogues of Neu5Ac reported in literature,[10],[11],[12] there is no general synthetic route for the preparation of C-9 modified Neu5Ac derivatives that tolerate a diverse range of functionality (ethers, esters, phosphates & sulfates etc). It should be noted that regioselective introduction of our desired functionalities at C-9 was troublesome due to the known high reactivity of the C-4 hydroxy group of Neu5Ac leading to di- and poly-functionalised derivatives.[11],[13],[14] Our synthetic route facilitates the use of benzyl ether protecting groups, which are typically not tolerated in nonulosonic acids due to the presence of the carboxylic acid moiety and 3-deoxy methylene group; resulting in the competing elimination side reaction, lactamisation, ring contraction products and other indistinguishable side products.[15],[16] Once introduced the benzyl groups are excellent protecting groups due to their stability but also their mild removal under neutral- or slightly acidic conditions allowing almost any substituent in the target structure, especially ester groups where known C-9 to C-7 acyl migration can be prevented during deprotection.

In order to utilise these C-9 modified derivatives in the retro-aldol condensation reaction and obtain synthetic pure model compounds to further elucidate their biologically significance, we embarked on their divergent synthesis.

Results and Discussion

Initially, it was envisaged that we could gain access to C-9 derivatised neuraminic acid analogues by regioselectively

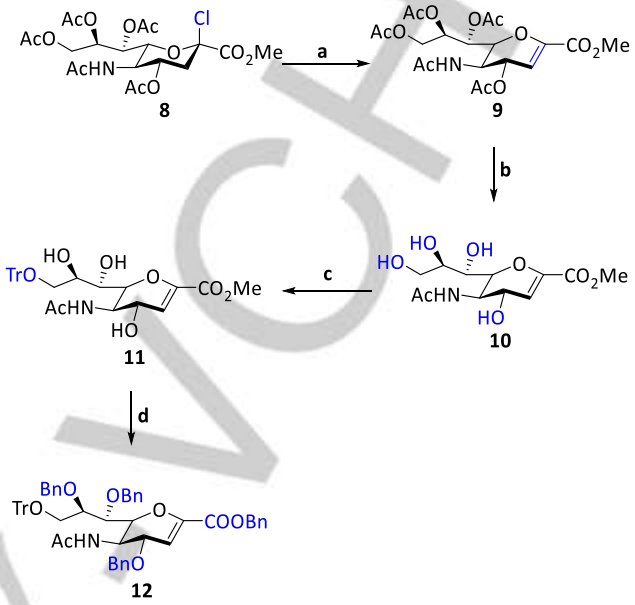
protecting the primary C-9 alcohol of a Neu5Ac thiophenol derivative, followed by global benzylation of the remaining hydroxy moieties (**Scheme 2)**. With this synthetic strategy, we planned to orthogonally mask our anomeric position with a stable thiophenol functionality and hence the known compound **5**[16] was prepared and tritylated to give **6**. However, subsequent benzylation of the triol **6** proved to be non-trivial.



Scheme 2: Failed synthetic sequence

Although there are a handful reported cases of benzylated neuraminic acid derivatives (albeit in low yield) mainly by Sharma and others, we found this reaction to be quite difficult (See SI for detailed benzylations attempts).[17],[18] One of the reasons for this difficulty can be attributed to the unique structural features of neuraminic acid namely, the electron withdrawing nature of the carboxylic acid moiety and the presence of the acidic 3-deoxy methylene protons. [19],[20] This led us to explore several benzylation methods using a variety of bases, acids, benzylating reagents and solvents. We found that strong bases, such as NaH, as expected resulted in a complex mixture of products (elimination, partial *O*- and *N*-benzylation, lactamisation, ring contraction amongst other indistinguishable products). When we switched to relatively milder bases, the desired per-benzylated compound **7** was not formed, instead partial benzylation with minor elimination product was observed when using $Ba(OH)_2$, while no progression of the reaction was detected with Ag_2CO_3, even at elevated temperatures. We then switched to acidic conditions using benzyl trichloroacetimidate and triflic acid in CH_2Cl_2,[21] the results were wistfully similar to their base mediated counterparts in addition to the observance of the trityl ether cleavage.

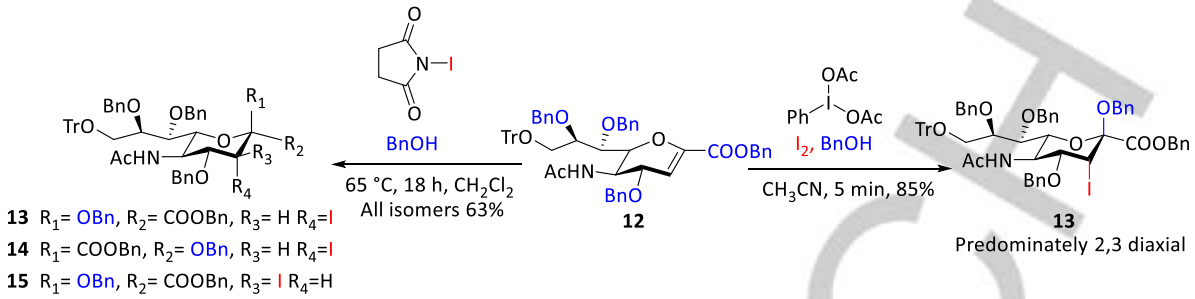
With these results, and inspired by work on Kdo (keto-3-deoxy-α-D-manno-oct-2-ulosonic acid) glycals by Kosma and our own group,[22],[23] we decided to revise our synthetic plan to incorporate the main competing elimination product into our synthetic sequence. Accordingly, per-acetylated glycal **9** was prepared by elimination of chloride **8** in a 91% yield (**Scheme 3**).[24] De-esterfication using freshly prepared 1 M sodium methoxide solution furnished 4,7,8,9-tetrahydroxy neuraminic acid glycal **10**. The alkaline solution was subsequently stirred with an acidic resin overnight to restore the methyl ester functionality. Complementary to our previous synthetic endeavour (**Scheme 2**), the primary alcohol at C-9 was temporarily masked as a trityl ether (**11**, 68%), followed by subsequent benzylation of the triol hydroxy moieties and transesterification to give benzyl ester **12** in 75% yield. The concomitant formation of the benzyl ester was beneficial to our synthesis as it facilitated a single global debenzylation step as opposed to an additional methyl hydrolysis step, which does not allow C-9 ester functionalities in our final target structures.



Scheme 3: Reagents & Conditions; (a) Et_3N, CH_2Cl_2, rt, 91%, (b) NaOMe, MeOH, rt, 9 h (c) TrCl, pyridine, 60 °C, 48 h, 68% (d) BnBr, $Ba(OH)_2{\cdot}8H_2O$, BaO, DMF, 0 °C – rt, 16 h, 75%.

