A Stereoselective Synthesis of 1,6-Dideoxynojirimycin by Double-Reductive Amination of Dicarbonyl Sugar†

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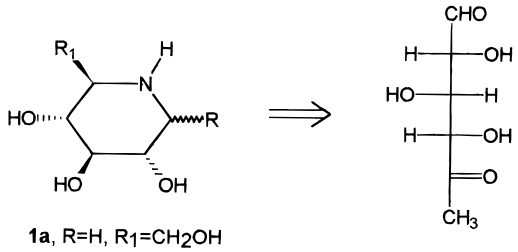
Polyhydroxylated piperidine alkaloids manifest promising therapeutic applications as antiviral agents[1] and in regulation of carbohydrate metabolic disorders.[2] In view of the particular attention on anti-HIV activity in the AIDS area, a number of chemical and enzymatic syntheses of deoxy aza sugars,[3] in particular, 1-deoxynojirimycin[4] (**1a**), have been reported in recent years. However, 1,6-dideoxynojirimycin (**1b**) is still a somewhat unexplored class of aza sugars in spite of their interesting glycosidase inhibitory activity.[4b] Only two syntheses are so far reported, the first approach[4b] involves preparation of azido keto sugar **11** via enzymatic aldol condensation of 3-azido-2-hydroxypropanal and dihydroxyacetone phosphate followed by ring closure using a palladium-catalyzed stereocontrolled reductive amination reaction, while the second sequence[5] makes use of an asymmetric Diels−Alder reaction of hexa-2,4-dienal *O*-methyloxime with a chiral chloronitroso derivative of D-mannose followed by osmylation to diol and nucleophilic ring opening of cyclic sulfate. Recent efforts[6] in our laboratory directed toward the synthesis of 6-deoxynojirimycin (**1c**) have led us to the development of a practical route to 1,6-dideoxynojirimycin (**1b**). Our approach hinges on the double-reductive amination of suitably protected 6-deoxy-5-keto-D-glucose, a dicarbonyl sugar, using simple reactions that allow good reproducibility on a multigram scale (Scheme 1). We have adopted this strategy because of the vital role played by the 5-keto sugars in the biogenesis of nojirimycin and analogs, wherein the carbon chain comes from D-glucose and the amino group in aza sugars has been introduced probably using the 5-keto functionality.[7]

Scheme 1



1a, R=H, R_1=CH_2OH
1b, R=H, R_1=CH_3
1c, R=OH, R_1=CH_3

Results and Discussion

Our previous report[8] describes a synthesis of sugar *β*-keto ester **3** by the reaction of 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pentodialdose (**2**) with ethyl diazoacetate in the presence of BF_3−OEt_2. Decarbalkoxylation[9] of **3** using sodium chloride in wet DMSO afforded 5-keto sugar **4** in good yield[10] (Scheme 2). Hydrolysis of the 1,2-*O*-isopropylidine functionality in **4** gave 6-deoxy-3-*O*-benzyl-α-D-*xylo*-hexofuran-5-ulose (**5**). The critical double-reductive amination reaction with benzhydrylamine, $NaCNBH_3$, and acetic acid in methanol at −78 °C afforded a diastereomeric mixture of piperidines **6a**,**b** corresponding to D-gluco and L-ido configurations in the ratio 86:14, respectively. The separation of diastereomers

† Dedicated to Prof. M. S. Wadia on the occasion of his 60th birthday.

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(10) Conversion of **2** to **4** via Grignard reaction using CH_3MgI followed by oxidation with PCC or Jones reagent is reported in ∼46% overall yield; see: (a) Kiely, D. E.; Morris, P. E., Jr.; *J. Carbohydr. Chem.* **1990**, *9*, 661−673. (b) Wolfrom, M. L.; Hanessian, S. *J. Org. Chem.* **1962**, *27*, 2107−2109. (c) Kraus, G. A.; Shi, J. *J. Org. Chem.* **1990**, *55*, 4922−4925; whereas our method, which is biomimetic, gives 68% yield. Surprisingly **4**, which is the logical precursor to **1b**, has not been earlier exploited for the synthesis of aza sugars.

