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Deoxyiminoalditols from Aldonolactones — V. Preparation of the Four Stereoisomers of 1,5-Dideoxy-1,5-iminopentitols. Evaluation of these Iminopentitols and Three 1,5-Dideoxy-1,5-iminoheptitols as Glycosidase Inhibitors

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Abstract—The four stereoisomeric 1,5-dideoxy-1,5-iminopentitols with D-*arabino* - (D-*lyxo*-) (**3**), *ribo*- (**9**), L-*lyxo*- (L-*arabino*-) (**13**) and *xylo*-(**18**) configurations were synthesized. The corresponding aldonolactones (**1**, **7** and **11**) or aldonic acid ester (**15b**) having a leaving group at C-5 gave by reaction with aqueous ammonia, the 5-amino-5-deoxy-1,5-lactams, **2**, **8**, **12** and **17**, respectively. Reduction of the lactam function using sodium borohydride/acetic or trifluoroacetic acid, or borane dimethyl sulfide complex yielded the iminopentitols. The compounds **3**, **9**, **13** and **18**, together with the three 1,5-dideoxy-1,5-iminoheptitols **19**, **20** and **21** were tested for inhibition of the glycosidase activities present in an extract from human liver. Compound **18** was a potent and **19** a moderately good inhibitor of β-glucosidase. Compound **3** together with **19**, **20** and **21**, all having D-*arabino*-configuration at the hydroxy-substituted carbon atoms, were good inhibitors of α-L-fucosidase. Copyright © 1996 Elsevier Science Ltd

Introduction

Both naturally occurring and synthetic polyhydroxylated piperidines and pyrrolidines have been shown to exhibit interesting biological activities as glycosidase inhibitors.[1–3] Glycosidases are key enzymes in the biosynthesis and processing of glycoproteins and catabolism of glycoconjugates. These macromolecules are involved in cell–cell recognition and thus in the control of biological mechanisms. Sugar pyranoses or furanoses, in which the ring oxygen has been replaced with nitrogen, are metabolically inert but can still be recognized by glycosidases and other carbohydrate recognizing proteins. They inhibit glycosidases by mimicking the pyranosyl or furanosyl moiety of the corresponding substrate. Thus, substances that are able to inhibit the processing glycosidases of the biosynthetic pathway of glycoproteins have become important as potential antiviral,[4] and antitumor[5] agents and those that inhibit intestinal disaccharidases as antidiabetic[6] agents. An examination of the structural features of hydroxylated piperidines and pyrrolidines that act as inhibitors may give information about the structural requirements necessary for the inhibition. It has been shown that 1,5-dideoxy-1,5-iminohexitols with D-*arabino*-configuration of the three hydroxy groups in the piperidine ring exihibit strong α-L-fucosidase inhibitor activity.[7,8] Recently we have developed procedures for preparation of 1,4-dideoxy-1,4-iminohexitols[9] and 1,5-dideoxy-1,5-iminoheptitols[10] from dibromohexono- and -heptonolactones, respectively. We envisioned that similar procedures could be applied to pentonolactones for synthesis of 1,5-dideoxy-1,5-iminopentitols.

The strategy involved preparation of the corresponding 5-amino-5-deoxy-pentono-1,5-lactams directly, by treatment of 5-bromo- or 5-mesyl substituted pentono 1,4-lactones with ammonia. From our previous work[9] we know that 6-bromo-6-deoxyhexono-1,4-lactones when treated with ammonia give the 5,6-epoxide of the hexonic acid amide followed by opening at C-6, to give a 6-amino-6-deoxy-derivative. We have also observed that a cyclic amide is preferred to an acyclic one, even when seven-membered.[11] Following our strategy, the pentono-1,5-lactams thus obtained should be reduced to the trihydroxypiperidines.

Aldonolactams having ring size five, six and seven, have previously been prepared by Hanessian[12] by displacement of ω-tosyloxy aldonolactones with sodium azide. Hydrogenation of the ω-azido derivatives thus obtained underwent ring enlargement of the ω-amino derivatives to give the sugar lactams.

5-Amino-5-deoxy-pentono-1,5-lactams can exist in four pairs of enantiomers. Reduction of the lactam function to give the hydroxylated piperidines decreases the number of possible isomers to four, namely with D- and L-*arabino*- (equal to D- and L-*lyxo*-)configuration, together with the two mesoforms with *ribo*- and *xylo*-configurations.

In the present paper we describe the synthesis of the four stereoisomeric 1,5-iminopentitols. These com-

pounds and the previously prepared 1,5-iminoheptitols[10] have been tested for potential inhibitor activity towards human liver glycosidases, including α-L-fucosidase, in order to evaluate/confirm the structural basis for the inhibition of human liver α-L-fucosidase.

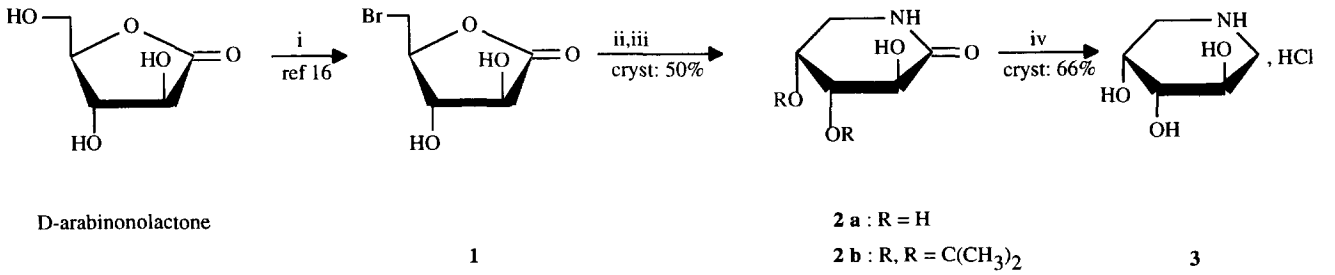
Results and Discussion

Chemistry

5-Bromo-5-deoxy-D-arabinonolactone (**1**) was obtained as described previously[13] by treatment of D-arabinonolactone or potassium D-arabonate with hydrogen bromide in acetic acid. To check our hypothesis discussed above, we followed the reaction of **1** with aq ammonia by running ^{13}C NMR spectra at intervals. Rapid changes took place: after 5 min the 5-bromo amide **A** was seen together with the epoxide **B** (Scheme 1, and Experimental; ca. 35 and 59%, respectively), while the 5-amino amide **C** (6%) just could be observed. After 20 min the lactam **2a** was observed (18%) together with **A** (7%), **B** (47%) and **C** (28%). After 1 h the relative amounts of **B**, **C** and **2a** were 11, 14, and 75%. After 2 h of reaction the product **2a** was the only one present. Thus, after treatment of **1** with aq ammonia for 2 h the lactam was isolated as the crystalline 3,4 -*O*-isopropylidene derivative **2b**. Reduction of the lactam **2b** was performed with $BH_3 \cdot Me_2S$ in dioxane,[14] but besides the iminopentitol, isopropylethers were also observed in the product. These were formed by reduction of the isopropylidene group.[15] Then $NaBH_4$ in the presence of 1 equiv of trifluoroacetic acid[16,17] was tried, and the lactam was cleanly reduced to 1,5-dideoxy-1,5-imino-D-arabinitol, which was isolated as the crystalline hydrochloride **3**. When acetic acid was used instead of trifluoroacetic acid in the reduction procedure, various amounts of *N*-alkylated products were observed. They may be formed by reduction of the acid to the aldehyde, which subsequently underwent reductive amination.[17] The iminoarabinitol has previously been synthesized from methyl-α-D-mannopyranoside in nine steps.[18] Very recently the synthesis of **3** has been considerably improved using a seven step procedure from D-arabinose with the 5-azido-5-deoxy-D-arabinofuranose as the key intermediate.[19] Our procedure involved three steps from D-arabinonolactone.

