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Deoxyiminoalditols from Aldonolactones. III. Preparation of 1,4-Dideoxy-1,4-imino-L-gulitol. - Evaluation of 1,4-Dideoxy-1,4-iminohexitols as Glycosidase Inhibitors

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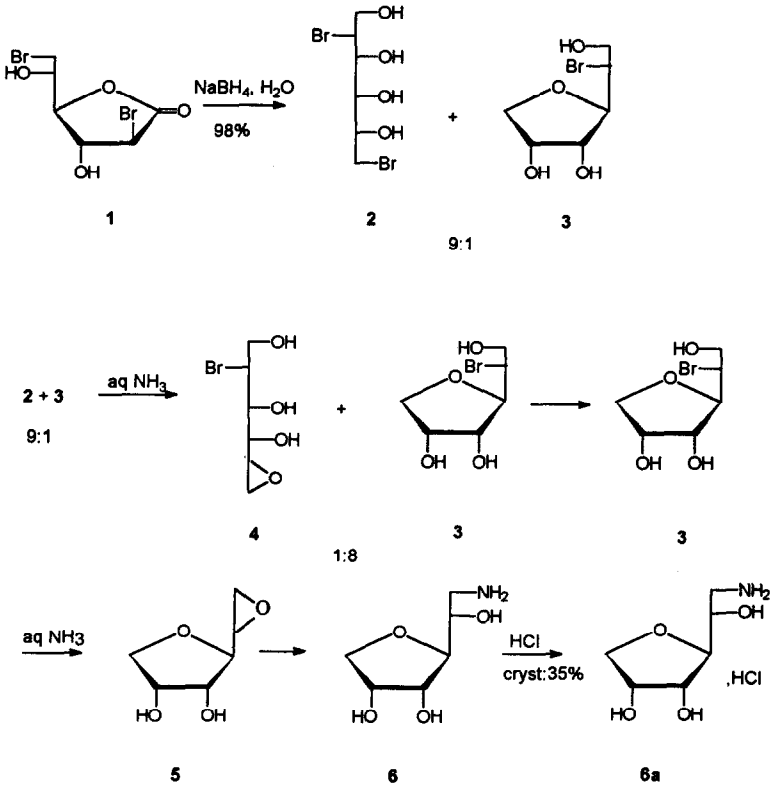
Abstract: 2,6-Dibromo-2,6-dideoxy-D-altrono-1,4-lactone (**1**) was converted into a mixture of 2,3-anhydro-6-bromo-6-deoxy-D-allono-1,4- (**7**) and -1,5-lactone (**8**), which by treatment with aqueous NH_3 (25%) gave 3,6-dideoxy-3,6-imino-D-gluconic acid (**9**). Convertion into the 1,4-lactone **10** followed by reduction with $NaBH_4$ gave 1,4-dideoxy-1,4-imino-L-gulitol (**11**). - Reduction of the dibromolactone **1** gave 2,6-dibromo-2,6-dideoxy-D-altritol (1,5-dibromo-1,5-dideoxy-D-talitol) (**2**) which was unstable since it was readily transformed into 3,6-anhydro-2-bromo-2-deoxy-D-altritol (**3**). Treatment of either **2** or **3** with aqueous NH_3 (25%) gave 1-amino-1-deoxy-3,6-anhydro-D-allitol (**6**). - The reaction of the bromo compounds with aqueous NH_3 were followed by ^{13}C NMR spectroscopy. - Evaluation of nine 1,4-dideoxy-1,4-iminohexitols with D- and L- *allo*, *talo*-, *galacto*-, *ido*- and with L-*gulo*-configurations as glycosidase inhibitors is reported.

