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A Simple Convergent Synthesis of the Mannosidase Inhibitor 1-Deoxymannonojirimycin from Sucrose

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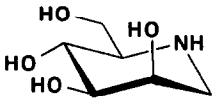
Abstract: The glycosidase inhibitor 1-deoxymannonojirimycin (1,5-dideoxy-1,5-imino-D-mannitol) was synthesized in four simple steps from sucrose *via* 6,6´-diazido-6,6´-dideoxysucrose and 6-azido-6-deoxy-D-fructofuranose. The "isomeric ballast" of the sequence, 6-azido-6-deoxy-D-glucose, could be partially converted into 6-azido-6-deoxy-D-fructofuranose with the aid of glucose isomerase (E.C. 5.3.1.5) demonstrating a novel synthetic application of this enzyme. The sequence allows access to multigramm quantities of 1-deoxymannonojirimycin in over 30% overall yield without the need for expensive reagents and protecting group manipulations.

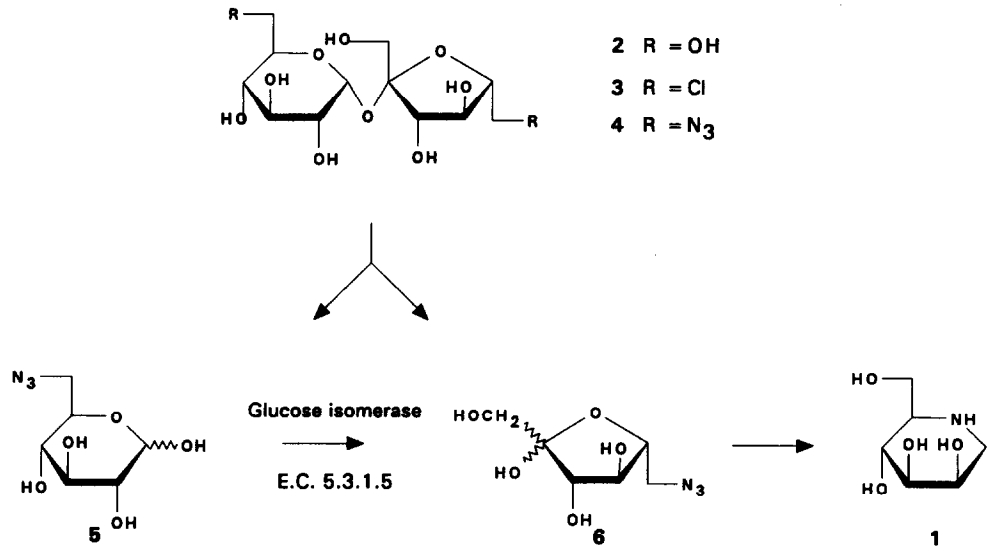
1-Deoxymannonojirimycin (1,5-dideoxy-1,5-imino-D-mannitol, **1**), a natural product first found in the legumes *Lonchocarpus sericeus* and *L. costaricensis*[1], is an inhibitor of several mannosidases[2], amongst them mannosidases 1A and 1B of glycoprotein processing[3], an efficient inhibitor of mammalian α-fucosidase[4], and thus a valuable tool in biochemical research.



1

For syntheses of **1**, D-mannose[2,5] and D-glucose[5b,6] have been the most frequently employed starting materials. However, L-gulonolactone[7], *(S)*-pyroglutamic acid[8], and other compounds[9] have also been used. Chemoenzymatic approaches have been published by three groups[5a,10,11], two of them taking advantage of an enzymatic aldol reaction[10,11]. Of the reasonably efficient syntheses the numbers of synthetic steps lie between 6 and 14 with overall yields ranging from 5 to about 25%. The best overall yield to date (35% over 11 steps) was reported by Fleet and coworkers[6c] for a synthesis of **1** from 1,2;5,6-di-*O*-isopropylidene-α-D-glucofuranose.

In context with a project concerned with the synthesis of biologically active derivatives of various glycosidase inhibitors we were interested in a simple approach to **1** allowing relatively quick access to multigramm quantities without the need for expensive reagents such as trifluoromethanesulfonic anhydride. Based on the pioneering work by Paulsen and coworkers[12] 6-azido-6-deoxy-D-fructofuranose had already been successfully used[10,11] as an intermediate for the synthesis of **1**. Consequently we turned our attention to sucrose (**2**) as an inexpensive, abundant source of D-fructose, the latter already protected at the anomeric centre and as the required 2,5-furanoside to allow access to C-6.



Commercially available sucrose **2** (51 g, 150 mmol) was treated with triphenylphosphine/ tetrachloromethane in pyridine employing the method of Anisuzzaman and Whistler[13], to give 6,6´-dichloro-6,6´-dideoxysucrose (**3**)[13,14], albeit as a syrup. The yields in our experiments ranged between 65 and 75%, unfortunately never reaching that (92%) previously reported for this reaction. Reaction of sucrose derivative **3** with sodium azide in *N,N*-dimethylformamide (DMF) led directly and without the need for protecting group manipulations to the known 6,6´-diazido-6,6´-dideoxysucrose (**4**)[14,15] in 81% yield (57% for both steps). This product was quantitatively hydrolyzed with the aid of ion exchange resin Amberlite IR 120 [H^+] in water to give a mixture of 6-azido-6-deoxy-D-glucose (**5**)[16] and 6-azido-6-deoxy-D-fructofuranose (**6**)[11b,16c], from which the less polar fructose derivative **6** could be isolated as a syrup by careful chromatographic separation[17] in 62% yield. Crystalline 6-azido-6-deoxy-D-glucose **5** was obtained in 64% yield. Compound **6** was reductively cyclized by hydrogenation in methanol/water in the presence of palladium-on-carbon to give after conventional purification on Amberlite CG 50 the desired 1,5-dideoxy-1,5-imino-D-mannitol **1** in 78% yield. The NMR spectroscopic features of this material were in perfect agreement with published data[5d,5e,6b,11b] and the spectra of the corresponding hydrochloride were identical with those obtained from an authentic sample (SIGMA D-9160). No evidence for concomitant formation of the corresponding L-*gulo* epimer could be found on the basis of ^1H NMR-spectroscopy.

