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Syntheses of (3*R*,4*R*,5*R*,6*R*)-tetrahydroxyazepane (1,6-dideoxy-1,6-imino-D-mannitol) and (3*S*,4*R*,5*R*,6*R*)-tetrahydroxyazepane (1,6-dideoxy-1,6-imino-D-glucitol)

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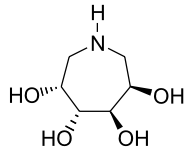
Abstract—Syntheses of 1,6-dideoxy-1,6-imino-D-mannitol (D-mannoazepane) (**1**) and 1,6-dideoxy-1,6-imino-D-glucitol (D-glucoazepane) (**3**) from D-isoascorbic acid and D-glucono-1,5-lactone, respectively, are described. The key step in both routes involved reductive aminative 1,6-cyclization with retention of configurations to give the corresponding lactams, which were subsequently reduced to afford compounds **1** and **3** in 24 and 28.5%, overall yield, respectively. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The syntheses and biological evaluation of polyhydroxy piperidine and pyrrolidine derivatives (azasugars), which are efficient inhibitors of glycosidases and glycoprotein-processing enzymes, have been investigated.[1] Seven-membered azasugars (polyhydroxyazepanes) have also been shown to possess potent inhibitory activities.[2] Compound **1** is a better inhibitor of β-*N*-acetylglucosaminidase than 1-deoxynojirimycin (**2**), which is often taken as a standard.[2c] Descriptions of their synthesis are not yet abundant. In some of those reported they have been obtained in admixture with their corresponding six-membered ring derivatives, requiring separation.[3]



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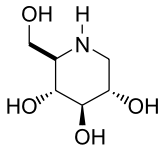

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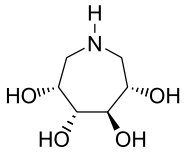

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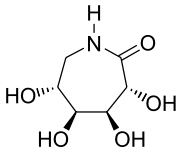

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In connection with studies on the development of simplified routes to azasugars, we now report the stereoselective synthesis of (3*R*,4*R*,5*R*,6*R*)-tetrahydroxyazepane (**1**) and the (3*S*,4*R*,5*R*,6*R*) configurational isomer **3** from D-mannonolactone (via D-isoascorbic acid) and D-glucono-1,5-lactone, respectively, both of which are cheap and readily available starting materials. The synthesis of **1** and its enantiomer, from D- and L-chiroinositols was reported[4] recently, but these cannot be considered generally as convenient starting materials. The use of D-galactono-1,4-lactone for preparing the lactam **4** and some derivatives thereof, has also been described.[5] More recently, nitrone addition to a pent-4-enofuranoside has been reported to be an expeditious route to some seven-membered ring derivatives.[6]

2. Results and discussion

Catalytic hydrogenation of the double bond of D-isoascorbic acid (**5**) using a modified[7] procedure furnished D-mannono-1,4-lactone **6** as the key starting material for the synthesis of azepane **1** (Scheme 1). The projected route from **6** required a C-1/C-6 aminative cyclization preceded by the introduction of a nitrogen function at either of these positions. Isopropylidenation of the lactone **6** gave the acetonide **7**. Compound **7** could also be obtained from D-mannose using an isopropylidenation–dimethylsulfoxide/acetic anhydride oxidation sequence.[8] Selective hydrolysis (80% aq. acetic acid) of compound **7** gave the 2,3-*O*-acetonide **8** with a free primary hydroxyl group at C-6. The introduction of an azide function at this position to give compound **9** was achieved using a one-pot procedure based on a combination

Keywords: azasugars; iminosugars; glycosidase inhibitors; D-mannoazepane; D-glucoazepane.