The access to a variety of compounds which may act as glycosidase inhibitors is of importance in for example the study of diabetes, cancer and viral diseases.[1] It has been shown that 1,4-dideoxy-1,4-iminohexitols[2,3] and -pentitols[3] inhibit the hydrolysis of glycopyranosidic linkages and such types of compounds are thus of interest in the above mentioned context. Since we have found a convenient two-step procedure for converting 2,6-dibromo-2,6-dideoxy-hexonolactones into crystalline 1,4-dideoxy-1,4-iminohexitols using cheap reagents in aqueous media,[4,5] we wanted to extend our investigations to 2,6-dibromo-2,6-dideoxy-D-altronolactone.[6] Our method involved reduction of the dibromohexonolactone with $NaBH_4$ in water to give the corresponding 2,6-(1,5) dibromoalditol, which then by treatment with aqueous NH_3 (25%) yielded the 1,4-iminohexitol as the only product.[4,5] Using this strategy, the dibromoaltronolactone **1** was treated with $NaBH_4$ in water to give 2,6-dibromo-2,6-dideoxy-D-altritol (1,5-dibromo-1,5-dideoxy-D-talitol) (**2**) contaminated with *ca.* 10% of an anhydride, presumably the 3,6-anhydro-2-bromo-2-deoxy-D-altritol (**3**), since a ^{13}C NMR spectrum showed a secondary bromide (δ 57.8, C-2) as well as a 5-membered ring (δ 80.6, C-3 and δ 64.6, C-6). Crystallization from EtOH at -78°C gave pure **2**. This was, however, not stable, since it was slowly converted into the anhydride **3**.

Because **2** was not stable on storage, we treated the crude, freshly prepared 2,6-dibromoaltritol **2** with aqueous NH_3. Monitoring the reaction by ^{13}C NMR spectroscopy revealed that the 3,6-anhydride **3** was formed rapidly (see Table). Traces of the intermediate 5,6-epoxide **4** were observed (δ 44.3, C-6, δ 53.9, C-5), and within 1 h only **3** was present. After 20 h **3** was present together with the 1-amino compound **6** in about

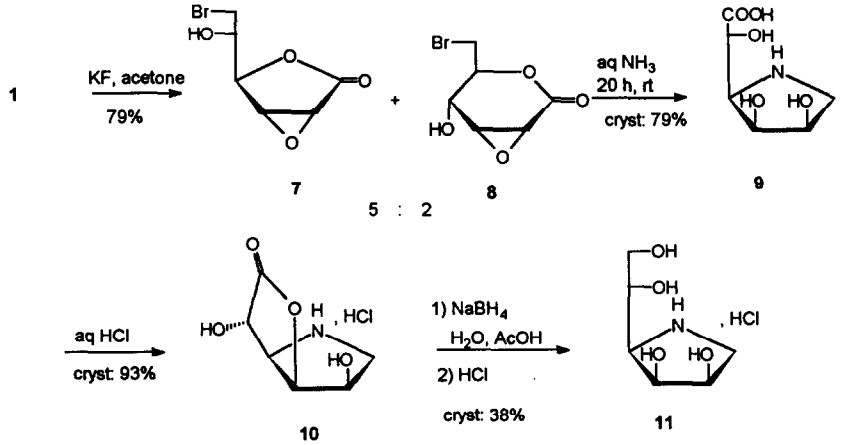
equal amounts. The reaction took 3 days to go to completion. During this time up to *ca.* 10% of the intermediate epoxide **5** (δ 49.0, C-1, δ 61.1, C-2) was observed. In all spectra *ca.* 10% of an 2,5-anhydride was present, since it was formed from **2** in a parallel reaction to the formation of the 3,6-anhydride **3**. The 1-amino-1-deoxy-3,6-anhydro-D-allitol (**6**) was isolated as the crystalline hydrochloride **6a**.



Scheme 1

The formation of a 3,6-anhydride instead of a 5,6-epoxide under basic conditions has not been observed in the reactions of other isomeric 2,6-dibromo-2,6-dideoxy-hexitols with NH_3.[4,5] Since the dibromoaltritol **2** did not give pyrrolidine derivatives when treated with NH_3, we investigated the similar reaction starting with the dibromoaltronolactone **1**. Previously,[4] we have shown that the reaction of the 2,6-dibromo-2,6-dideoxy-hexono-1,4-lactone with *manno*-configuration gave a pyrrolidine when treated with aqueous NH_3, while the corresponding lactone with *gluco*-configuration gave in addition an 2,5-anhydride (*ca.* 25%). When **1** was treated with aqueous NH_3 a complex mixture was obtained, in which anhydrides were recognized from the ^{13}C NMR spectrum. Since the OH-3 was probably involved in the anhydride formation, this group was blocked as a 2,3-epoxide prior to the NH_3-treatment. Thus, when **1** was treated with KF in acetone following our previously described method,[7] the 2,3-anhydro-6-bromo-6-deoxy-D-allonolactone was obtained as a mixture of the 1,4-(**7**) and the 1,5-lactone (**8**). This product was treated directly with aqueous NH_3 to give 3,6-dideoxy-