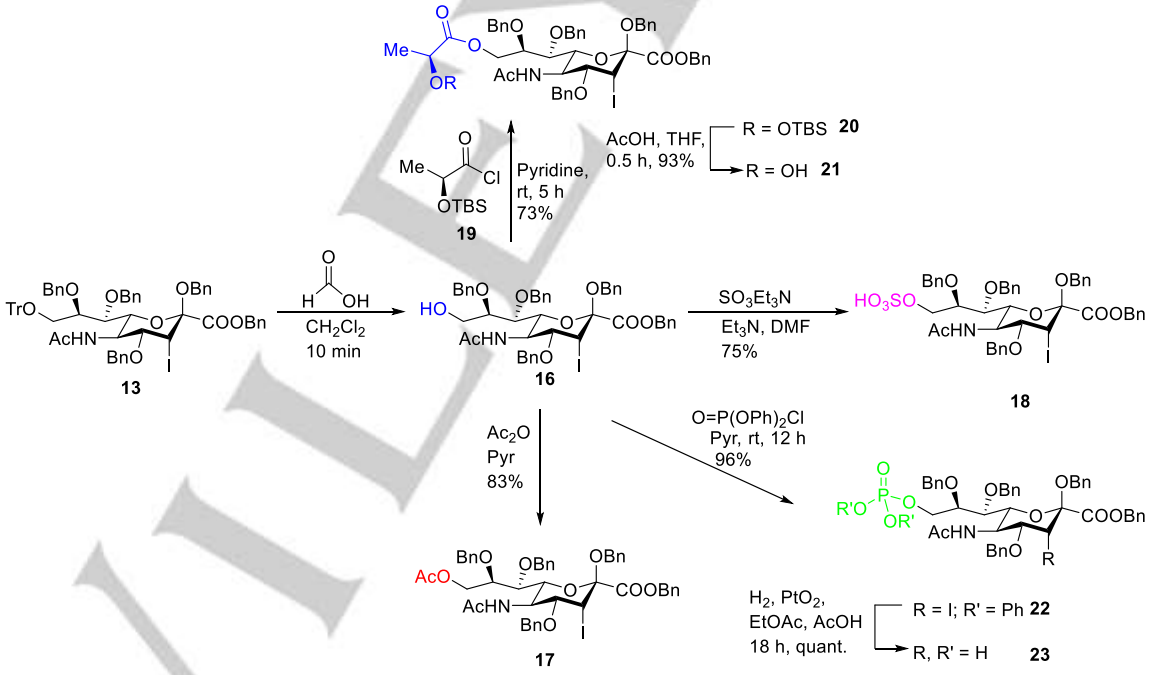
With our desired benzylated glycal in hand, we turned our attention to the olefin addition reaction used widely in the synthesis of 2-deoxy sugars.[25] Initially, we treated **12** with *N*-iodosuccinimide (NIS) in acetic acid at 65 °C (**Scheme 4**), however the harsh acidic conditions resulted in the cleavage of the trityl ether protecting group.[26] Subsequent replacement of acetic acid with benzyl alcohol as our nucleophile was beneficial in two folds; it prevented premature cleavage of the trityl moiety, whilst also masking our newly installed hydroxy anomer as a benzyl ether – ultimately reducing the total number of steps. However, this reaction resulted in a mixture of inseparable diastereomers as analysed by TLC and NMR. In the complex NMR, three distinct C-1 signals could be observed (in the ratio of 1: 0.7: 0.7), one with a $^3J_{C1\text{-}H3}$ of 3.7 Hz (compound **13**) and the other two being broad singlets, which we tentatively assign as compounds **14** and **15**. Although the anomeric configuration of our target compounds is insignificant to our studies, having some sort of diastereoselectivity would ease characterisation and purification attempts. In 2017, Li and co-workers reported the diastereoselective preparation of 2-deoxy-2-iodo-glycosides from their corresponding glycals and glycosyl acceptors using I_2 and diacetoxy(iodo)benzene to furnish the desired α-glycosides.[27] Extending Li's protocol by using I_2, $PhI(OAc)_2$ and benzyl alcohol in anhydrous CH_3CN, we were able to predominantly obtain the 2,3-diaxial 3-iodo-β-benzyl glycoside in an 85% yield. The presence of additional benzylic ^{1}H NMR peaks at 4.71 & 4.34 ppm, and the upfield shift of C-3 proton from 6.13 ppm to 4.83 ppm, confirmed formation of **13** (9:1, **13**:**14**; based on $^3J_{C1\text{-}H3}$).[28],[29] Whilst we could have reductively removed the 3-iodo substituent at this stage, we decided to retain it until the final step to avoid future elimination issues when functionalising the C-9 position. In

our hands, 3-iodo Neu5Ac compounds were stable under basic and acidic conditions.



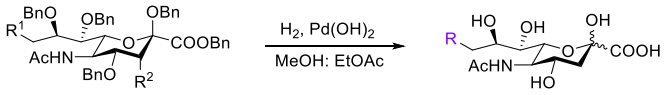
Scheme 4: Glycal addition reaction for formation of **13**

With the C-9 hydroxy liberated using miniscule equivalents of formic acid in CH_2Cl_2, we were able to functionalise the advanced common intermediate **16** (**Scheme 5**) with our desired substituents. The acetyl substituent was installed under conventional conditions using acetic anhydride in pyridine (**17**, 83%). Similarly, **16** was sulfated by the addition of 5 equivalents of SO_3Et_3N complex in DMF, furnishing sulfate **18** in 75% yield. The lactyl ester analogue was introduced via an acylation reaction between **16** and silyl protected lactyl chloride **19**, which itself was prepared in 3 steps (89% yield) from commercially available L-methyl lactate, to afford **20** in a 73% yield. Finally, phosphate **22** was prepared using diphenyl phosphoryl chloride in pyridine in a 96% yield.



Scheme 5: Divergent synthesis of C-9 functionalised Neu5Ac derivatives

With our divergently synthesised C-9 modified neuraminic acid derivatives in hand, we turned to their deprotection (**Scheme 6**). Hydrogenolysis of **22** using Adam's catalyst (PtO_2) selectively cleaved the phenyl and 3-iodo moieties to afford **23** in a quantitative yield. Removal of the TBS group in **20** was accomplished by treatment with acetic acid in THF and CH_2Cl_2 to give **21** in 93% yield. All four derivatives **17**, **18**, **21**, and **23**, were then globally de-benzylated by palladium (10% mol) catalysed hydrogenolysis under an atmosphere of H_2 in a solvent mixture of EtOAc and MeOH, which also concomitantly reduced the 3-iodo function in **17**, **18** and **21**. The polarity of the solvent mixture was gradually increased as the reaction progressed (80:20 → 10:90 v/v; EtOAc: MeOH). Following chromatography, we were able to isolate all four desired C-9 functionalised neuraminic acid derivatives in yields ranging from 61-85%.



17 R^1 = OAc, R^2 = I
18 R^1 = O-lactyl, R^2 = I
21 R^1 = OSO_3, R^2 = I
23 R^1 = OPO_3, R^2 = H

1 R = OAc (78%)
2 R = O-lactyl (82%)
3 R = OSO_3 (85%)
4 R = OPO_3 (61%)

Scheme 6: Catalytic hydrogenolysis to furnish desired target structures

Conclusion

In summary, we describe herein a general and robust synthetic protocol for the divergent preparation of naturally occurring C-9 functionalised sialic acid derivatives from *N*-acetylneuraminic acid in 9 short linear steps. The synthesis includes both an effective way to benzylated neuraminic acid derivatives as well as a working methodology towards β-linked neuraminic acid glycosides. The target compounds will be used as substrates for chemoenzymatic studies (i.e. retro-aldol condensation reactions), as a well as model synthetic compounds for understanding the biological implications of diversification of *N*-acetylneuraminic acid analogues at the terminal primary alcohol.