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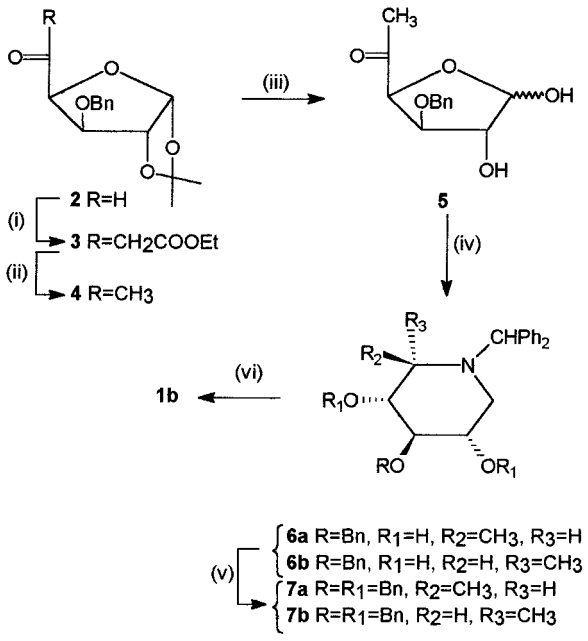
Scheme 2[a]

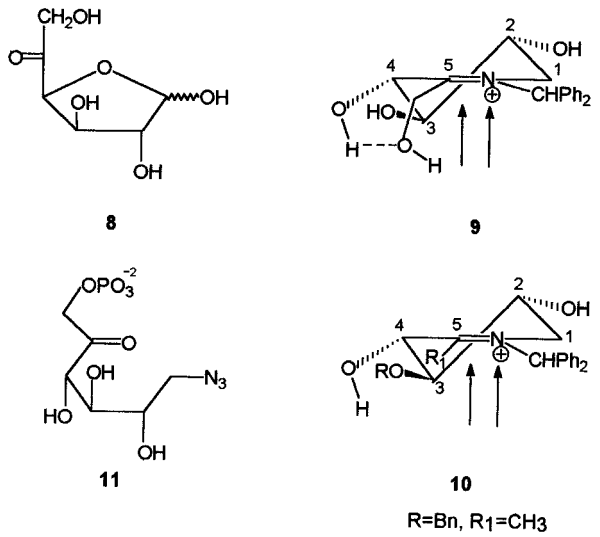


[a] Reagents and conditions: (i) ref 8; (ii) DMSO, H_2O, NaCl, 135 °C, 2 h; (iii) 3 N HCl, THF, 70 °C, 2 h; (iv) H_2NCHPh_2, $NaCNBH_3$, AcOH, MeOH, −78 °C to 20 °C, 22 h; (v) NaH, BnBr, nBu_4NI, 0 to 20 °C, 5 h; (vi) $HCOONH_4$, 10% Pd/C, MeOH, 70 °C, 30 min.

at this stage, by flash chromatography, was troublesome due to the close R_f values. However, benzylation of this diastereomeric mixture with benzyl bromide and NaH in THF afforded an easy access for purification, and the required diastereomer **7a** was isolated in good yield by chromatography. One-pot removal of -$CHPh_2$ and -Bn groups in the D-gluco isomer **7a** by hydrogenolysis with ammonium formate, 10% Pd/C in methanol at 70 °C for 30 min gave 1,6-dideoxynojirimycin (**1b**) as a colorless resin. The ^{1}H- and ^{13}C-NMR data and specific rotation of **1b** are known[4b,5] and were found to be parallel with those of the compound synthesized by us.

The observed diastereoselectivity in the double-reductive amination of **5** (86:14 D-gluco:L-ido) is intriguing in light of results reported by Reitz and co-workers[4a] with the substrate 5-keto-D-glucose (**8**) under identical reaction conditions, wherein the ratio of the product obtained is >95:5 for D-gluco and L-ido isomers, respectively. The substrates **5** and **8**, however, differ in two structural aspects: presence of -CH_3 instead of -CH_2OH at C-5 and -OBn rather than -OH at C-3 (Chart 1). It is evident that the $NaCNBH_3$ reductive amination reaction of cyclic iminium ion intermediate **9** is hydroxyl directed in which the -OH group at C-4 plays a significant stereodirecting effect.[4a] The substituent at C-3 is far away from the reactive site and therefore presumably has a lesser role in determining the stereoselectivity of hydride addition. Now we feel that the presence of -CH_2OH at C-5, instead of CH_3, also has a stereodirecting effect of hydride delivery. This difference in the stereoselectivity could be ascribed to -CH_2OH functionality which is oriented in a particular fashion, probably due to intramolecular hydrogen bonding as shown in the stereodetermining key intermediate **9**. This favors the attack of hydride from the α-face (axial orientation) due to the complexation of the reagent with -CH_2OH and C-4 hydroxyl groups. Such type of additional complexation effect is absent in cyclic iminium ion **10**, due to the presence of a -CH_3 instead of a CH_2OH group, which might result in small access for