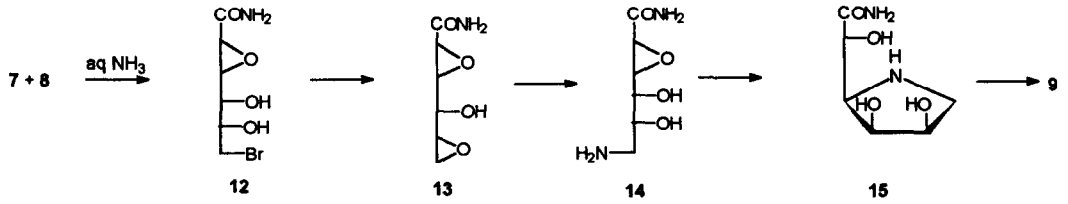
3,6-imino-D-gluconic acid (**9**) as the only product. After treatment with ion exchange resin, **9** was obtained as a crystalline residue (79%). Esters[4] or lactones[8] of carboxylic acids having an electron withdrawing group in the α-position can be reduced to an alcohol function using $NaBH_4$. Since we have observed that **9** easily formed a 1,4-lactone, it was coconcentrated with aqueous HCl to give the crystalline lactone **10**. Treatment of **10** with $NaBH_4$ in water buffered with AcOH[8] gave 1,4-dideoxy-1,4-imino-L-gulitol (**11**). Besides, some of the acid **9** was formed due to opening of the lactone prior to reduction. Work up by treatment with ion exchange resin (H^+) gave the iminohexitol **11** as the crystalline hydrochloride (38%). This compound has been synthesized previously in seven steps from D-glucose.[9]



Scheme 2

The reaction of the epoxylactones **7** and **8** with NH_3 was monitored by ^{13}C NMR spectroscopy (Scheme 3 and Table). The initial step was opening of the lactones to give the 6-bromo-epoxy-amide **12** which readily formed the diepoxy-amide **13**, observed as the major product after 5 min. After 20 min **13** was present together with the pyrrolidine amide **15** (3:2) and after 2 h the ring closure was completed. The amide function in **15** slowly hydrolysed to the acid **9**. The 5,6-epoxide in **13** was presumably opened by ammonia to give the 6-amino-2,3-epoxide **14**. The amino group subsequently opened the epoxide at C-3 in an 5-*exo* mode, according to Baldwins rules.[10] **14** was not observed in the spectra.

mechanism:



Scheme 3

We have now shown that 2,6-dibromo-2,6-dideoxy-hexonolactones can be transformed readily into crystalline 1,4-dideoxy-1,4-iminohexitols in gram amounts. The bromolactone may, prior to treatment with aqueous NH_3, either be converted into the 2,3-epoxide by treatment with KF or K_2CO_3 in acetone, or it may be reduced with $NaBH_4$ in water to give the bromohexitol.[4,5] In this way we have prepared nine isomeric iminohexitols (Scheme 4) which now have been tested as inhibitors towards a number of human liver glycosidases.

Table. ^{13}C NMR Data of Products Observed in the Reactions in Aqueous Ammonia (Scheme 1 and 3)