Experimental Section

General Methods:

All the starting material chemicals were purchased from commercial suppliers (Carbosynth, Sigma Aldrich, Flourochem and Acros) and used without further purification. Unless otherwise stated, all reactions containing air- and moisture sensitive reagents were carried out under an inert atmosphere of nitrogen in oven-dried glassware with magnetic stirring. Anhydrous solvents were obtained from PureSolv-EN™ solvent purification system or purchased from Sigma-Aldrich in AcrosSeal® bottles. All reactions were monitored by thin-layer chromatography (TLC) on Merck DC-Alufolien plates precoated with silica gel 60 F254. TLC plates were visualised with UV-light (254 nm) and stained with H_2SO_4 (8%) and/or ninhydrin solution. Silica gel column chromatography was carried out using Davisil silica gel or with automated flash chromatography suite (Buchi Reveleris X2 AND Biotage SP4 HPFC). ^{1}H NMR (300, 400 or 500 MHz), ^{13}C NMR (101 MHZ or 125 MHz) spectra were recorded on Varian-inova spectrometers at 25 °C in chloroform-d1 ($CDCl_3$), MeOH-d4 (CD_3OD), water-d2 (D_2O), acetone-d6 ($(CD_3)_2CO$), dimethylsulfoxide-d6 ($(CD_3)_2SO$). ^{1}H NMR spectra were standardised against the residual solvent peak ($CDCl_3$, δ = 7.26 ppm; CD_3OD, δ = 3.31 ppm; D_2O, δ = 4.79 ppm; $(CD_3)_2SO$ δ = 2.50 ppm; $(CD_3)_2CO$, δ = 2.84 ppm); or internal trimethylsilane, δ = 0.00 ppm). ^{13}C NMR spectra were standardised against the residual solvent peak ($CDCl_3$, δ = 77.16 ppm; CD_3OD, δ = 49.00 ppm; $(CD_3)_2SO$ δ = 39.52 ppm; $(CD_3)_2CO$, δ = 29.84 ppm). All ^{13}C NMR are ^{1}H decoupled. All NMR data is represented as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets, m = multiplet, br = broad signal, *a*d = apparent doublet, *a*t = apparent triplet), coupling constant in Hz, integration. Mass spectrometry was determined using either Waters Quattro Micro LC-MS/MS in electronspray ionisation (ESI) mode or by matrix -assisted laser deposition/ionization (MALDI) modes.

Experimental Procedure and Data:

Methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-2,6-anhydro-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-enonate (9) A pre-oven dried round bottom flask containing compound **8** (11.9 g, 23.3 mmol), pre-activated 4 Å molecular sieves and a stirring bar were dried on a Schlenk line for 15 mins. The reaction vessel was then charged with CH_2Cl_2 (233 mL) and anhydrous Et_3N (260 mL, 1.87 mol) was added dropwise to the flask in an ice-water bath. The suspension was stirred at room temperature for 2 h upon which the reaction mixture was concentrated down under reduced pressure. The resulting yellow coloured oil was diluted with CH_2Cl_2 (250 mL) and washed consecutively with $NaHCO_3$ (2 x 100 mL), H_2O (2 x 100 mL) and brine (2 x 100 mL). The combined organic fractions were dried over Na_2SO_4 and evaporated *in vacuo*. The crude glycal was purified by flash column chromatography (cHEX/EtOAc, 30:70 → 10:90 cHEX/EtOAc v/v) to give **9** as a white amorphous solid (10.0 g, 21.20 mmol, 91%). R_f: 0.52, cHEX/EtOAc (10:90); **^{1}H NMR** (300 MHz, CD_3OD) δ 5.97 (d, *J* = 2.8 Hz, 1H, H-3), 5.57 (dd, *J* = 8.4, 2.6 Hz, 1H, H-7), 5.52 (dd, *J* = 6.1, 2.6 Hz, 1H, H-8), 5.39 (ddd, *J* = 6.3, 2.8 Hz, 1H, H-4), 4.62 (dd, *J* = 12.4, 2.9 Hz, 1H, H-9a), 4.47 (dd, *J* = 10.2, 2.6 Hz, 1H, H-6), 4.24 – 4.12 (m, 2H, H-9b, H-5), 3.83 (s, 3H, OMe), 2.13 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.08 (s, 3H, OAc), 2.07 (s, 3H, OAc), 1.92 (s, 3H, NAc) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.76, 170.56, 170.19, 170.13, 170.08 (C=O x 5), 161.59 (C-1), 145.02 (C-2), 108.0 (C-3), 70.81 (C-6), 68.14 (C-7), 67.6 (C-4), 61.9 (C-9), 52.51 (CH_3), 46.34 (C-5), 23.02, 20.81, 20.79, 20.68, 20.66 (5 x Ac) ppm; **HRMS** (ESI): m/z calcd for $C_{20}H_{27}NNaO_{12}$: 496.1431 $[M + Na]^+$; found 496.1457.[30]

Methyl 5-acetamido-2,6-anhydro-3,5-dideoxy-9-*O*-trityl-D-*glycero*-D-*galacto*-non-2-enonate (11) Na (0.32 g, 13.7 mmol) was added to a vessel containing MeOH (21 mL) and the resulting solution was added dropwise to **9** (6.5 g, 13.7 mmol) in MeOH (5 mL). The reaction mixture was stirred at room temperature for 9 h. Upon complete de-acetylation (monitored by TLC analysis EtOAc, 100 %), the reaction was quenched with Amberlyst® 15 hydrogen form resin and stirred overnight. The resin was subsequently filtered off and the reaction mixture was concentrated *in vacuo* to give compound **10**, which was used in the next step without further purification. **10** (4.18 g, 13.7 mmol) was dissolved in anhydrous pyridine (45 mL) and trityl chloride (4.6 g, 16.44 mmol) was added. The reaction mixture was heated to 60 °C and stirred at this temperature overnight. The reaction mixture was poured into ice-water, extracted with an excess of CH_2Cl_2 (50 mL) and the combined organic layers was dried over Na_2SO_4. Toluene was added to the solution for co-evaporation

and the solvents were removed under reduced pressure. The crude residue was purified by flash column chromatography (Toluene/EtOAc, 40:60 → 10:90 v/v) to give **11** as a white foam (5.1 g, 9.32 mmol, 68%). R_f: 0.15, EtOAc (100%); **^{1}H NMR** (500 MHz, CD_3OD) δ 7.53 – 7.47 (m, 6H, ArH), 7.35 – 7.28 (m, 6H, ArH), 7.26 – 7.22 (m, 3H, ArH) 5.96 (d, *J* = 2.5 Hz, 1H, H-3), 4.46 (dd, *J* = 8.8, 2.5 Hz, 1H, H-4), 4.21 (dd, *J* = 10.8, 1.3 Hz, 1H, H-6), 3.98 (dd, *J* = 10.9, 8.8 Hz, 1H, H-5), 3.78 (s, 3H, OMe), 3.75 (dd, *J* = 9.5, 1.3 Hz, 1H, H-9a), 3.43 (dd, *J* = 9.5, 2.4 Hz, 1H, H-7), 3.27 (dd, *J* = 9.5, 5.4 Hz, 1H, H-8), 2.04 (s, 3H, NAc) ppm; **^{13}C NMR** (126 MHz, CD_3OD) δ 175.2 (NC=O), 164.9, 164.4 (C-1), 149.0 (C-2), 145.7, 145.2, 130.1, 129.3, 128.8 (C-Ar), 113.6 (C-3), 87.7 (C-Tr)), 78.2, 70.4, 69.9 (C-6), 67.8 (C-7), 66.9 (C-4), 61.6 (C-9), 52.9 (CH_3), 52.0 (C-5), 22.8 (NAc); **HRMS** (ESI): m/z calcd for $C_{31}H_{33}NO_8$: 570.2104 $[M + Na]^+$, found 570.2098. [31]

