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Concise Chemical Synthesis of β-Homonojirimycin and Related Compounds

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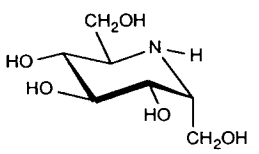
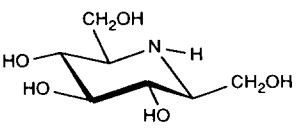
Summary: *β-Homonojirimycin **2** was prepared in 27% overall yield from tetra-O-benzyl-D-glucono-1,5-lactone by way of the double reductive amination of a 2,6-heptodiulose (**7**). This synthetic approach provided also access to the 1,N-anhydro derivative of **2**, compound **3**. Aziridines of this type are potential inactivators of glycosidases.*

Azasugars,[1] i.e., analogs of sugar hemiacetals or of anhydroalditols in which the ring oxygen atom is replaced by an -NH- group, have attracted recently a great deal of attention because of the spectacular biological activities that many members of this family exhibit.[2,3] As a result of the lability of the (anomeric) hemiaminal function in 5-amino-5-deoxy-hexopyranoses such as nojirimycin, most piperidine azasugars[4] are derivatives of 1,5-dideoxy-1,5-iminohexitols (e.g., deoxynojirimycin[4]) and thus lack an "orienting" group at the anomeric position which could contribute to a greater selectivity of the sugar analogs, for example, as glycosidase inhibitors. The insertion of a methylene group into the C_1–O_1 bond of 5-amino-5-deoxy-hexopyranoses provides a means of generating stable analogs of elusive hemiaminals and related "glycosides": the first such "homoazasugar," α-homonojirimycin (**1**),[5] was, in fact, found to occur naturally[6] soon after its



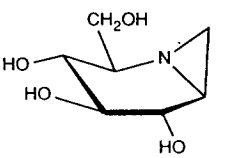
"α-Homonojirimycin"

1



"β-Homonojirimycin"