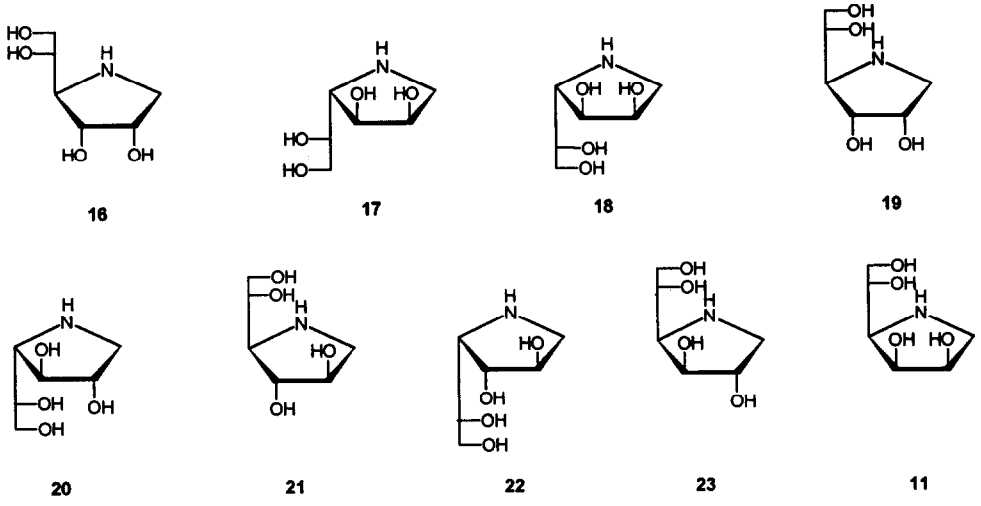
								Relative Amounts after				
Substrate	Product	C-1	C-2	C-3	C-4	C-5	C-6	5 min	20 min	2 h	10 h	1 d	3 d
3	**3**	64.1	58.4	80.0	74.7[a]	74.0[a]	71.3			84		46	
	5	49.0	61.1	-	-	-	-			8		8	
	6	43.4	72.7[a]	83.6	72.6[a]	71.7[a]	71.7[a]			8		46	100
7 + 8	**12**	172.9	53.7	58.7	74.4[a]	70.0[a]	37.1	13					
	13	172.7	54.1[a]	57.8	67.7	54.9[a]	45.9	81	60				
	15	179.5	71.1[a]	61.9	73.8[a]	72.7[a]	50.8	6	40	72	28		
	9	180.2	71.9[a]	63.0	73.9[a]	72.9[a]	50.7			28	72		

a: may be interconverted

1,4-Dideoxy-1,4-imino-D-allitol (**16**) which has been synthesised previously,[4,11,12] was found to be a weak inhibitor of β-D-glucosidase (I_{50}, 1 mM). (For experimental details see ref.[2]). In contrast, 1,4-dideoxy-1,4-imino-L-allitol (**17**), which has been synthesised [2,4,13] and tested before [2,11], was a moderate competitive inhibitor of lysosomal α-D-mannosidase (Ki, 1.2 x 10^{-4} M) and a weak inhibitor of neutral (cytosolic) α-D-mannosidase, β-D-glucosidase, N-acetyl-β-D-hexosaminidase and α-L-fucosidase. It can alter the metabolism of N-linked glycans in cells in culture in a way distinct from that of another inhibitor of α-mannosidase, swainsonine.[13] Neither of the 1,4-dideoxy-1,4-imino-allitols had any effect on the human immunodeficiency virus (HIV).[14]

1,4-Dideoxy-1,4-imino-D-talitol (**18**) has also been synthesised by several routes[4,13,15,16] and has a similar specificity of inhibition to 1,4-dideoxy-1,4-imino-L-allitol (**17**), with a Ki for the competitive inhibition of lysosomal α-D-mannosidase of 1.2 x 10^{-4} M.[11,16] It can also disrupt the metabolism of N-linked glycans in cells in culture. From a study of the oligosaccharides that accumulate in cells in the presence of **18** and **17**, it appears that they inhibit lysosomal α-mannosidase rather than the processing α-mannosidases I and II. Both compounds may have application as selective inhibitors of intracellular α-D-mannosidases. 1,4-Dideoxy-1,4-imino-L-talitol (**19**)[4,12] did not inhibit any of the glycosidases appreciably.

The two iminohexitols with *galacto* configurations, **20** and **21**, did not inhibit any glycosidases very strongly. α-D-Glucosidase was inhibited weakly by 1,4-dideoxy-1,4-imino-D-galactitol (**20**) (I_{50}, 1 mM) and very slightly by 1,4-dideoxy-1,4-imino-L-galactitol (**21**). The lack of inhibition of α-D-galactosidase suggests that this enzyme is not susceptible to inhibitors in the furano-configuration. It was not possible to test the inhibition of β-D-galactosidase accurately because this enzyme is selectively activated by Cl^-, and the compounds were prepared and tested in the form of hydrochloride salts.



Scheme 4

The novel compound 1,4-dideoxy-1,4-imino-D-iditol (**22**) was a moderate inhibitor of α-L-fucosidase (69% at 1mM). The enantiomer 1,4-dideoxy-1,4-imino-L-iditol (**23**) was a potent inhibitor of α-D-galactosidase and a weak inhibitor of α-D-arabinosidase, 95 and 62% respectively, at 1 mM. Compound **11**, the L-gulitol analogue did not inhibit any glycosidases.

