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Synthesis of 1-Amino-1,2,5-trideoxy-2,5-imino-D-mannitol, a Novel Analogue of the Powerful Glucosidase Inhibitor 2,5-Dideoxy-2,5-imino-D-mannitol, *via* an Amadori Rearrangement of 5-Azido-5-deoxy-D-glucofuranose

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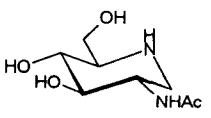
Abstract: By an Amadori rearrangement of easily available 5-azido-5-deoxy-D-glucofuranose with dibenzylamine and subsequent catalytic hydrogenation of the resulting 5-azido-1-dibenzylamino-1,5-dideoxy-D-fructopyranose, the new 1-amino-1,2,5-trideoxy-2,5-imino-D-mannitol was obtained in only two steps and excellent overall yield. Likewise, other amines and/or other 5-modified hexofuranoses can be used to advantage. The reported rearrangement reaction is a high yielding, convenient and apparently general entry to 1-aminodeoxyketopyranoses modified at C-5, facilitated by the ring enlargement of the aldofuranose to the ketopyranose as an additional driving force.

Various powerful sugar-shaped glycosidase inhibitors with basic nitrogen instead of oxygen in the ring have been found as natural products or have been synthesized by chemical as well as enzymatic methods[1]. Hexosaminidase inhibitors such as 2-acetamido-1,2-dideoxynojirimycin[1] (**1**) and 6-acetamido-6-deoxy-castanospermine[1] (**2**) have found considerable interest as biochemical probes as well as ligands for the purification of hexosaminidases by affinity chromatography[2]. Similar to the imino function in the ring, free amino groups instead of the acetamido moieties could offer useful anchor group properties as an alternative means of immobilisation on polymer supports.



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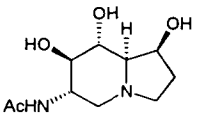

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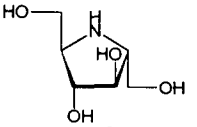

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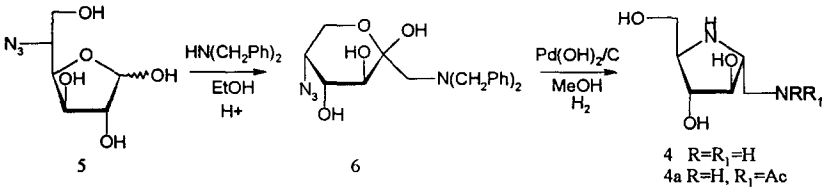
In the course of a project concerned with the synthesis of novel glycosidase inhibitors suitable for immobilisation procedures, we have become interested in a simple, reasonably versatile, and efficient synthetic route to aminodeoxy derivatives of 2,5-dideoxy-2,5-imino-D-mannitol (**3**), a powerful inhibitor of glucosidases and invertase[3], such as compound **4**.



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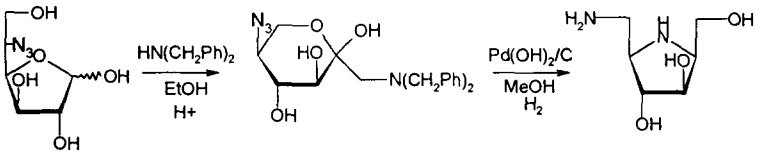
5-Azido-5-deoxy-D-glucofuranose (**5**), a direct precursor of compound **3**, is available in multi-gramm quantities[4]. We had been looking for suitable methods to utilise aldose **5** for the preparation of the desired compound **4**. Bearing in mind that the release of ring strain in 5-membered ring **5** is a strong driving force for the quantitative isomerisation[5] into the corresponding D-fructopyranose isomer, we expected that an Amadori rearrangement[6] reaction would introduce the desired amino group at C-1 under concomitant formation of the D-fructopyranose derivative **6** which, in turn, could be cyclized by intramolecular reductive amination to furnish **4**. Gratifyingly, by reaction of glucofuranose **5** with dibenzylamine in EtOH in the presence of glacial acetic acid at 40 °C, compound **6** was obtained in over 90% yield[7]. Ring closure to pyrrolidine derivative **4** and removal of the *N*-benzyl groups were achieved by hydrogenation of compound **6** in dry MeOH at ambient pressure in the presence of $Pd(OH)_2$-on-carbon (20%). For analytical purposes, the 1-acetamido derivative (**4a**), previously synthesised by a chemo-enzymatic approach and found to be a highly potent hexosaminidase inhibitor[8], was prepared (82% yield) by treatment with acetic anhydride in DMSO or, more conveniently, employing THF/MeOH as the solvent system. Under these conditions, the primary amine was highly chemo- and regioselectively *N*-acetylated in the presence of the unprotected imino function of the pyrrolidine ring.



