4-Octulose Derivatives; Part 8:[1] Highly Stereocontrolled Synthesis of 2-Deoxy-4-octulosononitriles by Reformatsky-Type Reaction

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Abstract: 2-Deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranosononitrile (**3**) and 2-deoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*gulo*-oct-4-ulo-4,7-furanosononitrile (**5**) were prepared by a high stereocontrolled indium-mediated Reformatsky-type reaction of 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose (**1**) and 2,3:4,6-di-*O*-isopropylidene-α-L-*xylo*-hexos-2-ulofuranose (**2**) with bromoacetonitrile, repectively. The configurations at C(3) in **3** and **5** were established by chemical correlation.

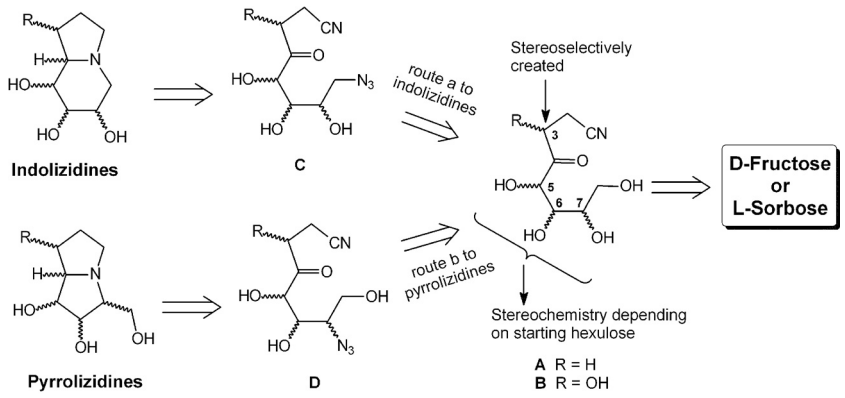
Key words: D-fructose, L-sorbose, stereoselective synthesis, 2-deoxy-4-octulosononitriles, indium

We have earlier reported the synthesis of 2,3-dideoxy-4-octulosononitriles (**A**), from common hexuloses (D-fructose and L-sorbose), as well as their use for the preparation of trihydroxylated indolizidines related with the potent glycosidase inhibitor castanospermine[2] (Scheme 1). The key step of these syntheses was a tandem double cyclization process, involving an internal reductive amination, followed by an addition-deamination reaction.

According to Scheme 1, 2-deoxy analogues **B** of the above mentioned nitriles would be excellent chiral intermediates for the preparation of tetrahydroxylated indolizidines (route a) and pyrrolizidines (route b), depending on the location of azide function [either C(8) or C(7), respectively], whereas the stereochemistry would depend on the starting hexulose. On the other hand, intermediate nitrile **B** could be synthesized by a Reformatsky-like reaction between an α-halonitrile and a suitably protected 'hexulose aldehyde'. With this objective in mind, the influence of the ring size, as well as the chirality at C(5,6,7), of the starting aldehyde-sugar on the stereochemical control of the new stereogenic centre C(3) must be investigated, prior to any other transformation leading to related azido hexuloses **C** and **D**. Thus, two readily available 'diacetone hexulose aldehyde', namely 2,3:4,5-di-*O*-isopropylidene-β-D-*arabino*-hexos-2-ulopyranose[3] (**1**) and 2,3:4,6-di-*O*-isopropylidene-α-L-*xylo*-hexos-2-ulofuranose[4] (**2**), were chosen as models.

Although α-halonitriles are less reactive under the Reformatsky conditions, recent modifications of this metodology[5] as well as the use of other metal promoter,[6] have overcame this drawback. In the present paper, we communicate the results from the above-mentioned reaction under different conditions as well as those aspects concerning the stereochemistry of the new products.

Aldehyde **1** reacted slowly with bromoacetonitrile in the presence of Zn-Cu couple[6a] to yield a 4.5:1 mixture (GC analysis) of 2-deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranosononitrile (**3**) and probably its 3-epimer, since the latter compound could not be isolated after workup and column chromatography (Scheme 2). When the same reaction was mediated by indium/TMSCl[6b] an impressive increase in the reaction rate as well as in the stereoselectivity was observed. Thus, the corresponding 3-*O*-TMS derivatives of **3** (**4**) and that of



Scheme 1 Retrosynthesis of polyhydoxyindolizidines and pyrrolizidines from 2,3-dideoxy- (**A**) and 2-deoxy-4-octulosononitriles (**B**).