Benzyl 5-acetamido-2,6-anhydro-4,7,8-tri-*O*-benzyl-3,5-dideoxy-9-O-trityl-D-*glycero*-D-*galacto*-non-2-enonate (12) Compound **11** (2.38 g, 4.35 mmol) was solubilised in anhydrous DMF (21.7 mL) and at O °C $Ba(OH)_2{\cdot}8H_2O$ (4.12 g, 13.05 mmol), BaO (1.33 g, 8.70 mmol) and BnBr (3.1 mL, 26 mmol) were added. The reaction mixture was allowed to warm up to room temperature and the suspension was stirred overnight. Upon completion (analysed by TLC), the reaction mixture was diluted with CH_2Cl_2 (100 mL), and the resulting insoluble inorganic salts were filtered through a bed of Celite and washed sequentially with $NaHCO_3$ (2 x 50 mL), H_2O (2 x 50 mL) and brine (2 x 50 mL). The combined organic fractions were concentrated and the resulting crude product was purified by flash column chromatography (cHEX/EtOAc, 70:30 → 10:90 v/v) to furnish compound **12** as an off-white amorphous foam (2.91 g, 3.26 mmol, 75%). R_f: 0.55, cHEX/EtOAc (50:50); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.48 (m, 6H, ArH), 7.36 – 7.29 (m, 8H, ArH), 7.29 – 7.17 (m, 19H, ArH), 7.17 – 7.12 (m, 2H, ArH), 6.13 (d, *J* = 3.6 Hz, 1H, H-3), 5.23 (d, *J* = 12.3 Hz, 1H, CH_2Ph), 5.16 (d, *J* = 12.3 Hz, 2H, CH_2Ph), 4.74 (ddd, *J* = 6.3, 4.3, 4.1 Hz, 1H, H-8), 4.68 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.51 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.44 (dd, *J* = 11.5, 6.3 Hz, 2H, H-7), 4.35 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.27 – 4.23 (m, 2H, CH_2Ph, H-4), 4.21 – 4.17 (m, 1H, H-5), 3.79 (dt, *J* = 6.0, 4.1 Hz, 1Hz, H-6), 3.75 (dd, *J* = 10.1, 4.3 Hz, 1H, H-9a), 3.31 (dd, *J* = 10.1, 4.0 Hz, 1H, H-9b), 1.84 (s, 3H, NAc) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4 (C=O), 133.9, 128.8, 128.55, 128.50, 128.41, 128.19, 128.16, 128 (C-Ar x 10), 127.7, 127.5, 126.9 (C-Ar), 109.6 (C-3), 78.1 (C-6), 77.3 (C-8) 74.72 (CH_2Ph), 74.1 (C-7), 72.51 (C-5), 71.6 (C-4), 70.70 (CH_2Ph), 67.11 (CH_2Ph), 62.41 (C-9), 23.5 (NAc) ppm; **HRMS** (ESI): m/z calcd for $C_{58}H_{55}NNaO_8$: 916.3825 $[M + Na]^+$; found 916.3822.

Benzyl (benzyl 5-acetamido-4,7,8-tri-*O*-benzyl-3,5-dideoxy-3-iodo-9-*O*-trityl-β-D-*erythro*-L-*manno*-non-2-ulopyranosid)onate (13) Compound **12** (0.83 g, 0.92 mmol) was dissolved in anhydrous CH_3CN (3.7 mL) and at 0 °C benzyl alcohol (0.9 mL, 5.10 mmol), (Diacetoxyiodo)benzene (0.36 g, 1.10 mmol) and iodine (0.14 g, 0.55 mmol) were added sequentially. The reaction vessel was then removed from the ice bath and stirred at ambient temperature for 10 min. The reaction mixture was diluted in EtOAc and washed sequentially with Na_2SO_3 (2 x 5 mL), water (2 x 5 mL) and brine (2 x 5 mL). The combined organic fractions were dried over $MgSO_4$ and evaporated under reduced pressure. The crude product was purified by flash column chromatography (cHEX/EtOAc, 70:30 v/v) to afford **13** (0.88 g, 0.78 mmol, 85%) as an amorphous foam. R_f: 0.68, cHEX/EtOAc (60:40); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.52 – 7.41 (m, 6H, ArH), 7.40 – 7.27 (m, 10H, ArH), 7.29 – 7.12 (m, 20H, ArH), 7.07 (dd, J = 8.4, 6.9 Hz, 2H, ArH), 6.74 – 6.68 (m, 1H, NH), 4.83 (d, *J* = 2.5 Hz, 1H, H-3), 4.80 (d, *J* = 10.3 Hz, 2H, CH_2Ph), 4.71 (d, *J* = 10.3 Hz, 1H, CH_2Ph), 4.65 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.60 (d, *J* = 8.8 Hz, 1H, CH_2Ph), 4.52 (d, *J* = 12.4 Hz, 1H, CH_2Ph), 4.45 – 4.42 (m, 2H, H-8, CH_2Ph), 4.41 – 4.35 (m, 3H, H-7, CH_2Ph), 4.26 (dd, *J* = 8.7, 1.4 Hz, 1H, H-6), 4.04 (dt, *J* = 8.9, 2.6 Hz, 1H, C-5), 3.98 (d, *J* = 11.3 Hz, 1H, CH_2Ph), 3.85 (dd, *J* = 10.7, 2.2 Hz, 1H, H-9a), 3.40 (dd, *J* = 9.9, 2.5 Hz, 1H, H-4), 3.28 (dd, *J* = 10.7, 3.1 Hz, 1H, H-9b), 2.06 (s, 3H, NAc); **^{13}C NMR (**151 MHz, CD_3OD) δ 172.1 (C=O), 166.3 (C=O), 143.9, 138.5, 138.3, 137.8, 136.1, 135.1, 128.2, 128.1, 127.92, 127.90, 127.7, 127.5, 127.3, 127.1, 126.8, 126.7, 126.6, 125.8 (35 x C-Ar), 100.6 (C-2), 86.3 (C-6), 77.2 (CH_2Ph), 74.6 (C-8), 74.4 (C-7), 73.6 (C-5), 71.8 (CH_2Ph), 70.3 (CH_2Ph), 67.2 (CH_2Ph), 66.7 (C-4), 60.5 (C-9), 34.2 (C-3), 21.6 (NAc) ppm; **HRMS (ESI)**: m/z calcd for $C_{65}H_{62}INNaO_9$: 1150.3367 $[M + Na]^+$; found 1150.3401

Benzyl (benzyl 5-acetamido-4,7,8-tri-*O*-benzyl-3,5-dideoxy-3-iodo-β-D-*erythro*-L-*manno*-non-2-ulopyranosid)onate (16) Formic acid (0.2 mL) was added to a solution of compound **13** (2.01 g, 1.78 mmol) in CH_2Cl_2 (9 mL) at 0 °C. The resulting yellow coloured reaction mixture was warmed to room temperature and stirred at this temperature until TLC showed complete cleavage of the trityl group (~ 10 min). MeOH (0.2 mL) was added to quench excess acid, and the solution was concentrated *in vacuo* and subsequently purified by flash column chromatography (cHex/EtOAc, 50:50 v/v) to give compound **17** as a pale yellow foam (1.50 g, 1.69 mmol, 95%). R_f: 0.41, cHEX/EtOAc (60:40); **^{1}H NMR** (500 MHz, CD_3OD) δ 7.64 – 7.50 (m, 2H, ArH), 7.37 – 7.20 (m, 16H, ArH), 7.20 – 7.07 (m, 5H, ArH), 6.98 – 6.64 (m, 2H, ArH), 5.19 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 5.15 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 5.08 (d, *J* = 12.2 Hz, 1H, CH_2Ph), 5.02 (d, *J* = 12.2 Hz, 1H, CH_2Ph), 4.83 (d, *J* = 3.2 Hz, 1H, H-3), 4.79 (d, *J* = 11.8 Hz, 1H, CH_2Ph), 4.73 (d, *J* = 10.2 Hz, 1H, CH_2Ph), 4.69 – 4.62 (m, 3H, CH_2Ph, H-7,), 4.55 (dd, *J* = 11.0, 9.3 Hz, 1H, H-6), 4.48 – 4.41 (m, 2H, CH_2Ph), 4.41 – 4.31 (m, 1H), 4.02 (d, *J* = 11.2 Hz, 1H, CH_2Ph), 3.99 (dd, *J* = 12.1, 2.5 Hz, 1H H-9a), 3.96 – 3.89 (m, 1H, H-4), 3.86 – 3.80 (m, 1H, H-8), 3.72 (dd, *J* = 12.1, 3.0 Hz, 1H, H-9b), 3.65 (dt, *J* = 8.9, 2.8 Hz, 1H, H-5), 1.94 (s, 3H, NAc).**^{13}C NMR** (126 MHz, $CDCl_3$) δ 170.8 (C=O), 166.2, 138.2, 138.1, 137.6, 136.0, 134.6, 129.2 – 127.1 (m) (C-Ar), 100.4 (C-Tr), 81.8 (C-6), 75.0 (C-8), 72.6 (C-7), 72.1 (CH_2Ph), 71.3,(CH_2Ph) 71.2 (C-6), 71.0 (CH_2Ph), 68.0 (CH_2Ph), 67.1 (C-9), 60.4 (C-4), 52.3, 36.9 (C-3), 23.5 (NAc); **HRMS** (ESI): m/z calcd for $C_{46}H_{48}INNaO_9$: 908.2271 $[M + Na]^+$; found 908.2263.