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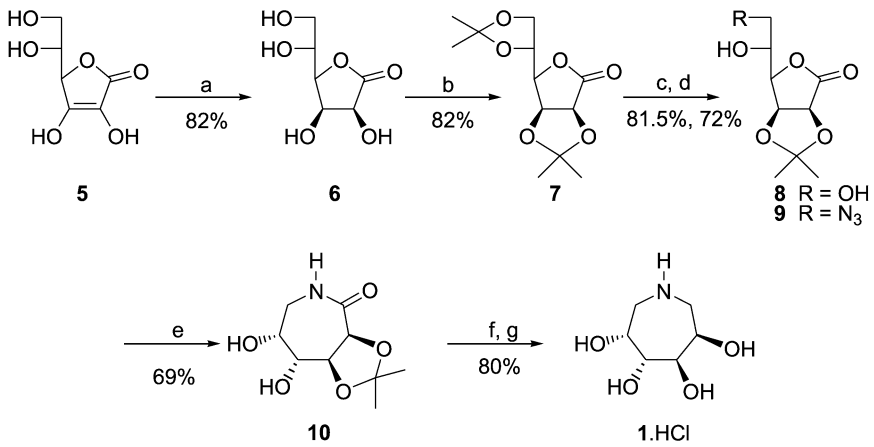
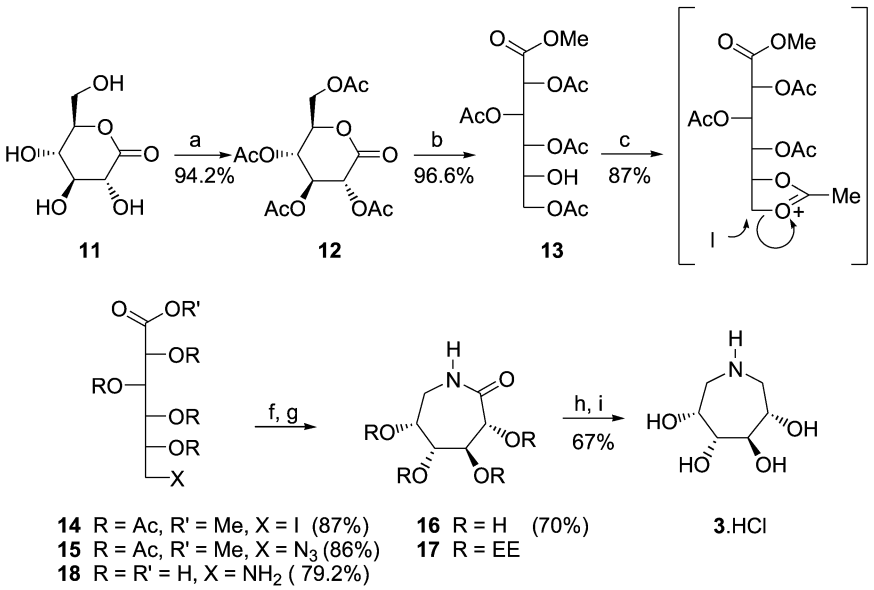


Scheme 1. (a) H_2, Pd–C, 50 psi, H_2O/MeOH; (b) DMP/MeOH, TsOH; (c) HOAc; (d) Ph_3P/CBr_4, LiN_3, DMF; (e) H_2, Pd/C, EtOH; (f) BH_3–THF, THF; (g) HCl, MeOH.

of methods in which a primary hydroxyl group is treated with a mixture of triphenylphosphine (Ph_3P)-carbon tetrabromide (CBr_4) and lithium azide[9] in *N*,*N*-dimethylformamide (DMF). This reaction is presumed to proceed via a bromo intermediate, formed in situ, followed by S_N2 displacement with azide. The use of lithium azide was useful in the reaction since it is more soluble than the corresponding sodium salt at ambient temperature.[9,10] This method of introducing an azide group is much less laborious than the conventional alternative involving selective sulfonation of the primary position followed by S_N2 displacement with azide, and has been applied successfully to nucleosides and polysaccharides.[10] Catalytic hydrogenation of **9** over palladium on charcoal (10%) proceeded with concomitant ring closure to produce the crystalline lactam **10**. Reduction of compound **10** with a borane–THF complex (1 M) followed by treatment with conc. HCl, gave **1** as the crystalline hydrochloride salt.

The synthesis of azepane **3** was achieved from D-glucono-1,5-lactone (**11**) via the acetylated ester **13** (Scheme 2). Treatment of the lactone **11** with a mixture of acetic anhydride and trifluoroacetic acid (TFA) followed by reaction of the resultant acetylated lactone **12** with methanol in the presence of a catalytic quantity of *p*-toluenesulfonic acid gave the methyl ester **13** in excellent yield (>95%). These reactions can be conducted as a one pot sequence and represent a distinct improvement on the pre-existing route to this compound, which involves the use of diazomethane.[11]

Treatment of the ester **13** with iodotrimethylsilane, obtained in situ from a mixture of chlorotrimethylsilane and sodium iodide yielded the primary iodide **14**. The reaction proceeds via a 5,6-acetoxonium ion intermediate, with selective attack by iodide ion on the primary carbon with retention of the original gluco configuration.[12] Reaction of compound **14** with lithium azide[9] in *N*,*N*-dimethylformamide (DMF) gave the crystalline azide **15** which was deacetylated (MeOH/KCN) and the resultant product (not isolated) was reductively cyclized (10% Pd/C, H_2, 3 atm) to give the expected pure lactam **16**. In another experiment reduction of the deprotected azide **15** at lower pressure (1 atm) afforded