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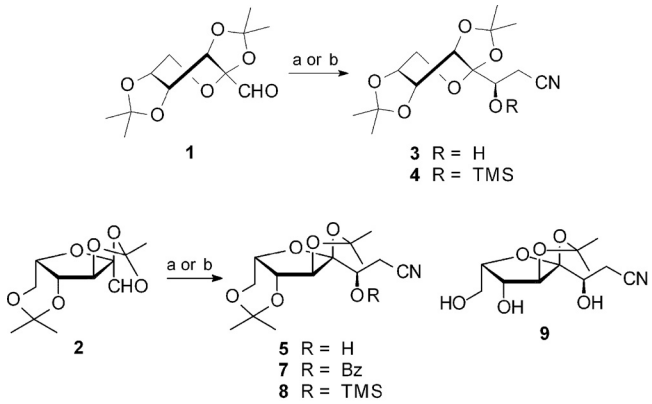

Scheme 2 *Reagents and conditions*: a) $XCH_2CN/Zn\text{-}Cu/I_2$ (cat.)/Δ; b) $BrCH_2CN/TMSCl/THF/In$/sonication.

its 3-epimer in a 19:1 ratio (GC evidence) was detected. Compounds **4** and **3** were obtained after basic and acidic workup of the reaction mixture, respectively. *O*-Desilylation of **4** gave **3**, confirming the same configuration at C(3) in both compounds.

In the same manner, reaction of aldehyde **2** with chloroacetonitrile mediated by the Zn-Cu couple (Scheme 2), gave an unresolvable mixture of 2-deoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*gulo*-oct-4-ulo-4,7-furanosononitrile (**5**) and probably its 3-epimer **6**. This mixture could partially be resolved after its *O*-benzoylation to afford the 3-*O*-benzoyl derivative of **5** (**7**). On the other hand, the indium/TMSCl-mediated reaction gave an unexpected result, since only **5** and its *O*-TMS derivative **8** was observed by GC analysis. Compound **8** could be isolated when the reaction was processed after 1 hour. Upon standing at room temperature, the reaction mixture containing **8** was transformed into the *O*-desilylated derivative **5**. In order to prove that **5** proceeding from latter reaction has the same stereochemistry to that previously prepared, it was transformed into the univocal benzoate **7**. When the workup of the reaction mixture was carried out with diethyl ether saturated with aqueous 10% HCl, compound **5** and its 6,8-deacetonated derivative **9** were obtained.

Attempts to synthesize **3** and **5** by the alkyllithium-mediated reaction of **1** and **2** with acetonitrile[6c] were unsuccessful.

The configurations at C(3) in **3** and **5** were determined as follows: **3** and the 3-*O*-benzoyl derivative of **5** (**7**) were transformed into the corresponding amides **11** and **13** by conventional treatment with H_2O_2 in basic medium. On the other hand, **11** and **13** were unequivocally obtained after transamidation of the already known methyl esters **10** and **12**[7] and hence an *R* configuration at C(3) was assigned according to Figure 1.

We can conclude that indium is an excellent metal-promoter for the synthesis of chiral β-hydroxy nitriles by Reformatsky-type reaction not only for the high yielding, but even for the high stereoselectivity of the procedure.

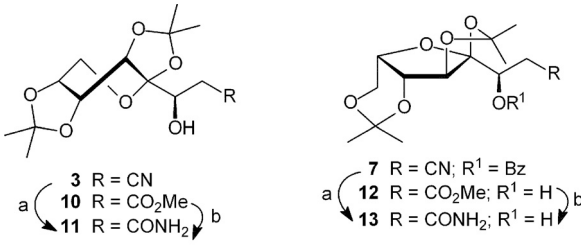

Figure 1 Preparation of Amides **11** and **13**. *Reagents and conditions*: a) H_2O_2/MeOH/aq NaOH; b) aq NH_3/MeOH/Δ.

