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A stereocontrolled synthesis of 3-acetamido-1,3,5-trideoxy- and 1,3,5,6-tetradeoxy-1,5-imino-D-glucitol

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ABSTRACT

3-Acetamido-5-amino-3,5,6-trideoxy-D-glucono-1,5-lactam and 3-acetamido-5-amino-3,5-dideoxy-D-glucono-1,5-lactam were synthesized from corresponding 3-acetamido-3-deoxy-β-D-glucopyranosides in 63% and 35% overall yield, respectively. Acetylation followed by reduction led to the title 3-acetamido-3-deoxy derivatives of both deoxynojirimycin and 1,6-dideoxynojirimycin. The procedure developed is useful for a multi-gram scale.

1. Introduction

Iminosugars have attracted a considerable attention as potent inhibitors of glycosidases and other glycoprotein-processing enzymes.[1–4] These inhibitors have therapeutic potential for the treatment of diabetes, cancer, inflammation and viral or bacterial infections.[5–13] Hence, this interest has generated a multitude of publications on the synthesis of new iminosugars or the development of improved protocols for the preparation of already known bioactive compounds, starting from either sugars or non-sugar substrates.[14–19] Among the polyhydroxylated piperidines, the naturally occurring 1-deoxy-D-nojirimycin (1,5-dideoxy-1,5-imino-D-glucitol) has occupied a prominent position due to its excellent inhibition of glycosidases.[20] Moreover, *N*-butyl-1-deoxy-D-nojirimycin (Zavesca®) and *N*-hydroxyethyl-1-deoxy-D-nojirimycin (miglitol, Glyset®) are used in the treatment of type 1 Gaucher disease and non-insulin-dependent diabetes, respectively.[21] Modification of the 1-deoxynojirimycin structure seems to be a promising strategy on the way to discover effective and more selective inhibitors towards glycosidases of therapeutic interest. In principle, there are two main strategies employing either alteration of the ring hydroxyls or introduction of different groups on the *endo*-amino moiety. Although a great effort was paid to understanding structure–activity relationship patterns required for rational design of inhibitors there is still a lack of information. In our ongoing study, we focus on the development of syntheses of 3-acetamido-1,3,5-trideoxy-1,5-iminohexitols with respective δ-lactam as a key intermediate following a retro synthetic analysis (Scheme 1).

At present, the preparation of 3-amino-1,3-dideoxy-D-nojirimycin or its *N*-acetyl derivative (**1**) besides other regio- and stereoisomers was described only in two papers.[22,23] Both multistep syntheses started from expensive 1-deoxy-D-nojirimycin employing the nucleophilic opening of intermediate 2,3-epoxide with azide. The overall yield of 3-amino- as well as 3-acetamido-D-deoxynojirimycin was rather low, 1% (lit.[23]) and 15% (lit.[22]), respectively. Moreover, the tedious chromatographic separations could not be avoided and therefore this synthetic strategy prevents a large scale synthesis.

Herein, we wish to report on our results concerning the stereocontrolled synthesis of 3-acetamido-1,3,5-trideoxy-1,5-imino-D-glucitol (**1**) and 3-acetamido-1,3,5,6-tetradeoxy-1,5-imino-D-glucitol (3-acetamido-1,3,6-trideoxy-D-nojirimycin, **2**).

2. Results and discussion

Starting methyl β-D-glucopyranoside was routinely synthesized by reaction of D-glucose with dimethyl sulfate[24,25] and was purified through methyl tetra-*O*-acetyl-β-D-glucopyranoside **3** by acetylation of a crude reaction mixture (Scheme 2). The crystalline acetate **3** was easily obtained by a simple crystallization from water in 40% yield if 1 mol (180 g) of D-glucose was utilized. A Zemplen's

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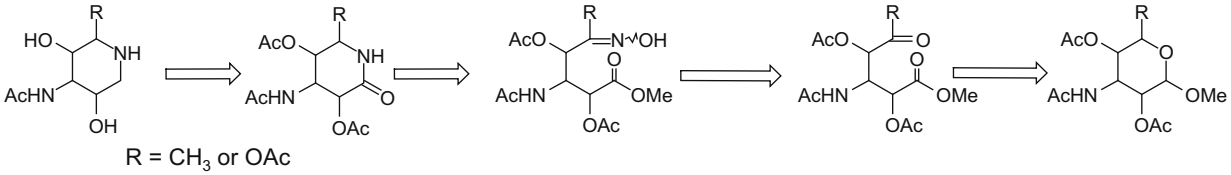
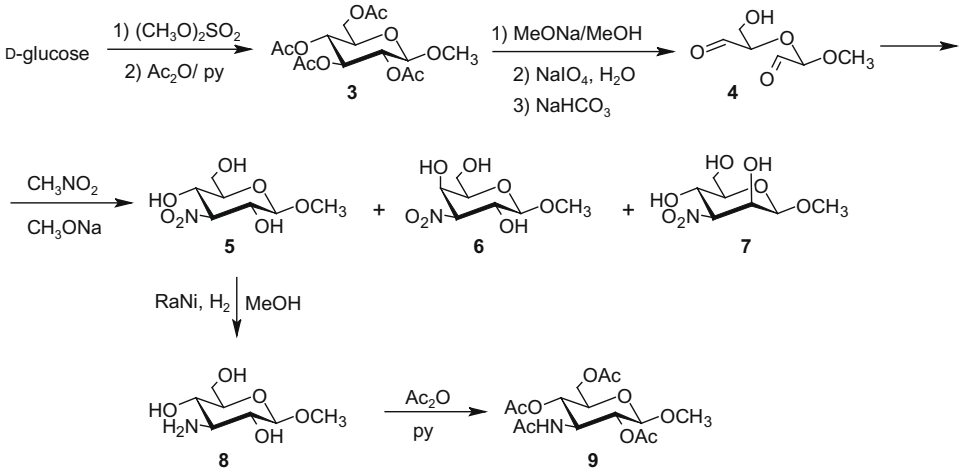


