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A general strategy for the stereoselective synthesis of L-1-deoxyallonojirimycin and D-1-deoxygulonojirimycin☆

Subhash Ghosh,* J. Shashidhar and Samit Kumar Dutta

Indian Institute of Chemical Technology, Hyderabad 500 007, India

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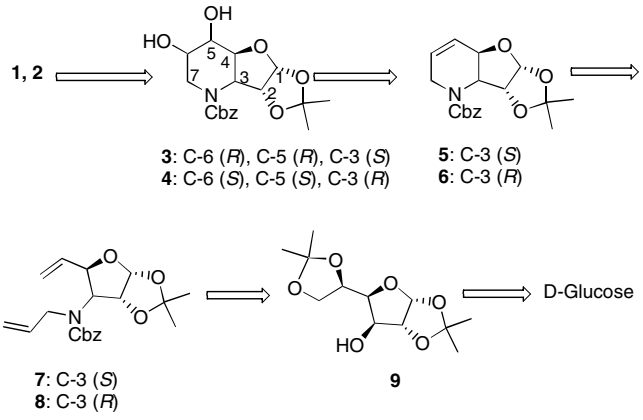
Abstract—A general strategy for the synthesis of deoxyazasugars from D-glucose is described. Ring-closing metathesis and stereoselective dihydroxylation reactions were used as key steps.

Polyhydroxylated piperidines, commonly known as azasugars (iminosugars), are a class of compounds in which the ring oxygen of the sugar ring is replaced by nitrogen. At physiological pH, this nitrogen can be protonated and mimics a glycopyranosyl cation. In recent years, these polyhydroxylated compounds have attracted a great deal of attention, mainly due to their special structural features and promising biological activities.[1] Polyhydroxylated piperidines have the ability to inhibit glycosidases and glycosyl transferases, the carbohydrate processing enzymes, which are responsible for the cleavage of glycosidic bonds.[2] Thus, this family of compounds have the potential to provide leads for the treatment of numerous diseases associated with carbohydrate-related metabolic disorders like diabeties,[3] cancer,[4] AIDS,[5] and viral infections.[6] Due to these promising biological activity profiles, a large number of strategies have been developed for their syntheses.[7] Here, we report a protocol (Scheme 1), which allows the total synthesis of the deoxyazasugars L-1-deoxyallonojirimycin **1**[8] and D-1-deoxygulonojirimycin **2**[9] (Fig. 1).

Our retrosynthetic analysis is shown in Scheme 1. Deoxy azasugars **1** and **2** could be synthesized from **3** and **4**, respectively, by cleavage of the sugar unit. Compounds **3** and **4** in turn could be obtained by stereoselective dihydroxylation of piperidines **5** and **6**, which would be prepared by ring-closing metathesis of bis-alkenes **7** and **8**. Compounds **7** and **8** could be synthesized from **9**, which in turn, would be derived from D-glucose according to the literature procedure.[10]



Scheme 1. Retrosynthetic analysis.

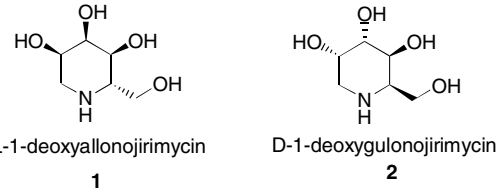


Figure 1.

The synthesis started from **9**, which was converted into **10**[11] in two steps, involving the formation of an imidazoyl sulfate with sulfuryl chloride and imidazole in

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* Corresponding author. Fax: +91 40 27193108; e-mail: subhashbolorg3@yahoo.com