Organic solutions were dried over $MgSO_4$ before concentration under reduced pressure. ^1H and ^{13}C NMR spectra were recorded on Bruker AMX-300, AM-300, and ARX-400 spectrometers in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin-Elmer 782 instrument, and mass spectra with a Hewlett-Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured in $CHCl_3$ (1 dm tube) with a Jasco DIP-370 polarimeter. GC was performed on a Hewlett-Packard 6890 gas chromatograph equipped with split/splitless injector, a flame-ionization detector, and a capillary HP-5 column (30 m × 0.25 mm i.d. × 0.25 μm film thickness) at: (A) 5 min at 200 °C, program to 250 °C, 10 °C/min; (B) 5 min at 180 °C program to 250 °C, 10 °C/min. The He flow rate was 1.1 mL/min, the injection port and the zone-detector temperatures were 275 °C. GC (conditions C) was performed on a Perkin-Elmer 8410 gas chromatograph equipped with a flame-ionization detector, and a steel column (2 m × 3 mm i.d.) packed with 5% OV-17 on Chromosorb W (100–120 mesh): 3 min at 200 °C, program to 230 °C, 15 °C/min. The He flow rate was 30 mL/min, the injection port and the zone-detector temperatures were 250 °C. TLC was performed on precoated silica gel 60 F_{254} aluminum sheets and detection by charring with H_2SO_4. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, MS and HRMS.

Reformatsky Reaction of Aldehyde 1 with Bromoacetonitrile; 2-Deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranosononitrile (3) and its Trimethylsilyl Derivative 4; Typical Procedures

a) *Zn-Cu Couple-Mediated*: To a stirred solution of 'diacetone aldehyde fructose'[3] **1** (400 mg, 1.55 mmol), in anhyd dioxane (20 mL) was added Zn-Cu couple (460 mg), bromoacetonitrile (200 μL, 3 mmol), and I_2 (108 mg, 0.43 mmol), and the mixture was heated at 80 °C for 40 h. GC (A) then revealed the presence of two new compounds (t_R 6.25 and 6.98 min, in a 4.5:1 ratio) and unreacted **1** (t_R 2.78 min, 30%). Additional Zn-Cu couple (150 mg), bromoacetonitrile (70 μL, 1 mmol), and I_2 (40 mg, 0.16 mmol) were needed in order to complete the reaction. The reaction mixture was filtered and concentrated to a residue that was dissolved in Et_2O (30 mL). The Et_2O layer was washed with aq 10% HCl (10 mL), H_2O, aq 10% $Na_2S_2O_3$ (10 mL), H_2O, and concentrated. Column chromatography (Et_2O–hexane, 2:1) gave pure **3;** yield: 150 mg (32%); t_R 6.25; white needles; mp 137–140 °C (Et_2O–hexane); $[\alpha]_D^{25}$ –1.5; $[\alpha]_{405}^{25}$ +6 (*c* = 1.2).

3

IR (KBr): 3410 (OH), 2256 (C≡N), 1383 and 1378 cm^{-1} (CMe_2).

^1H NMR (400 MHz): δ = 4.63 (dd, 1 H, $J_{5,6}$ = 2.7 Hz, $J_{6,7}$ = 7.9 Hz, H-6), 4.51 (d, 1 H, H-5), 4.25 (br d, 1 H, H-7), 3.99 (dt, 1 H, H-3), 3.90 (dd, 1 H, $J_{7,8ax}$ = 1.8 Hz, $J_{8ax,8eq}$ = 13 Hz, H-8*ax*), 3.77 (d, 1 H, H-8*eq*), 2.95 (dd, 1 H, $J_{2,3}$ = 3.2 Hz, $J_{2,2'}$ = 17 Hz, H-2), 2.73 (d, 1

H, $J_{3,HO}$ = 8.9 Hz, OH), 2.66 (dd, 1 H, $J_{2',3}$ = 9.3 Hz, H-2′), 1.55, 1.48, 1.45 and 1.36 [4 s, 12 H, 2 C(CH_3)$_2$].

^{13}C NMR (100 MHz): δ = 118.49 (C-1), 109.28 and 109.18 (2 *C*Me$_2$), 102.84 (C-4), 70.66 (C-7), 70.11 (C-6), 69.98 (C-5), 69.35 (C-3), 61.55 (C-8), 26.60, 25.91, 25.60 and 23.93 [2 C(*C*H$_3$)$_2$] and 21.15 (C-2).

Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.55; H, 6.85; N, 4.84.

b) *Indium/TMSCl-Mediated*: To a suspension of indium powder (220 mg, 1.9 mmol) in anhyd THF (2 mL), was added bromoacetonitrile (360 μL, 5.2 mmol) and the mixture was stirred at 0 °C for 10 min, and then at r.t. for additional 10 min. The reaction mixture was cooled at 0 °C and aldehyde **1** (310 mg, 1.2 mmol) dissolved in the same solvent (3 mL), and Me_3SiCl (460 μL, 3.8 mmol) were successively added and the whole mixture was stirred at 0 °C for 1 h. GC (A) revealed two main compounds (t_R 6.56 and 7.58 min, in a 19:1 ratio). The reaction mixture was diluted with Et_2O (15 mL) and the Et_2O layer was washed with aq 10% $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine and concentrated to a residue that was submitted to column chromatography (Et_2O–hexane, 1:2) to afford **4**; yield: 260 mg (58%); t_R 6.56 min; white needles mp 129–131 °C (Et_2O–hexane); $[\alpha]_D^{26}$ –3, $[\alpha]_{405}^{28}$ +2.5 (*c* = 1).

4

IR (KBr): 2248 (C≡N), 1382 and 1372 cm^{-1} (CMe$_2$).

^{1}H NMR (400 MHz): δ = 4.62 (dd, 1 H, $J_{5,6}$ = 2.6 Hz, $J_{6,7}$ = 7.9 Hz, H-6), 4.42 (d, 1 H, H-5), 4.24 (br d, 1 H, H-7), 4.01 (dd, 1 H, $J_{2,3}$ = 3 Hz, $J_{2',3}$ = 8.2 Hz, H-3), 3.87 (dd, 1 H, $J_{7,8ax}$ = 1.7, $J_{8ax,8eq}$ = 12.9 Hz, H-8*ax*), 3.74 (d, 1 H, H-8*eq*), 2.90 (dd, 1 H, $J_{2,2'}$ = 16.9 Hz, H-2), 2.68 (d, 1 H, H-2′), 1.53, 1.49, 1.41 and 1.36 [4 s, 12 H, 2 C(CH_3)$_2$], and 0.27 [s, 9 H, Si(CH_3)$_3$].

^{13}C NMR (100 MHz): δ = 119.16 (C-1), 109.04 and 108.83 (2 *C*Me$_2$), 103.33 (C-4), 70.96, 70.81, 70.35, and 69.41 (C-3,5,6,7), 61.17 (C-8), 26.65, 26.58, 25.51 and 23.97 [2 C(*C*H$_3$)$_2$], 21.48 (C-2), and 0.60 [Si(CH_3)$_3$].

Anal. Calcd for $C_{17}H_{29}NO_6Si$: C, 54.96; H, 7.87; N, 3.77. Found: C, 55.57; H, 8.10; N, 3.91.

When the reaction was carried out as above with indium powder (350 mg, 3 mmol), bromoacetonitrile (600 μL, 8.6 mmol), aldehyde **1** (500 mg, 1.94 mmol), and Me_3SiCl (740 μL, 6 mmol), but diluting with Et_2O saturated with aq 5% HCl and stirred for 10 min, followed by the same workup, the *O*-desilylated compound **3** was obtained; yield: 380 mg (66%).

O-Desilylation of Compound 4

To a stirred solution of **4** (230 mg, 0.62 mmol) in THF (3 mL) was added TBAF trihydrate (205 mg, 0.65 mmol) and the mixture was left at r.t. for 1 h. TLC (Et_2O–hexane, 2:1) then showed the presence of **3**. The reaction mixture was concentrated and the residue was partitioned between Et_2O (30 mL) and brine (10 mL). The organic phase was separated and concentrated. Column chromatography (Et_2O–hexane, 2:3) of the residue afforded pure **3**; yield: 170 mg (quantitative).

Reformatsky Reaction of Aldehyde 2 with Haloacetonitriles

a) *Zn-Cu Couple-Mediated*: The above typical procedure was applied to 'diacetone aldehyde L-sorbose'[4] **2** (2.6 g, 10.1 mmol), in anhyd dioxane (30 mL), with Zn-Cu couple (3 g), chloroacetonitrile (1.25 mL, 20 mmol), and I_2 (700 mg, 2.76 mmol) for 2 h at 80 °C. GC (C) then revealed the presence of two new compounds (t_R 6.73 and 7.59 min, in a 4:1 ratio). Workup of the reaction mixture as above gave an unresolvable mixture of **5** (t_R 6.73 min) and its 3-epimer **6** (t_R 7.59 min); yield: 1.30 g (43%).