Scheme 2. (a) Ac_2O/TFA; (b) MeOH, TsOH; (c) Me_3SiCl/NaI, CH_2Cl_2; (d) LiN_3/DMF; (e) KCN/MeOH; (f) (i) H_2/3 atm, 10% Pd–C, EtOH, (ii) H_2/1 atm, Pd–C, EtOH; (g) ethyl vinyl ether/DMF, TsOH; (h) BH_3–Me_2S, THF (i) Conc. HCl/MeOH.

the known[13] uncyclized 6-amino-6-deoxy-D-gluconic acid **18**.

The lactam **16** was insoluble in ethereal solvents and was converted into the per-*O*-(1′-ethoxyethyl) derivative **17** by reaction with ethyl vinyl ether in the presence of a catalytic quantity of *p*-toluenesulfonic acid to provide the soluble, base stable derivative **17** for the subsequent reductive step. Although ethoxyethyl groups have been suggested[14] as useful *O*-protecting functions, they have found limited applications, so far, in carbohydrate chemistry. They are readily introduced under mild conditions, are very stable under basic conditions, and are easily removed under very mild acidic conditions, even in the presence of other acetals. These derivatives are mixtures of diastereomers and are not usually characterized due to their complexity, especially in their ^{1}H NMR spectra. The protecting group is usually considered temporary and removed in the last stages of reactions. The protected derivative **17** was reduced directly with a 1 M borane–methylsulfide complex in boiling tetrahydrofuran followed by treatment with conc. HCl in methanol gave pure **3** as a non-crystalline hydrochloride salt.

3. Summary

In summary, we have developed simple syntheses of the azepanes **1** and **3** from cheap, readily available sugar lactones. The route further illustrates the use of D-glucono-1,5-lactone as a basic synthon.[15]

4. Experimental

4.1. General

Melting points were determined using a Reichert thermopan microscope equipped with cross polarizers and are uncorrected. IR spectra were determined on a Perkin Elmer 298 spectrophotometer. Optical rotations were determined with a Perkin Elmer automatic polarimeter model 241 MC on 1% solutions in the solvents indicated at 21°C. Column chromatography was performed using Silica Gel (E. Merck) using the eluents indicated. Thin layer chromatography (TLC) on pre-coated plates of Silica Gel GF_{254} (E. Merck) was conducted in the solvent mixtures given. Compounds were detected by spraying with 0.1 M $K_2Cr_2O_7$ in 0.05 M H_2SO_4 followed by heating at 140°C. ^{1}H and ^{13}C NMR were recorded on Brucker AC 100 (100 MHz), AC 300 (300 MHz) and Varian AM 400 (400 MHz) spectrometers at room temperature on solutions in $CDCl_3$, DMSO-d_6 (internal Me_4Si) or D_2O (external 1,4-dioxane, 76.8 ppm). Mass spectra were recorded using a double focusing VG 7070E spectrometer. Borane–tetrahydrofuran complex (1 M solution in tetrahydrofuran) and borane–methylsulfide complex (2 M solution in tetrahydrofuran) were purchased from Acros.

4.1.1. D-Mannono-1,4-lactone (6). The lactone was prepared from D-isoascorbic acid (**5**) according to the described method.[7] Mp 150–152°C, lit.[7]=mp 151–152°C; $[\alpha]_D$=+51.4 (*c* 1, H_2O), lit.[7] $[\alpha]_D$=+51.2 (H_2O). The spectral characteristics were identical with those reported earlier.[7]

4.1.2. 2,3;5,6-Di-*O*-isopropylidene-D-mannono-1,4-lactone (7). Compound **7** was prepared as described previously.[16,17] Mp 124–125°C, lit.[17] mp 126°C; $[\alpha]_D$=+51 (*c* 1, $CHCl_3$), lit.[17] $[\alpha]_D$=+50.6; ν_{max}(KBr) 1770 cm^{-1} (lactone). ^{1}H NMR ($CDCl_3$ 100 MHz) δ 4.85–4.78 (m, 2H, H-2, H-3), 4.41–4.30 (m, 2H, H-4, H-5), 3.94–4.06 (m, 2H, H-6, H-6′), 1.39–1.30 (4s, each 3H, CMe_2).