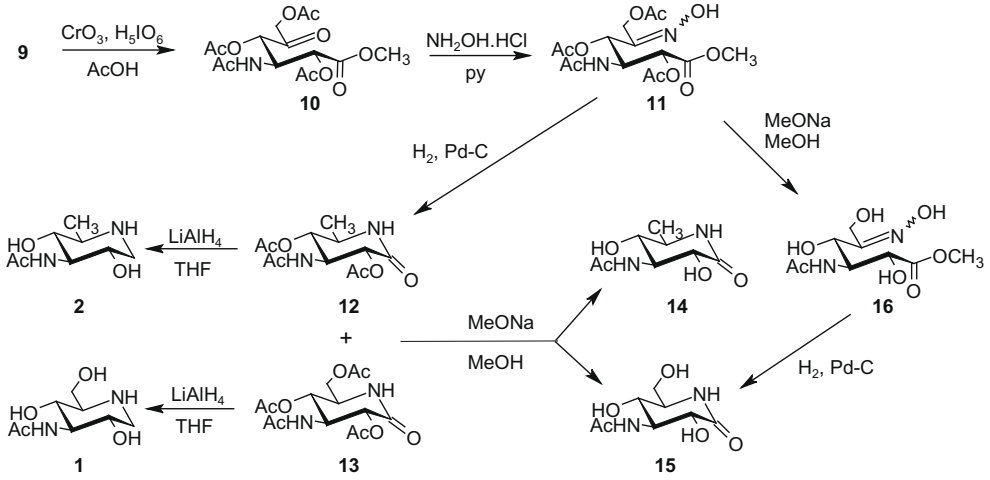
Scheme 1. Retrosynthesis of 3-acetamido-1,3,5-trideoxy- and 1,2,3,6-tetradeoxy-1,5-iminohexitols.



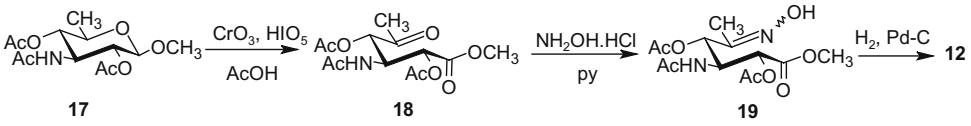
Scheme 2. The synthesis of methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-glucopyranoside (**8**).

deacetylation followed by crystallization gave methyl β-D-glucopyranoside in 90% yield. In the next step, methyl β-D-glucopyranoside was subjected to the periodate cleavage and crude dialdehyde **4** was then treated[26] with nitromethane producing a mixture of three nitropyranosides with D-*gluco* (**5**), D-*galacto* (**6**) and D-*manno* (**7**) configuration. The major 3-deoxy-3-nitro-β-D-glucopyranoside **5** was isolated by crystallization from ethyl acetate in 44% yield. The nitro group in **5** was reduced by palladium on charcoal-catalyzed hydrogenation only in low yield of 46% but using Raney nickel catalyst in methanol and increasing the hydrogen pressure the course of reduction was nearly quantitative. Pure amine **8** was obtained by crystallization in 84% yield or a crude **8** was directly peracetylated to 3-acetamido-3-deoxy-D-glucopyranoside **9** isolated again by crystallization in 90% yield. This optimized procedure makes methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-β-D-glucopyranoside (**9**) available in a multi-gram scale with crystallization as the only purification method needed.

Following the retro synthetic scheme, glucopyranoside **9** was further oxidized with chromium trioxide (2.4 equiv) according to Angyal's[27] approach producing the keto-ester **10** in 90% yield (Scheme 3). It is worth mentioning that the starting glycoside must be the β-anomer because the α-anomer gives exclusively the 1-*O*-formate. Keeping a protocol originally developed for oxidation of primary alcohols to the carboxylic acids,[28] the oxidation of **9** was also carried out in acetic acid with only 10 mol % of chromium trioxide and 2.5 equiv of periodic acid within 2 h and the keto-ester **10** was isolated by flash chromatography in 83% yield. Thus, we obtained excellent results using only 0.1 equiv of chromium trioxide instead



Scheme 3. The synthesis of deoxynojirimycins **1** and **2**.



Scheme 4. Synthesis of lactam **11**.

of its large excess. The use of other oxidizing agents as chromium chloroformate (1.3 equiv) or chromium bichromate (1.3 equiv) resulted in the formation of **10** in comparable yields (85–88%) but the removal of chromium salts was tedious. The nucleophilic addition of hydroxylamine hydrochloride on the carbonyl group of keto-ester **10** produced an inseparable crystalline mixture of isomeric *Z*/*E* oximes **11** in 85% yield. The diastereoisomeric ratio was 2:1 as determined by analysis of the ^{1}H NMR spectrum of the mixture integrating the well-resolved H-4 signals of each isomer but the exact configuration could not be assigned.

