Synthesis of 4-deoxy-4-nitrosialic acid

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The synthesis of 4-deoxy-4-nitrosialic acid (3,4,5-trideoxy-4-nitro-D-glycero- β -D-galacto-non-2ulopyranosonic acid, **5**), was completed in seven steps starting from D-arabinose. Coupling of the 6-carbon fragment, 2-acetamido-1,2-dideoxy-1-nitro-D-mannitol (**6**) with ethyl α -(bromomethyl)acrylate afforded a 2 : 1 mixture of ethyl 5-acetamido-2,3,4,5-tetradeoxy-2methylene-4-nitro-D-galacto-nononate (**9a**-S) and ethyl 5-acetamido-2,3,4,5tetradeoxy-2-methylene-4-nitro-D-glycero-D-talo-nononate (**9a**-R). This mixture of enones was subjected to ozonolysis, and following reduction of the ozonide, the resultant products cyclised to the pyranosides. The target compound, ethyl 4-deoxy-4-nitrosialate (**11a**) was isolated by fractional crystallisation. Hydrolysis of the ethyl ester proved problematic; thus, the synthesis was modified by using *tert*-butyl α -(bromomethyl)acrylate. Following ozonolysis of the corresponding *tert*-butyl enoate esters and diastereomer separation, the *tert*-butyl ester of 4-nitrosialic acid (**11b**) could be deprotected under acidic conditions to afford **5**. The target compound is a useful intermediate for synthesis of a variety of C-4 substituted sialic acid derivatives, and it is synthesised by a modular route.

Introduction

Sialic acid (N-acetylneuraminic acid, Neu5Ac, 1) is a 9-carbon sugar often found α-ketosidically linked within many biologically important glycoconjugates.1 Indeed, it is often present on the termini of the oligosaccharide chain components of these biomolecules and as such plays many important roles in biological function, including cell recognition, cell ageing, tumour formation, and many other immunological events.¹ Sialic acid also plays a role in influenza infection, as it has been shown that the influenza virus particles recognise and bind to these residues that are present on the surface of host cells, an event that initiates infection.² Upon budding from the infected cell, the progeny virus particles clump together, as they are coated in cellular sialic acid residues. At this juncture, the viral sialidase (neuraminidase, EC 3.2.1.18) hydrolyses the glycosidic linkage between sialic acid residues and the glycoconjugates, a process that allows virus proliferation. Inhibition of this viral sialidase therefore provides an attractive target for developing anti-influenza therapeutics.³

Considerable effort has been made toward synthesising numerous derivatives of sialic acid substituted at various positions within the 9-carbon framework, for purposes that include being potential therapeutics for influenza infection. A common synthetic route to sialic acid derivatives uses the enzyme sialic acid aldolase (*N*acylneuraminate pyruvate lyase, EC 4.1.3.3) to couple pyruvate with an appropriate aldose, *N*-acetylmannosamine in the case of sialic acid synthesis (Scheme 1). This enzyme has been shown to accept a wide assortment of aldoses, allowing the synthesis of a variety of derivatives.^{4,5} However, since the reaction proceeds by nucleophilic attack of pyruvate's C-3 atom on the aldehyde carbon (C-1) of the aldose, an OH-group is necessarily generated at C-4 of the product. Chemical syntheses of sialic acid derivatives commonly use a similar strategy. For example, the



Scheme 1 Sialic acid aldolase-catalyzed synthesis of sialic acid from *N*-acetyl-D-mannosamine and pyruvate.

indium-mediated coupling of ethyl α -(bromomethyl)acrylate⁶ or α -(bromomethyl)acrylic acid⁷ with an aldose followed by ozonolysis of the resulting enone installs the α -ketoacid moiety. Strategies such as this also result in the generation of an OH-group on C-4 of the product.

Due to the prevalence of these synthetic strategies, there are few general routes leading to variously C-4 substituted sialic acid derivatives. An azido group has been introduced at C-4 by treatment of the peracetylated methyl ester of the glycal of sialic acid (2-deoxy-2,3-didehydro-*N*-acetylneuraminic acid, DANA) with BF₃·OEt₂, resulting in the formation of oxazoline **2**, which was opened with azide ion.⁸ Further functionalisation of the azido group led to 4-amino derivatives that could also be functionalised. Among other derivatives, this synthetic route was used to make zanamavir (**3**, sold as RelenzaTM), which became one of the first sialidase inhibitors on the market as an anti-influenza therapeutic.³ Oxazoline **2** has also been opened with chloride ion to generate a 4-chlorosialic acid derivative,⁹ a compound that was used in palladium(0)-mediated coupling reactions with various organotin reagents to install unsaturated functional groups at

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C-4.¹⁰ Various ether derivatives have been made at C-4 by reacting the free hydroxyl group with bromoacetonitrile and then further functionalisation of the nitrile group.¹¹ Zbiral and co-workers have synthesised derivatives of sialic acid modified at various positions, and have performed several functional group manipulations involving the C-4 hydroxyl group, including oxidation to a ketone, replacement of the ketone oxygen with a methylene group, and reduction of the methylene group to give a 4-deoxy-4-methyl sialic acid derivative.¹² They have also synthesised 2-deoxy versions of these derivatives¹³ and several 4-substituted sialic acid glycals.¹⁴ In addition, the 4-deoxy-4-methylene derivative was treated with MCPBA to give spiro-epoxide 4, which could be opened with a nucleophile to install an OH and a new substituent on C-4.15 The oxygen of the epoxide was delivered exclusively from the top face of the molecule to generate the 4S-diastereomer (the D-glycero-Dtalo isomer, 4), and nucleophilic ring opening by azide, methoxide, cyanide, and chloride all occurred with exclusive attack on the less-hindered exocyclic CH₂.