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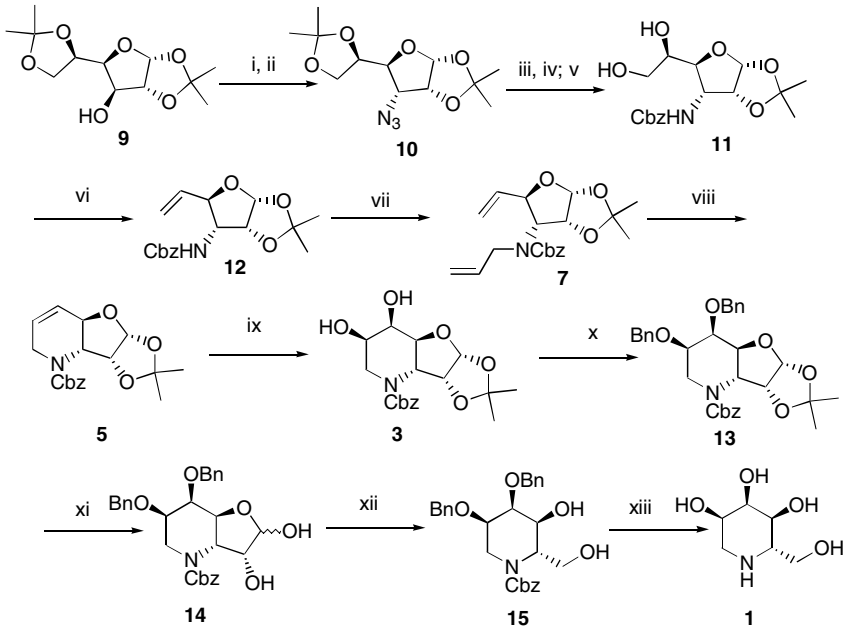
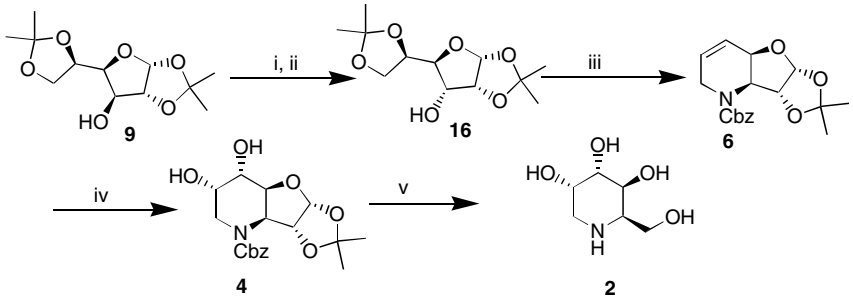
CH_2Cl_2, followed by azide displacement. Selective deprotection of the 5,6-*O*-isopropylidene group using 50% acetic acid in water at room temperature, followed by azide reduction with H_2 under atmospheric pressure in the presence of Pd/C, gave an intermediate amine, which on treatment with CbzCl afforded **11** in good yield. Compound **11** on treatment with imidazole, Ph_3P, and iodine in toluene at 50 °C afforded **12**.[12] N-Allylation of **12** using allyl bromide and NaH in DMF at 0 °C afforded the desired bis-alkene **7** in 88% yield. Next, the crucial ring-closing metathesis (RCM) of **7**, using Grubbs' first generation catalyst $Cl_2(PCy_3)_2Ru{=}CHPh$ (10 mol %) in CH_2Cl_2 under argon at 50 °C afforded piperidine **5** in 90% yield.[13] Stereoselective dihydroxylation of **5** using catalytic OsO_4 with two equivalents of NMO in acetone:water (2:1) at 0 °C for 12 h, afforded a separable diastereomeric mixture of 4:1 in favor of the required isomer **3**.[14] The structure of **3** was confirmed by extensive NMR study.[15] The hydroxyl groups of **3** were protected as benzyl ethers using BnBr, NaH, and TBAI (cat) in THF at 0 °C to afford **13**. Acetonide deprotection of **13** with 50% TFA in water at 0 °C afforded **14** in good yield. Cleavage of the diol in **14** using $NaIO_4$ in 50% ethanol, followed by $NaBH_4$ reduction, gave **15** in 80% yield. Finally, global deprotection by hydrogenation using Pd/C with under atmospheric pressure afforded L-1-deoxyallonojirimycin **1** in 90% yield, the physical properties of which were shown to be identical with previously reported spectral and analytical data.[8a,16]

For the synthesis of D-1-deoxygulonojirimycin, we started from **16**, which was prepared from **9** according to the reported procedure.[17] The key building block **6** required for the synthesis of **2** was synthesized in good yield using similar transformations to those used for the synthesis of **5** from **9** (Scheme 2). Stereoselective dihydroxylation of **6** using OsO_4 gave exclusively one