The recently developed hydrogenation protocol in the presence of palladium on charcoal was chosen for the subsequent reduction of oxime **11**.[29,30] These conditions were described for the preparation of 2,3,4-tri-*O*-acetyl-5-amino-5,6-dideoxy-D-*glucono*-1,5-lactam from methyl 2,3,4,6-tetra-*O*-acetyl-D-*xylo*-hex-5-ulosonate oxime and it was found that reduction combined with spontaneous stereoselective cyclization and reductive cleavage of the 6-acetoxy group. Nevertheless, access to the 6-hydroxy derivatives was readily achieved by deacetylation of the respective oxime prior to reduction.[29] In contrast to the published data, reduction of oxime **11** afforded an inseparable mixture of both 6-deoxy-2,4-di-*O*-acetyl lactam **12** and 2,4,6-tri-*O*-acetyl lactam **13** in 75% yield. The **12**/**13** ratio was 3 as indicated by integral intensity of H-6 protons in **12** (δ 1.21 ppm) and **13** (δ 4.23 and 4.00 ppm). After removing of acetyl groups by Zemplén's deacetylation, the corresponding lactams **14** and **15** were smoothly separated by silica gel chromatography, identified and transformed individually into acetyl lactams **12** and **13** for their characterization. Despite the presence of both (*Z*/*E*)-isomers in oxime **11**, cyclization was stereoselective and no L-derivatives were detected.

The selective access to 6-hydroxy lactam **15** was easily achieved by Zemplén's deacetylation of oxime **11** followed by catalytic hydrogenation of the crude oxime **16**. Lactam **15** was isolated in 50% yield as the only product over two steps (Scheme 3). The selective preparation of 6-deoxy lactam **12** started from methyl 3-acetamido-3,6-dideoxy-β-D-glucopyranoside **17** prepared from D-glucose.[25] Oxidation with chromium oxide and periodic acid led to the keto-ester **18** in 92% yield and subsequent reaction with hydroxylamine hydrochloride yielded a mixture of isomeric oxime **19** in 85% yield. Finally, catalytic hydrogenation of oxime **19** afforded the 6-deoxy lactam **12** as the only product in 80% yield (Scheme 4). In such a way, the key lactam **12** was synthesized in the overall yield of 63% from methyl 3-acetamido-3,6-dideoxy-β-D-glucopyranoside **17** and lactam **15** in the overall yield of 35% from methyl 3-acetamido-3-deoxy-β-D-glucopyranoside **3**.

The title compounds, 3-acetamido-1,3,5,6-tetradeoxy-1,5-imino-D-glucitol (**2**) and 3-acetamido-1,3,5-trideoxy-1,5-imino-D-glucitol (**1**) were then obtained by a common reduction of respective *O*-acetyl lactams **12** and **13** with lithium aluminium hydride in 83% and 77% yields, respectively. The remarkable chemoselectivity observed could be explained by the relative rates of three competitive reactions: reduction of lactam, reduction of acetamido group and deacetylation. In this particular case, the reduction of acetamido group is likely the slowest process. Once the *O*-acetyl groups are removed a solubility of iminoglucitols **1** and **2** decreases substantially so the acetamido group remains intact. The observation that reduction of lactams **14** and **15** was unsuccessful under identical conditions can support this hypothesis.

In conclusion, we developed an effective synthesis of 3-acetamido-3-deoxy derivatives of 1,6-dideoxynojirimycin and 1-deoxynojirimycin using β-glycosides as starting materials in a stereoselective hydrogenation–cyclization approach.[29] The evaluation of inhibition activity of compounds **1**, **2**, **14** and **15** is in progress and will be reported on later.

3. Experimental

3.1. General methods

Optical rotations were measured on a Jasco Model DIP-370 polarimeter and are given in 10^{-1} deg cm^2 g^{-1}. Melting points were determined with a Kofler hot block and are uncorrected. NMR spectra were recorded on a FT Varian Oxford-300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C) at 25 °C. Chemical shifts are expressed in parts per million downfield from Me_4Si. Assignments of ^{13}C and ^{1}H signals are based on APT, HMQC and COSY experiments. MS spectra were recorded on a ZAB-EQ mass spectrometer (VG Analytical) with Xe ionization and accelerating potential 8 kV in positive mode. Elemental analysis was performed on a CHN-Perkin–Elmer-2400 instrument. Reactions were followed on TLC on silica gel (10–40 μm, Merck) and column chromatography was carried out on silica gel (100–160 μm, Merck). Compounds on TLC plates were visualized or by spraying with 1% cerium(IV)sulfate in 10% sulfuric acid and subsequent mineralization. All solvents were dried prior to distillation and stored over molecular sieves. Solvents were removed under reduced pressure below 45 °C.

3.2. General method for the reduction of oximes

A soln of the respective oxime in glacial AcOH containing 10% palladium on charcoal was hydrogenated under H_2 pressure of 5 MPa for 48 h at 55 °C. The reaction mixture was filtered through Celite® and was concentrated to give a raw product that was eventually purified by flash chromatography.