Although several different types of functional groups have been installed at C-4, there are still few general and/or modular routes to C-4 substituted sialic acid derivatives. Given that the effects of a nitro group at C-4 have never been explored, a synthetic route was devised to give 4-deoxy-4-nitrosialic acid (5). The chosen synthetic route involves the synthesis of a 6-carbon fragment, 2-acetamido-1,2-dideoxy-1-nitro-D-mannitol (6), by known methods,^{16,17} followed by a key coupling step involving deprotonation of this nitroalditol and reaction of the resultant nitronate anion with an appropriate 3-carbon electrophile to afford the 9-carbon backbone of 4-nitrosialic acid. A conceptually similar synthetic route to sialic acid derivatives has been reported by the group of Vasella, and involves the deprotonation of a nitroaldopyranose followed by reaction with a 3-carbon electrophile (Scheme 2).^{18,19} Notably, in these syntheses alkylation of the nitro group gives a nitroketal functionality that was hydrolysed, presumably via a glycosyl oxacarbenium ion intermediate, to give a hemiketal (Scheme 2). This material was then further modified to yield sialic acid, 4-episialic acid and 4-deoxysialic acid.18,19 A limitation to this synthetic protocol is that glycosidic nitroketal groups are less synthetically versatile than acyclic nitroalkanes, however, Vasella's group have reported an ingenious synthesis of [6-2H]-sialic acid by a radicalinitiated reduction of a glycosidic nitroketal precursor.²⁰

Our proposed route is modular, as many different nitroalditols could be used in the coupling reaction to generate 4-nitrosialic acid derivatives. It is also general in that the secondary nitroalkyl group is a flexible unit for functional group interconversions; for



Scheme 2 Base-promoted nitroaldopyranose addition to *tert*-butyl α -(bromomethyl)acrylate followed by hydrolysis of the nitroketal leading to an intermediate in Vasella's sialic acid synthesis. *Reagents and conditions:* (*a*) 2 eq. DBU, THF, 0 °C, 24 h; (*b*) urea, phosphate buffer pH 6.6, RT, 3 days.¹⁸

instance, it can be reduced to several different nitrogen-containing functionalities (including oximes, hydroxylamines, or amines), hydrolysed to a ketone, alkylated *via* its nitronate anion, and made to undergo various radical-mediated processes.²¹

Results and discussion

Starting from D-arabinose, the method of Sowden *et al.*¹⁷ was used to synthesise D-*arabino*-tetraacetoxy-1-nitro-1-hexene (7) in three steps (Scheme 3). This sequence began with a base-promoted Henry reaction between D-arabinose and nitromethane, after which peracetylation of the diastereomeric nitromannitol and nitroglucitol products followed by elimination of HOAc gave nitrohexene 7. Of note, the crude products from the first two reaction steps could be used without purification, thus allowing the routine formation of multi-gram quantities of the nitroalkene (7), which could be recrystallised from ethanol to give a light yellow powder in 54% yield over three steps.

Subsequently, the Michael addition of NH_3 to the double bond of 7 (Scheme 3) was first attempted by bubbling ammonia



Scheme 3 Synthesis of 2-acetamido-1,2-dideoxy-1-nitro-D-mannitol 6. *Reagents and conditions*: (a) CH₃NO₂, NaOMe/MeOH, 18 h; (b) Amberlite H⁺; (c) Ac₂O, cat. H₂SO₄, 80 °C, 1 h; (d) NaHCO₃ (s), benzene, reflux, 3 h; (e) sat. NH₃/MeOH, 0 °C to RT, 16 h.

through a methanol suspension of the nitroalkene for 15 h according to Sowden's procedure. This reaction accomplished the installation of the desired amine on C-2 while also deacetylating and causing migration of an acetyl group onto the amine, forming acetamidonitromannitol **6**. Although this procedure worked, it never afforded greater than a 43% yield of the mannitol isomer after purification by recrystallisation from ethanol, a procedure that separated the mannitol isomer from the glucitol isomer and other impurities (Sowden obtained 51%). A higher-yielding procedure was developed by O'Neill, in which the nitroalkene was slowly added portionwise to a saturated solution of ammonia in methanol at 0 °C.¹⁶ This procedure afforded a modestly improved 56% yield of **6** (O'Neill reported 82%).

Slight difficulties were encountered while attempting to couple the acetamidonitromannitol 6 with an appropriate 3-carbon fragment to complete the synthesis of the necessary 9-carbon backbone. This involved deprotonation of the nitrosugar and using it as a nucleophile to attack a 3-carbon electrophile. Initially, ethyl bromopyruvate was used as an electrophile in a methanol solution of acetamidonitromannitol and NaOMe, but after 22 h no product was isolated. Addition of AgBF₄ to increase the electrophilicity of the alkyl bromide did not afford any product after 2 days. The electrophile was changed to allyl bromide, whose reaction product could be dihydroxylated and carefully oxidised to the α -ketoester moiety. This should then cyclise to give the desired sialic acid derivative. Although this reaction gave some coupled product after 24 h using NaOMe/MeOH, the majority of the crude product mixture was starting material. To rule out the possibility that the hydroxyl groups were reducing the reactivity of the acetamidonitromannitol, they were protected as isopropylidene ketals using acetone, $CuSO_4$, and catalytic H_2SO_4 (Scheme 4), a procedure that is a slight variation from that



Scheme 4 Isopropylidene protection of acetamidonitromannitol 6 and coupling with ethyl α -(bromomethyl)acrylate. *Reagents and conditions*: (a) acetone, CuSO₄, cat. H₂SO₄, 24 h; (b) ethyl α -(bromomethyl)acrylate, 0.5 M NaOH (aq.), THF, 2 days.

reported in the literature.²² Coupling of the diisopropylidene 8 with ethyl bromopyruvate was attempted using a variety of bases (0.5 M NaOH (aq.), EtNⁱPr₂, DBU, LDA) in THF, but in all cases only starting material was isolated. Coupling with allyl bromide was also attempted using NaOMe/MeOH and 0.5 M aqueous NaOH/THF, but very little coupled product was isolated. As a result, the electrophile ethyl α-(bromomethyl)acrylate was tested, with which nucleophilic attack could proceed via a Michael addition instead of an S_N2-type displacement.²³ The coupled product could then undergo ozonolysis to remove the methylene carbon, thus installing the desired α -ketoacid moiety. Ethyl α -(bromomethyl)acrylate, when stirred with unprotected acetamidonitromannitol 6 in NaOMe/MeOH solution, gave the coupled enoate ester 9a-(R,S) (Scheme 5) as a 2 : 1 (S : R) diastereomeric mixture in 72% yield on a 1 g scale. A lower yield (55%) was obtained on a larger scale (13 g), but the balance of unreacted acetamidonitromannitol (45%) was recovered and reused. Attempts to purify enoate ester 9a-(R,S) by crystallisation from EtOH-Et2O and EtOH-hexanes failed. Thus, column chromatography was used to purify the crude material, affording the diastereomeric mixture of enoate esters as a light vellow foam. The diisopropylidene-protected nitromannitol 8 was also coupled with ethyl α -(bromomethyl)acrylate using aqueous sodium hydroxide in THF to afford the enoate ester product 10-(R,S) in 81%yield as a 1.9 : 1.0 (S : R) diastereometric mixture. However, since the coupling could be performed with the unprotected nitromannitol 6, the diisopropylidene 8 was not used in this synthesis, as this avoided two unnecessary protection/deprotection steps.