Preparation of the 1,5-dideoxy-1,5-iminoribitol might be performed similarly, by treatment of 5-bromo-5-deoxy-D-ribono-1,4-lactone (**4**)[20] with aq ammonia (Scheme 2). When the reaction was performed in an NMR tube and followed by ^{13}C NMR the 4,5-epoxy amide **E** and the 2,5-anhydro carboxamide **6** were observed after 20 min in a ratio of ca. 2:5. Formation of a five-membered ether **6** is very easily recognized by the presence of a low field signal (C-2, δ 82.0). The epoxide **E** reacted within 4 h with ammonia to give the lactam **5**. In this case, the 5-bromoribono amide **D** did not give the epoxide **E** exclusively, but the attack from C-2 hydroxy group at the C-5 bromine to give **6** was a competing reaction. We have observed this competition between formation of three- and five-membered ethers earlier.[9a] Consequently, it was necessary to prepare a C-2 protected ribonolactone.

Previously we have described the synthesis of 2,3-*O*-isopropylidene-5-*O*-mesyl-D-ribono-1,4-lactone (**7**) from D-ribonolactone.[21] When **7** was treated with aq ammonia and worked up, the 2,3-*O*-isopropylidene ribonolactam **8** could be isolated crystalline in 84% yield. Reduction of the lactam with $NaBH_4$ in the presence of acetic acid gave the 1,5-dideoxy-1,5-iminori-



D-arabinonolactone

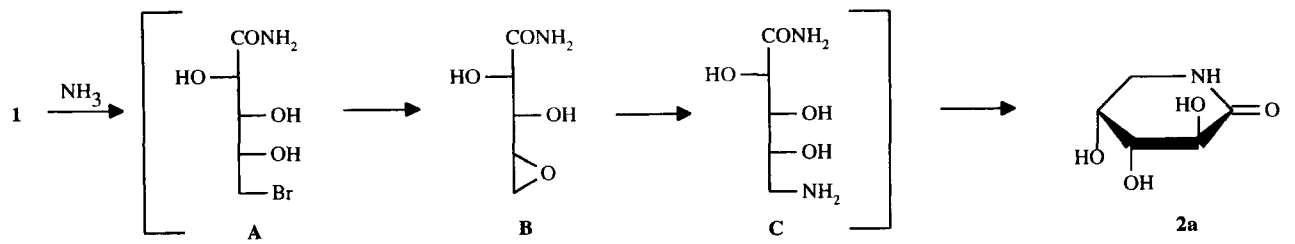
1

2 a : R = H

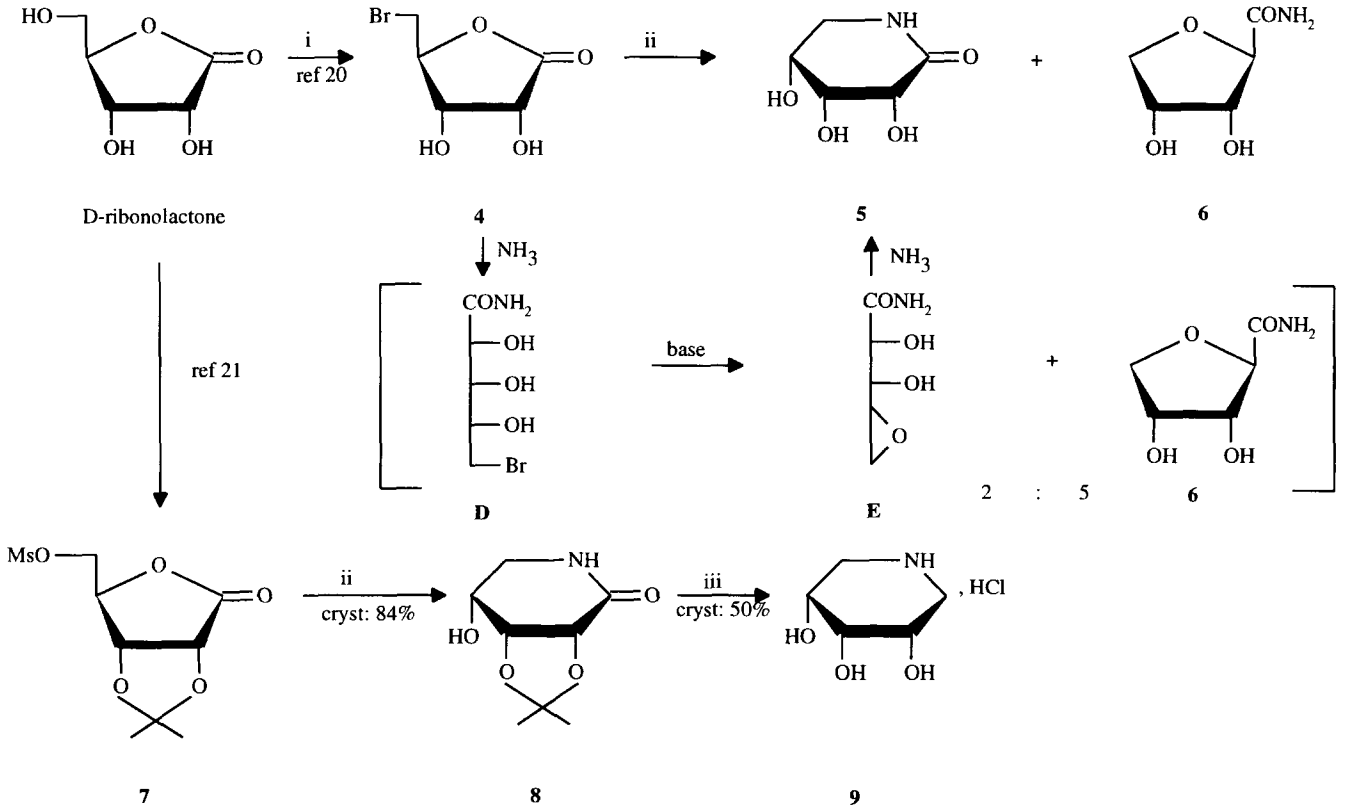
2 b : R, R = $C(CH_3)_2$

3

Reagents and conditions: i: HBr-HOAc; ii: 25% aq NH_3, 2 h, rt; iii: dimethoxypropane, TsOH; iv: $NaBH_4$, CF_3COOH, dioxane 100°C, 3 h; IR 120 (H^+); aq HCl



Scheme 1.