It is difficult to deduce the structural basis of the specificity of inhibition of these compounds, except for the effect of **17** and **18** on the multiple forms of α-D-mannosidase. Their specificity is in accord with the structural requirements of azafuranose analogues of mannose for inhibition of mammalian α-D-mannosidases.[17] However, it is surprising that 1,4-dideoxy-1,4-imino-L-gulitol (**11**) does not inhibit α-D-mannosidase, because it only differs from 1,4-dideoxy-1,4-imino-D-mannitol, the archetypal azafuranose inhibitor of α-D-mannosidase, at the "C-5" chiral centre. The compounds **17**, **18** and **22** showed weak/moderate inhibition of α-L-fucosidase. Although azafuranose analogues of fucose have been shown to inhibit α-L-fucosidase,[2,18] the structural criteria for inhibition have not been studied as fully as those for inhibition of α-D-mannosidase. Similarly, the lack of inhibition of α- and probably β-D-galactosidases by **20** and **21** suggests that these enzymes are not particularly susceptible to azafuranose analogues of galactose. The failure of **18**, which differs from **20** at only one chiral centre, to inhibit the galactosidases reinforces this view.

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 (δ = 67.4) was used as internal reference for ^{13}C NMR spectra and acetone (δ = 2.17) for ^1H-NMR spectra. For spectra in $CDCl_3$ (chloroform-d, δ=76.9) was used as internal reference for ^{13}C-NMR spectra. ^{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 bromodeoxyhexonolactones/hexitols with aqueous NH_3. ^{13}C NMR experiments. The substrate (150 mg) was dissolved in 25% aq NH_3 (1 ml) and D_2O (0.2 ml). ^{13}C NMR spectra were recorded at intervals on a Bruker AC-250 instrument using the spectrometer reference as a standard. The results obtained are listed in the Table.

2,6-Dibromo-2,6-dideoxy-D-altritol (**2**). 2,6-Dibromo-2,6-dideoxy-D-altrono-1,4-lactone (**1**) [6] (1.60 g, 5.26 mmol) was dissolved in CH_3OH (5 ml). H_2O (20 ml) and ion exchange resin (Amberlite IR-120, H^+, 5 ml) was added and the mixture was cooled in ice and stirred while $NaBH_4$ (320 mg, 8.46 mmol) was added during 10 min; the pH was kept around 5. Then more $NaBH_4$ (370 mg, 9.78 mmol) was added, increasing the pH to 9, and the stirring was continued at 0 °C for 20 min. Ion exchange resin (Amberlite IR-120, H^+, 20 ml) was added decreasing the pH to 3. The mixture was filtered and the filtrate concentrated and co-concentrated with methanol (3 x 20 ml) at 30 °C to leave **2** (1.59 g, 98%) as a syrup which was contaminated with 10% of the 3,6-anhydro-2-bromo-2-deoxy-D-altritol (**3**), as seen from a ^{13}C NMR spectrum. **2**: ^1H NMR (D_2O): δ 4.40 (H-2, J_{12} 7, $J_{1'2}$ 6, J_{23} 1), 4.06 (H-5, J_{45} 4, J_{56} 8, $J_{56'}$ 3), 3.88 (H-1', $J_{11'}$ 12), 3.85 (H-1), 3.80 (H-4, J_{34} 9), 3.76 (H-3), 3.65 (H-6', $J_{66'}$ 11) and 3.52 (H-6). ^{13}C NMR (D_2O): δ 73.9 (C-4), 73.6 (C-5), 70.8 (C-3), 64.5 (C-1), 59.2 (C-2) and 35.9 (C-6). Crystallization from EtOH at -78°C gave almost pure **2** (200 mg). At room temperature **2**, either as a syrup or as crystals, was converted into the 3,6-anhydride **3** (^{13}C NMR: δ 80.6, 75.0, 74.0, 71.8, 64.6 and 57.8) when kept overnight. **2** was not further purified.