3.3. Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-β-D-glucopyranoside (9)

A soln of methyl β-D-glucopyranoside (9.6 g, 49.4 mmol) in water (96 mL) was cooled below 10 °C by external bath and was stirred with $NaIO_4$ (23.0 g; 107.7 mmol) for 20 min. Cooling bath was then removed and stirring was continued for another 20 min. Solid $NaHCO_3$ (4.42 g; 52.6 mmol) was added portionwise and the reaction mixture was poured slowly into cooled EtOH (500 ml; 0 °C) and left in refrigerator for 1 h. Precipitated inorganic salts were removed and washed with cold EtOH (2 × 50 mL). The combined filtrate was concentrated in rotary evaporator at bath temperature below 25 °C. The residue was mixed with EtOH (100 mL), filtered and concentrated. The colourless syrup dialdehyde **4** (7.38 g, 92%) was dissolved in MeOH (63.4 mL) and treated with CH_3NO_2 (7.7 mL, 142.2 mmol).[26] After workup,[26] the residue was dissolved in MeOH (50 mL) and the soln decolourized with charcoal, concentrated and the residue was dissolved in AcOEt (100 mL) under reflux. After slow cooling at 0 °C, the 3-deoxy-3-nitro-D-glucopyranoside **5** crystallized spontaneously from the soln as white crystals (4.45 g, 44%): mp 201–202 °C, lit.[31] mp 202–204 °C. ^{1}H and ^{13}C NMR spectral data matched with those

reported.[32] The mother liquor was concentrated and crystallization from acetone (50 mL) gave a major portion of 3-deoxy-3-nitro-D-galactopyranoside **6**. Finally, the concentrated residue was separated on silica gel (petroleum ether/ethyl acetate 2:1 + 1% AcOH). Thus a combined yield 2.22 g (22%) was obtained for 3-deoxy-3-nitro-D-galactopyranoside **6**, mp 130–131 °C (lit.[33] mp 131–132 °C). ^{1}H and ^{13}C NMR spectral data matched with those reported.[34] 3-Deoxy-3-nitro-D-mannopyranoside **7** (0,74 g; 7%) was then obtained, mp 136–138 °C (lit.[33] mp 136–138 °C).

For **7**: MS (ESI) calcd for $C_7H_{14}NO_7$ [M+H$^+$]: 224, found 224.^{1}H NMR (D_2O): δ 3.36 (ddd, 1H, $J_{4,5}$ 10.0, $J_{5,6b}$ 2.3, $J_{5,6a}$ 5.9 Hz, H-5), 3.42 (s, 3H, OCH_3), 3.66 (dd, 1H, $J_{5,6a}$ 5.9, $J_{6a,6b}$ 12.3 Hz, H-6$_a$), 3.83 (dd, 1H, $J_{5,6b}$ 2.3, $J_{6a,6b}$ 12.3 Hz, H-6$_b$), 4.20 (dd, 1H, $J_{3,4}$ 10.3, $J_{4,5}$ 10.0 Hz, H-4), 4.38 (dd, 1H, $J_{1,2}$ 0.9, $J_{2,3}$ 3.2 Hz, H-2), 4.54 (d, 1H, $J_{1,2}$ 0.9 Hz, H-1), 4.73 (dd, 1H, $J_{2,3}$ 3.2, $J_{3,4}$ 10.3 Hz, H-3). ^{13}C NMR (D_2O): δ 57.0 (C-5), 60.6 (C-6), 62.3 (OCH$_3$), 69.0 (C-4), 75.8 (C-2), 89.2 (C-3), 100.5 (C-1).

Methyl 3-nitro-D-glucopyranoside **5** (5 g, 22.4 mmol) was dissolved in MeOH (300 mL) and RaNi catalyst (21 mL) was added. The reaction mixture was stirred under H_2 pressure (3.5 MPa) in autoclave for 3 h, then passed through Celite® and concentrated. Crystallization from MeOH and Et_2O yielded white crystals of 3-amino-3-deoxy-D-glucopyranoside **8** (3.64 g, 84%): mp 206–207 °C, lit.[35] mp 207–209 °C. The soln of amine **8** (3.0 g, 15.5 mmol) and Ac_2O (9.0 mL) in pyridine (5.0 mL) was stirred at rt overnight. The reaction mixture was then diluted with CH_2Cl_2 and washed three times with water. The organic layer was dried over Na_2SO_4, and then concentrated. Crystallization from EtOH gave white crystals of 3-acetamido-3-deoxy-D-glucopyranoside (**9**) (5.05 g, 90%): mp 160–162 °C, lit.[36] mp 163–164 °C.

3.4. Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-D-*xylo*-hex-5-ulosonate (10)

3.4.1. Procedure A using CrO_3

To a soln of **9** (3.86 g, 10.69 mmol) in AcOH (73.3 mL) and Ac_2O (7.7 mL), CrO_3 (2.55 g, 25.5 mmol) was added at 55 °C and the mixture was stirred for 2 h. After cooling at rt the reaction was quenched with EtOH (1 mL), the solvent evaporated and ulosonate **10** was obtained by flash chromatography on silica gel ($CHCl_3$/MeOH 40:1) as a syrup (3.41 g, 85%).

3.4.2. Procedure B using CrO_3 and H_5IO_6

To a soln of **9** (0.10 g, 0.3 mmol) in AcOH (1 mL) and Ac_2O (0.1 mL), CrO_3 (3 mg, 0.03 mmol) and H_5IO_6 (1.60 g, 7 mmol) in AcOH (5 mL) were added and the mixture was stirred at rt for 2 h. The workup according to Section 3.4.1 gave ulosonate **10** (0.08 g, 80%) as a colourless oil.