Conventional benzoylation of above mixture (1 g, 3.3 mmol) in CH_2Cl_2 (25 mL) with BzCl (0.5 mL, 4.3 mmol) and Et_3N (1.2 mL, 8.7 mmol) for 6 h, gave after workup and column chromatography (Et_2O–hexane, 1:3) pure **7**; yield: 1 g (72%); colorless syrup; $[\alpha]_D^{25}$ –22 (*c* = 1.2).

7

IR (neat): 2255 (C≡N), 1733 (C=O benzoate), 1386 and 1376 cm^{-1} (CMe$_2$).

^{1}H NMR (400 MHz): δ = 8.12 (d, 2 H-*ortho*, PhCO), 7.60 (t, 1 H-*para*, PhCO), 7.46 (t, 2 H-*meta*, PhCO), 5.71 (dd, 1 H, $J_{2,3}$ = 4.7 Hz, $J_{2',3}$ = 7.2 Hz, H-3), 4.38 (s, 1 H, H-5), 4.33 (d, 1 H, $J_{6,7}$ = 2.3 Hz, H-6), 4.17 (br dd, 1 H, H-7), 4.08 (dd, 1 H, $J_{7,8}$ = 2.1 Hz, $J_{8,8'}$ = 13.6 Hz, H-8), 4.03 (br d, 1 H, H-8′), 3.14 (dd, 1 H, $J_{2,2'}$ = 17.2 Hz, H-2), 3.09 (dd, 1 H, H-2′), 1.52, 1.45, and 1.43 [3 s, 12 H, 2 C(CH_3)$_2$].

^{13}C NMR (100 MHz): δ = 165.01 (Ph*C*O), 133.65, 130.10, 129.08 and 128.62 (*C*$_6$H$_5$CO), 116.81 (C-1), 113.43 and 113.30 (C-4 and *C*Me$_2$ dioxolane), 97.69 (*C*Me$_2$ dioxane), 84.84 (C-5), 73.36 (C-6), 73.00 (C-7), 68.68 (C-3), 60.25 (C-8), 28.95 and 18.85 [C(CH_3)$_2$, dioxane], 27.55 and 26.76 [C(CH_3)$_2$, dioxolane] and 18.90 (C-2).

HRMS (LSIMS): *m*/*z* calcd for $C_{21}H_{25}NNaO_7$: 426.1529; found: 426.1528 [M$^+$ + Na] (deviation + 0.2 ppm).

A second fraction (200 mg) contained **7** slightly contaminated with its 3-epimer.

b) *Indium/TMSCl-Mediated*: To a suspension of indium powder (350 mg, 3 mmol) in anhyd THF (3 mL), was added bromoacetonitrile (480 μL, 6.9 mmol) and the mixture stirred at 0 °C for 10 min, and then at r.t. for an additional 10 min. The reaction mixture was cooled at 0 °C and aldehyde **2** (415 mg, 1.6 mmol), dissolved in the same solvent (4 mL), and Me_3SiCl (610 μL, 5.1 mmol) were successively added and the whole mixture was stirred at 0 °C for 4 h. GC (B) revealed the presence of **2** (20%) and two new compounds (t_R 8.96 and 9.66 min, in a 8:1 ratio). The reaction mixture was diluted with Et_2O (15 mL) and the Et_2O layer was washed with aq 10% $NaHCO_3$. The organic phase was separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic extracts were washed with brine and concentrated to a residue that was submitted to column chromatography (Et_2O–hexane, 2:1) to afford **5**; yield: 300 mg (78%); t_R 8.96 min; colorless thick syrup; $[\alpha]_D^{28}$ +7, $[\alpha]_{405}^{28}$ +24.5 (*c* = 1).

5

IR (neat): 3445 (OH), 2253 (C≡N), 1385, 1380, and 1376 cm^{-1} (CMe$_2$).

^{1}H NMR (400 MHz): δ = 4.55 (br s, 1 H, H-5), 4.36 (br d, 1 H, $J_{6,7}$ = 2.1 Hz, H-6), 4.17 (dt, 1 H, H-3), 4.14 (br t, 1 H, H-7), 4.08 (dd, 1 H, $J_{7,8}$ = 2.1 Hz, $J_{8,8'}$ = 13.6 Hz, H-8), 4.02 (br d, 1 H, H-8′), 2.97 (dd, 1 H, $J_{2,3}$ = 3.4 Hz, $J_{2,2'}$ = 16.9 Hz, H-2), 2.75 (d, 1 H, $J_{3,OH}$ = 8.8 Hz, HO-3), 2.73 (dd, 1 H, $J_{2',3}$ = 8.9 Hz, H-2′), 1.52, 1.45, 1.44, and 1.39 [4 s, 12 H, 2 C(CH_3)$_2$].