Benzyl (benzyl 5-acetamido-9-*O*-acetyl-4,7,8-tri-*O*-benzyl-3,5-dideoxy-3-iodo-β-D-*erythro*-L-*manno*-non-2-ulopyranosid)onate (17) Acetic anhydride (0.25 mL, 2.67 mmol) was added to solution of **16** (1.57 g, 1.78 mmol) in anhydrous pyridine (3.56 mL). The solution was stirred at room temperature overnight (17 h). Upon completion, the reaction mixture was diluted in EtOAc and washed sequentially with NaHCO3 (2 x 10 mL), water (2 x 10mL) and brine (2 x 10 mL). The combined organic fractions were dried over MgSO4 and concentrated under reduced pressure. The crude acetate was purified by flash column chromatography (70:30, cHex: EtOAc v/v) to give **17** as pale-yellow foam (1.36 g, 1.47 mmol, 83%). R_f: 0.45, cHEX/EtOAc (60:40); **^{1}H NMR** (600 MHz, CD_3OD, conformational rotamers observed. Spectral data for 1 of the rotamers is reported) δ 7.47 – 7.42 (m, 3H, ArH), 7.40 – 7.23 (m, 15H, ArH), 7.24 – 7.14 (m, 6H, ArH), 7.14 – 7.06 (m, 1H, ArH), 5.22 – 5.17 (m, 1H, CH_2Ph), 5.14 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 4.89 (d, *J* = 2.8 Hz, 1H, H-3), 4.86 – 4.83 (m, 2H, C-8), 4.80 (d, *J* = 12.1 Hz, 1H, CH_2Ph), 4.66 – 4.59 (m, 2H), 4.58 – 4.52 (m, 1H, H-4), 4.51 – 4.45 (m, 1H, H-7), 4.35 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.15 – 4.07 (m, 2H, CH_2Ph, H9a), 4.01 (ddd, *J* = 8.6, 5.1, 2.3 Hz, 1H, H-6), 3.91 – 3.82 (m, 1H, H-5), 3.62 (dd, *J* = 7.8, 1.4 Hz, 1H, H-9b), 2.04 (s, 3H, OAc), 1.74 (s, 3H, NAc). ppm; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.7 (C=O), 165.9 (NC=O), 138.2, 138.0, 137.8, 137.7, 137.5, 136.3, 129.0, 128.9, 128.7, 128.57, 128.52, 128.47, 128.45, 128.41, 128.3 (C x 5, C-Ar), 128.1, 127.9, 127.88, 127.86, 127.79, 127.75, 127.6, 127.59, 127.50, 127.3 (C-Ar), 100.5 (C-2), 99.9 (C-8), 81.1 (C-6), 78.2, 75.3, 74.6, 74.0 (CH_2Ph), 73.4, 73.2 (CH_2Ph), 72.9 (CH_2Ph),

72.8, 72.1, 71.8, 71.4, 70.7, 67.7 (C-5), 67.5 (C-9), 66.9 (CH_2Ph), 66.2, 63.4 (C-4), 62.8, 30.85 (C-3), 23.5 (OAc), 21.0 (NAc) ppm; **HRMS** (MALDI-TOF): m/z calcd for $C_{48}H_{50}INNaO_{10}$: 950.2377 $[M + Na]^+$; found 950.2379

Benzyl (benzyl 5-acetamido-4,7,8-tri-*O*-benzyl-3,5-dideoxy-3-iodo-9-*O*-sulfo-β-D-*erythro*-L-*manno*-non-2-ulopyranosid)onate (18) Compound **16** (0.5 g, 0.58 mmol) was solubilised in dry DMF (5.8 mL) and at O °C, $SO_3.Et_3N$ (0.525 g, 2.9 mmol) powder was added portion-wise. Et_3N (0.40 mL, 2.9 mmol) was subsequently injected into the pale-yellow solution. The reaction mixture warmed to room temperature and stirred at this temperature overnight. Upon completion of the reaction (monitored by TLC), the solution was concentrated under reduced pressure (co-evaporation toluene) and re-dissolved in CH_2Cl_2 before being washed sequentially with $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL) and brine solution (2 x 10 mL). The combined organic fractions were dried over Na_2SO_4 and concentrated *in vacuo* before being purified by flash column chromatography (60:40, cHex: EtOAc v/v) to give **18** as a white amorphous solid (0.42 g, 0.43 mmol, 75%). R_f: 0.34, cHEX/EtOAc (60:40); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.40 – 7.35 (m, 5H, ArH), 7.33 – 7.16 (m, 14H, ArH), 7.17 – 7.07 (m, 6H, ArH), 4.82 (d, *J* = 3.1 Hz, 1H, C-3), 4.79 – 4.76 (m, 1H, CH_2Ph), 4.73 (d, *J* = 11.9 Hz, 1H, CH_2Ph), 4.65 (m, 2H,CH_2Ph, H8), 4.59 – 4.52 (m, 3H, CH_2Ph, H-7), 4.51 – 4.45 (m, 2H, CH_2Ph), 4.44 – 4.38 (m, 2H, H-9b) 4.08 – 4.00 (m, 2H, H-9b, H-6, H-4), 3.75 (ddd, *J* = 7.4, 4.6, 2.5 Hz, 1H, H-5), 1.97 (s, 3H, NAc) ppm; **^{13}C NMR** (126 MHz, $CDCl_3$) δ, 170.7 (C=O), 166.1 (C-1), 136.3, 134.8, 134.7, 134.65, 134.61, 128.36, 128.34, 128.32, 128.31, 128.2, 127.3, (C-Ar x 20), 100.3 (C-2), 74.9 (C-6), 72.5 (C-7), 72.0 (CH_2Ph), 71.2 (C-5), 71.1 (CH_2Ph), 70.9 (CH_2Ph), 67.9 (C-9), 67.0 (C-8), 60.5 (CH_2Ph), 52.2 (C-4), 36.8 (C-3), 23.4 (NAc) ppm; **HRMS** (MALDI-TOF): m/z calcd for $C_{46}H_{48}INNaO_{12}S$: 988.1840 $[M + Na]^+$; found 988.1856.