4.1.3. 2,3-*O*-Isopropylidene-D-mannono-1,4-lactone (8). A solution of compound **7** (2.5 g, 9.62 mmol) in 80% aqueous acetic acid (25 mL) was set aside at room temperature for 18 h. The mixture was concentrated in vacuo and water (4×20 mL) and toluene (25 mL) were distilled in vacuo consecutively from the residue to give a colourless gel, which crystallized on standing at room temperature. The crude material was recrystallized from isopropyl ether/ethyl acetate to give **8** (1.72 g, 81.5%) as white crystals, mp 129–131°C, lit.[17] mp 133°C; $[\alpha]_D$=+49.6 (*c* 1, acetone), lit.[17] +55 (H_2O); ν_{max} (KBr), 3450–3120 (OH), 1790 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 100 MHz) δ 4.94–4.86 (m, 2H, H-3, H-2), 4.51 (m, 1H, H-4), 3.96 (m, 1H, H-5), 3.88–3.71 (m, 2H, H-6, 6′), 2.79–2.32 (bs, OH), 1.49–1.44 (2s, each 3H, CMe_2).

4.1.4. 6-Azido-2,3-*O*-isopropylidene-D-mannono-1,4-lactone (9). A stirred mixture of **8** (1.5 g, 6.88 mmol), triphenylphosphine (1.84 g, 7.02 mmol, 1.02 equiv.), lithium azide[9] (3.3 g, 68.8 mmol, 10 equiv.) and carbon tetrabromide (2.33 g, 7.02 mmol, 1.02 equiv.) was set aside at room temperature overnight, treated with methanol (3 mL), stirred for 30 min longer, and then concentrated in vacuo. Column chromatography (hexane–EtOAc, 3:1) of the residue afforded **9** (1.28 g, 77%) as a colourless gel, $[\alpha]_D$=+34 (*c* 1, $CHCl_3$); ν_{max}(neat) 2990, 2960 (OH), 2100 (–N=N=N), 1790 (C=O) cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.95 (d, 1H, H-2, $J_{2,3}$=5.4 Hz), 4.86 (dd, 1H, H-3, $J_{3,2}$=5.4 Hz, $J_{3,4}$=3.6 Hz), 4.61 (dd, 1H, H-4, $J_{4,3}$=3.6 Hz, $J_{4,5}$=7.3 Hz), 4.23–3.92 (m, 1H, H-5), 3.7 (br s, 1H, OH), 3.60 (dd, 1H, H-6a, $J_{6a,5}$=8.0 Hz, $J_{6a,6b}$=13.0 Hz), 3.56 (dd, 1H, H-6b, $J_{6b,5}$=5.2 Hz, $J_{6b,6a}$=13.0 Hz), 1.39 and 1.38 (s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.61 (C=O), 115.16 (qC), 80.58 (C-2), 77.13 (C-3), 76.65 (C-4), 70.63 (C-5), 53.04 (C-6), 27.30 and 26.35 (CMe_2). Anal. calcd for $C_9H_{13}N_3O_5$. C 44.44; H 5.35; N 17.28. Found (%): C 44.43; H 5.36; N 17.23.

4.1.5. 1,6-Dideoxy-2,3-*O*-isopropylidene-4,5-dihydroxy-1,6-imino-D-mannonolactam (10). A solution of compound **9** (1.0 g, 4.12 mmol) in ethanol (10 mL) was treated with palladium on charcoal (10%, 0.1 g) and then hydrogenated (1 atm) for 18 h at room temperature. The mixture was filtered through a layer of celite, the inorganic material washed with ethanol (10 mL) and the combined filtrate and washings concentrated in vacuo to give crude crystalline material which was recrystallized from isopropyl ether to give compound **10** (614 mg. 68.8%) as white fine crystals, mp 185–188°C, $[\alpha]_D$=+6.4 (*c* 1, $CHCl_3$); ν_{max}(KBr) 3430–3475 (OH, NH),1663 (lactam C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.40–4.32 (m, 2H,

H-6a/6b), 3.97 (t, 1H, H-3), 3.87 (d, 1H, H-2), 2.96–2.73 (m, 2H, H-4/5), 1.42, 1.32 (s, 6H, C*Me*$_2$). ^{13}C NMR (D_2O, 75 MHz) δ 174.98 (C=O), 112 (qC), 75.66, 75.49 (C-2/3), 73.59 (C-4), 68.30 (C-5), 43.57 (C-6), 27.41 and 25.38 (C*Me*$_2$). Anal. calcd for $C_9H_{15}NO_5$: C 49.76; H 6.96; N 6.45. Found (%): C 49.48; H 6.86; N 6.32.