1-Amino-3,6-anhydro-D-allitol hydrochloride (**6a**). To a mixture of **2** and **3**, obtained from **1** (6.7 g) as described above, was added aq NH_3 (25%, 50 ml). After 3 days at room temp the mixture was concentrated to a residue, which was poured on a column of ion exchange resin (Amberlite, IRA 400, OH^-, 250 ml) and washed with H_2O until neutral. Concentration of the eluent followed by co-concentration with aq 4 M HCl gave a residue (3.1 g, 70.5% based on **1**) which was crystallized from CH_3OH to give **6** (1.54 g, 35% based on **1**), mp. 120-123 °C. Recrystallization from CH_3OH-Et_2O gave mp. 125.5-127 °C, $[\alpha]_D^{20}$ -54.1° (*c* 1, H_2O). *Anal.* Found: C, 36.04: H, 7.03; N, 6.93; Cl, 17.50. Calc. for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; Cl, 17.76; N, 7.02 ^1H NMR (D_2O): δ 4.09–4.13 (H–5, H–4), 3.9–3.85 (H–6, H–2), 3.65 (H–6, $J_{56'}$ 2.2, $J_{66'}$ 10.0), 3.61 (H-3, J_{23} 5.0, J_{34} 6.0), 3.07 (H-1, J_{12} 3.2, $J_{11'}$ 13.8), 2.90 (H-1', $J_{1'2}$ 9.5). ^{13}C NMR (D_2O): δ 82.8 (C-3), 73.4 (C-6), 72.6 (C-4), 72.0 (C-5), 68.6 (C-2), 42.1 (C-1).

2,3-Anhydro-6-bromo-6-deoxy-D-allono-1,4 (**7**) *and 1,5-lactone* (**8**). Potassium fluoride (21.0 g, 361 mmol) was dried ovenright at 150 °C and 1 mmHg. 2,6-Dibromo-2,6-dideoxy-D-altrono-1,4-lactone (**1**) (16.0 g, 52.6 mmol) was dissolved in acetone (120 ml, dried with magnesium sulfate) and added to the potassium fluoride. The mixture was stirred for 5 h, filtered and concentrated to a syrupy residue (9.24 g, 79%), consisting of **7** and **8** in the ratio 5:2 as seen from a ^{13}C NMR spectrum. **7**: ^{13}C NMR ($CDCl_3$): δ 169.7 (C-1), 79.1 (C-

4), 69.5 (C-5), 55.4 (C-2), 48.9 (C-3), 33.3 (C-6). **8**: ^{13}C NMR ($CDCl_3$): δ 165.1 (C-1), 74.0 (C-5), 65.6 (C-4), 55.1 (C-2), 50.0 (C-3), 32.0 (C-6). The syrup containing **7** and **8** was used for the next step without further purification.

3,6-Dideoxy-3,6-imino-D-gluconic acid (**9**). The syrupy mixture of **7** and **8** (9.24 g, 41.4 mmol) was dissolved in 25% aq NH_3 (60 ml) and stirred for 20 h. Evaporation of the solvent and co-evaporation with H_2O gave a residue which was dissolved in H_2O. Ion exchange resin (Amberlite IR-120, H^+, 320 ml) was added and the mixture was stirred slowly for 2 h. The resin was filtered off and poured into H_2O. The mixture was cooled in ice and stirred while 25% aq NH_3 (220 ml) was added. The stirring was continued for 1 h at room temperature. The resin was then filtered off and the filtrate filtered through activated carbon. Evaporation left crystalline **9** (5.83 g, 79%), mp. 70-80 °C, which was pure as seen from a ^{13}C NMR spectrum. The product was not further purified before the next step, but could be recrystallized from H_2O to give an analytical sample which decomposed above 150 °C, $[\alpha]_D^{20}$ -6.3° (*c* 5, H_2O). *Anal.* Found: C, 40.24; H, 6.28; N, 7.27. Calc. for $C_6H_{11}NO_5$: C, 40.68; H, 6.26; N, 7.91. ^1H NMR (D_2O): δ 4.46 (H-5, J_{45} 4, $J_{56'}$ 8, J_{56} 8), 4.34 (H-4, J_{34} 4), 4.34 (H-2, J_{23} 8), 3.73 (H-3), 3.50 (H-6', $J_{66'}$ 12), 3.18 (H-6). ^{13}C NMR (D_2O): δ 177.9 (C-1), 71.2 (C-4 or C-2), 71.0 (C-5), 69.1 (C-2 or C-4), 64.4 (C-3), 47.8 (C-6).