Benzyl (benzyl 5-acetamido-4,7,8-tri-*O*-benzyl-3,5-dideoxy-3-iodo-9-*O*-L-lactyl-β-D-*erythro*-L-*manno*-non-2-ulopyranosid) onate (21) L-Lactyl chloride **19** (75 mg, 0.33 mmol) in DMF (0.8 mL) was added slowly to **16** (0.250 g, 0.28 mmol) solubilised in anhydrous pyridine (2 mL) at O °C. The reaction mixture was then allowed to warm to room temperature and stirred at this ambient temperature upon completion of the reaction (5 h). MeOH (1 mL) was added to the solution before evaporation under reduced pressure. The crude material was diluted in CH_2Cl_2 and washed sequentially with $NaHCO_3$ (2 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL). The combined organic fractions were dried over MgSO4, concentrated *in vacuo* and then purified by column chromatography (50:50, cHEX:EtOAc v/v) to generate **20** as a pale-yellow foam (0.19 g, 0.18 mmol, 73%). Subsequently, glacial acetic acid (0.5 mL) was added to **20** dissolved in THF (1.8 mL) and the solution was stirred at room temperature for 30 min. The resulting solution was concentrated down and purified by flash flash column chromatography (60:40. cHex:EtOAc v/v) to furnish **21** (0.16 g, 0.17 mmol, 93%) as white foam. R_f: 0.49, cHex:EtOAc (50:50); **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 6H, ArH), 7.37 – 7.27 (m, 13H, ArH), 7.24 – 7.16 (m, 3H, ArH), 7.14 – 7.06 (m, 3H, ArH), 5.23 – 5.16 (m, 4H, CH_2PH), 5.14 (dd, *J* = 12.1, 7.8 Hz, 1H, CH_2Ph), 4.86 – 4.84 (m, 2H, C-3, CH_2Ph), 4.80 (d, *J* = 12.0 Hz, 1H, CH_2Ph), 4.64 – 4.59 (m, 2H, CH_2Ph, H-7), 4.56 – 4.53 (m, 2H, CH_2Ph, H-8), 4.50 (d, *J* = 6.1 Hz, 1H), 4.48 – 4.46 (m, 2H,H-6, H-9a), 4.13 (d, *J* = 11.4 Hz, 1H, CH_2Ph), 4.03 – 3.99 (m, 2H, H9b), 3.78 (dd, *J* = 5.0, 1.9 Hz, 1H, H-4), 3.75 (ddd, *J* = 7.4, 5.0, 2.5 Hz, 1H, H-5), 2.04 (s, 3H, NAc), 1.74 (s, 3H, lactyl CH_3) ; **^{13}C NMR** (151 MHz, $CDCl_3$) δ 170.7 (C=O), 170.6 (C=O), 169.7 (C=O), 136.3, 134.8, 129.0, 128.9, 128.7, 128.57, 128.55, 128.52, 128.46, 128.45, 128.41, 128.38, 128.36, 128.34, 128.31, 128.13, 128.10, 128.0, 127.9, 127.8, 127.79, 127.75, 127.6, 127.59, 127.50, 127.3 (C-Ar), 99.9 (C-2), 81.1 (C-6), 75.3 (CH_2Ph), 74.0 (CH_2Ph), 73.4 (CH_2Ph), 72.8 (CH_2Ph), 72.1 (C-7), 71.8 (CH_2Ph), 71.4 (C-8), 70.7, 67.5 (C-9), 66.2 (C-5), 51.7 (C-4), 36.3 (C-3), 21.00 (NAc); **HRMS (MALDI-TOF)**: m/z calcd for $C_{55}H_{66}INNaO_{11}Si$: 1094.3348 $[M + Na]^+$; found 1094.3352.

Benzyl (benzyl 5-acetamido-4,7,8-tri-*O*-benzyl-3,5-dideoxy-3-iodo-9-*O*-(diphenyl)phosphoryl-β-D-*erythro*-L-*manno*-non-2-ulopyranosid)onate (22) Compound **16** (0.27 g, 0.31 mmol) was dissolved in anhydrous pyridine (1.1 mL), and, at 0 °C, diphenyl phosphoryl chloride (0.17 g, 0.62 mmol) was added portion-wise. The reaction mixture was then stirred at room temperature (12 h). The reaction was quenched with MeOH (1 mL) before being evaporated under reduced pressure (co-evaporation with toluene). The resulting crude phosphate was purified by silica gel flash column chromatography (70:30, cHEX: EtOAc v/v) to furnish **23** as an off-white amorphous solid (0.33 g, 0.29 mmol, 96%). R_f: 0.31, cHEX:EtOAc, (1:1); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 – 7.36 (m, 2H, ArH), 7.35 – 7.18 (m, 33H, ArH),, 5.17 – 5.11 (m, 2H, CH_2Ph, NH), 5.08 (dd, *J* = 12.1, 7.8 Hz, 1H, CH_2Ph), 4.96 (d, *J* = 3.8 Hz, 1H, H-3), 4.80 – 4.77 (m, 2H, H-7, CH_2Ph), 4.74 (d, *J* = 11.7 Hz, 2H, CH_2Ph), 4.60 – 4.54 (m, 2H, H-6, CH_2Ph), 4.52 – 4.46 (m, 2H, CH_2Ph), 4.45 – 4.39 (m, 3H, H-9a, H-8, CH_2Ph), 4.10 – 4.02 (m, 2H, H-4), 3.96 (ddd, *J* = 8.6, 5.1, 2.3 Hz, 1H, H-5), 3.85 – 3.76 (m, 1H, H9b), 3.73 (dd, *J* = 5.0, 1.9 Hz, 1H, H-7), 3.56 (dd, *J* = 7.8, 1.9 Hz, 1H, H-6), 1.98 (s, 3H, NAc) ppm; **^{13}C NMR** (126 MHz, cdcl$_3$) δ 171.3 (C=O), 166.6 (C=O), 138.6, 138.5, 138.0, 136.5, 135.0, 129.5, 129.4, 129.1, 129.0, 128.88, 128.85, 128.7, 128.48, 128.3, 128.2, 128.1, 127.95, 127.90 (C-Ar), 100.8 (C-2), 82.2 (C-6), 73.0 (C-7), 72.5 (CH_2Ph), 71.7 (C-8), 71.6 (CH_2Ph), 71.4 (CH_2Ph), 68.50 (CH_2Ph), 67.53 (C-5), 60.8 (CH_2Ph), 52.7 (C-4), 37.3 (C-3), 23.9 (NAc); **HRM S** (MALDI-TOF): m/z calcd for $C_{58}H_{57}INNaO_{12}P$: 1140.2561 $[M + Na]^+$; found 1140.2592

General Procedure for catalytic de-benzylation of C-9 functionalised Neu5Ac derivatives:

C-9 functionalised Neu5Ac (1 eq) was solubilised in a mixture of EtOAc and MeOH (80:20 0.2 M). Pd/C (10% wt) was added and the reaction mixture was stirred under H_2 atmosphere (10 bar). After stirring the mixture at room temperature overnight, the polarity of the reaction solvent was increased to 10:90 (EtOAc: MeOH v/v) and the reaction was continued for a further 12 h. The reaction was then filtered, concentrated *in vacuo* and purified by flash column chromatography (EtOAc:MeOH 85:15 v/v).

5-Acetamido-9-*O*-acetyl-3,5-dideoxy-D-*glycero*-D-*galacto*-non-2-ulopyranosonic acid (1) Compound **1** was prepared from **17** according to the General Procedure to afford the title compound as an off-white amorphous solid (162 mg, 462 mmol, 78%). **^{1}H NMR** (500 MHz, DMSO) δ 4.11 – 4.02 (m, 2H, H-9a, H-8), 3.93 (t, *J* = 10.2 Hz, 1H, H-7), 3.84 (dd, *J* = 11.9, 2.7 Hz, 1H, H-9b), 3.79 – 3.71 (m, 1H, H-5), 3.71 – 3.53 (m, 2H, H-6, H-4), 2.72 (dd, *J* = 12.9, 4.5 Hz, 0.05H, H-3eq), 2.32 (dd, *J* = 13.1, 5.0 Hz, 1H, H-3eq), 2.05 (s, 3H, NAc), 1.88 (dd, *J* = 13.1, 11.5 Hz, 1H, H-3ax); **^{13}C NMR** (125 MHz, DMSO) δ 173.2 (C1), 171.5 (C=O), 169.9 (C=O), 95.3 (C-2), 70.5 (C-6), 69.0 (C-8), 66.79 (C-7), 66.75 (C-4), 65.7 (C-9), 53.0 (C-5), 39.4 (C-3), 23.4 (OAc), 20.7 (NAc) ppm; **HRMS** (ESI): m/z calcd for $C_{13}H_{21}NNaO_{10}$: 374.1063 $[M + Na]^+$; found 374.1097. NMR signals consistent with previously reported spectral data [32]