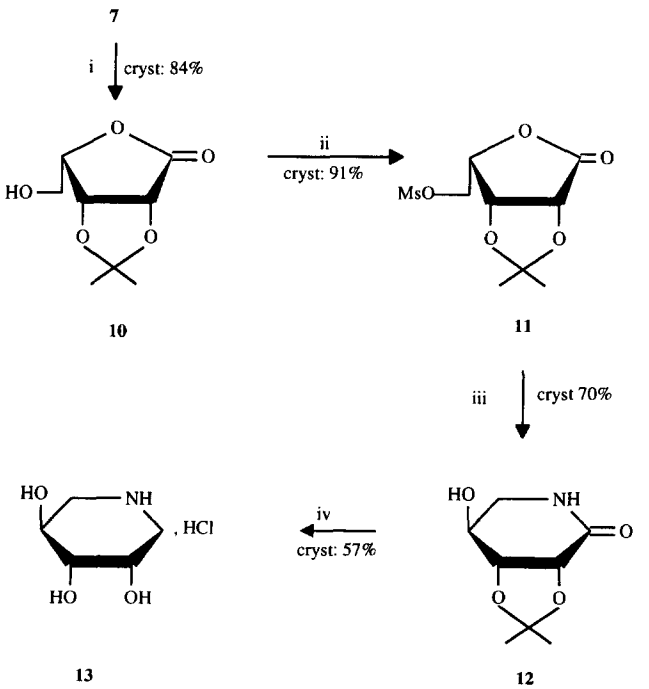


Reagents and conditions: i: CBr_4, Ph_3P; ii: aq NH_3; iii: $NaBH_4$, CH_3COOH, dioxane, 100 °C, 5 h; IR 120 (H^+); aq HCl.

Scheme 2.

bitol, isolated as the crystalline hydrochloride **9**. In this case acetic acid was used, since using trifluoroacetic acid in the reduction, gave an isopropylether of the iminoribitol as a side product. Compound **9** is a new compound, while both **8** and the unprotected 5-amino-5-deoxy-D-ribono-1,5-lactam have been described.[12]

As mentioned in the Introduction the 1,5-amino-1,5-dideoxy-L-arabinitol might also be viewed as the corresponding L-lyxitol. Thus, **13** can either be prepared analogously to the D-arabinitol **3**, from L-arabinonolactone, or from L-lyxonolactone. We chose the latter method, since we have published a convenient method to prepare L-lyxonolactone by isomerization of the mesylated D-ribonolactone **7** selectively at C-4, by treatment with strong aqueous potassium hydroxide, followed by acid work up.[21] When **7**, after treatment with strong base, was worked up keeping the pH above 3 a high yield of crystalline 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**10**) was obtained (Scheme 3). Mesylation gave the crystalline 5-*O*-mesyl-2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**11**) which by treatment with aq ammonia gave the crystalline 5-amino-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,5-lactam (**12**). Reduction with $NaBH_4$–CH_3COOH gave the corresponding 1,5-imino-1,5-dideoxy-L-lyxitol (-L-arabinitol) as the crystalline hydrochloride **13**. This compound has been prepared previously from methyl-D-galactopyranoside in a nine step procedure.[18]



Reagents and conditions: i: KOH/H_2O, 3 h; aq HCl to pH 3; ii: MsCl, pyridine, 1 h, 0 °C; iii: 25% aq NH_3, 4 h, rt; iv: $NaBH_4$, CH_3COOH, dioxane 100 °C, 5 h; IR 120 (H^+); aq HCl.

Scheme 3.

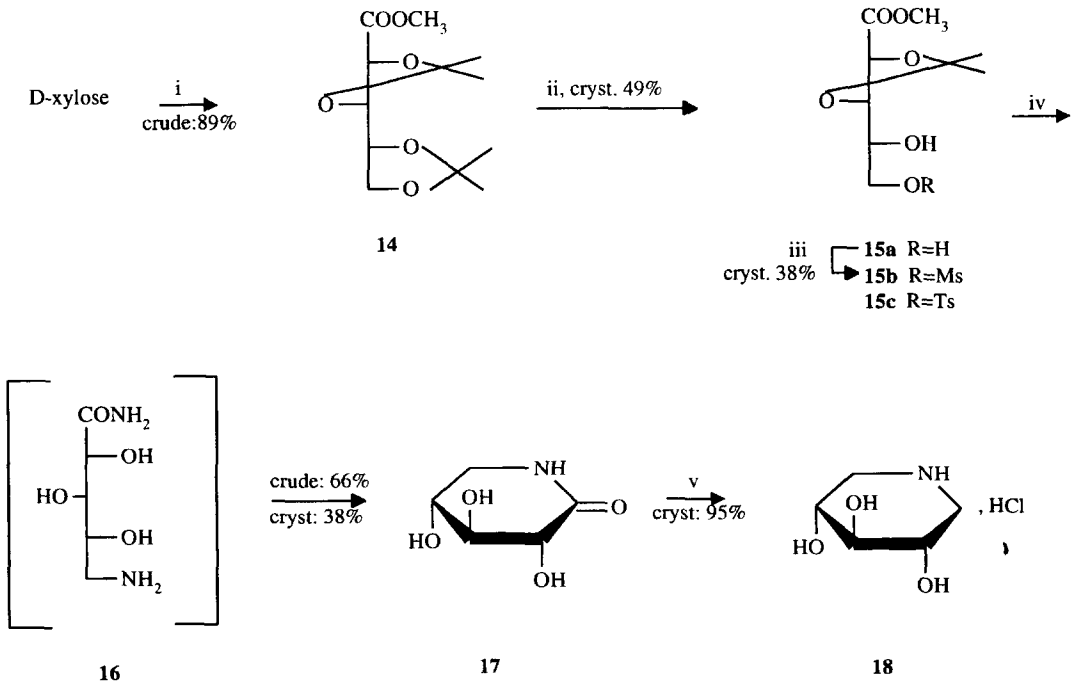
Finally, the iminopentitol with *xylo*-configuration, **18** (mesoform), was targeted (Scheme 4). Iminoxylitol as the free base has previously been synthesized analogously to **13** from methyl 6-bromo-6-deoxy-α-D-glucopyranoside,[18] while Paulsen had already prepared hydroxylated piperidines with *xylo*-configuration in 1967.[22] In both cases no data were given of the noncrystalline products. For our stategy a 5-*O*-mesylated-D-xylono-1,4-lactone was needed. D-xylonic acid is normally prepared by oxidation of D-xylose with bromine, but it is not possible to obtain the pure γ-lactone, since a mixture of open form, γ- and δ-lactones exists.[23] Therefore, the D-xylonic acid was converted into the 2,3–4,5-di-*O*-isopropylidene methyl ester, followed by selective deprotection of the 4,5-acetal group to give, without any purification from D-xylose, crystalline 2,3-*O*-isopropylidene-D-xylonic acid methyl ester **15a** in a 49% overall yield. Mesylation or tosylation gave the 5-sulfonated esterases **15b** (38%) or **15c** (37%). Treatment of the mesylate **15b** with aq ammonia, gave, after methanolysis and lactamization, the 5-amino-5-deoxy-D-xylono-1,5-lactam (**17**). This hitherto unknown lactam was very recently obtained by an intramolecular Schmidt rearrangement of an aldehydo 5-azido-5-deoxy-D-xylose precursor.[24] The melting point reported was, however, ca. 100 °C lower than the one obtained for our compound **17**. The lactam was silylated in situ and reduced using $BH_3 \cdot SMe_2$ to give the 1,5-dideoxy-1,5-imino-xylitol, isolated as the hydrochloride **18**.