The diastereomeric mixture of enoate esters 9a-(R,S) was subjected to ozonolysis followed by reductive workup to cleave the terminal vinylic CH_2 and replace it with an oxygen to install the necessary α -ketoester (Scheme 5). The ozonised product spontaneously cyclised to the pyranoside, and the desired 4Sisomer precipitated out of solution while the 4R-isomer remained in the CH₂Cl₂-MeOH solution. After filtration, a second crop of the 4S-isomer was obtained by concentrating the filtrate and crystallising it from MeOH to give a 55% yield of ethyl 4-deoxy-4nitrosialate (11a). The stereochemistry at C-4 was assigned after analysis of the H-3/H-4 and H-4/H-5 coupling constants, where the large values indicated *trans*-diaxial coupling $(J_{3ax,4} = J_{4,5} =$ 11.2 Hz versus $J_{3eq.4} = 5.0$ Hz) and that H-4 was axial, possessing the S configuration. After concentration of the filtrate, the 4Risomer was separated from most of the contaminating DMSO by column chromatography in 33% yield. The small values of all coupling constants to H-4 indicated its equatorial orientation $(J_{3eq,4} = 3.2 \text{ Hz}, J_{3ax,4} = 5.0 \text{ Hz}, J_{4,5} = 4.0 \text{ Hz})$ allowing assignment of the minor product as the 4R-isomer. From the product ratio of



Scheme 5 Synthesis of ethyl 4-deoxy-4-nitrosialate (11a) and *tert*-butyl 4-deoxy-4-nitrosialate (11b) from acetamidonitromannitol 6. *Reagents and conditions*: (a) NaOMe/MeOH, 18 h; (b) O₃, CH₂Cl₂-MeOH, -78 °C, 1 h; (c) DMS, -78 °C to RT, 16 h, fractional crystallisation.

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the ozonolysis reaction it can be reasoned that the major isomer of enone 9a possesses the 4*S*-configuration and the minor isomer is the 4*R*-isomer.

Hydrolysis of the ethyl ester proved to be problematic. The presence of an acidic proton α - to the nitro group on C-4 is the likely cause for complicating the normally straightforward basic hydrolysis of an ethyl ester. When compound 11a was treated with lithium hydroxide in THF-water at 0 °C, the major product lacked the ethyl ester but did not have the expected spectral characteristics. The signals for the protons on C-3 in the ¹H NMR spectrum were shifted downfield to 2.7 and 2.9 ppm from their normal positions at 2.4-2.5 ppm and their respective coupling constants to H-4 had decreased to 4.4 and 8.3 Hz, showing a lack of trans-diaxial coupling. In the ¹³C NMR spectrum a peak for the C-2 hemiketal carbon was not observed at its normal frequency at around 94 ppm, but an HMBC spectrum showed correlations between the H-3 protons and a carbon at 200 ppm, indicating that C-2 was a ketone; in addition, the IR spectrum showed a peak for a ketone carbonyl stretch at 1712 cm⁻¹. This, along with the lack of *trans*-diaxial coupling, seemed to indicate that the reaction product was acyclic. Also of note, the frequency for the H-4 resonance had shifted upfield from a chemical shift of 5.00 ppm to one of 4.04 ppm, and the IR spectrum showed no NO₂ stretching bands. As a consequence, it was apparent that the nitro group on C-4 had undergone a reaction. After a variety of nucleophilic de-esterification conditions failed to afford the desired material, the synthetic route was modified to use a tert-butyl ester, which can be removed under acidic conditions, in place of the ethyl ester.

Thus, acetamidonitromannitol 6 was stirred with tert-butyl α-(bromomethyl)acrylate in NaOMe/MeOH solution for 16 h to afford the enoate *tert*-butyl ester product 9b(R,S) after chromatography in 79% yield as a tan foam. The 1.4 : 1.0 (S : R) diastereometric mixture of these products was subjected to ozonolysis and reductive workup, after which the desired 4Sdiastereomer precipitated out of solution, while a mixture of 4R- and 4S-diastereomers remained in solution. The precipitate was isolated by filtration, affording the 4S-isomer of tert-butyl 4-deoxy-4-nitrosialate 11b in 33% yield, while a further 25% was isolated from the filtrate after chromatography. As with the ethyl ester, the stereochemistry at C-4 was assigned based on the large trans-diaxial coupling between H-4/H-3_{ax} and H-4/H-5 ($J_{3ax,4} = 12.9$ Hz, $J_{4,5} = 10.6$ Hz versus $J_{3eq,4} = 4.6$ Hz) for the major product isomer, as compared to the smaller coupling constants for the minor product isomer $(J_{3,4} = 3.2,$ 5.0 Hz). Using this information, the enoate ester precursors can be assigned as 4S (major diastereomer) and 4R (minor diastereomer).

Hydrolysis of the *tert*-butyl ester **11b** proceeded smoothly by stirring overnight in aqueous trifluoroacetic acid (Scheme 6). After the solvent was evaporated, 4-deoxy-4-nitrosialic acid **5** was obtained as an off-white powder in 90% yield. Attempts to improve the purity of this compound through recrystallisation or column chromatography were fruitless, as the compound partially decomposed during these attempts. These attempts were unnecessary, however, because the compound, when isolated directly from the deprotection medium, was analytically pure as determined by NMR spectroscopy and elemental analysis.