2

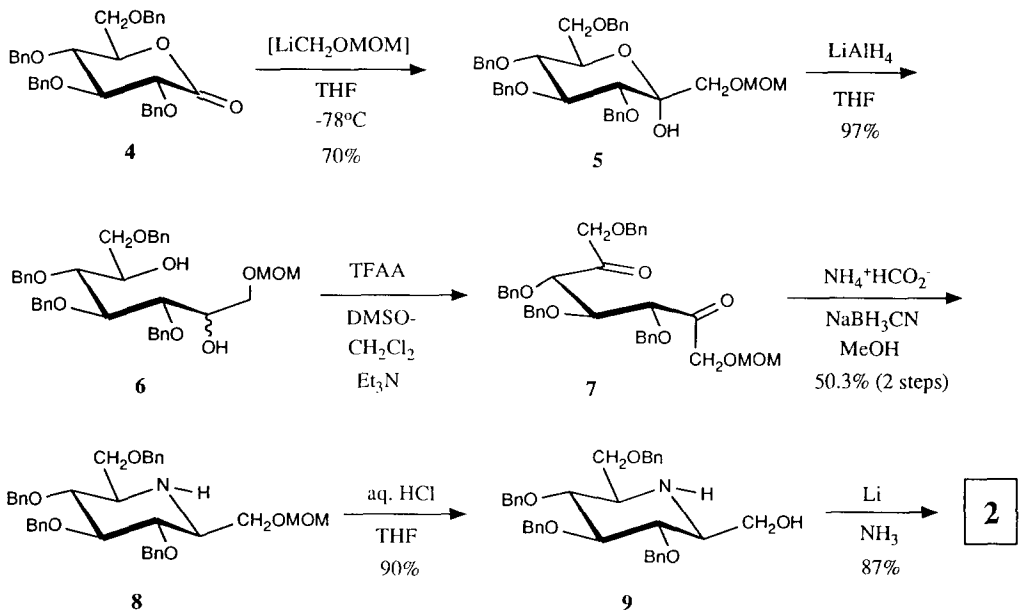


3

synthesis.[5] Both **1** and its 7-*O*-β-D-glucopyranosyl derivative are potent inhibitors of intestinal α-glucosidases.[5,6] In addition to **1**,[5-8] "homo" analogs of L-fuconojirimycin[9,10] and of mannojirimycin[11,12] have been recently prepared by chemical and chemoenzymatic approaches, respectively. Interestingly, both α- and β-epimers of L-homofuconojirimycin were found to be powerful inhibitors of human α-L-fucosidases.[10,13] We report, in this communication, the first chemical synthesis of the β-anomer of **1**, namely β-homonojirimycin **2**, and of its 1,*N*-anhydro derivative **3**, a potential inactivator of glucosidases.[14] A chemoenzymatic synthesis of **2**, in which the key step is an aldolase-mediated chain-extension, was very recently reported by Holt.[11]

Our synthesis of **2** is based on the double reductive amination[15] of a 2,6-heptodiulose (**7**). This approach appeared to be particularly well suited to the preparation of the all-equatorial piperidine derivative **2** since the reduction step was expected to provide predominantly, if not exclusively, the desired configuration at C-2 and C-6: such stereochemical control was anticipated on the basis of extensive studies on the synthesis of deoxynojirimycin itself, by internal reductive amination,[1,16] and from dicarbonyl sugars.[15b]

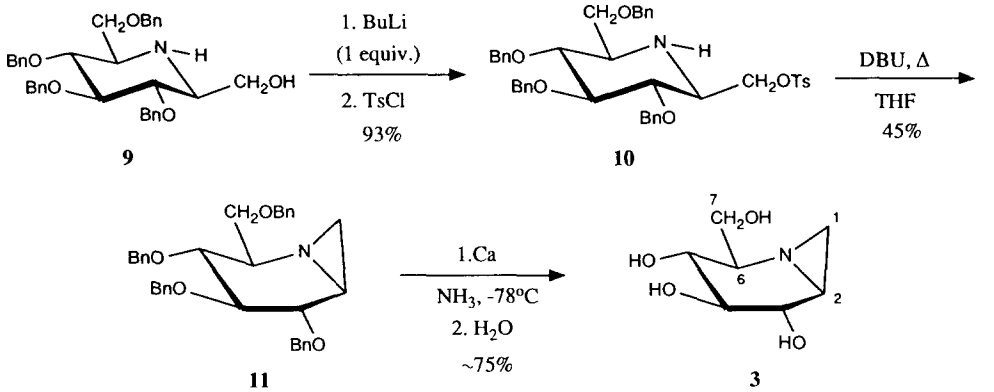
The required diketone, compound **7**, was prepared in three steps from tetra-*O*-benzyl-D-glucono-1,5-lactone **4**: addition of (methoxymethoxy)methyllithium[17] (see also ref. 18), reduction of the resulting 2-heptulose derivative **5** using $LiAlH_4$ (1M solution in THF), which gave heptitols **6** (~1:1 mixture of epimers at C–2) in nearly quantitative yield, and oxidation of diol **6** under the conditions described by Fukase and



Scheme 1

Horii.[19] Because of its tendency to undergo internal aldol addition,[19] compound **7** was submitted without purification[20] to reductive amination using ammonium formate and $NaBH_3CN$.[21] This reaction led to the desired β-homonojirimycin derivative **8**[22] *as a single isomer*, in 50.3% yield (from **6**) after purification by flash chromatography. The synthesis of **2** was completed by removal of the MOM group under mildly acidic conditions, to form amino alcohol intermediate **9**, and of the benzyl groups under dissolving-metal reduction conditions; this sequence afforded **2** in 27% overall yield from **4**. The ^1H- and ^{13}C-NMR spectra[23] of **2** exhibited only 5 and 4 signals, respectively, as expected from its symmetrical structure.