In summary, a simple method for the preparation of the four stereoisomeric 1,5-dideoxy-1,5-iminopentitols from 5-substituted aldonolactones/aldonic acid derivatives is presented. When the latter compounds were treated with aq ammonia, 5-amino-5-deoxy-1,5-lactams were formed in a single step. The lactams were subsequently reduced to the target molecules. In the synthesis only cheap and readily available reagents have been used, and the compounds have been crystallized directly.

Biochemistry

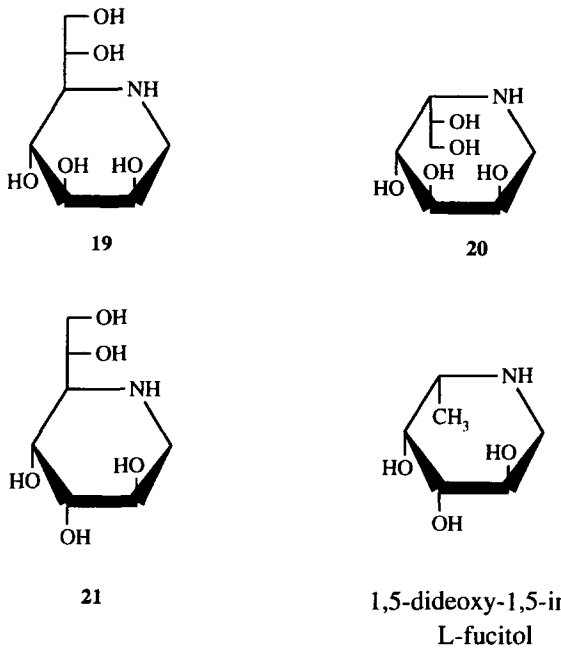
5-Amino-5-deoxy-aldono-1,5-lactams have been reported to exhibit glycosidase inhibitor activity as well as the hydroxylated piperidines.[2] In the present work only the latter compounds have been tested.

The 1,5-dideoxy-1,5-iminopentitols, **3**, **9**, **13**, **18**, and the three 1,5-dideoxy-1,5-iminoheptitols, 1,5-dideoxy-1,5-imino-L-*glycero*-D-*manno*-heptitol (**19**), 1,5-dideoxy-1,5-imino-D-*glycero*-L-*gulo*-heptitol (**20**) and 1,5-dideoxy-1,5-imino-L-*glycero*-D-*altro*-heptitol (**21**) (Scheme 5) which we have prepared from bromodeoxyheptonolactones or -alditols by reaction with ammonia[10] were tested for inhibition of the glycosidase activities present in an extract of human liver.[7] A preliminary screen was carried out using a mixture of human liver enzymes and a panel of 4-methylumbelliferyl glycosides under optimal conditions of assay for each substrate.[7] The concentrations of the test compounds and substrates were 1 and 0.5 mM, respectively, which give a very sensitive assay for inhibition of the enzymes studied. Compound **18**, in which the hydroxy groups in the ring have the same configuration as in D-glucose, almost



Reagents and conditions: i: Br_2, $NaHCO_3$, H_2); acetone, dimethoxypropane, MsOH, 5 h reflux; ii: CH_3OH-H_2O, IR 120 (H^+); iii: MsCl or TsCl, 1.2 eq., pyridine, 0 °C, 0.5–1.5 h; iv: aq NH_3, rt, 16 h; 1% HCl/MeOH, 60 °C, 4 h IRA 400 (HCO_3^-); v: HMDS, TMSCl, CH_3CN, 1 h, 82 °C; $BH_3 \cdot SMe_2$, dioxane, 100 °C, 5 h; 1 M HCl, 100 C, 1 h.

Scheme 4.



Scheme 5.

completely inhibited (97%) β-D-glucosidase under these conditions. None of the other glycosidases was inhibited appreciably. Alteration of the configuration at C3 as in compound **9** decreased the inhibition (61%), whereas alteration of the configuration at C4 as in compound **13** abolished inhibition altogether.

The 1,5-dideoxy-1,5-imino-D-arabinitol (**3**) and the iminoheptitols **19**, **20** and **21** all selectively inhibited α-L-fucosidase by over 85%. This is comparable to other polyhydroxylated piperidines with the same configuration at C2, C3 and C4, which is the minimal structural motif necessary for the inhibition of α-L-fucosidase.[7] These preliminary inhibition studies show that 1,5-dideoxy-1,5-iminopentitols and iminoheptitols have similar inhibitory properties to the corresponding 1,5-dideoxy-1,5-iminohexitols.[19]

Experimental

Melting points are uncorrected. Optical rotations were determined on a Perkin–Elmer 241 polarimeter. NMR spectra were recorded on Bruker AC-250 and AM-500 instruments. Chemical shifts were measured in ppm and coupling constants (J) in Hz. For NMR spectra in D_2O dioxane ($\delta = 67.4$) was used as the internal reference for ^{13}C NMR spectra and acetone ($\delta = 2.17$) for ^1H NMR spectra. For spectra in $CDCl_3$ (chloroform-d, $\delta = 76.9$) was used as the internal reference for ^{13}C NMR spectra while (CD_3, $\delta = 29.8$) was used for ^{13}C spectra and (CD_2H, $\delta = 2.05$) for ^1H spectra in acetone-d_6. ^{13}C NMR signals were assigned through CH-correlated NMR spectra. All evaporations were carried out below 40 °C in vacuo. Microanalyses were performed by Leo Microanalytical Laboratory.

Reaction of the bromodeoxylactones 1 and 4 with aq ammonia followed by ^{13}C NMR spectroscopy. The bromolactone (150 mg) was dissolved in 25% aq ammonia (1 mL) and 10 drops of D_2O were added. The ^{13}C NMR spectra were recorded on a Brucker AC-250 instrument at intervals, using the external instrument reference in water as a reference. ^{13}C chemical shifts for intermediates in these reactions: From **1** (Scheme 1): **B**: δ 179.0 (C-1), 73.5, 72.6 (C-2, C-3), 53.8 (C-4), 47.8 (C-5); **C**: δ 180.4 (C-1), 74.5, 72.3, 72.3 (C-2, C-3, C-4), 45.3 (C-5); **2a**: δ 175.0 (C-1), 73.3, 70.9, 68.2 (C-2, C-3, C-4), 46.5 (C-5). From **4** (Scheme 2): **E**: δ 74.5, 73.4 (C-2, C-3), 52.6 (C-4), 47.0 (C-5); **6**: δ178.1 (C-1), 82.0 (C-2), 76.8, 74.3, 72.4 (C-3, C-4, C-5); **5**: δ175.0 (C-1), 72.5, 69.7, 66.2 (C-2, C-3, C-4), 44.2 (C-5).