Chart 1



β-face attack on **10** giving information of L-*ido*-piperidine (**6b**) still as a minor product (14%). Our results are found to be parallel to those reported by Wong and co-workers,[4b] wherein the piperidine ring closure in azido keto sugar **11** is achieved by hydrogenation under palladium-catalyzed conditions resulting in a ~90:10 mixture of C-5 epimers.

In conclusion, we have demonstrated a concise and practical approach for the synthesis of 1,6-dideoxynojirimycin (**1b**) by exploiting dicarbonyl sugar **4**. In addition it has been demonstrated that, in the reductive amination process of cyclic iminium ion intermediate **10**, the presence of a -CH_3 group at C-5 reduces the stereodirecting effect of hydride delivery, thus indicating that the complexation with both C-4 hydroxy and C-5 methylenehydroxy groups is responsible for stereoselectivity in such types of reductive amination processes.

Experimental Section

General. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR 300S spectrometer using $CDCl_3$ and D_2O as solvents. Chemical shifts are reported in ppm (δ) relative to internal standard Me_4Si, TSP. FT IR spectra were obtained with a Perkin-Elmer 1600 spectrophotometer. Optical rotations were measured at 25 °C with a JASCO DIP 181 polarimeter. Elemental analyses were performed on a Hosli carbon−hydrogen analyzer. Melting points were measured with a Thomas Hoover capillary melting point apparatus and are uncorrected. Whenever required the reactions were conducted in oven-dried glassware under dry N_2. On workup, the solvents were evaporated at reduced pressure with a Buchi rotary evaporator. Thin layer chromatography was performed on 0.25 mm precoated silica gel polygram Sil G/UV 254. Flash chromatography was carried out on silica gel 230−400 mesh. All the solvents, *n*-hexane, THF, diethyl ether, chloroform, methanol, petroleum ether (60−80 °C), and ethyl acetate, were purified and dried before use. Ethyl 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hepto-5-ulo-furanuronate (sugar β-keto ester) (**3**) was prepared from **2** in 85% yield as reported earlier.[8] Benzhydrylamine, $NaCNBH_3$, and 10% Pd/C were purchased from Fluka.

3-*O*-Benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hexofuran-5-ulose (4). A solution of sugar β-keto ester **3** (5.0 g, 13.7 mmol) and sodium chloride (0.8 g, 13.7 mmol) in DMSO (15 mL) and water (0.5 mL) was heated at 135 °C for 2 h. After being cooled, the reaction mixture was poured into ice−water and extracted with ether (20 mL × 6). The combined extract was washed with water and brine and dried over anhyd Na_2SO_4. Removal of the solvent left a residue which was purified by chromatography using petroleum ether:ether acetate = 19:1

to give a white solid (3.21 g, 80%): mp 54−55 °C (lit.[10] mp 55−56 °C); $[\alpha]_D = -48.0$ (*c* 1.2, MeOH); IR (Nujol, cm^{-1}) ν 1735, 1365, 1225, 1170; ^1H NMR ($CDCl_3$) δ 1.30 (s, 3H), 1.46 (s, 3H), 2.21 (s, 3H), 4.26 (d, $J = 2.7$ Hz, 1H), 4.47 (d, $J = 11.7$ Hz, 1H), 4.58 (d, $J = 13.8$ Hz, 1H), 4.56−4.63 (m, 2H), 6.07 (d, $J = 2.7$ Hz, 1H), 7.20−7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 26.5, 27.1, 28.5, 72.6, 82.0, 83.9, 85.7, 106.1, 112.0, 127.9, 128.3, 128.7, 137.1, 206.9. Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.70; H, 6.87.