4.1.6. (3*R*,4*R*,5*R*,6*R*)-Tetrahydroxyazepane (1,6-dideoxy-1,6-imino-D-mannitol) (1). A solution of compound **10** (300 mg, 1.38 mmol) in tetrahydrofuran (10 mL) containing borane–tetrahydrofuran (1.5 mL) was heated under reflux for ca. 20 h, cooled to room temperature and concentrated in vacuo. A solution of the residue **11** in methanol (10 mL) was treated with two drops of concentrated hydrochloric acid and kept at room temperature for 24 h, concentrated in vacuo and the resultant material was dissolved in water (15 mL) and extracted with ether (2×10 mL). The aqueous layer was concentrated in vacuo and water (3×10 mL) was distilled in vacuo from the residue to give a crude white solid which was recrystallized from methanol/ether (5:1, v/v) to give compound **1** (220.6 mg, 80%) as the HCl salt. Mp 184–186°C, lit.[2b] mp 183–185°C; $[\alpha]_D$=−45 (*c* 1, H_2O), lit.[2b] $[\alpha]_D$=−38; ^{1}H NMR (D_2O, 300 MHz) δ 3.86 (m, H-2), 3.62 (s, H-3), 2.71 (dd, H-1b, $J_{1b,2}$=8.3 Hz, $J_{1b,1a}$=13.3 Hz), 2.63 (dd, 1H, $J_{1a,2}$=3.38 Hz, $J_{1a,1b}$=13.3 Hz). ^{13}C NMR (D_2O, 75 MHz) δ 75.73, 73.08 (C-2/3), 53.84 (C-1). Anal. calcd for $C_6H_{14}ClNO_4$: C 36.10, H 7.07, N 7.02. Found (%): C 35.92; H 6.98; N 6.91.

4.1.7. 2,3,4,6-Tetra-*O*-acetyl-D-glucono-1,5-lactone (12). A stirred solution of D-glucono-1,5-lactone (5 g, 28.09 mmol) in acetic anhydride (30 mL) containing trifluoroacetic acid (2.5 mL) was kept at room temperature for 3 h. The mixture was concentrated in vacuo and toluene (3×20 mL) was distilled in vacuo from the residue to give **12** as a colourless syrup (9.15 g, 94%). $[\alpha]_D$=+76.1 (*c* 1, $CHCl_3$), lit.[18] +79.7; ν_{max}(neat) 1720–1730 (acetate C=O, lactone C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.58 (m, 1H, H-3), 5.37 (m, 1H, H-4), 5.16 (d, 1H, H-2), 4.60 (m, 1H, H-5), 4.39–4.26 (m, 2H, H-6, 6′), 2.25–2.00 (m, 4s, each 3H, 4×acetyl CH_3).

4.1.8. Methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate (13). A stirred solution of **12** (9.0 g, 26.0 mmol) in methanol (100 mL) containing *p*-toluenesulfonic acid (150 mg) was kept at room temperature for 1 h when analysis (TLC) indicated completion of the reaction. The mixture was neutralized by ion-exchange resin (IRA 400, HCO_3^- form), filtered, and the filtrate concentrated in vacuo to give white crystals which were recrystallized from methanol to give **13** (9.5 g, 97%). Mp 114–116°C, lit.[11] mp 111–112°C; $[\alpha]_D$=+20.6 (*c* 1, $CHCl_3$), lit.[11] $[\alpha]_D$=+16.8; ν_{max}(KBr) 1730 (acetate, ester C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.71 (t, 1H, H-3), 5.31 (d, 1H, H-2), 5.19 (dd, 1H, H-4), 4.14 (m, 2H, H-6), 3.86 (d, 1H, H-5), 3.74 (s, 3H, OMe), 3.03 (br s, 1H, OH), 2.17, 2.16, 2.14, 2.10 (s, 12H, 4×COC*H*$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.10 (C=O ester), 170.43, 169.70, 167.30 (C=O acetate), 71.55 (C-2), 70.66, 69.44 (C-3/4), 68.34 (C-5), 64.64 (C-6), 52.75 (O*C*H$_3$-methoxy), 20.70, 2×20.50, 20.39 (4×CO*C*H$_3$). Anal. calcd for $C_{15}H_{22}O_{11}$: C 47.62; H 5.86. Found (%): C 47.36; H 5.81.