Scheme 2. Reagents and conditions: (i) SO_2Cl_2, imidazole, CH_2Cl_2, rt, 5 h; (ii) NaN_3, DMF, 70 °C, 3 h, 50% in two steps; (iii) 50% aq AcOH, rt, 5 h; (iv) H_2, Pd/C, MeOH, 1 h; (v) CbzCl, Et_3N, CH_2Cl_2, 30 min, 60% in three steps; (vi) Ph_3P, imidazole, I_2, toluene, 50 °C, 90%; (vii) NaH, DMF, allyl bromide, 0 °C, 2 h, 88%; (viii) 10 mol % $(PCy_3)_2RuCl_2{=}CHPh$, CH_2Cl_2, 24 h, 90%; (ix) NMO, $NaIO_4$, OsO_4, acetone:water (2:1), 0 °C, 12 h, 72%; (x) NaH, BnBr, TBAI (cat), THF, 0 °C to rt, 4 h, 95%; (xi) 50% TFA in water, 0 °C, 8 h; (xii) $NaIO_4$, 50% aq EtOH, 45 min, followed by $NaBH_4$, 10 min, 80% in two steps; (xiii) Pd/C, H_2 under atmospheric pressure, 12 h, 90%.



Scheme 3. Reagents and conditions: (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C; (ii) $NaBH_4$, MeOH, 0 °C, 85% in two steps; (iii) same as in Scheme 2 for the conversion **9** to **5**, 49% in eight steps; (iv) OsO_4, NMO, acetone:water (2:1), 50 °C, 12 h, 80%; (v) same as in Scheme 2 for the conversion **3** to **1**, 43% in four steps.

diol **4**, as expected, since the β-face is blocked by the bulky NCbz group as well as the adjacent C4-β oxygen.[15] Finally, diol **4** was converted into D-1-deoxygulonojirimyan **2** following the same set of reactions as in Scheme 3 (for **3** to **1**). The spectroscopic and analytical data of **2** were in good agreement with the literature data.[9g,i,18]

In conclusion, we have devised a strategy for the synthesis of deoxyazasugars from the commercially available, cheap starting material D-glucose. Making library synthesis and a study of their biological activities are currently under progress and will be reported in due course.

Acknowledgments

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15. The structures of **3** and **4** were confirmed by extensive NMR studies at 500 MHz in DMSO-d_6 at 30 °C. The assignments were carried out with the help of ^{1}H and double quantum filtered correlation spectroscopy (DQF-COSY) experiments. Nuclear Overhauser effect spectroscopy (NOESY) experiments provided information about the proximity of the protons. In **3**, $^3J_{H4-H5} = 2.6$, $^3J_{H5-H6} = 3.0$, $^3J_{H6-H7'} = 5.8$, and $^3J_{H6-H7} = 10.5$ Hz, and characteristic NOE correlations between H3–C5OH, H7–C5OH, H3–H7, H4–H6, and H4–CH_3*proR* confirm the structure in Figure A. The six-membered ring adopts a $^3C_6$ chair form. For **4**, $^3J_{H4-H5} = 4.0$, $^3J_{H6-H7} = 3.8$, and $^3J_{H6-H7'} = 7.8$ Hz and characteristic NOE correlations between H3–H7′, H3–C5OH, H7′–C5OH, H1–H6, H2–H6, H3–CH_3*proR*, and H4–CH_3*proR* confirm the structure given in Figure B. The nuclear Overhauser correlations for **3** and **4** are shown in Figures A and B, respectively.