3-*O*-Benzyl-6-deoxy-α-D-*xylo*-hexofuran-5-ulose (5). A solution of **4** (2.7 g, 9.2 mmol) in 3 N HCl (10 mL) and THF (20 mL) was heated at 70 °C for 2 h. After being cooled, the reaction mixture was neutralized with saturated Na_2CO_3 solution to pH 7 and concentrated, and the residue was extracted with ethyl acetate (20 mL × 5). The combined extract was dried over anhyd Na_2SO_4 (twice) and ethyl acetate evaporated to give **5** as an oil (2.1 g, 90%) which was immediately used for the next reaction.

1,5-Imino-1,5,6-trideoxy-*N*-benzhydryl-3-*O*-benzyl-D-glucitol (6a). To a solution of benzhydrylamine (1.22 g, 6.7 mmol) and acetic acid (0.4 g, 6.7 mmol) in MeOH (60 mL) at −78 °C was added **5** (2.1 g, 8.33 mmol) in MeOH (60 mL) over a period of 30 min followed by addition of $NaCNBH_3$ (1.05 g, 16.64 mmol) in three portions (10 min). The mixture was stirred at −78 °C for 2 h, allowed to warm at room temperature, and concentrated after 20 h. Saturated aqueous Na_2CO_3 solution was added to the residue, solution was extracted with $CHCl_3$ (20 mL × 3), and combined extract was dried over anhyd Na_2SO_4. Removal of chloroform afforded a liquid that was purified by chromatography using petroleum ether:ethyl acetate = 9:1 to give a diastereomeric mixture of **6a**,**b** as a thick oil (2.02 g, 60%). The ^1H NMR indicated percentage composition of **6a**:**6b** = 86:14; R_f 0.66 (*n*-hexane:ethyl acetate = 1:1). Diastereomer **6a**: ^1H NMR δ 1.30 (d, $J = 6.4$ Hz, 3H), 1.64 (bs, 1H), 2.14 (dd, $J = 11.9$, 7.7 Hz, 1H), 2.52 (bs, 1H), 2.62 (dq, $J = 6.4$, 6.2 Hz, 1H), 2.95 (dd, $J = 11.9$, 3.7 Hz, 1H), 3.22 (dd, $J = 6.8$, 6.6 Hz, 1H), 3.46 (dd, $J = 6.6$, 6.4 Hz, 1H), 3.78 (ddd, $J = 7.7$, 6.8, 3.7 Hz, 1H); 4.72 (AB quartet, $J = 11.7$ Hz, 2H), 5.16 (s, 1H), 7.05−7.45 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 13.6, 49.6, 57.2, 66.5, 70.1, 73.7, 74.8, 84.2, 126.8, 127.0, 127.1, 127.2, 127.3, 127.7, 127.9, 128.3, 128.6, 128.7, 129.5, 138.7, 142.6.

For diastereomer **6b**, additional and detectable signals: ^1H NMR δ 0.97 (d, $J = 6.7$ Hz, 3H), 2.41 (dd, $J = 1.7$, 11.95 Hz, 1H), 2.78 (dd, $J = 5.5$, 11.7 Hz, 1H), 4.76 (AB quartet $J = 11.0$ Hz, 2H); ^{13}C NMR δ 29.7, 48.5, 53.5, 59.8, 70.9, 71.5, 72.7, 83.9.