Scheme 6 Hydrolysis of *tert*-butyl ester 11b to afford 4-deoxy-4-nitrosialic acid 5. *Reagents and conditions*: (a) CF_3COOH , H_2O , RT, 18 h.

Conclusions

A synthetic route has been developed that gives access to gram quantities of 4-deoxy-4-nitrosialic acid esters, compounds that when used as synthetic intermediates open up potential pathways to previously inaccessible 4-substituted sialic acid analogues. The key synthetic step in this route was the carbon backbone extension from the coupling of the 6-carbon acetamidonitromannitol 6 with an alkyl a-(bromomethyl)acrylate. The products of this reaction could then be ozonised to give the sialic acid pyranose structure, the tert-butyl ester of which could be hydrolysed under acidic conditions. This synthetic route is modular in that many different nitroalditols could potentially be used to generate a number of α -ketoacid sugar analogues, and the products of these reactions are synthetically versatile due to the large variety of reaction types that the nitro group can undergo. Currently, the syntheses of a number of 4-modified sialic acid analogues from the compounds reported here are being pursued, in order to test these materials as substrates and/or inhibitors of various sialidase enzymes.

Experimental

Thin-layer chromatography (TLC) was performed on aluminumbacked TLC plates pre-coated with Merck silica gel 60 F_{254} . Compounds were visualised with UV light and/or staining with phosphomolybdic acid (5% solution in EtOH). Flash chromatography was performed using Avanco silica gel 60 (230-400 mesh). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Solvents used for anhydrous reactions were dried and distilled immediately prior to use. Methanol was dried and distilled over magnesium methoxide. Dichloromethane was dried and distilled over calcium hydride. Glassware for anhydrous reactions was flame-dried and cooled under a nitrogen atmosphere immediately prior to use. NMR spectra were recorded on a Varian Unity 500 MHz spectrometer. Chemical shifts (δ) are listed in ppm downfield from TMS using the residual solvent peak as an internal reference. ¹H and ¹³C NMR peak assignments are made based on ¹H–¹H COSY and ¹H–¹³C HMQC experiments. IR spectra were recorded on a Bomem IR spectrometer and samples were prepared as cast evaporative films on NaCl plates from CH₂Cl₂. Optical rotations were measured using a Perkin–Elmer 341 polarimeter and are reported in units of deg cm² g⁻¹ (concentrations reported in units of g per 100 cm³). 2-Acetamido-1,2-dideoxy-1-nitro-D-mannitol (6) was prepared from D-arabinose according to literature procedures,^{16,17} as was ethyl α -(bromomethyl)acrylate from diethyl malonate and formaldehyde;²⁴ the spectral characteristics of these molecules matched those reported in the literature.

2-Acetamido-1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1-nitro-Dmannitol (8)

2-Acetamido-1,2-dideoxy-1-nitro-D-mannitol (**6**, 15.2 g, 60.3 mmol) was dissolved in reagent-grade acetone (500 cm³). Anhydrous CuSO₄ (9.7 g, 60.8 mmol) was added along with 1 cm³ of concentrated H₂SO₄, and the light blue suspension was vigorously stirred for 24 h. The reaction was filtered through a Celite pad (3 cm) and the Celite was washed with acetone (100 cm³). The resultant filtrate was diluted with CHCl₃ (400 cm³) and washed with brine (3 × 500 cm³); the aqueous layer was neutral after the second wash. The organic layer was dried (MgSO₄), filtered, and concentrated under reduced pressure to give the diisopropylidene product **8** as a white solid (14.9 g, 44.8 mmol, 74%). The material exhibited identical NMR spectral data to that reported in the literature.²² The purity was deemed adequate for further use (mp 131–133 °C) but this could be improved by recrystallisation from CH₂Cl₂–hexanes (1 : 4) (mp 134.0–134.5 °C).

Ethyl 5-acetamido-2,3,4,5-tetradeoxy-2-methylene-4-nitro-D*glycero*-D-*galacto*-nononate, ethyl 5-acetamido-2,3,4,5-tetradeoxy-2-methylene-4-nitro-D-*glycero*-D-*talo*-nononate (9a-(*R*,*S*))

2-Acetamido-1,2-dideoxy-1-D-nitromannitol (6, 13.0 g, 51.5 mmol) was suspended in dry methanol (150 cm³). To this suspension was added a solution of sodium methoxide in methanol that had been prepared by adding sodium metal (1.3 g, 56.6 mmol) to dry methanol (75 cm³). The resulting clear light brown solution was stirred for 10 min, after which time ethyl α -(bromomethyl)acrylate (10.9 g, 56.6 mmol) was added. After 18 h, the solution was concentrated under reduced pressure to give a yellow foam which was purified by column chromatography (hexanes-EtOAc gradient solvent system from 5:1 v/v to 3:1 v/v), to afford the acrylate-coupled enone product 9a as a light yellow foam (10.3 g, 28.3 mmol, 55%) in a 2 : 1 4S : 4R diastereomeric mixture. In addition, a quantity of unreacted nitromannitol (5.8 g, 23 mmol, 45%) was also isolated and could be re-used. IR (cm⁻¹): 1374 (NO₂), 1549 (NO₂), 1666 (amide C=O), 1711 (unsaturated ester C=O), 3369 (OH). ¹H NMR (D₂O) 4S isomer: δ : 1.29 (t, 3H, J = 7.1 Hz, CH_3CH_2O), 2.07 (s, 3H, NHCOC H_3), 2.90 (dd, 1H, $J_{3a,3b} = 14.8$ Hz, $J_{3a,4} = 4.9$ Hz, H-3a), 2.98 (dd, 1H, $J_{3a,3b} =$ 14.8 Hz, $J_{3b,4} = 9.8$ Hz, H-3b), 3.45 (d, 1H, $J_{7,8} = 9.2$ Hz, H-7), $3.60 (dd, 1H, J_{8,9a} = 6.3 Hz, J_{9a,9b} = 11.9 Hz, H-9a), 3.69 (ddd, 1H,$ $J_{7,8} = 9.0$ Hz, $J_{8,9a} = 6.2$ Hz, $J_{8,9b} = 2.7$ Hz, H-8), 3.81 (dd, 1H, $J_{8,9b} = 2.7$ Hz, $J_{9a,9b} = 11.7$ Hz, H-9b), 3.86 (d, 1H, $J_{5,6} = 10.3$ Hz, H-6), 4.24 (q, 2H, J = 7.2 Hz, CH₃CH₂O), 4.55 (dd, 1H, $J_{4,5} =$ $3.3 \text{ Hz}, J_{5.6} = 10.3 \text{ Hz}, \text{H-5}, 5.35 \text{ (ddd, 1H, } J_{3a,4} = 5.0 \text{ Hz}, J_{3b,4} =$ 9.6 Hz, $J_{4.5} = 3.4$ Hz, H-4), 5.79 (s, 1H, C=C H_aH_b), 6.32 (s, 1H, C=CH_a H_b); 4*R* isomer: δ : 1.29 (t, 3H, J = 7.1 Hz, C H_3 CH₂O), 2.02 (s, 3H, NHCOCH₃), 2.91 (dd, 1H, $J_{3a,3b} = 15.0$ Hz, $J_{3a,4} =$