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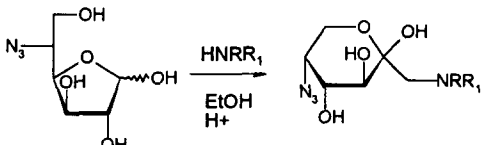
When 5-azido-5-deoxy-L-idofuranose[5] (**7**), the epimer of **5** at C-5, was subjected to the same reaction conditions, the corresponding 1-aminodeoxy derivative of L-sorbopyranose (**8**) could be isolated in 80% yield. From compound **8**, the new 6-amino-2,5,6-trideoxy-2,5-imino-D-glucitol (**9**) was readily prepared.

Furthermore, compound **5** was successfully reacted with terminally functionalised amines such as 6-aminohexanol to give D-fructose derivative **10** (96% isolated yield) and 3-(benzylamino)propionitrile to furnish compound **11** (83% yield after chromatography). These are clearly suitable for the preparation of spacer-arm bearing derivatives of inhibitors **4** and **4a** with a view to immobilisation studies.



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10 R=$(CH_2)_6OH$, R_1=H
11 R=$(CH_2)_2CN$, R_1=CH_2Ph

In terms of yields and reaction conditions, the results obtained in this study stand in marked contrast to the outcomes of conventional Amadori rearrangement reactions with simple sugar. These transformations have to be performed under more forced conditions and frequently fail to give more than moderate yields of the desired 1-aminoketose derivatives[6]. These findings support conclusions drawn from results with the quantitative isomerisation of D-gluco- as well as L-idofuranoses into the coresponding D-fructo- and L-sorbopyranoses with the aid of immobilised glucose isomerase. Observations suggest that energy release by reduction of ring strain and unfavourable sterical interactions of substituents around the five-membered ring of hexofuranoses is a general and crucial pre-requisit for the efficiency of the type of aldose-to-ketose rearrangement reactions under consideration.

Biological evaluation of compound **4** as well as the syntheses of 1-*N*-modified derivatives thereof are currently in progress and results will be reported in a full account.