5-Amino-5-deoxy-3,4-*O*-isopropylidene-D-arabinono-1,4-lactam (2b). 5-Bromo-5-deoxy-D-arabinono-1,4-lactone[13] 12.0 g, 56.9 mmol) was dissolved in aq NH_3 (25%, 50 mL) and stirred for 2 h. Evaporation of the solvent and co-evaporation with CH_3OH left a syrupy residue which was dissolved in boiling CH_3OH (25 mL). To the warm solution was added *p*-toluenesulfonic acid monohydrate (1.8 g) and 2,2-dimethoxypropane (125 mL) and the mixture was stirred at room temperature for 24 h. The mixture was then neutralized with K_2CO_3, diluted with CH_3OH (100 mL) and filtered. The filtrate was concentrated to a yellow crystalline residue which was washed with hot acetone (100 mL) and an additional amount of potassium salts (5.7 g) was filtered off. The filtrate was poured onto a column of ion-exchange resin (Amberlite MB-3, H^+ and OH^-, 75 mL), which was eluted with CH_3OH. The eluate was concentrated to a crystalline residue which on recrystallization from acetone yielded **2b** (5.32 g, 50%), mp 170–172 °C. Additional recrystallizations from the same solvent gave an analytical sample; mp 177–178 °C, $[\alpha]_D^{20}$ −27° (*c* 2, H_2O). Anal.: Found: C, 51.30; H, 7.05; N, 7.45; calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48%. ^{13}C NMR (D_2O): 174.8 (C-1), 112.1 (O—C—O), 78.4 (C-3), 72.1 (C-4), 71.4 (C-2), 42.1 (C-5), 26.3 and 24.3 (2 × CH_3). ^1H NMR (D_2O): δ 4.58 (ddd, H-4, $J_{4,5} = 6.2$ Hz, $J_{4,5'} = 5.0$ Hz, $J_{3,4} = 7.7$ Hz), 4.40 (dd, H-3, $J_{2,3} = 5.9$ Hz), 4.23 (d, H-2), 3.53 (dd, H-5′, $J_{5,5'} = 13.6$ Hz), 3.22 (dd, H-5), 1.45 and 1.36 (s, CH_3).

1,5-Dideoxy-1,5-imino-D-arabinitol hydrochloride (3). To a stirred solution of 5-amino-5-deoxy-3,4-*O*-isopropylidene-D-arabinono-1,5-lactam **3** (5.00 g, 26.7 mmol) in dioxane (80 ml) was added sodium borohydride (4.50 g, 119 mmol). Then a solution of trifluoroacetic acid (12.0 g, 105 mmol) in dioxane (10 ml) was added at room temperature during 15 min and the mixture heated at 100 °C for 2 h. After being cooled to room temperature H_2O (40 ml) was added slowly and a crystalline precipitate (5.9 g) was filtered off and discarded. To the filtrate was added ion-exchange resin (Amberlite IR-120, H^+, 250 mL) and the mixture was stirred slowly for 2 h. The resin was filtered off and poured into ice-cooled water. NH_3 (25%, 180 mL) was added with stirring, which was continued for 1 h at

room temperature. The resin was then filtered off and the filtrate was filtered through activated carbon, concentrated and co-concentrated with H_2O to leave a residue, which was dissolved in 3 M HCl (25 mL). Concentration left a syrup which crystallized from CH_3OH by seeding, to give **3** (2.97 g, 66%), mp 194–195 °C, $[\alpha]_D^{20}$ −22° (*c* 0.8, CH_3OH) (lit.:[18] mp 191–192 °C, $[\alpha]_D^{20}$ −16° (*c* 0.9, CH_3OH)). ^{13}C NMR (D_2O): 71.8 (C-3), 66.0 (C-2), 65.6 (C-4), 47.0 (C-5) and 46.5 (C-1). The ^1H NMR data are in accordance with the published values.[18] ^1H NMR (D_2O): δ 4.19 (H-4, m, $J_{4,5'}=6.0$ Hz, $J_{4,5}=2.8$ Hz, $J_{3,4}=3.0$ Hz), 4.05 (dt, H-2, $J_{2,3}=8.0$ Hz, $J_{1',2}=4.0$ Hz, $J_{1,2}=8.5$ Hz), 3.73 (dd, H-3), 3.37 (dd, H-1′, $J_{1,1'}=12.8$ Hz), 3.25 (dd, H-5′, $J_{5,5'}=13.0$ Hz), 3.17 (dd, H-5) and 2.91 (dd, H-1).

5-Amino-5-deoxy-2,3-*O*-isopropylidene-D-ribono-1,4-lactam (8). 2,3-*O*-Isopropylidene-5-*O*-mesyl-D-ribono-1,4-lactone[21] (**7**; 17.0 g, 63.8 mmol) was dissolved in aq NH_3 (65 mL, 25%) and allowed to stand for 18 h at room temperature in a sealed flask. Concentration and co-concentration twice with EtOAc gave a residue which was extracted with boiling EtOAc (2 × 200 mL). The combined organic phases were treated with activated carbon, dried (Na_2SO_4), filtered and concentrated to give **8** (10.1 g, 84%) as colorless crystals, mp 123–127 °C. Recrystallization from EtOAc/EtOH gave **8**; mp 133–134 °C, $[\alpha]_D^{20}$ + 8.3° (*c* 1.0, CH_3OH). Anal.: found: C, 51.30; H, 7.11; N, 7.42; calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48% (lit.[15]: mp 139–140 °C, $[\alpha]_D^{20}$ +26.8° (*c* 1.02, $CHCl_3$)]. ^{13}C NMR (D_2O): δ 172.3 (C-1), 112.1 (acetal C), 75.9, 73.5 (C-2, C-3), 64.1 (C-4), 42.2 (C-5), 26.3 and 25.0 (2 × CH_3). ^1H NMR (D_2O): δ 4.62 (dd, H-3, $J_{2,3}=6.5$ Hz, $J_{3,4}=3.0$ Hz), 4.60 (d, H-2), 4.25 (ddd, $J_{4,5}=8.0$ Hz, $J_{4,5'}=4.0$ Hz), 3.45 (dd, H-5, $J_{5,5'}=13.0$ Hz), 3.33 (dd, H-5′), 1.48 (s, CH_3) and 1.44 (s, CH_3).

1,5-Dideoxy-1,5-imino-ribitol, hydrochloride (9). 5-Amino-5-deoxy-2, 3-*O*-isopropylidene-D-ribono-1,5-lactam (**8**; 4.0 g, 21 mmol) was dissolved in dioxane (70 mL). $NaBH_4$ (8.1 g, 210 mmol, 10 equiv.) was added with stirring, followed by dropwise addition of acetic acid (11.6 ml, 200 mmol, 9.5 equiv.) and the mixture was heated at 100 °C for 5 h. The solution was then cooled to room temperature and H_2O (60 mL) was added slowly. The resulting crystalline precipitate (12.4 g) was filtered off. The filtrate was stirred with ion-exchange resin (Amberlite IR-120, H^+, 200 mL) for 2 h. The resin was filtered off, washed with H_2O, poured into a beaker and aq NH_3 (150 ml, 25%) was added at 0 °C. After stirring for 1 h the resin was filtered off and the filtrate concentrated and co-concentrated with H_2O. The residue was dissolved in 3 HCl (20 mL), concentrated and co-concentrated with 1‰ concd HCl in CH_3OH leaving a crystalline residue, which on recrystallization from CH_3OH/H_2O gave **8** (1.8 g, 50%) as colorless crystals; mp 179–181 °C. Further recrystallizations from the same solvent furnished an analytical sample; mp 185–187 °C, $[\alpha]_D^{20}$ ≈0.0° (*c* 1.0, H_2O). Anal.: found: C, 35.39; H, 7.11; N, 8.37; Cl^-, 20.25; calcd for $C_5H_{12}ClNO_3$: C, 35.41; H, 7.13; N, 8.26; Cl 20.90%. ^{13}C NMR (D_2O): δ 69.1 (C-3), 66.3 (C-1, C-5), 45.0 (C-2, C-4). ^1H NMR (D_2O): δ 4.08 (ddd, H-2, H-4, $J_{1,2}=J_{4,5}=4.5$ Hz, $J_{1',2}=J_{4,5'}=7.2$ Hz, $J_{2,3}=J_{3,4}=2.9$ Hz), 4.04 (t, H-3), 3.26 (dd, H-1, H-5, $J_{1,1'}=J_{5,5'}=13.0$ Hz), 3.22 (dd, H-1′, H-5′).