4.1.9. Methyl 6-deoxy-6-iodo-2,3,4,5-tetra-*O*-acetyl-D-gluconate (14). A stirred mixture of methyl 2,3,4,6-tetra-*O*-acetyl-D-gluconate **13**, (1.0 g, 2.65 mmol) chlorotrimethylsilane (1.15 g, 10.58 mmol, 4 equiv.) and sodium iodide (1.59 g, 10.6 mmol, 4 equiv.) in dichloromethane (10 mL) mainatained under nitrogen was set aside at room temperature for 18 h. The mixture was treated with a mixture of acqueous 5% sodium thiosulfate and saturated sodium hydrogen carbonate solution (50 mL, 1:1) and the separated organic layer was washed with a mixture of 5% sodium thiosulfate and saturated sodium hydrogen carbonate (25 mL, 1:1), brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Recrystallization of the crude crystalline material from ether afforded **14** (1.12 g, 87%) as white crystals. Mp 124–125°C, $[\alpha]_D$=+18 (*c* 1, $CHCl_3$); ν_{max}(KBr) 1730 (acetate, ester C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz), δ 5.52 (t, 1H, H-3, $J_{3,2}$=4.2 Hz), 5.39 (dd, 1H, H-4, $J_{4,3}$=4.2 Hz, $J_{4,5}$=6.85 Hz), 5.20 (d, 1H, H-2, $J_{2,3}$=4.3 Hz), 4.96–4.90 (m, 1H, H-5), 3.8 (s, 3H, O*Me*), 3.4 (dd, 1H, H-6a, $J_{6a,5}$=3.4 Hz, $J_{6a,6b}$=11.4 Hz), 3.2 (dd, 1H, H-6b, $J_{6b,5}$=5.1 Hz, $J_{6b,6a}$=11.4 Hz), 2.2, 2.1, 2.1, 2.0 (s, 12H, 4×CO*CH*$_3$) ^{13}C NMR ($CDCl_3$, 300 MHz) δ 169.69, 169.53, 169.43 (2×) (4×*C*OCH$_3$), 167.18 (C=O, ester), 71.26 (C-2), 70.62, 69.75 (C-4/5), 68.33 (C-3), 52.84 (OMe), 20.77, 20.69, 20.42 (2×), (4×CO*C*H$_3$), 2.37 (C-6); Anal. calcd for $C_{15}H_{21}IO_{10}$: C 36.90; H 4.34. Found (%): C 37.05; H 4.33.

4.1.10. Methyl 6-azido-6-deoxy-2,3,4,5-tetra-*O*-acetyl-D-gluconate (15). A stirred solution of **14** (1.09 g, 2.05 mmol) in *N*,*N*-dimethylformamide (5 mL) was treated with lithium azide (0.462 g, 10.27 mmol, 5 equiv.) and set aside at 60°C for 20 h. The mixture was poured into ice-water (20 mL) and the product extracted with ethyl acetate (2×30 mL). The combined organic layers were washed once with water (20 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo to give crystalline material on standing at room temperature. Recrystallization from ether gave compound **15** (712 mg, 86%) as white crystals. Mp 68–69°C, $[\alpha]_D$=+16 (*c* 1, $CHCl_3$); ν_{max}(neat) 2105 (–N=N=N), 1735 (acetate, ester C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.55 (t, 1H, H-3, $J_{3,2}$=4.4 Hz, $J_{3,4}$=4.4 Hz), 5.46 (dd, 1H, H-4, $J_{4,3}$=4.4 Hz, $J_{4,5}$=6.8 Hz), 5.2 (d, 1H, H-2, $J_{2,3}$=4.4 Hz), 5.06–5.03 (m, 1H, H-5), 3.75 (s, 3H, O*Me*), 3.53 (dd, 1H, H-6a, $J_{6a,5}$=3.9 Hz, $J_{6a,6b}$=13.4 Hz), 3.39 (dd, 1H, H-6b, $J_{6b,5}$=6.1 Hz, $J_{6b,6a}$=13.4 Hz), 2.18, 2.12, 2.09, 2.08 (s, 12H, 4×COCH$_3$). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 169.52, 169.40, 2×169.30 (4×*C*OCH$_3$), 168.94 (C=O, ester), 70.33 (C-2), 69.23, 69.12 (C-3/4), 68.18 (C-5), 52.72 (OMe), 49.97 (C-6), 22.43, 20.62, 20.46, 20.37 (4×COC*H*$_3$). Anal. calcd for $C_{15}H_{21}N_3O_{10}$: C 44.67; H 5.25; N 10.42. Found C 44.83; H 5.16; N 10.34%.