3.9 Hz, H-3a), 2.96 (dd, 1H, $J_{3a,3b} = 14.9$ Hz, $J_{3b,4} = 10.6$ Hz, H-3b), 3.47 (d, 1H, $J_{7.8} = 9.3$ Hz, H-7), 3.61 (dd, 1H, $J_{8.9a} =$ $6.3 \text{ Hz}, J_{9a,9b} = 11.8 \text{ Hz}, \text{H-9a}, 3.70 \text{ (ddd}, 1\text{H}, J_{7,8} = 9.0 \text{ Hz}, J_{8,9a} =$ 6.2 Hz, $J_{8,9b} = 2.7$ Hz, H-8), 3.82 (dd, 1H, $J_{8,9b} = 2.7$ Hz, $J_{9a,9b} =$ 11.8 Hz, H-9b), 3.97 (d, 1H, $J_{5.6} = 10.4$ Hz, H-6), 4.19–4.28 (m, 2H, CH₃CH₂O), 4.84 (dd, 1H, $J_{4,5} = 4.8$ Hz, $J_{5,6} = 10.4$ Hz, H-5), 5.23 (ddd, 1H, $J_{3a,4} = 4.4$ Hz, $J_{3b,4} = 10.4$ Hz, $J_{4,5} = 4.4$ Hz, H-4), 5.78 (s, 1H, C= CH_aH_b), 6.30 (s, 1H, C= CH_aH_b). ¹³C NMR (D₂O) 4S isomer: δ : 13.4 (CH₃CH₂O), 22.0 (NHCOCH₃), 33.1 (C-3), 51.2 (C-5), 62.4 (CH₃CH₂O), 63.28 (C-9), 68.4 (C-6), 69.2 (C-7), 70.61 (C-8), 86.3 (C-4), 130.6 (C=CH₂), 134.5 (C=CH₂), 168.1 (C=O), 174.5 (C=O); 4*R* isomer: δ: 13.4 (CH₃CH₂O), 21.9 (NHCOCH₃), 30.4 (C-3), 52.4 (C-5), 62.4 (CH₃CH₂O), 63.30 (C-9), 69.08 (C-6/7), 69.11 (C-6/7), 70.57 (C-8), 87.2 (C-4), 130.3 (C=CH₂), 134.6 (C=CH₂), 168.2 (C=O), 174.4 (C=O). Anal. calcd. for C14H24N2O9: C 46.15, H 6.64, N 7.69; found: C 46.51, H 6.96, N 7.47.

Ethyl 5-acetamido-2,3,4,5-tetradeoxy-6,7:8,9-di-*O*-isopropylidene-2-methylene-4-nitro-D-*glycero*-D-*galacto*-nononate, ethyl 5-acetamido-2,3,4,5-tetradeoxy-6,7:8,9-di-*O*-isopropylidene-2methylene-4-nitro-D-*glycero*-D-*talo*-nononate (10-(*R*,*S*))