2,3-*O*-Isopropylidene-L-lyxono-1,4-lactone (10). 2,3-*O*-Isopropylidene-5-*O*-methane-sulfonyl-D-ribono-1,4-lactone (43.3 g, 163 mmol) was dissolved in H_2O (250 mL) containing KOH (31 g, 470 mmol) and stirred for 3 h at room temperature. The solution was then acidified with 3 M HCl to exactly pH = 3.0 and concentrated. The residue was stirred twice with boiling acetone (250 mL) for 30 min. The remaining salts were dissolved in H_2O (250 mL) and pH was adjusted to 3 with 3 M HCl. As above, the solution was then concentrated and the residue extracted with acetone. The procedure was repeated once. The combined organic phases were dried ($MgSO_4$), filtered and concentrated leaving **10** as a crystalline product (28.3 g). Further purifications were carried out by dissolving in boiling acetone followed by hot filtration through a short column of charcoal. Concentration of the filtrate gave colorless needles of **10** (25.8 g, 84%); mp 92–93 °C, $[\alpha]_D^{20}$ −85.6° (*c* 1.0, acetone). Anal.: found: C, 50.85; H, 6.42; calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.43%. ^{13}C NMR (D_2O): δ 177.9 (C-1), 115.5 (acetal C), 81.8 (C-4), 77.2 (C-2), 77.0 (C-3), 60.5 (C-5), 26.6 and 25.6 (2 × CH_3). ^1H NMR (D_2O): δ 5.10 (d, H-2, $J_{2,3}=5.6$ Hz), 5.03 (dd, H-3, $J_{3,4}=3.7$ Hz), 4.76 (ddd, H-4, $J_{4,5}=4.2$ Hz, $J_{4,5'}=8.0$ Hz), 3.91 (dd, H-5, $J_{5,5'}=12.5$ Hz), 3.87 (dd, H-5′), 1.40 (s, CH_3) and 1.36 (s, CH_3).

2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-L-lyxono-1,4-lactone (11). Methanesulfonyl chloride (4.55 ml, 58.4 mmol) was added dropwise with stirring to an ice-cooled solution of 2,3-*O*-isopropylidene-L-lyxono-1,4-lactone (**10**; 10.0 g, 53.1 mmol) in pyridine (30 mL) and the mixture was kept for 1 h at 0 °C. H_2O (1 mL) was then added slowly followed by CH_2Cl_2 (150 mL). The mixture was washed successively with 10% aq HCl (30 mL) until the extract became acidic and then with an additional portion of 10% aq HCl (30 mL) followed by aq $NaHCO_3$ (30 mL). The organic phase was dried ($MgSO_4$), treated with activated carbon, filtered and concentrated to give **11** as colorless crystals (12.8 g, 91%); mp 122–124 °C. According to NMR the product was pure enough for further synthesis. Recrystallization from EtOAc furnished an analytical sample; mp 133–133.5 °C, $[\alpha]_D^{20}$ −75.9° (*c* 1.0, CH_3OH). Anal.: found: C, 40.71; H, 5.35; S, 11.93; calcd for $C_9H_{14}O_7S$: C, 40.60; H, 5.30; S, 12.04%. ^{13}C NMR (acetone-d_6): δ 173.9 (C-1), 114.6 (acetal C), 77.4 (C-4), 77.0 (C-2), 77.0 (C-3), 68.9 (C-5), 37.4 (Ms), 26.9 and 25.9 (2 × CH_3). ^1H NMR (acetone-d_6): δ 5.11 (d, H-2, $J_{2,3}=6.3$ Hz), 5.05 (dd, H-3, $J_{3,4}=3.8$ Hz), 4.95 (ddd, H-4, $J_{4,5}=3.5$ Hz, $J_{4,5'}=8.2$ Hz), 4.65 (dd, H-5, $J_{5,5'}=11.5$ Hz), 4.45 (H-5′), 3.19 (Ms), 1.42 (s, CH_3) and 1.36 (s, CH_3).

5-Amino-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,5-lactam (12). 2,3-*O*-Isopropylidene-5-*O*-mesyl-L-lyxono-

1,4-lactone (**11**; 12.7 g, 47.7 mmol) was dissolved in aq NH_3 (25%, 50 mL) and left for 4.5 h at room temperature in a sealed flask. Concentration and co-concentration twice with EtOAc gave a residue which was extracted with boiling EtOAc (2 × 150 mL). The combined organic phases were treated with activated carbon and dried (Na_2SO_4), filtered and concentrated to give **12** (6.25 g, 70%) as colourless crystals; mp 110–115 °C. Purification by flash chromatography (EtOH:EtOAc 1:4), furnished a product with mp 121–122 °C, $[\alpha]_D^{20}$ + 6.2° (*c* 1.0, CH_3OH). Anal.: found: C, 51.52; H, 7.03; N, 7.36; calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48%. ^{13}C NMR (D_2O, acetone δ = 29.8): δ 170.9 (C-1), 110.8 (acetal), 77.3 (C-3), 72.0 (C-2), 65.6 (C-4), 42.0 (C-5), 25.4 and 23.7 (2 × CH_3). ^1H NMR (D_2O): δ 4.61 (d, H-2, $J_{2,3}$ = 6.8 Hz), 4.46 (ddd, H-3, $J_{3,4}$ = 5.3 Hz, $J_{3,5'}$ = 0.7 Hz), 4.02 (ddd, H-4, $J_{4,5}$ = 3.2 Hz, $J_{4,5'}$ = 6.0 Hz), 3.47 (dd, H-5, $J_{5,5'}$ = 13.5 Hz), 3.22 (dd, H-5′), 1.41 (s, CH_3) and 1.38 (s, CH_3).