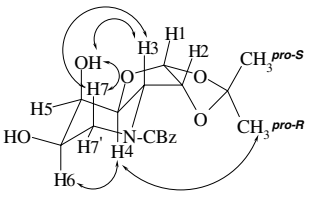

Figure A

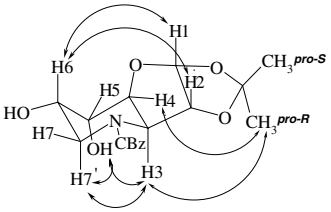

Figure B

Spectral data of **3**: $[\alpha]_D^{27}$ +66.7 (*c* 1.54, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6): δ 7.42–7.31 (m, 5H, aromatic protons), 5.72 (d, 1H, H1, $J = 3.3$ Hz), 4.98 (m, 1H, H2), 4.95 (d, 1H, C5–OH, $J = 3.5$ Hz), 4.91 (d, 1H, C6–OH, $J = 6.2$ Hz), 4.06 (ddd, 1H, H5, $J = 2.6$, 3.0, 3.5 Hz), 3.70 (dd, 1H, H4, $J = 2.6$, 10.0 Hz), 3.68 (dd, 1H, H7′, $J = 5.8$, 11.6 Hz), 3.61 (dddd, 1H, H6, $J = 3.0$, 5.8, 6.2, 10.5 Hz), 3.14 (dd, 1H, H3, $J = 3.7$, 10.7 Hz), 2.86 (dd, 1H, H7, $J = 10.5$, 11.6 Hz), 1.41 (s, 3H, CH_3*proR*), 1.21 (s, 3H, CH_3*proS*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.4, 136.0, 128.5, 128.2, 128.1, 112.8, 105.0, 79.0, 76.3, 67.9, 66.4, 66.8, 55.1, 46.4, 26.4, 26.0; HRMS (ESI) calcd for $C_{18}H_{23}NO_7Na$ $[M+Na]^+$ 388.1372, found 388.1387. Spectral data of **4**: $[\alpha]_D^{27}$ −39.7 (*c* 1.1, $CHCl_3$); ^1H NMR (500 MHz, DMSO-d_6): δ 7.41–7.30 (m, 5H, aromatic protons), 5.76 (d, 1H, H1, $J = 3.8$ Hz), 5.13 (m, 1H, C5–OH), 4.83 (d, 1H, C6–OH, $J = 5.0$ Hz), 4.76 (d, 1H, H2, $J = 3.8$ Hz), 4.25 (dd, 1H, H4, $J = 4.0$, 5.4 Hz), 3.99 (d, 1H, H3, $J = 5.4$ Hz), 3.76 (m, 1H, H6), 3.74 (m, 1H, H5), 3.40 (dd, 1H, H7′, $J = 7.5$, 12.5 Hz), 3.25 (dd, 1H, H7, $J = 3.8$, 12.5 Hz), 1.41 (s, 3H, CH_3*proR*), 1.24 (s, 3H, CH_3*proS*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157, 136, 128.4, 128.3, 128.0, 127.7, 111.9, 103.7, 85.1, 77.9, 67.6, 66.2, 64.2, 58.5, 44.0, 26.7, 26.2; HRMS (ESI) calcd for $C_{18}H_{23}NO_7$ $[M+1]^+$ 366.155, found 366.1562.

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17. Spectral data of **1**: $[\alpha]_D^{27}$ −29.6 (*c* 0.24, MeOH); ^1H NMR (500 MHz, D_2O): δ 4.08 (t, 1H, H5, $J = 2.8$ Hz), 3.90 (ddd, 1H, H6, $J = 2.8$, 5.0, 11.5 Hz), 3.85 (dd, 1H, H2, $J = 3.3$, 12.6 Hz), 3.77 (dd, 1H, H2′, $J = 5.5$, 12.6 Hz), 3.73 (dd, 1H, H4, $J = 2.8$, 10.4 Hz), 3.23 (ddd, 1H, H3, $J = 3.3$, 5.5, 10.4 Hz), 3.17 (dd, 1H, H7, $J = 5.0$, 12.1 Hz), 3.03 (dd, 1H, H7′, $J = 11.5$, 12.1 Hz); ^{13}C NMR (D_2O, 100 MHz) δ 69.0, 67.6, 63.0, 59.4, 55.9, 42.8; HRMS (ESI) calcd for $C_6H_{13}NO_4$ $[M+1]^+$ 164.0922, found 164.0924.
18. Spectral data of **2**: $[\alpha]_D^{27}$ −13.07 (*c* 0.5, H_2O); ^1H NMR (500 MHz, D_2O): δ 4.29 (ddd, 1H, H6, $J = 3.0$, 5.0, 11.4 Hz), 4.16 (dd, 1H, H4, $J = 2.0$, 4.6 Hz), 4.09 (dd, 1H, H5, $J = 3.0$, 4.6 Hz), 3.94 (dd, 1H, H2, $J = 4.7$, 12.3 Hz), 3.85 (dd, 1H, H2′, $J = 9.0$, 12.3 Hz), 3.58 (ddd, 1H, H3, $J = 2.0$, 4.8, 9.0 Hz), 3.35 (dd, 1H, H7, $J = 5.0$, 12.0 Hz), 3.17 (dd, 1H, H7′, $J = 11.4$, 12.0 Hz); ^{13}C NMR (D_2O, 150 MHz) δ 70.4, 65.1, 63.2, 58.2, 53.3, 42.7; HRMS (ESI) calcd for $C_6H_{13}NO_4$ $[M+1]^+$ 164.0920, found 164.0926.