2-Acetamido-1,2-dideoxy-3,4:5,6-di-O-isopropylidene-1-nitro-Dmannitol (8, 14.9 g, 44.8 mmol) was dissolved in THF (500 cm³) along with ethyl α -(bromomethyl)acrylate (11.2 g, 58.0 mmol). An aqueous solution of NaOH (0.5 M; 116 cm³, 58 mmol) was added dropwise via an addition funnel over 30 min and the turbid yellow solution was stirred at room temperature. After 2 days, the reaction was diluted with 400 cm³ water and extracted with CH_2Cl_2 (3 × 300 cm³). The organic layer was dried (MgSO₄), filtered, and concentrated under reduced pressure to a dark yellow oil. This was purified by flash chromatography (CH₂Cl₂-methanol gradient solvent system from pure CH_2Cl_2 to 20: 1 v/v) to afford the product 10 as a light yellow syrup (16.2 g, 36.4 mmol, 81%) in a 1.9 : 1 diastereomeric mixture. 4S isomer: $[a]_{D}^{20}$ -29.4 (c 1.14, CHCl₃). IR (cm⁻¹): 1372 (NO₂), 1553 (NO₂), 1634 (C=C), 1666 (amide C=O), 1714 (unsaturated ester C=O), 3295 (amide NH). ¹H NMR (CDCl₃) 4S-isomer: δ : 1.31 (t, 3H, J = 7.1 Hz, CH₃CH₂O), 1.34 (s, 6H, CMe₂), 1.38 (s, 3H, CMe₂), 1.39 (s, 3H, CMe₂), 2.07 (s, 3H, NHCOCH₃), 2.88–2.90 (m, 2H, H-3_{ax}, H-3_{eq}), 3.828 (dd, 1H, $J_{9a,9b} = 8.8$ Hz, $J_{8,9a} = 12.2$ Hz, H-9a), 3.829 (d, 1H, $J_{7,8} = 8.8$ Hz, H-7), 3.93–3.98 (m, 2H, H-6, H-8), 4.13 (dd, 1H, $J_{9a,9b} = 8.8$ Hz, $J_{8,9b} = 6.3$ Hz, H-9b), 4.23 (q, 2H, J = 7.1 Hz, CH_3CH_2O , 4.56 (dt, 1H, $J_{4.5} = 2.9$ Hz, $J_{5.6} = J_{5.NH} = 9.8$ Hz, H-5), 5.26 (ddd, 1H, $J_{3a,4} = 5.9$ Hz, $J_{3b,4} = 8.8$ Hz, $J_{4,5} = 2.9$ Hz, H-4), 5.71 (s, 1H, C=C H_aH_b), 6.15 (d, 1H, $J_{5,NH}$ = 9.8 Hz, NHCOCH₃), 6.30 (s, 1H, C=CH_a H_b); 4*R*-isomer: δ : 1.32 (t, 3H, J = 7.1 Hz, CH₃CH₂O), 1.37 (s, 6H, CMe₂), 1.41 (s, 3H CMe₂), 1.42 (s, 3H, CMe₂), 2.01 (s, 3H, NHCOCH₃), 2.94 (dd, 1H, $J_{3a,3b} = 14.9$ Hz, $J_{3a,4} = 3.7$ Hz, H-3a), 3.02 (dd, 1H, $J_{3a,3b} = 14.9$ Hz, $J_{3b,4} = 10.5$ Hz, H-3b), 3.80–3.84 (m, 2H, H-7, H-9a), 3.95–4.01 (m, 1H, H-8), 4.10 (dd, 1H, $J_{5,6} = 9.5$ Hz, $J_{6,7} = 5.8$ Hz, H-6), 4.18 (dd, 1H, $J_{9a,9b} +$ $J_{8,9b} = 14.9$ Hz, H-9b), 4.24 (q, 2H, J = 7.1 Hz, CH₃CH₂O), 4.66 (dt, 1H, $J_{4,5} = 4.9$ Hz, $J_{5,6} = J_{5,NH} = 8.8$ Hz, H-5), 5.10 (dt, 1H, $J_{3b,4} = 10.7$ Hz, $J_{3a,4} + J_{4,5} = 8.5$ Hz, H-4), 5.71 (s, 1H, $C=CH_{a}H_{b}$, 6.11 (d, 1H, $J_{5,NH} = 8.3$ Hz, NHCOCH₃), 6.28 (s, 1H, C=CH_a H_b). ¹³C NMR (CDCl₃) 4S isomer: δ : 13.9 (CH₃CH₂O), 23.2 (NHCOCH₃), 25.1, 26.4, 27.0, 27.4 (C(CH₃)₂ × 2), 34.0 (C-3), 51.9 (C-5), 61.0 (CH₃CH₂O), 67.6 (C-9), 76.7 (C-8), 79.2 (C-6), 80.5 (C-7), 85.4 (C-4), 109.6, 110.7 (C(CH₃)₂ × 2), 129.7 (C=CH₂), 134.0 (C=CH₂), 165.5 (C=O), 170.2 (C=O); 4R isomer: δ : 13.9 (CH₃CH₂O), 23.0 (NHCOCH₃), 25.1, 26.4, 26.5, 27.2 (C(CH₃)₂ × 2), 31.8 (C-3), 53.7 (C-5), 61.0 (CH₃CH₂O), 67.9 (C-9), 77.0 (C-8), 79.3 (C-6), 80.5 (C-7), 87.1 (C-4), 109.8, 110.9 (C(CH₃)₂ × 2), 128.9 (C=CH₂), 134.5 (C=CH₂), 165.8 (C=O), 170.2 (C=O). Anal. calcd. for C₂₀H₃₂N₂O₉ C 54.04, H 7.26, N 6.30; found: C 54.01, H 7.21, N 6.31.

Ethyl 5-acetamido-3,4,5-trideoxy-4-nitro-D-*glycero*-β-D-*galacto*non-2-ulopyranosonate (11a)

Ozone was bubbled through a cooled $(-78 \degree C)$ solution of enoate ester **9a** (10.0 g, 27.4 mmol, ~ 2 : 1 diastereomeric mixture) in a 1 : 1 v/v mixture of dry CH₂Cl₂ and dry methanol (300 cm³) for 1 h, after which time the reaction became light blue in colour. Addition of dimethyl sulfide (5 cm^3) caused the product to precipitate. The resulting mixture was allowed to warm to room temperature over 16 h with stirring, after which time the cloudy white suspension was cooled in ice and vacuum-filtered. The white flocculent solid was washed with CH₂Cl₂ (100 cm³) and dried under vacuum to give the sialoside **11a** (4.8 g, 13.1 mmol, 48%). A second crop was obtained by concentrating the filtrate under reduced pressure to give a yellow syrup, adding methanol (20 cm³), and isolating the resultant white flocculent solid as above to give a further 0.68 g of sialoside **11a** (1.9 mmol, 7%), mp 175–177 °C (dec.). [a]_D²⁰ –28.9 (c 0.63, DMSO). IR (cm⁻¹): 1373 (NO₂), 1544 (NO₂), 1658 (amide C=O), 1735 (ester C=O), 3330 (OH). ¹H NMR (D₂O) δ: 1.15 (t, $3H, J = 7.1 Hz, CH_3CH_2O$, 1.84 (s, $3H, NHCOCH_3$), 2.40–2.50 (m, 2H, H- 3_{ax} , H- 3_{eq}), 3.44 (d, 1H, $J_{7,8} = 9.3$ Hz, H-7), 3.46 (dd, 1H, $J_{9a,9b} = 11.7$ Hz, $J_{9a,8} = 6.1$ Hz, H-9a), 3.59 (ddd, 1H, $J_{7,8} =$ 9.2 Hz, $J_{8,9a} = 6.2$ Hz, $J_{8,9b} = 2.7$ Hz, H-8), 3.68 (dd, 1H, $J_{9a,9b} =$ 11.9 Hz, $J_{8,9b} = 2.7$ Hz, H-9b), 4.11 (d, 1H, $J_{5,6} = 10.5$ Hz, H-6), 4.10–4.21 (m, 2H, CH₃CH₂O), 4.44 (t, 1H, $J_{4,5} = J_{5,6} = 10.7$ Hz, H-5), 5.00 (dt, 1H, $J_{3eq,4} = 5.0$ Hz, $J_{3ax,4} = J_{4,5} = 11.2$ Hz, H-4). ¹³C NMR (CD₃OD) δ: 13.1 (CH₃CH₂O), 21.3 (NHCOCH₃), 35.9 (C-3), 49.0 (C-5), 62.1 (CH₃CH₂O), 63.5 (C-9), 68.6 (C-7), 70.1 (C-6), 70.4 (C-8), 83.3 (C-4), 94.3 (C-2), 169.1 (C=O), 172.8 (C=O). Anal. calcd. for C₁₃H₂₂N₂O₁₀: C 42.62, H 6.05, N 7.65; found: C 42.77, H 6.12, N 7.51.