5-Acetamido-3,5-dideoxy-9-*O*-L-lactyl-D-*glycero*-D-*galacto*-non-2-ulopyranosonic acid (2) Compound **2** was prepared from **21** according to the General Procedure to afford the title compound as a white foamy solid (56 mg, 148 mmol, 82%). **^{1}H NMR** (500 MHz, D_2O) 3.94 (dt, *J* = 11.3, 2.7 Hz, 2H, H-9a, H-4), 3.87 – 3.76 (m, 1H, H-6), 3.73 (dd, *J* = 11.7, 2.6 Hz, 1H, H-9b),

3.64 (ddd, *J* = 8.8, 6.1, 2.4 Hz, 1H, H-8), 3.56 – 3.49 (m, 1H, H-5), 3.45 (t, *J* = 7.2 Hz, 1H, H-7), 2.68 – 2.54 (m, 1H, minor alpha H-3eq), 2.20 (dd, *J* = 13.0, 4.7 Hz, 1H, H-3eq), 1.94 (s, 3H, NAc), 1.89 – 1.63 (m, 4H, H-3ax, lactyl CH_3); **^{13}C NMR** (125 MHz, DMSO-d_6) δ 173.8 (C=O), 172.5 (C=O), 170.1 (C=O), 107.3 (C-2), 71.0 (C-4), 69.4 (C-5), 68.4 (C-7), 66.63 (C-8), 66.61 (C-6), 58.1 (C-9), 41.9 (C-3), 24.6 (NAc), 21.7 (Ac) ppm; **HRMS** (MALDI-TOF): m/z calcd for $C_{14}H_{23}NNaO_{11}$: 404.1169 [M + Na] $^+$; found 404.1206. NMR signals consistent with previously reported spectral data [33]

5-Acetamido-3,5-dideoxy-9-*O*-sulfo-D-*glycero*-D-*galacto*-non-2-ulopyranosonic acid (3) Compound **3** was prepared from **18** according to the General Procedure to afford the title compound as a white solid (134 mg, 343 mmol, 85%). **^{1}H NMR** (500 MHz, D_2O) δ 3.98 – 3.87 (m, 2H, H-6, H-7), 3.82 – 3.74 (m, 1H, H-8), 3.69 (dd, *J* = 11.8, 2.6 Hz, 1H, H-9a), 3.60 (ddd, *J* = 9.2, 6.3, 2.7 Hz, 1H, H- H-5), 3.47 (dd, *J* = 11.8, 6.3 Hz, 1H, H-9b), 3.41 (dd, *J* = 9.2, 1.2 Hz, 1H, H-4), 2.17 (dd, *J* = 13.1, 5.0 Hz, 1H, H-3eq), 1.90 (s, 3H, NAc), 1.73 (dd, *J* = 13.1, 11.4 Hz, 1H, H-3ax) ppm; **^{13}C NMR** (125 MHz, D_2O) δ 173.4 (C=O), 172.7 (C=O), 103.3 (C-2), 73.3 (C-6), 71.5 (C-8), 70.73 (C-7), 70.71 (C-4), 68.7 (C-9), 52.8 (C-5), 35.2 (C-3), 23.2 (OAc) ppm; **HRMS** (MALDI-TOF): m/z calcd for $C_{11}H_{19}NNaO_{12}S$: 412.0526 [M + Na] $^+$; found 412.0610 NMR signals consistent with previously reported spectral data [34]

5-Acetamido-3,5-dideoxy-9-*O*-phosphoryl-D-*glycero*-D-*galacto*-non-2-ulopyranosonic acid (4) Compound **4** was prepared from **23** according to the General Procedure to afford the title compound as an off white solid (78 mg, 201 mmol, 61%). **^{1}H NMR** (500 MHz, DMSO) δ 4.24 – 4.16 (m, 2H), 4.06 (t, *J* = 10.2 Hz, 1H), 3.97 (dd, *J* = 11.9, 2.7 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.75 (dd, *J* = 11.8, 6.3 Hz, 1H), 3.69 (dd, *J* = 9.3, 1.2 Hz, 1H), 2.85 (dd, *J* = 12.9, 4.5 Hz, 5% alpha), 2.45 (dd, *J* = 13.1, 5.0 Hz, 1H), 2.18 (d, *J* = 0.9 Hz, 3H), 2.01 (dd, J = 13.1, 11.5 Hz, 1H) ppm; **^{13}C NMR** (125 MHz DMSO-d_6) δ 172.7, 170.9, 103.2, 71.9, 70.1, 69.7, 68.3, 68.1, 58.2, 43.4, 22.9 ppm; **HRMS** (MALDI-TOF): m/z calcd for $C_{11}H_{20}NNaO_{12}P$: 412.0621 [M + Na] $^+$; found 412.0956. Data consistent with reported spectral data. [34]

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Keywords: Carbohydrates • sialic acid • aldolase • total synthesis • neuraminic acid

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FULL PAPER

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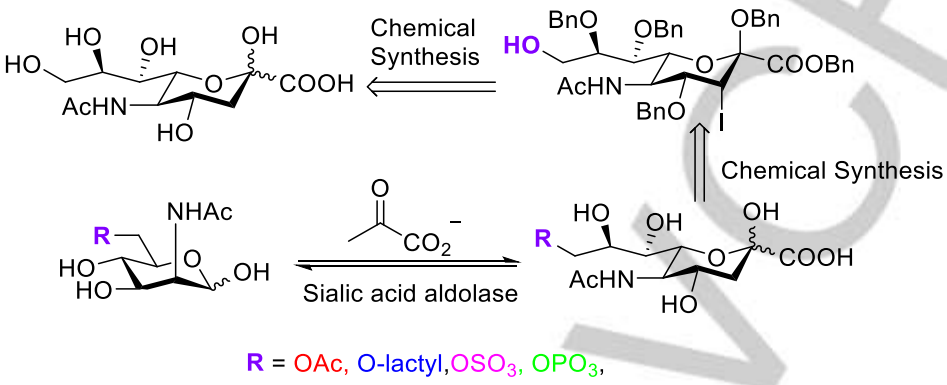
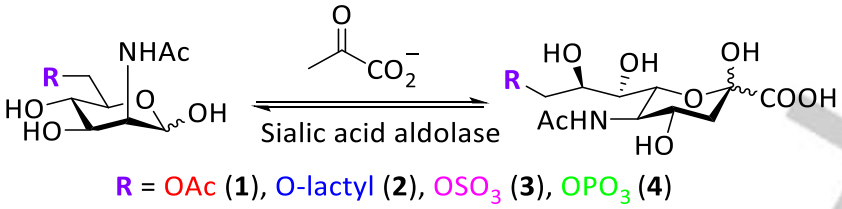


A general and operationally simple protocol for the synthesis of C-9 functionalised neuraminic acid derivatives from *N*-acetylneuraminic acid is described. During the synthetic endeavor, an efficient way to introduce sialic acid 'unfriendly' benzyl groups was established. Additionally, a working methodology towards unnatural β-configured neuraminic acid glycosides is reported.