By this sequence 1-deoxymannonojirimycin (**1**) was obtained in four steps from sucrose (**2**) in an average overall yield of 27%[18].

Initial attempts to utilize azidodeoxyaldose **5**, the "isomeric ballast" of the above sequence, by conversion into azidodeoxyketose **6** *via* an acid- or base-catalyzed Lobry de Bruyn - Alberda van Ekenstein rearrangement[19] did not meet any satisfying success employing acetic and trifluoroacetic acid as

well as a variety of bases, such as pyridine, quinoline, calcium hydroxide and ammonia in various concentrations (all of which had been previously used successfully in such rearrangement reactions[19b]). As an alternative, a biochemical approach was investigated employing glucose isomerase, E.C. 5.3.1.5, for the required transformation. This industrially very important enzyme for the large scale conversion of glucose into glucose/fructose syrup has also been demonstrated to isomerize 6-deoxy- as well as 6-O-methyl-D-glucose into the corresponding D-fructose derivatives, albeit in lower yields (15 and 21%, respectively) than the parent compound (over 40%)[20].

In a typical experiment a 30% solution of glucose derivative **5** (8-10 g) in distilled water (containing 10 mg magnesium sulfate and adjusted to pH 8.4 with sodium carbonate) was shaken at 60 °C for 60 h with polymer supported glucose isomerase (SWEETZYME T, 2.5 g) to give a mixture containing approximately 15% (estimated from NMR spectra) of the desired product **6**. After filtration and removal of the solvent under reduced pressure compound **6** could be obtained in 8-10% yield by chromatographic separation. Two recycling steps with recovered starting material **5** led to a total yield of 25% of fructose derivative **6** from this isomerization reaction (about 50% "by recovery"). Conventional hydrogenation gave an additional crop of compound **1** (7-8% overall) increasing the total yield of this convergent 1-deoxymannonojirimycin synthesis to 35%[21].

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17 Silica gel 60, 230-400 mesh (MERCK 9305); petroleum ether/ethyl acetate 1:3, v/v or dichloromethane/methanol 20:1, v/v, followed by ethyl acetate or ethyl acetate/ethanol/water 45:5:2, v/v/v; TLC on MERCK 5554 precoated sheets, ethyl acetate/methanol 7:1, v/v.

18 In a typical sequence compound **3** (40 g, 105 mmol) was stirred with sodium azide (70 g, 10 equ.) in DMF (400 mL, 100 °C, 16 h). After removal of the salts the solution was concentrated under reduced pressure and the residue chromatographed on silica gel (petroleum ether/ethyl acetate 1:3 could no longer be detected by TLC. After filtration the solvent was removed *in vacuo* followed by chromatography[17] of the syrupy residue to give 10.7 g (62%) essentially pure 6-azido-6-deoxy-D-fructofuranose (**6**), several mixed fractions and pure 6-azido-6-deoxy-D-glucose **5** (11 g, 64%). A 10% solution of compound **6** (10 g, 49 mmol) in methanol/water (1:1, v/v) was hydrogenated on a PARR-apparatus (600 mg Pd/C 5%, 4 bar H_2,72 h). After removal of the catalyst the solvent was evaporated under reduced pressure and the residue purified on Amberlite CG 50 (0.05-0.1 M aqueous ammonia as eluent). Crystallization from methanol/diethyl ether gave 5.7 g (78%) pure 1-deoxymannonojirimycin (**1**).
Mixed fractions of compounds **5** and **6** from the hydrolysis of **4** can be recycled.

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21 Physical and spectral data of compounds confirm the structures proposed and are in full agreement with published values. NMR Spectra were recorded on a BRUKER MSL 300 spectrometer at 300 MHz (^{1}H) and 75.47 MHz (^{13}C). Selected data: **4**: ^{13}C NMR (in D_2O, δ in ppm): 104.9 (C-2´), 93.2 (C-1), 80.9 (C-4´), 77.6, 76.6 (C-3´,5´), 73.5, 72.3, 72.2, 71.5 (C-2,3,4,5), 62.5 (C-1´), 54.1, 52.4 (C-6,6´). **5**: mp 128-133 °C; **5α**: ^{13}C NMR: 93.1 (C-1), 73.6, 72.4, 71.5 (C-2,3,5), 71.1 (C-4), 51.9 (C-6); **5β**: 97.0 (C-1), 76.5, 75.4, 75.1 (C-2,3,5), 71.4 (C-4), 51.9 (C-6); ^{1}H NMR (D_2O, δ in ppm): 5.16 (d, H-1α, $J_{1,2}$ 3.6 Hz), 4.59 (d, H-1β, $J_{1,2}$ 7.9 Hz); **5α:5β**, 2:3. **6**: $[\alpha]_D$ +20 (c 0.6, water); **6β**: ^{13}C NMR: 102.7 (C-1), 79.9 (C-5), 75.9 (C-3,4), 63.5 (H-1), 53.4 (H-6).

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