1,5-Dideoxy-1,5-imino-L-lyxitol, hydrochloride (13). 5-Amino-5-deoxy-2,3-*O*-isopropylidene-L-lyxono-1,5-lactam (**12**; 6.2 g, 33 mmol) was dissolved in dioxane (100 mL). $NaBH_4$ (12.6 g, 333 mmol) was added with stirring followed by dropwise addition of acetic acid (19.0 mL, 316 mmol) and the mixture was heated at 100 °C for 5 h. The solution was cooled to room temperature and H_2O (100 mL) was added slowly and a crystalline precipitate (17.2 g) was filtered off. The filtrate was stirred with ion-exchange resin (Amberlite IR-120, H^+, 200 mL) for 2 h. The resin was filtered off, washed with water, poured into a beaker and aq NH_3 (200 mL, 25%) was added to the resin at 0 °C. After stirring for 1.5 h the resin was filtered off and the filtrate was concentrated and co-concentrated with H_2O. The residue was dissolved in 3 M HCl (30 ml), concentrated and co-concentrated with 1‰ concd HCl in methanol leaving a crystalline residue. Addition of CH_3OH:EtOAc (1:1) gave crystalline **12** (3.23 g, 57%); mp 193–194 °C. Recrystallization from 85% aq CH_3OH gave an analytical sample; mp 195.5–196 °C, $[\alpha]_D^{20}$ = +22.7° (*c* 0.8, CH_3OH; lit.:[18] mp 191–192 °C, $[\alpha]_D^{20}$ + 16° (*c* 0.5, CH_3OH)]. ^{13}C NMR (D_2O, reference acetone δ = 29.8): δ 70.4 (C-3), 64.6 (C-2), 64.3 (C-4), 45.6 (C-5) and 45.1 (C-1). ^1H NMR (D_2O): δ 4.19 (m, H-4, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 6.0 Hz, $J_{4,5'}$ = 2.8 Hz), 4.05 (dt, H-2, $J_{1,2}$ = 4.0 Hz, $J_{1',2}$ = 8.5 Hz, $J_{2,3}$ = 8.0 Hz), 3.73 (dd, H-3), 3.37 (ddd, H-1, $J_{1,1'}$ = 12.8 Hz, $J_{1,5}$ = 1.0 Hz), 3.25 (ddd, H-5, $J_{5,5'}$ = 13.0 Hz), 3.17 (dd, H-5′) and 2.92 (dd, H-1).

2,3-*O*-Isopropylidene-D-xylonic acid methyl ester (15a). D-xylose (25.0 g, 166 mmol) and $NaHCO_3$ (34.9 g, 415 mmol) were dissolved in H_2O (300 mL), and Br_2 (8.5 mL, 166 mmol) was added slowly. After stirring for 3 h at room temperature the color had disappeared. More Br_2 (1.0 mL, 19 mmol) was added to the solution which was stirred for an additional 1.5 h and then concentrated. The residue was redissolved in water, acidified with concd HCl, concentrated and co-concentrated with methanol. To the residue was added acetone (250 mL), dimethoxypropane (80 mL) and methanesulfonic acid (1.0 mL). The mixture was refluxed for 5 h and left overnight at room temperature. The suspension was then neutralized with solid $NaHCO_3$, filtered and concentrated. The residue was dissolved in CH_2Cl_2 (200 mL), washed with H_2O (3 × 100 mL) and dried ($MgSO_4$). Filtration and concentration gave **14** as a colorless syrup (38.5 g, 89%). The syrup was dissolved in MeOH:H_2O (9:1, 400 mL) and ion exchange resin (Amberlite IR-120, H^+, 30 g, pre-washed with CH_3OH and dried for 10 min before use) was added. After stirring for 16 h the resin was separated from the solution by filtration through celite. The filtrate was concentrated, redissolved in H_2O (200 mL) and washed with Et_2O (3 × 100 mL). The ether phases were combined and concentrated to give a residue (5.2 g), which mostly consisted of 2,3–4,5-di-*O*-isopropylidene-D-xylonic acid methyl ester (**14**). The water phase was concentrated and co-concentrated with twice MeOH. The residue was dissolved in CH_2Cl_2 (200 mL), and under vigorously stirring hexane (200 mL) was added. The precipitate [consisting of D-xylonic acid methyl ester/2,3-*O*-isopropylidene-D-xylonic acid methyl ester (**15a**), 3:2] was removed from the solution by decanting through celite. Concentration of the filtrate gave **15a** as colorless crystals (15.3 g, 42%); mp 66–72 °C. The residue from the ether phase above was again hydrolysed by stirring for 16 h in MeOH:H_2O (9:1, 50 mL) with ion-exchange resin (Amberlite IR-120, H^+, 3 g). The resin was filtered off through celite, and the filtrate was concentrated, redissolved in H_2O (40 mL) and washed with Et_2O (3 × 20 mL) which was discharged. The water phase was mixed with the precipitate from above and extracted with EtOAc (10 × 40 mL). The combined organic phases were dried ($MgSO_4$), and concentrated to give an additional amount of **15a** which crystallized on standing, bringing the total yield to 49%. Recrystallization from EtOAc furnished an analytical sample; mp 75–76.5 °C, $[\alpha]_D^{20}$ −39.3° (*c* 1.0, CH_3OH). Anal.: found: C, 49.22; H, 7.37; calcd for $C_9H_{16}O_6$: C, 49.09; H, 7.32%. ^{13}C NMR ($CDCl_3$): δ 171.1 (C-1), 111.6 (acetal), 79.7 (C-3), 75.2 (C-2), 70.2 (C-4), 64.4 (C-5), 52.4 (OCH_3), 26.5 and 25.6 (2 × CH_3). C-H corr. ^1H NMR ($CDCl_3$): δ 4.62 (d, H-2, $J_{2,3}$ = 7.6 Hz), 4.23 (dd, H-3, $J_{3,4}$ = 2.9 Hz), 3.84 (m, H-4), 3.81 (s, OCH_3), 3.80 (dd, H-5, $J_{4,5}$ = 4.8 Hz, $J_{5,5'}$ = 11.5 Hz), 3.76 (dd, H-5′, $J_{4,5'}$ = 4.6 Hz), 1.50 (s, CH_3) and 1.44 (s, CH_3).

2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-D-xylonic acid methyl ester (15b). 2,3-*O*-Isopropylidene-D-xylonic acid methyl ester (**15a**; 10 g, 45.4 mmol) was dissolved in pyridine (50 ml) and cooled to 0 °C. Methanesulfonyl chloride (3.88 mL, 50.0 mmol) in pyridine (25 mL) was added slowly during 1.5 h at 0 °C. After stirring for 2 h at room temperature CH_2Cl_2 (150 mL) and ice were added and the mixture was acidified with concd HCl. The organic layer was washed with aq satd $NaHCO_3$, treated with activated carbon and dried ($MgSO_4$). Filtration and concentration left a slightly colored syrup (11.7 g), which crystallized on prolonged standing. The semi-crystalline residue was stirred with EtOH and crystals were filtered off (5.21 g, 38%) to

give **15b**; mp 91–97 °C. Recrystallization from EtOH furnished an analytical sample; mp 97–98 °C. $[\alpha]_D^{20}$ −27.3° (*c* 1.0, CH_3OH). Anal.: found: C, 40.32; H, 6.18; calcd for $C_{10}H_{18}O_8S$: C, 40.26; H, 6.08%. ^{13}C-NMR ($CDCl_3$): δ 170.8 C-1), 112.0 (acetal), 77.4 (C-3), 74.9 (C-2), 70.3 (C-5), 68.2 (C-4), 52.5 (OCH_3), 37.6 (Ms), 26.5 and 25.6 (2 × CH_3). ^{1}H NMR ($CDCl_3$): δ 4.59 (d, H-2, $J_{2,3}$ = 7.5 Hz), 4.36 (dd, H-5, $J_{4,5}$ = 7.1 Hz, $J_{5,5'}$ = 11.0 Hz), 4.29 (dd, H-5′, $J_{4,5'}$ = 4.8 Hz), 4.23 (dd, H-3, $J_{3,4}$ = 2.4 Hz), 4.08 (ddd, H-4), 3.81 (s, OCH_3), 3.08 (s, Ms), 2.28 (s, OH-4), 1.50 (s, CH_3) and 1.43 (s, CH_3). Chromatography of the mother liquour with a gradient (EtOAc:Hexane 1:3→EtOAc) gave 2,3-*O*-isopropylidene-4,5-di-*O*-methanesulfonyl-D-xylonic acid methyl ester (ca 1 g) and a mixture of 2,3-*O*-isopropylidene-4-*O*-methanesulfonyl-D-xylonic acid methyl ester and 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-D-xylonic acid methyl ester 1:2 (160 mg).

