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EFFICIENT SYNTHESIS OF (+)-NOJIRIMYCIN AND (+)-1-DEOXYNOJIRIMYCIN

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Summary: (+)-Nojirimycin (**1a**) and (+)-1-deoxynojirimycin (**2**) have been prepared from 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (**3**) by a route involving stereoselective reductive amination of 5-hydroxy-1,2-O-isopropylidene-α-D-*xylo*-hexofuranurono-6,3-lactone (**5a**).

(+)-Nojirimycin (**1a**)[1] and (+)-1-deoxynojirimycin (**2**)[1b,2] are two naturally occurring aza-sugar antibiotics that are quite potent and specific glycohydrolase (GH) inhibitors.[3] Because of this activity, analogs of **2** in particular, have been the focus of much recent attention as potential anti-diabetic[4] and anti-AIDS agents.[5]

During the course of an in-house program of GH inhibition, several derivatives of **1** and **2** were selected for further study. As a result, we required, efficient syntheses which would be readily amenable to scale-up.

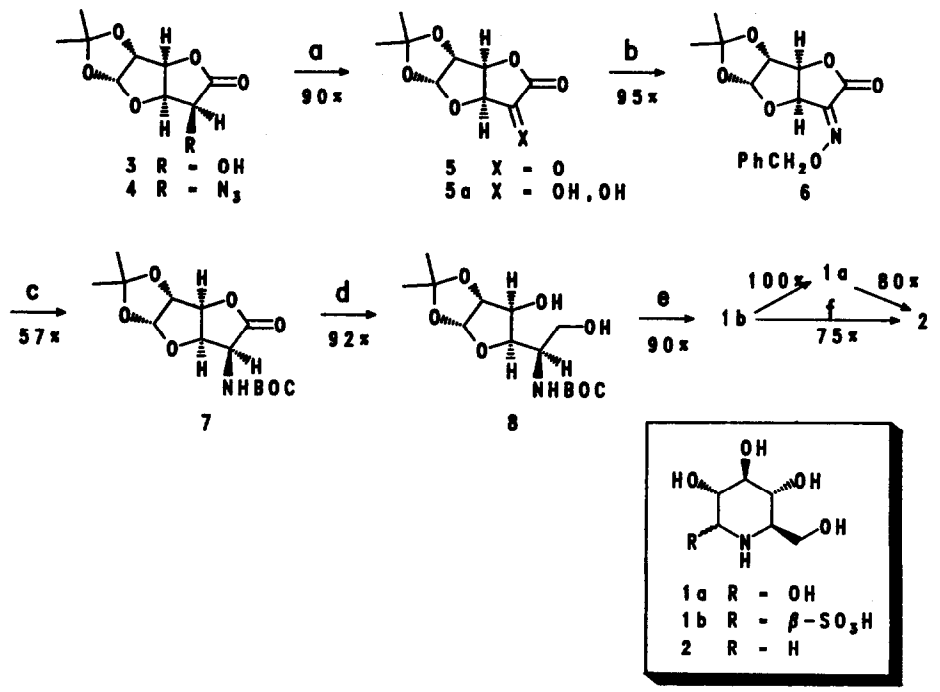
A number of total syntheses of both **1** and **2** have been reported.[1b,6-8] These have been by classical chemical[1b,6,7] (glucose-based for the most part[1b,6]) or combined chemical and enzymatic[8] routes. In this letter, we describe practical, highly stereoselective syntheses of **1** and **2** which compete quite effectively with the most efficient of these.[6e,h,k,m,8e]

Our route begins with readily available 1,2-O-isopropylidene-α-D-glucofuranurono-6,3-lactone (**3**)[9,10] (**Scheme 1**) and relies on stereoselective reductive amination of its 5-oxo derivative, **5**.

For **3** to be elaborated to **1** and **2**, its C-5 hydroxyl must be replaced by a nitrogen function with retention of stereochemistry. This problem was solved independently by Fleet et al.[10] and Lockhoff and Hayauchi[11] who prepared *gluco*-azide **4**[12] from **3** by successive stereospecific S_N2 invertive displacements.

Based on both an inspection of models of **5** and the reported X-ray structure of its stable ketone hydrate **5a**,[13] we reasoned that this requisite stereochemistry might be introduced by reductive amination. Reduction of an intermediate imine or oxime should occur preferentially from the less hindered, convex face, providing predominantly *gluco*-amine.