For **10**: $[\alpha]_D^{20}$ +13 (*c* 1.7, $CHCl_3$); MS (FAB) calcd for $C_{15}H_{22}NO_{10}$ [M+H$^+$]: 376.3, found 376.0; ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H, NHCOCH_3), 2.14 (s, 3H, OAc), 2.15 (s, 3H, OAc), 2.16 (s, 3H, OAc), 3.76 (s, 3H, OCH$_3$), 4.75 (d, 1H, $J_{6a,6b}$ 17.1 Hz, H-6$_a$), 4.83 (d, 1H, $J_{6a,6b}$ 17.1 Hz, H-6$_b$), 5.07 (m, 1H, H-3), 5.28 (d, 1H, $J_{2,3}$ 3.2 Hz, H-2), 5.40 (d, 1H, $J_{3,4}$ 4.4 Hz, H-4), 6.28 (d, 1H, $J_{3,NH}$ 9.7 Hz, N*H*COCH$_3$). ^{13}C NMR ($CDCl_3$): δ 20.5, 20.6, 20.6 (3 × CO*C*H$_3$), 23.2 (NHCO*C*H$_3$), 49.2 (C-3), 53.1 (OCH$_3$), 70.0 (C-6), 70.2 (C-2), 74.1 (C-4), 168.1 (C-1), 169.5, 169.6, 170.2 (3 × *C*OCH$_3$), 170.2 (NH*C*OCH$_3$), 198.5 (C-5). Anal. Calcd for $C_{15}H_{21}NO_{10}$: C, 48.00; H, 5.64; N, 3.73. Found: C, 48.20; H, 5.58; N, 3.59.

3.5. Methyl 3-acetamido-2,4,6-tri-*O*-acetyl-3-deoxy-D-xylo-*hex*-5-ulosonate oxime (11)

To a soln of **10** (3.41 g, 9.09 mmol) in pyridine (8 mL), $NH_2OH{\cdot}HCl$ (0.98 g, 14.8 mmol) was added at 0 °C. After 15 min the reaction mixture was allowed to warm up to rt then stirred for 2 h. The solvent was evaporated, the residue was dissolved in $CHCl_3$ and filtered through silica gel column ($CHCl_3$/MeOH 40:1). (*Z*/*E*)-Oxime **11** was obtained as white crystals (3.04 g, 86%). MS (FAB) calcd for $C_{15}H_{23}N_2O_{10}$ [M+H$^+$]: 391.3, found 391.2. Anal. Calcd for $C_{15}H_{22}N_2O_{10}$: C, 46.15; H, 5.68; N, 7.18. Found: C, 46.09; H, 5.57; N, 7.23.

For major **11**: ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H, NHCOCH_3), 2.02 (s, 3H, OAc), 2.10 (s, 3H, OAc), 2.15 (s, 3H, OAc), 3.69 (s, 3H, OCH$_3$), 4.95 (s, 2H, H-6$_{ab}$), 5.18 (m, 1H, H-3), 5.19 (s, 1H, H-2), 5.67 (d, 1H, $J_{3,4}$ 7.3 Hz, H-4), 5.88 (d, 1H, $J_{3,NH}$ 9.9 Hz, N*H*Ac), 9.41 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 20.6, 20.8 and 20.8 (3 × COCH$_3$), 23.2 (NHCOCH$_3$), 50.3 (C-3), 53.0 (OCH$_3$), 57.3 (C-6), 70.2 (C-4), 71.5 (C-2), 151.1 (C-5), 168.1 (C-1), 169.8, 170.4 and 170.4 (3 × *C*OCH$_3$), 170.5 (NHCOCH$_3$).

For minor **11**: ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, NHCOCH_3), 2.09 (s, 3H, OAc), 2.16 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.69 (s, 3H, OCH$_3$), 4.56 (d, 1H, $J_{6a,6b}$ 12.7 Hz, H-6$_a$), 4.92 (d, 1H, $J_{6a,6b}$ 12.7 Hz, H-6$_b$), 5.06 (d, 1H, $J_{2,3}$ 2.9 Hz, H-2), 5.18, (m, 1H, H-3), 5.89 (d, 1H, $J_{3,NH}$ 10.0 Hz, N*H*Ac), 6.33 (d, 1H, $J_{3,4}$ 7.9 Hz, H-4), 9.71 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 20.6, 20.8 and 20.8 (3 × CO*C*H$_3$), 23.2 (NHCO*C*H$_3$), 50.6 (C-3), 61.8 (OCH$_3$), 66.7 (C-6), 71.0 (C-4), 71.5 (C-2), 150.9 (C-5), 168.1 (C-1), 169.8, 170.4 and 170.4 (*C*OCH$_3$), 170.5 (NHCOCH$_3$).

3.6. 3-Acetamido-2,4-di-*O*-acetyl-5-amino-3,5,6-trideoxy-D-glucono-1,5-lactam (12), 3-acetamido-2,4,6-tri-O-acetyl-5-amino-3,5-dideoxy-D-glucono-1,5-lactam (13), 3-acetamido-5-amino-3,5,6-trideoxy-D-glucono-1,5-lactam (14) and 3-acetamido-5-amino-3,5-dideoxy-D-glucono-1,5-lactam (15)

Starting from oxime **11** (3.04 g, 7.79 mmol) in glacial AcOH (300 mL) with Pd/C catalyst (1.20 g) the hydrogenation[29] afforded an inseparable mixture of lactams **12** and **13** (1.74 g) in a 3:1 ratio. The mixture was dissolved in MeOH (100 mL), a catalytic amount of MeONa was added and the soln was stirred for 1 h. Neutralization with Dowex 50W-X (H$^+$ cycle, MeOH), filtration and evaporation of solvent gave a mixture of lactams **14** and **15**. Flash chromatography on silica gel ($CHCl_3$/MeOH 1:1) afforded the crystalline lactam **14** (0.90 g, 57% overall yield) and the syrupy lactam **15** (0.26 g, 15% overall yield).