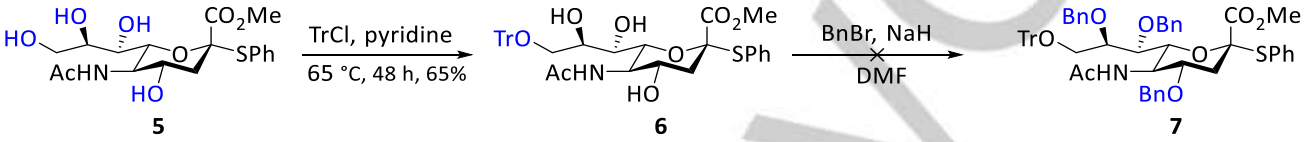
Institute and/or researcher Twitter usernames: @Abdi509

Key Topic: Carbohydrate synthesis

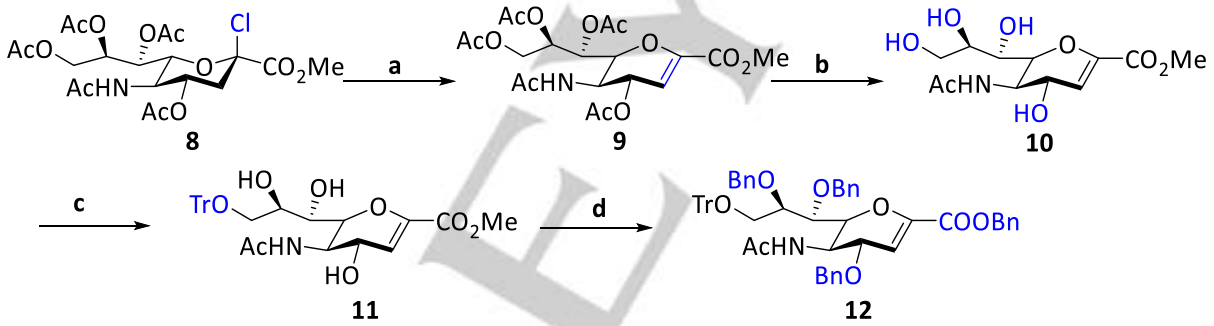


R = OAc (**1**), O-lactyl (**2**), OSO_3 (**3**), OPO_3 (**4**)

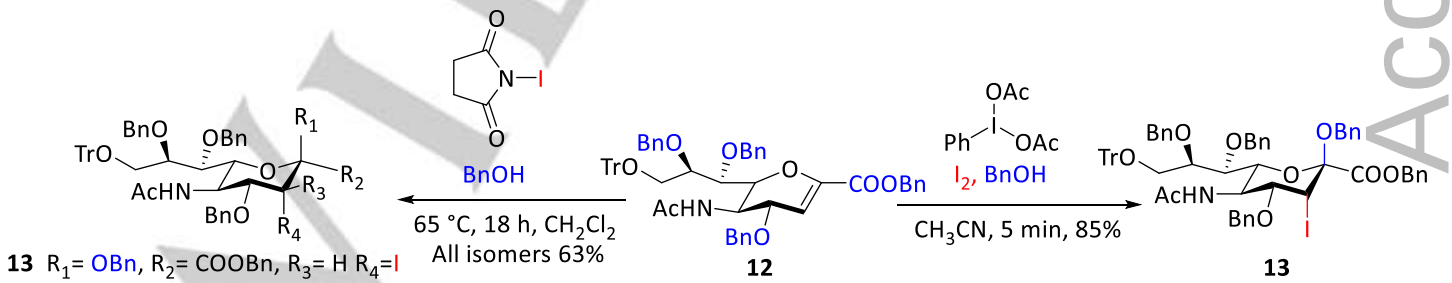
Scheme 1: Chemoenzymatic synthesis of C-9 functionalised Neu5Ac derivatives



Scheme 2: Failed synthetic sequence

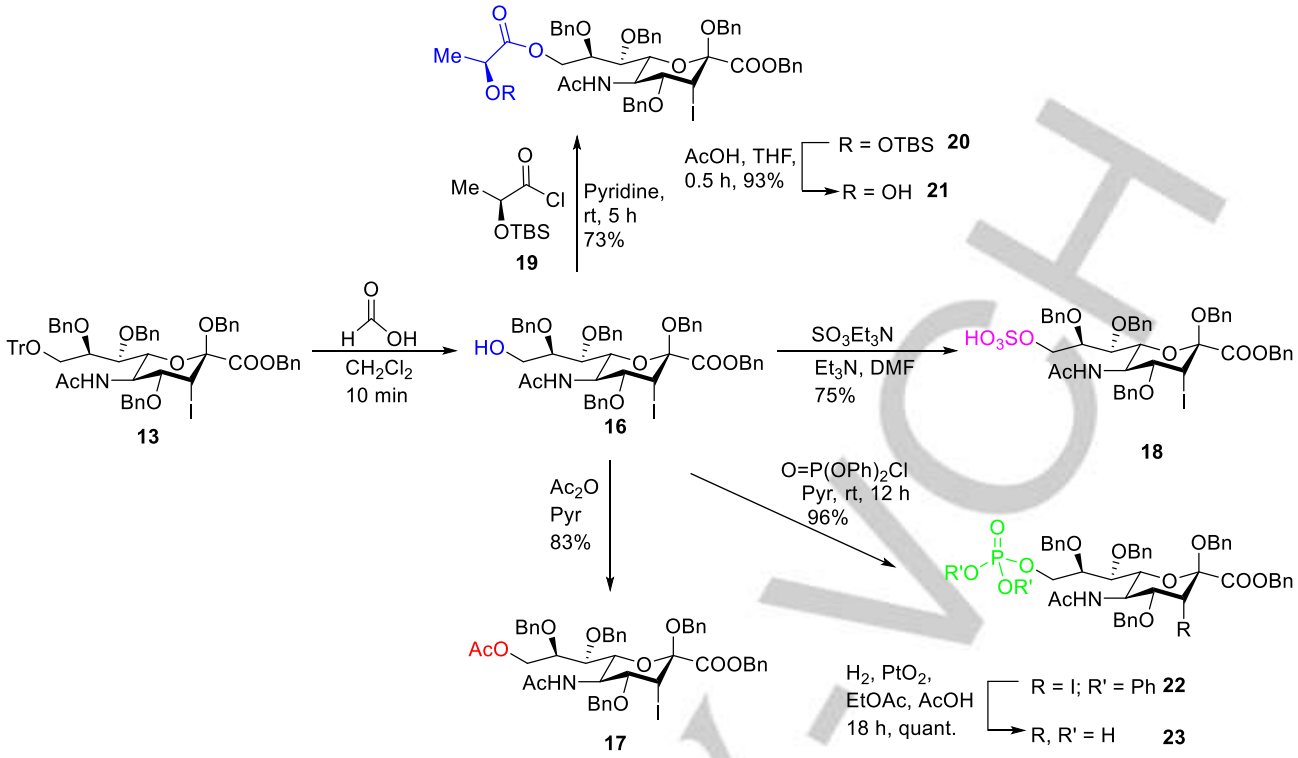


Scheme 3: Reagents & Conditions; (a) Et_3N, CH_2Cl_2, rt, 91%, (b) NaOMe, MeOH, rt, 9 h (c) TrCl, pyridine, 60 °C, 48 h, 68% (d) BnBr, $Ba(OH)_2{\cdot}8H_2O$, BaO, DMF, 0 °C – rt, 16 h, 75%.

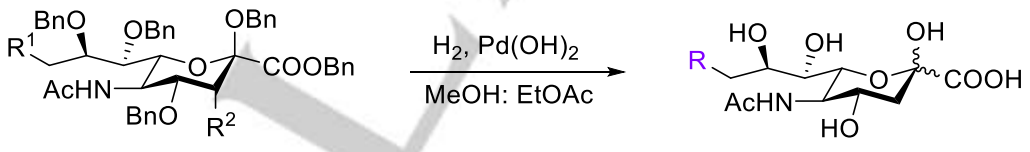


13 R_1= OBn, R_2= COOBn, R_3= H R_4=I
14 R_1= COOBn, R_2= OBn, R_3= H R_4=I
15 R_1= OBn, R_2= COOBn, R_3= I R_4=H

Scheme 4: Glycal addition reaction for formation of **13**



Scheme 5: Divergent synthesis of C-9 functionalised Neu5Ac derivatives



17 R^1 = OAc, R^2 = I
18 R^1 = O-lactyl, R^2 = I
21 R^1 = OSO_3, R^2 = I
23 R^1 = OPO_3, R^2 = H

1 R = OAc (78%)
2 R = O-lactyl (82%)
3 R = OSO_3 (85%)
4 R = OPO_3 (61%)

Scheme 6: Catalytic hydrogenolysis to furnish desired target structures