1,5-Imino-1,5,6-trideoxy-*N*-benzhydryl-2,3,4-tri-*O*-benzyl-D-glucitol (7a). A mixture of **6a**,**b** (1.57 g, 3.89 mmol) in THF (12 mL) was added to NaH (0.47 g, 11.69 mmol) at 0 °C under N_2. After 10 min benzyl bromide (1.67 g, 9.74 mmol) in THF (5 mL) followed by tetrabutylammonium iodide (0.072 g, 0.195 mmol) was added. The reaction mixture was stirred at room temperature for 5 h and poured into ice−water. Evaporation of THF left a residue which was extracted with ether (20 mL × 3); combined extract was washed with water and brine and dried over anhyd Na_2SO_4. Removal of ether gave an oil which was purified by chromatography. Elution first with petroleum ether:ethyl acetate = 19:1 gave major diastereomer **7a** as a pale yellow oil (1.7 g, 75%): R_f 0.70 (*n*-hexane:ethyl acetate = 7:3); $[\alpha]_D = -12.56$ (*c* 0.2, $CHCl_3$); IR (neat, cm^{-1}) ν 1601, 1494, 1367, 1178, 1069; ^1H NMR ($CDCl_3$) δ 1.41 (d, $J = 6.04$ Hz, 3H), 1.78 (dd, $J = 11.3$, 10.62 Hz, 1H), 2.38 (dq, $J = 8.79$, 6.04 Hz, 1H), 3.04 (dd, $J = 11.3$, 4.49 Hz, 1H), 3.22 (t, $J = 8.79$ Hz, 1H), 3.39 (t, $J = 8.79$ Hz, 1H), 3.63 (ddd, $J = 10.62$, 8.79, 4.49 Hz, 1H), 4.53 (d, $J = 11.8$ Hz, 1H), 4.58 (d, $J = 11.8$ Hz, 1H), 4.61 (d, $J = 10.9$ Hz, 1H), 4.76 (d, $J = 11.05$ Hz, 1H), 4.94 (d, $J = 11.05$ Hz, 1H), 4.96 (d, $J = 10.9$ Hz, 1H), 5.42 (s, 1H), 7.05−7.48 (m, 25H); ^{13}C NMR ($CDCl_3$) δ 16.4, 49.31, 58.1, 64.1, 72.1, 75.1, 78.8, 79.0, 84.9, 86.7, 126.51, 127.43, 127.54, 127.59, 127.65, 127.70, 127.76, 127.86, 127.92, 127.97, 128.03, 128.08, 128.14, 128.19, 128.24, 128.30, 128.35, 128.41, 128.46, 128.51, 129.17, 130.03, 133.89, 135.11, 135.72, 141.81. Anal. Calcd for $C_{40}H_{41}NO_3$; C, 82.30; H, 7.08. Found: C, 82.08; H, 6.90.

Further elution with petroleum ether:ethyl acetate = 17:3 afforded a mixture of diastereomer **7b** and different di-O-benzylated derivatives as an oil (0.31 g). The ^1H-NMR spectrum indicated the presence of three diastereomers as evidenced by three methyl doublets at δ 0.98 (d, $J = 6.7$ Hz, 3H), 1.18 (d, $J = 6.7$ Hz, 3H), 1.25 (d, $J = 6.4$ Hz, 3H) in the ratio 1:1.3:1.1. Our attempt to separate this mixture was unsuccessful.

1,5-Imino-1,5,6-trideoxy-D-glucitol (1b). A solution of **7a** (1.4 g, 2.4 mmol), 10% Pd/C (3.3 g), and ammonium formate (1.06 g, 16.8 mmol) in MeOH (35 mL) was heated at 70 °C for 30 min. The reaction mixture was brought to room temperature, the suspension was filtered through Celite and washed with 95% aqueous MeOH (70 mL), and the filtrate was concentrated to give a thick viscous liquid. The residue was dissolved in water (25 mL) and the water layer washed with $CHCl_3$ (20 mL × 3) to remove diphenylmethane. Lyophilization of water solution afforded a colorless resin (0.31 g, 87%): $[\alpha]_D = +12.7$ (*c* 0.8, H_2O): [lit.[4b] $[\alpha]_D = +12$ (*c* 2.5, H_2O), lit.[5] $[\alpha]_D = +13$ (*c* 1, H_2O)], $[\alpha]_D = +10.46$ (*c* 0.77, MeOH) [lit.[5] $[\alpha]_D = +11$ (*c* 1, MeOH)]; ^1H NMR (D_2O) δ 1.19 (d, $J = 6.4$ Hz, 3H), 2.54 (t, $J = 11.8$ Hz, 1H), 2.64 (dq, $J = 9.4$, 6.4 Hz, 1H), 3.07 (dd, $J = 9.9$, 9.4 Hz, 1H), 3.14 (dd, $J = 11.8$, 5.0 Hz, 1H), 3.30 (dd, $J = 9.9$, 9.4 Hz, 1H), 3.55 (ddd, $J = 11.8$, 9.4, 5.0 Hz, 1H); ^{13}C NMR (D_2O) δ 17.6, 48.9, 57.9, 70.2, 75.6, 78.9.

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