tert-Butyl α-(bromomethyl)acrylate

2-Methylpropene (25.6 g, 0.456 mol) was condensed in a Schlenk tube at -78 °C. To this was added a solution of α -(bromomethyl)acrylic acid (26.2 g, 0.159 mol, prepared according to ref. 19) in dry CH₂Cl₂ (120 cm³), along with 0.5 cm³ conc. H₂SO₄. The Schlenk tube was sealed, and the reaction mixture was allowed to warm to room temperature. Some α -(bromomethyl)acrylic acid that had precipitated at -78 °C re-dissolved upon reaching room temperature, and the solution was stirred overnight. The solution was then concentrated to half its volume under reduced pressure to remove excess 2-methylpropene and was diluted with CH₂Cl₂ (300 cm³) and washed with sat. NaHCO₃ (2 × 400 cm³). The organic layer was dried (MgSO₄), filtered, and concentrated under reduced pressure to afford the product as a light yellow oil (27.6 g, 0.125 mmol, 79%). The material exhibited identical spectra data to those reported in the literature.²⁵

tert-Butyl 5-acetamido-2,3,4,5-tetradeoxy-2-methylene-4-nitro-Dglycero-D-galacto-nononate, *tert*-butyl 5-acetamido 2,3,4,5tetradeoxy-2-methylene-4-nitro-D-glycero-D-talo-nononate (9b-(R,S))

2-Acetamido-1,2-dideoxy-4-nitro-D-mannitol (6, 12.0 g, 47.6 mmol) was suspended in dry methanol (150 cm³). A solution of sodium methoxide, prepared by reacting sodium metal (1.5 g, 65 mmol) with dry methanol (75 cm³), was then added. The resulting clear, brown solution was stirred for 10 min, after which time tertbutyl α-(bromomethyl)acrylate (12.6 g, 39.2 mmol) was added. The solution was stirred under nitrogen for 20 h and was concentrated under reduced pressure to a dark brown foamy syrup. This was purified by flash chromatography (CH2Cl2-MeOH gradient solvent system from 5:1 v/v to 3:1 v/v) to afford the product **9b** as a tan foam (12.2 g, 31.1 mmol, 79%) in a 1.4 : 1.0 4S : 4R diastereomeric ratio. IR (cm⁻¹): 1152 (C–O–C), 1370 (NO₂), 1552 (NO₂), 1659 (amide C=O), 1707 (unsaturated ester C=O), 3316 (OH). ¹H NMR (D₂O) 4S-isomer: δ : 1.49 (s, 9H, C(CH₃)₃), 2.07 (s, 3H, NHCOCH₃), 2.86 (dd, 1H, $J_{3a,3b} = 14.5$ Hz, $J_{3a,4} =$ 4.8 Hz, H-3a), 2.94 (dd, 1H, $J_{3a,3b} = 14.6$ Hz, $J_{3b,4} = 9.9$ Hz, H-3b), 3.44 (d, 1H, $J_{7.8} = 9.2$ Hz, H-7), 3.60 (dd, 1H, $J_{9a,9b} = 11.8$ Hz, $J_{8,9b} = 6.2$ Hz, H-9a), 3.67–3.71 (m, 1H, H-8), 3.81 (dd, 1H, $J_{9a,9b} =$ 11.8 Hz, $J_{8.9b} = 2.8$ Hz, H-9b), 4.53 (dd, 1H, $J_{4.5} = 3.3$ Hz, $J_{5.6} =$ 10.2 Hz, H-5), 5.36 (ddd, 1H, $J_{3a,4} = 4.8$ Hz, $J_{3b,4} = 9.8$ Hz, $J_{4,5} =$ 3.5 Hz, H-4), 5.71 (s, 1H, C= CH_aH_b), 6.22 (s, 1H, C= CH_aH_b); 4*R*-isomer: δ : 1.49 (s, 9H, C(CH₃)₃), 2.02 (s, 3H, NHCOCH₃), 2.84–2.94 (m, 2H, H-3a, H-3b), 3.48 (d, 1H, $J_{7.8} = 9.2$ Hz, H-7), 3.61 (dd, 1H, $J_{9a,9b} = 11.7$ Hz, $J_{8,9b} = 6.22$ Hz, H-9a), 3.67–3.71 (m, 1H, H-8), 3.82 (dd, 1H, $J_{9a,9b} = 11.8$ Hz, $J_{8,9b} = 2.8$ Hz, H-9b), $3.97 (d, 1H, J_{5,6} = 10.4 Hz, H-6), 4.83 (dd, 1H, J_{4,5} = 5.0 Hz, J_{5,6} =$ 10.5 Hz, H-5), 5.21 (dt, 1H, $J_{3a,4} + J_{3b,4} + J_{4,5} = 19.8$ Hz, H-4), 5.71 (s, 1H, C=C H_aH_b), 6.21 (s, 1H, C=C H_aH_b). ¹³C NMR (D₂O) 4S isomer: δ: 22.0 (NHCOCH₃), 27.3 (C(CH₃)₃), 33.4 (C-3), 51.2 (C-5), 63.3 (C-9), 68.4 (C-6), 69.2 (C-7), 70.6 (C-8), 83.6 (C(CH₃)₃), 86.5 (C-4), 129.8 (C=CH₂), 136.0 (C=CH₂), 167.3 (C=O), 174.4 (C=O); 4*R* isomer: δ : 21.9 (NHCOCH₃), 27.3 (C(CH₃)₃), 30.7 (C-3), 52.3 (C-5), 63.3 (C-9), 69.10 (C-6), 69.14 (C-7), 70.6 (C-8), 83.6 ($C(CH_3)_3$), 87.5 (C-4), 129.5 (C= CH_2), 136.1 ($C=CH_2$), 167.5 (C=O), 174.5 (C=O). Anal. calcd. for C₁₆H₂₈N₂O₉: C 48.97, H 7.19, N 7.14; found: C 49.04, H 6.97, N 7.06.