2,3-*O*-Isopropylidene-5-*O*-p-toluenesulfonyl-D-xylonic acid methyl ester (15c). 2,3-*O*-Isopropylidene-D-xylonic acid methyl ester **15a** (2.00 g, 9.1 mmol) was dissolved in pyridine (10 mL) and cooled to 0 °C. During 1 h a solution of *p*-toluenesulfonyl chloride (2.08 g, 10.9 mmol) and pyridine (5 mL) was added dropwise. After stirring for 30 min at 0 °C and 30 min at room temperature, CH_2Cl_2 (20 mL) and ice were added. The mixture was acidified with concd HCl. The organic layer was collected, washed with aq $NaHCO_3$, treated with activated carbon and dried ($MgSO_4$). Filtration and concentration left a slightly colored syrup (2.68 g). The syrup was dissolved in EtOH (3 mL), cooled to −70 °C followed by slowly warming to room temperature, whereby crystalline **15c** (1.24 g, 37%) was obtained; mp 84–89 °C. Recrystallization from EtOH furnished an analytical sample; mp 90–91.5 °C, $[\alpha]_D^{20}$ −13.5° (*c* 1.0, $CHCl_3$). Anal: found: C, 51.43; H, 5.97, S, 8.62; calcd for $C_{16}H_{22}O_8S$: C, 51.33; H, 5.92; S. 8.56%. ^{13}C NMR ($CDCl_3$): δ 170.6 (C-1), 145.0, 132.5, 129.8, 127.9 (aromatic carbon), 111.8 (acetal), 77.6 (C-3), 74.8 (C-2), 70.4 (C-5), 67.7 (C-4), 52.4 (OCH_3), 26.4 (CH_3), 25.5 (CH_3) and 21.5 (CH_3-Ph). ^{1}H NMR ($CDCl_3$): δ 7.81 (d, H′-3, H′-5, $J_{2,3}$ = $J_{5,6}$ = 8.1 Hz), 7.36 (d, H′2, H′-6), 4.56 (d, H-2, $J_{2,3}$ = 7.6 Hz), 4.17 (dd, H-3, $J_{3,4}$ = 2.1 Hz), 4.14 (dd, H-5, $J_{4,5}$ = 6.9 Hz, $J_{5,5'}$ = 10.3 Hz), 4.01 (ddd, H-4), 3.80 (s, OCH_3), 2.46 (s, CH_3-Ph), 1.45 (s, CH_3) and 1.39 (s, CH_3).

5-Amino-5-deoxy-D-xylono-1,5-lactam (17). 2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-D-xylonic acid methyl ester (**15b**; 6.24 g, 20.9 mmol) was dissolved in aq NH_3 (25%, 60 mL). After standing for 16 h at room temperature in a sealed flask, the mixture was concentrated and co-concentrated with CH_3OH (2 × 50 mL) followed by stirring at 60 °C with 1% HCl in methanol (100 mL) for 4 h. The solution was cooled and diluted with CH_3OH (100 mL) and was slowly run through a column of ion-exchange resin (Amberlite IR-400, HCO_3^-, 100 ml). The eluate was concentrated to give a semi-crystalline residue (2.06 g, 66%). Crystallization from EtOH/H_2O gave **17** (0.56 g, 18%); mp 169–171 °C. Unlactamized impurities (**16**) were removed by running the filtrate through a column of ion exchange resin (Amberlite IR-120, H^+, 15 mL) followed by washing with H_2O (100 mL). The eluate was concentrated to give **17** as a colorless syrup (0.62, 20%) which crystallized on standing. According to NMR it was pure enough for further synthesis. Recrystallization from H_2O/EtOH/acetone furnished an analytical sample; mp 172–173 °C, $[\alpha]_D^{20}$ +7.4° (*c* 1.0, H_2O). Anal.: found: C, 40.59; H, 6.16; N, 9.53; calcd for $C_5H_9NO_4$: C, 40.82; H, 6.17; N, 9.52% (lit.:[24] mp 68–71 °C). ^{13}C NMR (D_2O, reference AcOH δ = 20.0): δ 173.0 (C-1), 74.3 (C-3), 70.8 (C-2), 67.1 (C-4), 43.5 (C-5). C-H corr. ^{1}H NMR (D_2O, reference AcOH δ 2.03): δ 3.95 (d, H-2, $J_{2,3}$ = 9.2 Hz), 3.89 (dt, H-4, $J_{3,4}$ = 9.0 Hz, $J_{4,5}$ = 5.7 Hz, $J_{4,5'}$ = 8.9 Hz), 3.64 (t, H-3), 3.44 (dd, H-5, $J_{5,5'}$ = 12.4 Hz), 3.07 (dd, H-5′).

1,5-Dideoxy-1,5-imino-xylitol, hydrochloride (18). D-xylono-1,5-lactam (**17**; 0.53 g, 3.6 mmol) was suspended in acetonitrile (5 ml) and a mixture of hexamethyldisilizane (2.5 mL, 11.4 mmol) and trimethylsilylchloride (0.1 mL, 0.6 mmol) was added. After stirring for 1 h at 82 °C a precipitate had formed and was filtered off, and washed with $CHCl_3$. The filtrate was concentrated. The residue was dissolved in dioxane (20 mL) and under a N_2 atmosphere, $BH_3 \cdot Me_2S$ (10 M, 1.8 mL, mmol) was added. The mixture was then stirred for 5 h at 100 °C and allowed to stand for 16 h at rt. 1M HCl (15 mL) was added and the mixture was heated to 100 °C for 1 h, then concentrated and co-concentrated with 1% concd HCl in methanol (3 × 30 ml). The residue was kept in vacuo over KOH whereby it crystallized. The product was washed on a filter with MeOH and EtOH giving **18** (0.26 g, 43%) as colorless crystals; mp 135–140 °C. Concentration of the filtrate gave 0.32 g (52%) of slightly colored crystals, raising the total yield to 95%. Recrystallization from H_2O/MeOH/EtOAc furnished an analytical sample; mp 126.5–127.5 °C, $[\alpha]_D^{20}$ 0.0° (*c* 0.5, H_2O). Anal.: found: C, 35.30; H, 7.09; N, 8.31; Cl^-, 20.40; calcd for $C_5H_{12}ClNO_3$: C, 35.41; H, 7.13; N, 8.26, Cl^-, 20.90%. ^{13}C NMR (D_2O, reference AcOH δ = 20.0): δ 74.2 (C-3), 66.4 (C-2, C-4), 45.8 (C-1, C-5). ^{1}H NMR (D_2O, reference AcOH δ = 2.03): δ 3.76 (ddd, H-2, H-4, $J_{2,3}$ = $J_{3,4}$ = 8.4 Hz, $J_{1,2}$ = $J_{4,5}$ = 4.5 Hz, $J_{1',2}$ = $J_{4,5'}$ = 10.2 Hz), 3.50 (t, H-3), 3.44 (dd, H-1, H-5, $J_{1,1'}$ = $J_{5,5'}$ = 12.7 Hz), 2.93 (ddd, H-1′, H-5′).

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