^{13}C NMR (100 MHz): δ = 118.15 (C-1), 114.47 and 113.23 (C-4 and *C*Me$_2$ dioxolane), 97.64 (*C*Me$_2$ dioxane), 84.57 (C-5), 73.03 and 73.00 (C-6,7), 68.48 (C-3), 60.35 (C-8), 28.98 and 18.62 [C(CH_3)$_2$ dioxane], 27.69 and 26.85 [C(CH_3)$_2$ dioxolane], and 21.47 (C-2).

HRMS (LSIMS): *m*/*z* calcd for $C_{14}H_{21}NNaO_6$: 322.1267; found: 322.1270 [M$^+$ + Na] (deviation –1.2 ppm).

When the reaction was processed after 1 h as above, a small sample of the 3-*O*-trimethylsilyl derivative **8** was obtained; yield: 50 mg, (11%); t_R 9.66 min; $[\alpha]_D^{25}$ +7, $[\alpha]_{405}^{26}$ +24.3 (*c* = 1).

8

IR (neat): 2247 (C≡N), 1384 and 1376 cm^{-1} (CMe_2).

^1H NMR (400 MHz): δ = 4.43 (br s, 1 H, H-5), 4.31 (d, 1 H, $J_{6,7}$ = 1.8 Hz, H-6), 4.20 (dd, 1 H, H-3), 4.12 (br s, 1 H, H-7), 4.06 (dd, 1 H, $J_{7,8}$ = 1.8 Hz, $J_{8,8'}$ = 13.6 Hz, H-8), 3.99 (br d, 1 H, H-8′), 2.90 (dd, 1 H, $J_{2,3}$ = 2.9 Hz, $J_{2,2'}$ = 16.8 Hz, H-2), 2.74 (dd, 1 H, $J_{2',3}$ = 8.7 Hz, H-2′), 1.50, 1.44, 1.40 and 1.39 [4 s, 12 H, 2 $C(CH_3)_2$], and 0.27 [s, 9 H, $Si(CH_3)_3$].

^{13}C NMR (100 MHz): δ = 118.95 (C-1), 115.01 and 112.84 (C-4 and *C*Me_2 dioxolane), 97.47 (*C*Me_2 dioxane), 84.40 (C-5), 73.12 and 73.05 (C-6,7), 70.08 (C-3), 60.36 (C-8), 28.03 and 18.57 [$C(CH_3)_2$ dioxane], 27.62 and 26.45 [$C(CH_3)_2$ dioxolane], 21.61 (C-2), and 0.56 [$Si(CH_3)_3$].

HRMS (LSIMS): *m*/*z* calcd for $C_{17}H_{29}NNaO_6Si$: 394.1661; found 394.1662 [M^+ + Na] (deviation –0.1 ppm).

Conventional benzoylation of **5** (50 mg, 0.17 mmol) in anhyd CH_2Cl_2 (2 mL) with Et_3N (0.1 mL) and benzoyl chloride (0.1 mL) gave after usual workup and column chromatography (Et_2O–hexane, 1:2 → 1:1) pure **7** (45 mg, 66%).

When the reaction was carried out as above, but diluting with Et_2O saturated with aq 10% HCl and stirred for 5 min, followed by the same workup, the *O*-desilylated compound **5** together with a more polar compound were detected in TLC. Column chromatography of the reaction mixture gave pure **5** as the first fraction; yield: 220 mg (54%).

The more polar compound was shown to be the 6,8-*O*-deacetonated derivative of **5** (**9**; yield: 150 mg (45%); colorless thick syrup; $[\alpha]_D^{25}$ +4; $[\alpha]_{405}^{25}$ +11 (*c* = 1, MeOH).

9

^1H NMR (400 MHz): δ = 4.44 (br s, 1 H, H-5), 4.26 (ddd, 1 H, H-7), 4.12 (br d, 1 H, $J_{6,7}$ = 2.8 Hz, H-6), 3.95 (dd, 1 H, $J_{2,3}$ = 3 Hz, $J_{2'3}$ = 9.7 Hz, H-3), 3.77 (dd, 1 H, $J_{7,8}$ = 4.9 Hz, $J_{8,8'}$ = 11.7 Hz, H-8), 3.71 (dd, 1 H, $J_{7,8'}$ = 6.4 Hz, H-8′) 2.93 (dd, 1 H, $J_{2,2'}$ = 17 Hz, H-2), 2.63 (dd, 1 H, $J_{2',3}$ = 9.8 Hz, H-2′), 1.44 and 1.36 [2 s, 6 H, $C(CH_3)_2$].