For **14**: $[\alpha]_D^{20}$ +66 (*c* 0.4, H_2O), MS (FAB) calcd for $C_8H_{15}N_2O_4$ [M+H$^+$]: 203.2. Found *m*/*z* 203.1. ^{1}H NMR (D_2O): δ 1.16 (d, 3H, $J_{5,6}$ 6.2 Hz, H-6), 1.94 (s, 3H, NHCOCH_3), 3.30 (m, 1H, H-5), 3.38 (dd, 1H, $J_{3,4}$ 9.1, $J_{4,5}$ 9.1 Hz, H-4), 3.93 (d, 1H, $J_{2,3}$ 9.1 Hz, H-2), 3.98 (dd, 1H, $J_{2,3}$ 9.1, $J_{3,4}$ 9.1 Hz, H-3). ^{13}C NMR (D_2O): δ 18.2 (C-6), 22.4 (NHCO*C*H$_3$), 52.6 (C-5), 55.7 (C-3), 69.4 (C-2), 71.5 (C-4), 171.5 (C-1), 175.1 (NHCOCH$_3$). Anal. Calcd for $C_8H_{14}N_2O_4$: C, 47.52; H, 6.98; N, 13.85. Found: C, 47.48; H, 6.82; N, 14.10.

For **15**: $[\alpha]_D^{20}$ +58 (*c* 1.0, H_2O), MS (FAB) calcd for $C_8H_{15}N_2O_5$ [M+H$^+$]: 219.2. Found *m*/*z* 219.0. ^{1}H NMR (D_2O): δ 1.93 (s, 3H, NHCOCH_3), 3.30 (m, 1H, H-5), 3.62 (dd, 1H, $J_{5,6a}$ 3.8, $J_{6a,6b}$ 12.4 Hz, H-6$_a$), 3.65 (dd, 1H, $J_{3,4}$ 10.3, $J_{4,5}$ 10.3 Hz, H-4), 3.66 (dd, 1H, $J_{5,6b}$ 9.1, $J_{6a,6b}$ 12.4 Hz, H-6$_b$), 3.91 (d, 1H, $J_{2,3}$ 10.3 Hz, H-2), 4.02 (dd, 1H, $J_{2,3}$ 10.3, $J_{3,4}$ 10.3 Hz, H-3). ^{13}C NMR (D_2O): δ 22.4 (NHCO*C*H$_3$), 55.4, (C-3) 58.1 (C-5), 60.4 (C-6), 66.0 (C-4), 68.9 (C-2), 173.3 (C-1), 175.1 (NH*C*OCH$_3$). Anal. Calcd for $C_8H_{14}N_2O_5$: C, 44.03; H, 6.47; N, 12.84. Found: C, 44.11; H, 6.52; N, 12.54.

Standard acetylation of **14** and **15** in pyridine afforded lactams **12** and **13**, respectively.

For **12**: $[\alpha]_D^{20}$ +107 (*c* 1.0, $CHCl_3$), mp 202–204 °C, MS (FAB) calcd for $C_{12}H_{19}N_2O_6$ [M+H$^+$]: 287.3. Found *m*/*z* 287.1. ^{1}H NMR ($CDCl_3$): δ 1.21 (d, 3H, $J_{5,6}$ 6.2 Hz, H-6), 1.92 (s, 3H, NHCOCH_3), 2.10 (s, 3H, OAc), 2.13 (s, 3H, OAc), 3.67 (dq, 1H, $J_{4,5}$ 9.4, $J_{5,6}$ 6.2 Hz, H-5), 4.67 (ddd, 1H, $J_{2,3}$ 10.6, $J_{3,4}$ 10.9, $J_{3,NH}$ 9.7 Hz, H-3), 4.84 (dd, 1H, $J_{3,4}$ 10.9, $J_{4,5}$ 9.4 Hz, H-4), 5.14 (d, 1H, $J_{2,3}$ 10.6 Hz, H-2), 5.96 (d,

1H, $J_{3,NH}$ 9.7 Hz, N*H*Ac), 6.44 (br s, 1H, N*H*-ring). ^{13}C NMR ($CDCl_3$): δ 19.1 (C-6), 20.9 and 20.9 (2 × CO*C*H$_3$), 23.4 (NHCO*C*H$_3$), 50.2 (C-5), 52.0 (C-3), 70.6 (C-2), 72.7 (C-4), 167.0 (C-1), 170.5 (NH*C*OCH$_3$), 171.0 and 171.2 (2 × *C*OCH$_3$). Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.7. Found: C, 50.51; H, 6.32; N, 10.00.

For **13**: $[\alpha]_D^{20}$ +75 (*c* 1.3, $CHCl_3$), MS (FAB) calcd for $C_{14}H_{21}N_2O_8$ [M+H$^+$]: 345.3. Found *m*/*z* 345.0. ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H, NHCOC*H*$_3$), 2.09 (s, 6H, 2 × OAc), 2.13 (s, 3H, OAc), 3.83 (m, 1H, H-5), 4.00 (dd, 1H, $J_{6a,6b}$ 11.8, $J_{5,6a}$ 6.5 Hz, H-6$_a$), 4.23(dd, 1H, $J_{5,6b}$ 2.6, $J_{6a,6b}$ 11.8 Hz, H-6$_b$), 4.70 (ddd, 1H, $J_{2,3}$ 10.8, $J_{3,4}$ 10.6, $J_{3,NH}$ 9.7 Hz, H-3), 5.06 (dd, 1H, $J_{3,4}$ 10.6, $J_{4,5}$ 10.6 Hz, H-4), 5.17 (d, 1H, $J_{2,3}$ 10.8 Hz, H-2), 6.01 (d, 1H, $J_{3,NH}$ 9.7 Hz, N*H*COCH$_3$), 6.51 (br s, 1H, N*H*-ring). ^{13}C NMR ($CDCl_3$): δ 20.8, 20.8 and 20.9 (3 × CO*C*H$_3$), 23.1 (NHCO*C*H$_3$), 51.7 (C-3), 53.6 (C-5), 63.3 (C-6), 67.9 (C-4), 70.0 (C-2), 162.8 (C-1), 170.7 (*C*OCH$_3$), 170.8 (NH*C*OCH$_3$), 170.9 and 171.00 (2 × *C*OCH$_3$). Anal. Calcd for $C_{14}H_{20}N_2O_8$: C, 48.84; H, 5.85; N, 8.14. Found: C, 48.80; H, 6.01; N, 8.10.