Scheme 1



Reagents: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -70°C; (b) $H_2NOBn \cdot HCl$, C_6H_6, reflux; (c) H_2, 10% Pd/C, $(BOC)_2O$ (1.1 equiv), EtOAc; (d) LAH, THF, 0°C; (e) sat. aq. SO_2, 35-40°C; (f) H_2, Ra-Ni, $Ba(OH)_2 \cdot 8H_2O$, H_2O.

Of several reported methods[9,14] for the preparation of ketone hydrate **5a**, the best[9] is oxidation of **3** with a 10-fold excess of activated MnO_2. In our hands, yields of **5a** by this procedure were variable and usually low. We investigated several other oxidation methods and found Swern conditions (oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -70°C) to be the most convenient and reliable, giving **5a** in 90% yield.

Treatment of **5a** with O-benzylhydroxylamine hydrochloride in refluxing benzene, with azeotropic removal of water, gives crystalline O-benzyloxime **6**[15] in 95% yield as a single oxime isomer.[16] This was shown by X-ray analysis to be the E-isomer, i.e.,that in which the N-O bond is syn to the carbohydrate framework.

When oxime **6** was hydrogenated over 10% Pd on carbon in the presence of BOC-anhydride,[17] BOC-protected *gluco*-amine **7**[18] was produced in modest yield (~40%) and no amine product of *ido* configuration was observed. In attempts to increase this yield, we studied the hydrogenation varying catalyst, solvent, hydrogen pressure and reaction temperature. Under no

conditions did we see any *ido*-amine products. This contrasts with all previous syntheses of **1** and **2** that relied on reductive amination of acyclic ketone intermediates to introduce nitrogen.[1b,6a,h] In each case, mixtures of *gluco* and *ido* compounds were produced.

Thus far, best results are obtained using either 10% Pd on carbon or $Pd(OH)_2$ on carbon as catalyst (25% by weight of **6**) and hydrogenating at 50 psi in ethyl acetate containing 1.1 mol of BOC-anhydride/mol of **6**. In this way, yields of BOC-amino-lactone **7** averaging 57% are obtained.

Reduction of **7** with LAH in THF at 0°C proceeds smoothly, affording BOC-amino-alcohol **8** in 92% yield. Treatment of **8** with saturated aq. SO_2 at 35-40°C gives a 90% yield of nojirimycin bisulfite (**1b**), identical to that obtained from natural **1a**.

As reported,[1b,7b] (+)-nojirimycin (**1a**) is obtained in quantitative yield from **1b** by treatment with Dowex 1X2 basic ion exchange resin. (+)-1-Deoxynojirimycin (**2**) is obtained in 75% yield directly from **1b** by hydrogenation over Raney-Ni in the presence of barium hydroxide.[19]

In summary, reductive amination of **5** represents an efficient approach to 5-amino-5-deoxy-glucofuranoses. By our route, (+)-nojirimycin (**1a**) and (+)-1-deoxynojirimycin (**2**) can be prepared in five and six steps from lactone **3**, in overall yields of 40 and 30%, respectively.

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15. All new compounds reported were fully characterized by IR, ^{1}H and ^{13}C NMR and mass spectrometry. Each gave satisfactory analytical data (C,H,N). Physical data: **6**, mp 83-85°C, $[\alpha]_D^{20}$ + 152.9° (c 1.0, $CHCl_3$); **7**, mp 157-159°C, $[\alpha]_D^{20}$ + 60.2° (c 1.0, $CHCl_3$); **8**, mp 115-116°C, $[\alpha]_D^{20}$ + 45.5° (c 0.89, $CHCl_3$).
16. The stereochemical integrity of **6** was shown by its ^{1}H and ^{13}C NMR spectra. We had no success in preparing either the O-unsubstituted or O-methyl oxime of **5**.
17. See Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837 for the preparation of BOC- protected amines by catalytic hydrogenation of alkyl azides in the presence of BOC-anhydride.
18. This compound was identical in all respects to that obtained from azide **4** (prepared by the method of reference 10) by hydrogenation over Pd/C in the presence of BOC-anhydride. The BOC-protected *ido*-amine isomer of **7** (mp 156-157°C, $[\alpha]_D^{25}$ + 97.0 (c 2.0, $CHCl_3$)) was prepared in the same manner from the corresponding *ido*-azide (reference 10). All of our attempts to isolate pure, unprotected amine **7**, either as free base or acid salt, by hydrogenating **6** in the absence of BOC-anhydride were unsuccessful.
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