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7. In a typical rearrangement experiment, to a 5% ethanolic solution of the respective aldofuranose, 1 equv. amine and 1 equv. glacial acetic acid were added consecutively and the mixture was kept at 40 °C for about 1 h, when TLC indicated that all starting material and glycosyl amine intermediates had been converted. The mixture was conc. under reduced pressure and the remaining material was subjected to chromatography on silica gel. From reaction mixtures containing higher carbohydrate concentrations, products frequently crystallize upon cooling. All new compounds were fully characterised. Selected data (signals of benzyl groups are in the expected regions and not listed explicitly): **6**: $[\alpha]_D^{20}$ -84 (c 3.1, CH_2Cl_2); ^{13}C-NMR ($CDCl_3$) in δ: 97.0 (C-2), 71.6, 71.0 (C-3, C-4), 61.8, 61.1 (C-5, C-6), 56.2 (C-1); ^{1}H-NMR: 4.12-3.82 (m, 4 H, H-3, H-4, H-5, H-6), 3.64 (dd, 1 H, $J_{5,6}$ 1.7 Hz, $J_{6,6'}$ 12.6 Hz, H-6'), 3.06 (d, 1 H, $J_{1,1'}$ 13.6 Hz, H-1), 2.72 (d, 1 H, H-1'). **8**: $[\alpha]_D^{20}$ -83.6 (c 1.8, CH_2Cl_2); ^{13}C-NMR ($CDCl_3$) in δ: 96.5 (C-2), 74.6, 73.9 (C-3, C-4), 61.0, 60.4 (C-5, C-6), 56.2 (C-1); ^{1}H-NMR: 3.72-3.57 (m, 3 H, H-3, H-4, H-6), 3.44 (m, 1 H, H-5), 3.09-2.98 (m, 2 H, H-1, H-6'), 2.64 (d, 1 H, H-1'). **10**: ^{13}C-NMR (D_2O) in δ: 95.4 (C-2), 69.8, 69.3 (C-3, C-4), 62.3, 61.8, 61.3 (C-5, C-6, C-6'), 52.5 (C-1), 48.4 (C-1'), 30.5, 25.4, 25.0, 24.5 (C-2', C-3', C-4', C-5'); ^{1}H-NMR (CD_3OD): 4.12-4.00 (m, 2 H), 3.91 (m, 1 H), 3.73-3.53 (m, 4 H), 3.23-3.16 (m, 2 H), 2.99 (m, 2 H), 1.80-1.26 (m, 8 H). **11**: $[\alpha]_D^{20}$ -88 (c 2.8, CH_2Cl_2); ^{13}C-NMR ($CDCl_3$) in δ: 118.9 (C-1'), 97.2 (C-2), 71.2, 70.8 (C-3, C-4), 61.2, 60.4 (C-5, C-6), 57.8 (C-1), 50.3 (C-3'), 18.8 (C-2'). **9** (free base): $[\alpha]_D^{20}$ +24.1 (c 0.7, H_2O); ^{13}C-NMR (D_2O, pH 1) in δ: 73.8, 71.4 (C-3, C-4), 64.8, 63.5, 57.8 (C-2, C-5, C-6), 40.2 (C-6). **4** (free base): $[\alpha]_D^{20}$ +49.4 (c 0.9, H_2O); ^{13}C-NMR (D_2O, pH 1) in δ: 76.1, 73.6 (C-3, C-4), 63.1 (C-6), 58.1, 57.9 (C-2, C-5), 38.5 (C-1); ^{1}H-NMR: 3.76-3.60 (m, 2 H, H-3, H-4), 3.50 (dd, 1 H, $J_{6,6'}$ 12.5 Hz, $J_{5,6}$ 4.0 Hz, H-6), 3.38-3.18 (m, 3 H, H-2, H-5, H-6'), 3.10 (d, 2 H, $J_{1,2}$ 6.7 Hz, H-1, H-1'). **4a**: $[\alpha]_D^{20}$ +32 (c 0.7, MeOH); ^{13}C-NMR (free base in D_2O): 175.5 (C=O), 80.3, 78.7 (C-3, C-4), 62.8, 62.6, 60.7 (C-2, C-5, C-6), 42.7 (C-1), 22.9 (CH_3); ^{1}H-NMR: 3.78 (m, 2 H, H-3, H-4), 3.67 (dd, 1 H, $J_{5,6}$ 4 Hz, $J_{6,6'}$ 10.8 Hz, H-6), 3.38 (dd, $J_{5,6'}$ 7 Hz, H-6'), 3.38 (dd, 1 H, $J_{1,1'}$ 14 Hz, $J_{1,2}$ 5.2 Hz, H-1), 3.25 (dd, 1 H, $J_{1',2}$ 7.0 Hz, H-1'), 3.11-2.93 (m, 2 H, H-2, H-5).

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