4.1.11. 6-Amino-6-deoxy-D-glucono-1,6-lactam (3*S*,4*R*,5*R*,6*R*-tetrahydroxy-azepan-2-one) (16). A solution of the protected azide **15** (600 mg, 1.49 mmol) in methanol (20 mL) containing a catalytic amount of potassium cyanide (10 mg) was set aside for 48 h. The mixture was filtered through a layer of silica gel and the filtrate concentrated in vacuo to give a brown residue which was purified by passage through a short column of silica gel (dichloromethane–methanol, 4:1) to give a colourless gel which was not characterized but used immediately in the following

step. A solution of the gel (0.32 g, 1.36 mmol) in ethanol (5 mL) was treated with palladium on charcoal (10%, 40 mg) and then hydrogenated (3 atm) for 18 h at room temperature. The mixture was filtered through a layer of celite, the inorganic material washed with ethanol (10 mL) and the combined filtrate and washings concentrated in vacuo to give crude crystalline material which was recrystallized from methanol to give **16** (168 mg, 70%) as white crystals, mp 209–213°C, lit.[19] mp 212°C, $[\alpha]_D=-67$ (c 1, H_2O), lit.[19] −70; ν_{max} (KBr) 3500–3100 (OH), 2920 (C–H), 1660 (C=O), 1470 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 4.31 (d, 1H, J=9.9 Hz, H-2), 4.1 (dd, 1H, J=3.4, 0.7 Hz, H-5), 3.71 (dd, 1H, J=6.0, 3.4 Hz, H-3/H-4), 3.6 (dd, 1H, J=9.9, 6.0 Hz, H-4/H-3), 3.47–3.38 (m, 2H, H-6a/H-6b). ^{13}C NMR (D_2O, 75 MHz), 175.80 (C=O), 2×75.70 (C-4/5), 70.1 (C-2/C-3), 68.2 (C-2/3), 42.6 (C-6). Anal. calcd for $C_6H_{11}NO_5$: C 40.68; H 6.26; N 7.91. Found C 40.73; H 5.71; N 8.03%.

4.1.12. 6-Amino-6-deoxy-D-gluconic acid (18). In another experiment the deprotected azido derivative (320 mg, 1.36 mmol) in ethanol (5 ml) was treated with palladium on charcoal (10%, 30 mg) and then hydrogenated at 1 atm for 18 h at room temperature. The mixture was filtered through a layer of celite, the inorganic material washed with ethanol (10 mL) and the combined filtrate and washings concentrated in vacuo. The resultant material was treated as described[13] to give **18** as white crystals (210 mg, 79.2%); mp 200–202°C, lit.[13] 202°C; $[\alpha]_D=+23$ (c 1, H_2O), lit.[13] $[\alpha]_D=+21.5$ (H_2O); ^1H NMR (D_2O, 300 MHz), δ 3.65 (m, 1H, H-2), 3.46 (dd, 1H, $J_{3,2}$=5.3 Hz, $J_{3,4}$=1.6 Hz, H-3), 3.38–3.20 (m, 2H, H-4, H-5), 2.90 (dd, 1H, $J_{1a,2}$=3.5 Hz, $J_{1a,1b}$=15 Hz, H-6a), 2.69 (dd, 1H, $J_{1b,2}$=3.5 Hz, $J_{1b,1a}$=15.1 Hz, H-6b); ^{13}C NMR (D_2O, 75 MHz) δ 177.0 (C=O), 76.8 (C-2), 75.7 (C-5), 72.3 (C-4), 70.1 (C-3), 44.5 (C-6).