^{13}C NMR (100 MHz): δ = 119.87 (C-1), 115.89 and 113.81 (C-4 and *C*Me_2), 86.65 (C-5), 83.71 (C-6), 75.59 (C-7), 69.51 (C-3), 61.24 (C-8), 27.96 and 27.01 [$C(CH_3)_2$], and 21.28 (C-2).

Anal. Calcd for $C_{11}H_{17}NO_6$: C, 50.96; H, 6.61; N, 5.40. Found: C, 51.21; H, 6.56; N, 5.53.

2-Deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranosonamide (11)

a) *From β-Hydroxy Ester **10***: A stirred solution of methyl 2-deoxy-4,5:6,7-di-*O*-isopropylidene-β-D-*manno*-oct-4-ulo-4,8-pyranosonate[7] (**10**; 188 mg, 0.56 mmol) in MeOH (3 mL) containing aq 30% NH_3 (2 mL) was heated in a sealed tube at 100 °C for 3 h. TLC (Et_2O–hexane, 2:1) then revealed a not mobile compound. The reaction mixture was chromatographed on silica gel (Et_2O–MeOH, 20:1) to afford pure **11**; yield: 150 mg (84%); colorless thick syrup; $[\alpha]_D^{26}$ –0.3; $[\alpha]_{405}^{26}$ +10 (*c* = 1.3).

IR (neat): 3431 and 3356 (OH and NH_2), 1675 ($CONH_2$), 1384 and 1373 cm^{-1} (CMe_2).

^1H NMR (400 MHz): δ = 6.14 and 6.06 (2 br s, 2 H, $CONH_2$), 4.60 (m, 2 H, H-6,7), 4.39 (br s, 1 H, OH), 4.22 (d, 1 H, $J_{5,6}$ = 7.6 Hz, H-5), 4.03 (dd, 1 H, H-3), 3.39 (d, 1 H, $J_{8,8'}$ = 12.9 Hz, H-8), 3.72 (d, 1 H, H-8′), 2.76 (dd, 1 H, $J_{2,3}$ = 2.6 Hz, $J_{2,2'}$ = 15.9 Hz, H-2), 2.55 (dd, 1 H, $J_{2',3}$ = 9.2 Hz, H-2′), 1.52, 1.46, 1.43 and 1.33 [4 s, 12 H, 2 $C(CH_3)_2$].

^{13}C NMR (100 MHz): δ = 175.85 (C-1), 108.99 and 108.72 (2 *C*Me_2), 103.90 (C-4), 70.82, 70.32, 69.82, and 69.71 (C-3,5,6,7), 61.11 (C-8), 36.01 (C-2), 26.64, 25.87, 25.59, and 23.92 [2 $C(CH_3)_2$].

HRMS (LSIMS): *m*/*z* calcd for $C_{14}H_{23}NNaO_7$: 340.1372; found: 340.1374 [M^+ + Na] (deviation –0.6 ppm).

b) *From β-Hydroxy Nitrile* **3**: An ice-H_2O cooled and stirred solution of **3** (350 mg, 1.2 mmol) in MeOH (5 mL) was treated with aq 30% H_2O_2 (0.5 mL) and aq 6 N NaOH (0.26 mL) and the mixture was left at r.t. for 5 h. TLC (Et_2O–hexane, 2:1) then revealed a not mobile compound. The reaction mixture was neutralized with AcOH, and chromatographed on silica gel (Et_2O–MeOH, 20:1) to afford pure **11**; yield: 310 mg (84%).

2-Deoxy-4,5:6,8-di-*O*-isopropylidene-a-L-*gulo*-oct-4-ulo-4,7-furanosonamide (13)

a) *From β-Hydroxy Ester* **12**: A stirred solution of methyl 2-deoxy-4,5:6,8-di-*O*-isopropylidene-α-L-*gulo*-oct-4-ulo-4,7-furanosonate[7] (**12**; 190 mg, 0.59 mmol) in MeOH (10 mL) containing aq 30% NH_3 (10 mL) was heated in a sealed tube at 100 °C for 4 h. TLC (Et_2O–hexane, 2:1) then revealed a not mobile compound. Workup of the reaction mixture as for **10** afforded pure **13**; yield: 170 mg (93%); colorless thick syrup; $[\alpha]_D^{25}$ +18 (*c* = 1.9).