The partially protected β-homonojirimycin **9** constituted a convenient precursor for the preparation of 1,*N*-anhydro derivative **3**: such aziridines are extremely interesting as potential active site-directed, irreversible inhibitors of glycosidases.[14] However, very few examples of compounds of this type have yet been reported: the 6,*N*-anhydro derivatives of 1,5-dideoxy-1,5-imino-D- and L-galactitols[14,24] and an aziridine derived from aza-neuraminic acid.[25] For the preparation of **3**, the alcohol function of **9** was selectively sulfonylated in 93% yield by conversion into its lithium alkoxide form followed by reaction with purified tosyl chloride (1 equiv.) (Scheme 2). The resulting sulfonate **10** was separated from LiCl by extraction (CH_2Cl_2/H_2O). On treatment



Scheme 2

with DBU in THF at reflux temperature, compound **10** gave protected aziridine **11**; although the reaction appeared to be quantitative, some loss occurred during purification by flash chromatography on silica gel and compound **11** was isolated in 45% yield. Most remarkably, *the derivative **11** could be debenzylated without affecting the aziridine ring using dissolving-metal reduction conditions.*[26] This provided the free aziridine **3**,[27,28] the first example of a compound of this kind related to glucosides: its 7-carbon constitution and β-D-*gluco* configuration make it a useful probe to further study the mechanism of enzymatic glucoside hydrolysis. Enzymatic assays designed to probe the activity of both **2** and **3** as glycosidase inhibitors are in progress.

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20. The reaction mixture was only diluted with CH_2Cl_2, washed with 2N HCl, then with brine, dried (Na_2SO_4) and concentrated.
21. Conditions: Ammonium formate (10 mmol), $NaBH_3CN$ (10 mmol), powdered 3Å molecular sieves and diketone **7** (5 mmol) in methanol, room temperature, 14h. The solvent was removed *in vacuo*, the residue taken in water (50 mL) and CH_2Cl_2 (50 mL), the aqueous phase extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic phases were dried and concentrated. Note: the reaction was not successful with benzylamine-acetic acid.
22. New compounds gave satisfactory elemental analyses and/or mass spectral data.
23. ^{13}C-NMR (90 MHz, D_2O, ref. internal CH_3OH, δ 49.60): δ 60.37 (C-2/6), 62.14 (C-1/7), 72.16 (C-3/5), 78.88 (C-4). ^{1}H-NMR (360 MHz, D_2O, ref. internal CH_3OD, δ 3.35): δ 2.65 (ddd, 2H, *J* 3.0, 6.7 and 9.5 Hz, H-2/6), 3.24 (t, 2H, *J* 9.1 and 9.5 Hz, H-3/5), 3.39 (t, 1H, *J* 9.1 and 9.5 Hz, H-4), 3.63 (dd, 2H, *J* 11.6 and 6.7 Hz, H-1A/7A), 3.88 (dd, 2H, *J* 11.6 and 3.0 Hz, H-1B/7B).
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26. The reduction was successful with Li, Na or Ca. Ca was preferred since $Ca(OH)_2$ was much easier to separate from the final product than LiOH or NaOH.
27. Compound **3** appears to be notably more stable than the aziridine described by Paulsen.[24] However it did not survive standard purification methods.
28. ^{13}C-NMR (90 MHz, D_2O): δ 26.76 (C-1), 37.33 (C-2), 61.92 (C-6), 62.38 (C-7), 66.29, 71.52, 76.78 (C-3–5). ^{1}H-NMR (360 MHz, D_2O): δ 1.73 (d, 1H, $J_{1A,2}$ 3.8, $J_{1A,1B}$ ~ 0 Hz, H-1A), 1.87 (d, 1H, $J_{1B,2}$ 6.0 Hz, H-1B), 2.12 (ddd, 1H, $J_{2,3}$ 1.8 Hz, H-2), 3.08 (ddd, 1H, $J_{5,6}$ 10.0, $J_{6,7A}$ 6.9, $J_{6,7B}$ 2.9 Hz, H-6), 3.22 (t, 1H, $J_{4,5}$ 10.1 Hz, H-5), 3.43 (dd, 1H, $J_{3,4}$ 8.7 Hz, H-4), 3.76 (dd, 1H, $J_{7A,7B}$ 12.1 Hz, H-7A), 3.89 (dd, 1H, H-3), 3.94 (dd, 1H, H-7B).

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