4.1.13. (3*S*,4*R*,5*R*,6*R*)-Tetrahydroxyazepane (1,6-dideoxy-1,6-imino-D-glucitol) (3). A stirred cooled (−10°C) solution of the lactam **16** (120 mg, 0.7 mmol) in *N*,*N*-dimethylformamide (2 mL) containing *p*-toluenesulfonic acid (5 mg) was treated with ethyl vinyl ether (1.5 mL) and after 20 min was set aside at room temperature until the mixture just started to turn pale yellow (~10 min), whereon, it was poured into ice-water (ca. 10 mL) containing triethylamine (0.2 mL). The mixture was extracted with ether (3×15 mL), and the combined extracts dried (Na_2SO_4) and concentrated in vacuo to yield a pale yellow gel. A solution of the material in tetrahydrofuran (20 mL) containing borane-dimethyl sulfide (3 mL) was heated under reflux for ca. 20 h, cooled to room temperature and concentrated in vacuo. A solution of the residue in methanol (10 mL) was treated with three drops of concentrated hydrochloric acid and kept at room temperature for 24 h, concentrated in vacuo and the resultant material was dissolved in water (20 mL) and extracted with ether (2×10 mL). The aqueous layer was concentrated in vacuo, and water (3×10 mL) was distilled in vacuo from the residue to give a crude white gum (90.6 mg, 67%) which resisted crystallization from methanol–ether, $[\alpha]_D=-15$ (c 1, H_2O); lit.[3b] $[\alpha]_D=-23$; ν_{max}(KBr) 3565–3349 (OH, NH), 1589, 1181 (NH); ^1H NMR (D_2O, 300 MHz), δ 3.65 (m, H-2), 3.46 (dd, H-3, $J_{3,2}$=5.3 Hz, $J_{3,4}$=1.6 Hz), 2.90 (dd, H-1a, $J_{1a,2}$=3.5 Hz, $J_{1a,1b}$=15.1 Hz), 2.69 (dd, H-1b, $J_{1b,2}$=3.5 Hz, $J_{1b,1a}$=15.1 Hz); ^{13}C NMR (D_2O, 75 MHz) δ 2×76.8, 2×75.7 (C-2/3, 4/5), 52.5 (C-1/6); Anal. calcd for $C_6H_{14}ClNO_4$: C 36.10, H 7.07, N 7.02. Found (%): C 36.40; H 6.93; N 6.86.

References

1. Sütz, A. E. *Iminosugars as Glycosidase Inhibitors*; Wiley–VCH: Weinheim, 1999.
2. (a) Poitout, L.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron Lett.* **1994**, *35*, 3293–3296. (b) Qian, X.; Moris, F.-V.; Wong, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1117–1122. (c) Moris, F.-V.; Qian, X.-H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7647–7662.
3. (a) Bernotas, R. C.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 165–168. (b) Legler, G.; Jülich, E. *Carbohydr. Res.* **1984**, *128*, 61–72. (c) Dax, K.; Gaigg, V.; Koblinger, B.; Stutz, A. E. *J. Carbohydr. Chem.* **1990**, *9*, 479–499. (d) Lohray, B. B.; Jayamma, Y.; Chatterjee, M. *J. Org. Chem.* **1995**, *60*, 5958–5960. (e) Poitout, L.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 1613–1616.
4. Painter, F. G.; Falshaw, A. *J. Chem. Soc.* **2000**, *7*, 1157–1160.
5. Long, D. D.; Stetz, R. J. E.; Nash, R. J.; Marquess, D. G.; Lloyd, J. D.; Winters, A. L.; Asano, N.; Fleet, G. W. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 901–908.
6. Gallos, J. K.; Demeroudi, S. C.; Stathopoulou, C. C.; Dellios, C. C. *Tetrahedron Lett.* **2001**, *42*, 7497–7499.
7. Vekemans, J. A. J. M.; Boerkamp, J.; Godefroi, E. F.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bis* **1985**, *104*, 266–271.
8. Horton, D.; Jewell, J. S. *Carbohydr. Res.* **1966**, *2*, 251–260.
9. Hofmann-Bang, N. *Acta Chem. Scand.* **1957**, *11*, 581–582.
10. Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297–368.
11. Hegley, E. J.; Meresz, O.; Overend, W. G. J. *J. Chem. Soc.* **1967**, 888–894.
12. Heck, M. P.; Monthiller, S.; Mioskowski, C.; Guidot, J. P.; Gall, T. L. *Tetrahedron Lett.* **1994**, *35*, 5445–5448.
13. Kefurt, K.; Capek, K.; Kefurtová, Z.; Jary, J. *Collect. Czech. Chem. Commun.* **1979**, *44*, 2526–2535.
14. Wijnbergen, F.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F.; Rehnberg, N. *Carbohydr. Res.* **1996**, *280*, 151–156.
15. Mazzini, C.; Sambri, L.; Regeling, H.; Zwanenburg, B.; Chittenden, G. J. F. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3351–3356, and references cited therein.
16. Buchanan, J. G.; Lumbard, K. W.; Sturgeon, R. J.; Thompson, D. K.; Wightman, R. H. *J. Chem. Soc. Trans 1* **1990**, 699–706.
17. Goodyear, E. H.; Haworth, W. N. *J. Chem. Soc.* **1927**, 3136–3146.
18. Nelson, C. R. *Carbohydr. Res.* **1982**, *106*, 155–159.
19. Kefurt, K.; Kefurtová, Z.; Jary, J. *Collect. Czech. Chem. Commun.* **1988**, *53*, 1795–1805.