3.7. Methyl 3-acetamido-2,4-di-*O*-acetyl-3,6-dideoxy-D-*xylo*-hex-5-ulosonate (18)

Methyl 3-acetamido-3,6-dideoxy-β-D-glucopyranoside **17** (0.40 g, 1.3 mmol)[25] was diluted with AcOH (7.6 mL) and Ac_2O (0.7 mL), CrO_3 (0.26 g, 2.6 mmol) was added at 55 °C and the mixture was stirred for 2 h. The reaction was quenched by EtOH (1 mL) and the solvent was evaporated. The residue dissolved in $CHCl_3$ was purified by flash chromatography ($CHCl_3$/MeOH 40:1). Methyl 3-acetamido-2,4-di-*O*-acetyl-3,6-dideoxy-D-*xylo*-hex-5-ulosonate (**18**) was isolated (0.39 g, 92%) as colourless oil.

For **18**: $[\alpha]_D^{20}$ +18 (*c* 1.7, $CHCl_3$). MS (FAB) calcd for $C_{13}H_{20}NO_8$ [M+H$^+$]: 318.3. Found *m*/*z* 318.0. ^{1}H NMR ($CDCl_3$): δ 1.87 (s, 3H, NHCOC*H*$_3$), 2.01 (s, 3H, OAc), 2.03 (s, 3H, OAc), 2.10 (s, 3H, H-6), 3.63 (s, 3H, OC*H*$_3$), 4.97 (ddd, 1H, $J_{2,3}$ 4.1, $J_{3,4}$ 2.4, $J_{3,NH}$ 10.0 Hz, H-3), 5.08 (d, 1H, $J_{2,3}$ 4.1 Hz, H-2), 5.18 (d, 1H, $J_{3,4}$ 2.4 Hz, H-4), 6.38 (d, 1H, $J_{3,NH}$ 10.0 Hz, N*H*COCH$_3$). ^{13}C NMR ($CDCl_3$): δ 20.5 and 20.6 (2 × *C*OCH$_3$), 22.9 (NHCO*C*H$_3$), 26.6 (C-6), 48.8 (C-3), 52.9 (OCH$_3$), 70.7 (C-2), 76.6 (C-4), 168.1 (C-1), 169.4 and 169.5 (*C*OCH$_3$), 170.1 (NH*C*OCH$_3$), 170.1 (C-5). Anal. Calcd for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.04; N. 4.41. Found: C, 49.65; H, 5.97; N, 4.28.

3.8. Methyl 3-acetamido-2,4-di-*O*-acetyl-3,6-dideoxy-D-*xylo*-hex-5-ulosonate oxime (19)

To a soln of ulosonate **18** (0.39 g, 1.21 mmol) in pyridine (0.9 mL), NH_2OH·HCl (0.11 g, 1.6 mmol) was added at 0 °C. After 15 min the reaction mixture was allowed to reach rt and stirring continued for 2 h. The solvent was evaporated, the residue was dissolved in $CHCl_3$ and purified by flash chromatography on silica gel ($CHCl_3$/MeOH 40:1). A crystalline mixture of (*Z*/*E*)-oxime **19** (ratio 2:1) was obtained (0.34 g, 85%). MS (FAB) calcd for $C_{13}H_{21}N_2O_8$ [M+H$^+$]: 333.3. Found *m*/*z* 333.2. Anal. Calcd for $C_{13}H_{20}N_2O_8$: C, 46.99; H, 6.07; N, 8.43. Found: C, 47.10; H, 6.02; N, 8.36.

For major **19**: ^{1}H NMR ($CDCl_3$): δ 1.94 (s, 3H, H-6), 1.97 (s, 3H, NHCOC*H*$_3$), 2.09 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.73 (s, 3H, OCH$_3$), 4.95 (ddd, 1H, $J_{2,3}$ 2.3, $J_{3,4}$ 7.9, $J_{3,NH}$ 10.0 Hz, H-3), 5.05 (d, 1H, $J_{2,3}$ 2.3 Hz, H-2), 5.47 (d, 1H, $J_{3,4}$ 7.9 Hz, H-4), 5.92 (d, 1H, $J_{3,NH}$ 10.0 Hz, N*H*COCH$_3$), 8.19 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 10.8 (C-6), 20.7 and 21.0 (2 × CO*C*H$_3$), 23.2 (NHCO*C*H$_3$), 50.3 (C-3), 53.1 (OCH$_3$), 71.1 (C-2), 73.4 (C-4), 153.5 (C-5), 168.1 (C-1), 169.9 and 170.3 (2 × *C*OCH$_3$), 170.3 (NH*C*OCH$_3$).