3,6-Dideoxy-3,6-imino-D-glucono-1,4-lactone hydrochloride (**10**). 3,6-Dideoxy-3,6-imino-D-gluconic acid (**9**) (5.83 g, 32.9 mmol) was dissolved in 4 M aq HCl (40 ml). Concentration and co-concentration with toluene left a hygroscopic crystalline residue which was washed with cold EtOH, filtered and dried in a desiccator overnight to give **10** (6.04 g, 93%), mp. 65-75 °C, which was pure according to a ^{13}C NMR spectrum. Attempts at recrystallization from hydroxylic solvents resulted in opening of the lactone ring. An analytical sample was prepared by washing several times with CH_3OH; mp. 187-188 °C (dec.), $[\alpha]_D^{20}$ +33° (*c* 3, H_2O) → 1.6° (4 days). *Anal.* Found: C, 36.70; H, 5.15;Cl, 17.86; N, 7.11. Calc. for $C_6H_{10}ClNO_4$: C, 36.84; H; 5.15; Cl, 18.12; N, 7.16.

^1H NMR (D_2O): δ 5.24 (H-4, J_{34} 9, J_{45} 4), 4.94 (H-2, J_{23} 7), 4.60 (H-5, $J_{56'}$ 1, J_{56} 3), 4.49 (H-3), 3.61 (H-6', $J_{66'}$ 13) and 3.49 (H-6). ^{13}C NMR (D_2O): δ 177.0 (C-1), 80.1 (C-4), 70.7 (C-2), 68.1 (C-5), 63.3 (C-3) and 52.9 (C-6).

1,4-Dideoxy-1,4-imino-L-gulitol hydrochloride (**11**). Crude **10** (6.04 g, 30.9 mmol), obtained as described above, was dissolved in H_2O (80 ml) and acidified with HOAc (900 mg, 15 mmol). The mixture was cooled in ice and stirred, while $NaBH_4$ (1.40 g, 37.0 mmol) was added at such a rate that the pH was kept around 5. Then a further amount of $NaBH_4$ (2.20 g, 58.2 mmol) was added increasing the pH to 8-9, and the solution was stirred for 1 h at room temperature. EtOH (80 ml) was then added and the solution was kept at -4 °C for 1 h to precipitate sodium borates. Filtration afforded 5.11 g of white crystals (mp. 73-75 °C) which were discarded. Ion exchange resin (Amberlite IR-120, H^+, 370 ml) was added to the filtrate and the mixture was stirred for 2 h. The resin was filtered off and poured into water. The mixture was cooled in ice and stirred while 25% aq NH_3 (260 ml) was added. The stirring was continued for 1 h at room temperature. Filtration and concentration of the filtrate, followed by co-concentrated with H_2O gave a residue which was dissolved in 4 M aq HCl (40 ml). Concentration and co-concentration with CH_3OH (3 x 20 ml) gave a partly crystalline residue, which was washed with hot CH_3OH, cooled and filtered to give **11** (2.34 g, 38%), mp. 170-172 °C. Recrystallization from 90% aq CH_3OH gave a product with mp. 182-183 °C, $[\alpha]_D^{20}$ +6.0° (*c* 4, H_2O) (Lit[9]: mp. 170-173 °C, $[\alpha]_D^{20}$ +7.1° (*c* 0.48, H_2O)). *Anal.* Found: C, 36.14; H, 7.05; Cl, 17.22; N, 6.94. Calc. for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07; Cl, 17.76; N, 7.02. ^1H NMR (D_2O): δ 4.47 (H-2, J_{23} 4, $J_{1'2}$ 8, J_{12} 8), 4.25

(H-3, J_{34} 4), 4.10 (H-5, J_{45} 9, $J_{56'}$ 3, J_{56} 5), 3.73 (H-6', $J_{66'}$ 12), 3.60 (H-6), 3.60 (H-4), 3.52 (H-1', $J_{11'}$ 12) and 3.13 (H-1). ^{13}C NMR (D_2O): 71.2 (C-2), 70.5 (C-3), 69.0 (C-5), 63.8 (C-6), 63.8 (C-4) and 47.2 (C-1). The NMR data are in accordance with those reported previously.[9] A ^{13}C NMR spectrum of the CH_3OH from the washing showed a complex mixture of several compounds, namely **11** together with the unreduced compounds **9**, **10**, probably the methyl ester of **9**, and some minor products.

Acknowledgement

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