IR (neat): 3439 and 3362 (OH and NH_2), 1675 and 1669 ($CONH_2$), 1385 and 1376 cm^{-1} (CMe_2).

^1H NMR (400 MHz): δ = 6.12 and 5.72 (2 br s, 2 H, $CONH_2$), 4.56 (s, 1 H, H-5), 4.29 (br d, 1 H, $J_{6,7}$ = 1.9 Hz, H-6), 4.19 (dd, 1 H, H-3), 4.08 (br s, 1 H, H-7), 4.06 (dd, 1 H, $J_{7,8}$ = 2.1 Hz, H-8), 3.99 (d, 1 H, $J_{8,8'}$ = 12.9 Hz, H-8′) 2.78 (dd, 1 H, $J_{2,3}$ = 2.9 Hz, $J_{2,2'}$ = 15.5 Hz, H-2), 2.55 (dd, 1 H, $J_{2',3}$ = 9 Hz, H-2′), 1.48, 1.41 and 1.34 [3 s, 12 H, 2 $C(CH_3)_2$].

^{13}C NMR (100 MHz): δ = 175.21 (C-1), 115.44 (C-4), 112.67 (*C*Me_2 dioxolane), 97.54 (*C*Me_2, dioxane), 84.46 (C-5), 73.28 (C-6), 72.51 (C-7), 69.20 (C-3), 60.39 (C-8), 36.38 (C-2), 28.99 and 18.66 [$C(CH_3)_2$ dioxane], 27.76 and 26.73 [$C(CH_3)_2$ dioxolane].

Anal. Calcd for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41. Found: C, 52.61; H, 6.96; N, 4.40.

b) *From β-Benzoyloxy Nitrile* **7**: An ice-H_2O cooled and stirred solution of **7** (68 mg, 0.16 mmol) in MeOH (2 mL) was treated with aq 30% H_2O_2 (0.1 mL) and aq 6 N NaOH (0.05 mL) and the mixture was left at r.t. for 4 h. Workup of the reaction mixture as above gave pure **13**; yield: 36 mg (70%).

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References

(1) Izquierdo, I.; Plaza, M.-T.; Robles, R.; Mota, A.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 4509.
(2) (a) Izquierdo, I.; Plaza, M.-T.; Robles, R.; Rodríguez, C.; Ramírez, A.; Mota, A.-J. *Eur. J. Org. Chem.* **1999**, 1269. (b) Izquierdo, I.; Plaza, M.-T.; Robles, R.; Mota, A.-J. *Eur. J. Org. Chem.* **2000**, 2071.
(3) Izquierdo, I.; Plaza, M.-T. *Carbohydr. Res.* **1990**, *205*, 293.
(4) Izquierdo, I.; Plaza, M.-T.; Kari, N. *Carbohydr. Res.* **1994**, *261*, 231.
(5) Han, B.-H.; Boudjouk, P. *J. Org. Chem.* **1982**, *47*, 5030.

(6) (a) Zn/Cu-Mediated: Smith, R. D.; Simmons, H. E. *Org. Synth.* **1961**, *41*, 72. (b) See also: Corbin, T. F.; Hahn, R. C.; Shechter, H. *Org. Synth.* **1964**, *44*, 30. (c) See also: Chung, W. J.; Higashiya, S.; Welch, J. T. *J. Fluorine Chem.* **2001**, *112*, 343. (d) Indium-Mediated: Araki, S.; Yamada, M.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 1126. (e) See also: Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633. (f) Alkyllithium-Mediated: Zhou, J. J. P.; Zhong, B.; Silverman, R. B. *J. Org. Chem.* **1995**, *60*, 2261. (g) Tin-Mediated: Sun, P.; Shi, B. *J. Chem. Res., Synop.* **1999**, 318. (h) Samarium-Mediated: Caracoti, A.; Flowers, R. A. II *Tetrahedron Lett.* **2000**, *41*, 3039.

(7) Izquierdo, I.; Plaza, M.-T.; Robles, R.; Mota, A.-J. *Tetrahedron: Asymmetry* **1997**, *8*, 2597.