For minor **19**: ^{1}H NMR ($CDCl_3$): δ 1.89 (s, 3H, H-6), 1.99 (s, 3H, NHCOC*H*$_3$), 2.09 (s, 3H, OAc), 2.18 (s, 3H, OAc), 3.73 (s, 3H, OCH$_3$), 4.96 (ddd, 1H, $J_{2,3}$ 2.3, $J_{3,4}$ 7.0, $J_{3,NH}$ 9.1 Hz, H-3), 5.02 (d, 1H, $J_{2,3}$ 2.3 Hz, H-2), 5.95 (d, 1H, $J_{3,NH}$ 9.1 Hz, N*H*COCH$_3$), 6.28 (d, 1H, $J_{3,4}$ 7.0 Hz, H-4), 8.45 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 15.9 (C-6), 20.7 and 20.9 (2 × CO*C*H$_3$), 23.3 (NHCO*C*H$_3$), 50.1 (C-3), 53.1 (OCH$_3$), 67.2 (C-4), 71.1 (C-2), 153.8 (C-5), 168.2 (C-1), 170.0 and 170.1 (2 × *C*OCH$_3$), 170.1 (NH*C*OCH$_3$).

3.9. 3-Acetamido-1,3,5-trideoxy-1,5-imino-D-glucitol (1)

To a soln of lactam **13** (0.11 g; 0.32 mmol) in THF (5 ml) was added $LiAlH_4$ (200 mg; 5 mmol). The reaction mixture was stirred under argon for 5 h and after this period the reaction was quenched by addition of SiO_2. The solvent was removed under vacuum and chromatography on silica gel (*i*PrOH/H_2O 4:1) yielded deoxynojirimycin analogue **1** (0.05 g; 77%) as colourless solid.

For **1**: $[\alpha]_D^{20}$ +45 (*c* 0.5, H_2O), lit.[22] +40; MS (APEI) calcd for $C_8H_{17}N_2O_4$ [M+H$^+$]: 205.2. Found *m*/*z* 205.0. ^{1}H NMR (D_2O): δ 1.90 (s, 3H, NHCOC*H*$_3$), 2.42 (dd, 1H, $J_{1ax,1eq}$ 12.2, $J_{1ax,2}$ 11.3 Hz, H-1$_{ax}$), 2.52 (m, 1H, H-5), 3.07 (dd, 1H, $J_{1ax,1eq}$ 12.2, $J_{1eq,2}$ 5.3 Hz, H-1$_{eq}$), 3.14 (dd, 1H, $J_{3,4}$ 9.7, $J_{4,5}$ 9.7 Hz, H-4), 3.40 (ddd, 1H, $J_{1ax,2}$ 11.3, $J_{2,3}$ 9.7, $J_{1eq,2}$ 5.3 Hz, H-2), 3.49 (dd, 1H, $J_{6a,6b}$ 12.0, $J_{5,6a}$ 4.1 Hz, H-6$_a$), 3.56 (dd, 1H, $J_{2,3}$ 9.7, $J_{3,4}$ 9.7 Hz, H-3); 3.69 (dd, 1H, $J_{6a,6b}$ 12.0, $J_{5,6}$ 2.9 Hz, H-6$_b$). ^{13}C NMR (D_2O): δ 22.3 (NHCO*C*H$_3$), 49.2 (C-1), 59.7 (C-3), 61.0 (C-6), 62.5 (C-5), 65.8 (C-2), 69.6 (C-4), 175.2 (NH*C*OCH$_3$). Anal. Calcd for $C_8H_{16}N_2O_4$: C, 47.05; H, 7.90; N, 13.72. Found: C, 51.17; H, 8.44; N, 14.82.

3.10. 3-Acetamido-1,3,5,6-tetradeoxy-1,5-imino-D-glucitol (2)

Following the protocol described in Section 3.9 and starting from lactam **12** (0.11 g; 0.38 mmol) dideoxynojirimycin **2** (0.06 g; 86%) was obtained as a colourless solid.

For **2**: $[\alpha]_D^{20}$ +88 (*c* 0.4, H_2O), MS (APEI) calcd for $C_8H_{17}N_2O_3$ [M+H$^+$]: 189.22. Found *m*/*z* 189.1. ^{1}H NMR (D_2O): δ 1.05 (d, 3H, $J_{5,6}$ 6.2 Hz, H-6), 1.89 (s, 3 H, NHCOC*H*$_3$), 2.47 (dd, 1H, $J_{1ax,1eq}$ 12.0, $J_{1ax,2}$ 11.4 Hz, H-1$_{ax}$), 2.57 (m, 1H, H-5), 2.95 (dd, 1H, $J_{3,4}$ 9.7, $J_{4,5}$ 9.7 Hz, H-4), 3.06 (dd, 1H, $J_{1ax,1eq}$ 12.0 Hz, $J_{1eq,2}$ 4.7 Hz, H-1$_{eq}$), 3.42 (ddd, 1H, $J_{1ax,2}$ 11.4, $J_{2,3}$ 10.0 Hz, $J_{1eq,2}$ 4.7 Hz, H-2), 3.53 (dd, 1H, $J_{2,3}$ 10,0, $J_{3,4}$ 9.7 Hz, H-3). ^{13}C NMR (D_2O): δ 16.7 (C-6), 22.3 (NHCO*C*H$_3$), 49.0 (C-1), 55.8 (C-5), 59.4 (C-3), 68.9 (C-2), 74.1 (C-4), 175.2 (NH*C*OCH$_3$). Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.88. Found: C, 51.17; H, 8.44; N, 14.82.

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