tert-Butyl 5-acetamido-3,4,5-trideoxy-4-nitro-D-*glycero*-β-D*galacto*-non-2-ulopyranosonate (11b)

A solution of *tert*-butyl enoate ester **9b**-(R,S) (10.7 g, 27.3 mmol, 1.4 : 1.0 diastereomeric mixture) was prepared in a 1 : 1 v/v mixture of dry CH₂Cl₂ and dry methanol (300 cm³), which was cooled to -78 °C. Ozone was bubbled through the cold solution for 1 h 45 min, after which time the colour was light green. The ozonides were reduced with dimethyl sulfide (5 cm³), which caused the product to precipitate. The reaction was stirred overnight and allowed to warm to room temperature, and was then cooled in ice and filtered. The white solid was washed with CH₂Cl₂ (75 cm³) and dried to afford the product **11b** as a white solid (3.58 g, 9.08 mmol, 33%). The filtrate, which contained a mixture of DMSO, **11b** and its C-4 epimer, was concentrated and purified by flash chromatography (CH₂Cl₂-methanol gradient solvent system from 10 : 1 v/v to 3 : 1 v/v) to afford a further 2.70 g of sialoside

11b (6.8 mmol, 25%) as a white foamy solid, mp 147–149 °C (dec.). [*a*]₂₀²⁰ –25.9 (*c* 0.695, DMSO). IR (cm⁻¹): 1371 (NO₂), 1556 (NO₂), 1652 (amide C=O), 1724 (ester C=O), 3358 (OH). ¹H NMR (D₂O) δ : 1.50 (s, 9H, C(CH₃)₃), 1.98 (s, 3H, NHCOCH₃), 2.52 (dd, 1H, $J_{3ax,3eq} = J_{3ax,4} = 12.9$ Hz, H-3_{ax}), 2.61 (dd, 1H, $J_{3ax,3eq} = 13.0$ Hz, $J_{3eq,4} = 4.6$ Hz, H-3_{eq}), 3.59 (d, 1H, $J_{7,8} = 8.2$ Hz, H-7), 3.63 (dd, 1H, $J_{9a,9b} = 11.8$ Hz, $J_{8,9a} = 6.3$ Hz, H-9a), 3.75 (ddd, 1H, $J_{7,8} = 8.9$ Hz, $J_{8,9a} = 6.2$ Hz, $J_{8,9b} = 2.6$ Hz, H-8), 3.83 (dd, 1H, $J_{9a,9b} = 11.8$ Hz, $J_{8,9b} = 2.7$ Hz, H-9b), 4.23 (d, 1H, $J_{5,6} = 10.5$ Hz, H-6), 4.57 (dd, 1H, $J_{4,5} = J_{5,6} = 10.6$ Hz, H-5), 5.13 (dt, 1H, $J_{3eq,4} = 4.6$ Hz, $J_{3ax,4} + J_{4,5} = 23.1$ Hz). ¹³C NMR (CD₃OD) δ : 22.6 (NHCOCH₃), 28.1 (C(CH₃)₃), 50.3 (C-5), 64.8 (C-9), 70.0 (C-7), 71.4 (C-6), 71.8 (C-8), 84.3 (*C*(CH₃)₃), 84.6 (C-4), 95.6 (C-2), 169.6 (C-1), 174.1 (NHCOCH₃). Anal. calcd. for C₁₅H₂₆N₂O₁₀: C 45.68, H 6.65, N 7.10; found: C 45.81, H 6.71, N 7.09.

3,4,5-Trideoxy-4-nitro-D-*glycero*-β-D-*galacto*-non-2ulopyranosonic acid (5)

Trifluoroacetic acid (6.0 cm³) was added to a suspension of tertbutyl ester **11b** (148 mg, 0.375 mmol) in water (12 cm³). The clear, colourless solution was stirred at room temperature for 16 h, after which time the solution took on a light pink tinge. The solution was concentrated under reduced pressure to afford the de-esterified product 5 as an off-white powder (114 mg, 0.338 mmol, 90%), mp 175–177 °C (dec.). $[a]_{D}^{20}$ –23 (c 0.21, DMSO). IR (cm⁻¹): 1372 (NO₂), 1557 (NO₂), 1664 (amide C=O), 1721 (acid C=O), 3338 (OH/NH). ¹H NMR (D₂O) δ : 1.98 (s, 3H, NHCOCH₃), 2.50 (dd, $1H, J_{3ax,3eq} = J_{3ax,4} = 12.8 Hz, H-3_{ax}), 2.58 (dd, 1H, J_{3ax,3eq} = 12.9 Hz,$ $J_{3eq,4} = 4.6$ Hz, H-3_{eq}), 3.56 (d, 1H, $J_{7,8} = 9.4$ Hz, H-7), 3.60 (dd, 1H, $J_{9a,9b} = 11.8$ Hz, $J_{8,9a} = 6.3$ Hz, H-9a), 3.75 (ddd, 1H, $J_{7,8} =$ 9.2 Hz, $J_{8,9a} = 6.3$ Hz, $J_{8,9b} = 2.6$ Hz, H-8), 3.83 (dd, 1H, $J_{8,9b} =$ 2.6 Hz, $J_{9a,9b} = 11.8$ Hz, H-9b), 4.21 (d, 1H, $J_{5,6} = 10.3$ Hz, H-6), 4.56 (dd, 1H, $J_{4,5} = J_{5,6} = 10.5$ Hz, H-5), 5.13 (dt, 1H, $J_{3ax,4} +$ $J_{4,5} = 23.1$ Hz, $J_{3eq,4} = 4.6$ Hz). ¹³C NMR (DMSO-d₆) δ : 22.5 (NHCOCH₃), 35.4 (C-3), 48.5 (C-5), 63.3 (C-9), 68.4 (C-7), 69.3 (C-6), 69.9 (C-8), 83.7 (C-4), 93.5 (C-2), 170.06 (C=O), 170.13 (C=O). Anal. calcd. for $C_{11}H_{18}N_2O_{10}$: C 39.06, H 5.36, N 8.28; found: C 39.32, H 5.24, N 8.36.

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