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Intramolecular Michael addition of benzylamine to sugar derived α,β-unsaturated ester: a new diastereoselective synthesis of a higher homologue of 1-deoxy-L-*ido*-nojirimycin

Vijaya N. Desai, Nabendu N. Saha and Dilip D. Dhavale*

Department of Chemistry, Garware Research Centre, University of Pune, Pune - 411 007, India.
E-mail: ddd@chem.unipune.ernet.in

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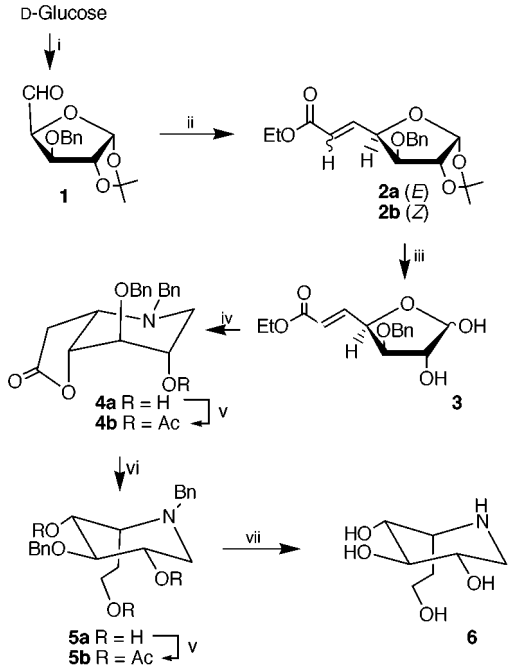
The diastereoselective intramolecular Michael addition of the benzylamine generated *in situ* from hemiacetal 3 leads to the lactone 4a with the required homoazasugar ring skeleton; reduction of the lactone functionality and removal of the protecting groups afford 1-deoxy-L-*ido*-homonojirimycin.

Naturally occurring polyhydroxylated piperidine alkaloids such as nojirimycin and mannonojirimycin are glycosidase inhibitors of great potential therapeutic value.[1] In order to examine the structure–activity relationship, a number of synthetic analogues of nojirimycin have been synthesised and evaluated for glycosidase inhibition in the treatment of various diseases such as diabetes, cancer, AIDS and viral infections. This includes synthesis of 6-deoxynojirimycin,[2a] 1-deoxynojirimycin,[2b] *N*-alkyl nojirimycin[2c] and *N*-linked disaccharide units.[2d] In recent years, preparation and evaluation of homoazasugars with a CH_2 homologation either at C-1 or in the C-5 side chain and nojirimycin with D and L sugar derivatives have received much attention.[3] As a part of our continuing efforts in the synthesis of nojirimycin analogues[4] we report herewith the synthesis of a one carbon higher (in the C-5 side chain) homologue of 1-deoxy-L-*ido*-nojirimycin **6**. We envisioned that the removal of the 1,2-*O*-isopropylidene in the D-glucose derived α,β unsaturated ester **2** (Scheme 1) followed by reductive amination at the anomeric carbon and concomitant intramolecular conjugate addition should lead to the homoazasugar ring skeleton. Reduction of the ester group and removal of the protecting groups should lead the target molecule. Although the intramolecular Michael addition of amines to α,β-unsaturated carbonyl compounds is widely utilized in the synthesis of polyhydroxylated pyrrolidenes and piperidine derivatives,[5] its application to the homoazasugars is highly restricted.[6]



Scheme 1 *Reagents and conditions* i, ref 8; ii, PPh_3CHCO_2Et (1.3 equiv.), MeCN, reflux, 2 h; iii, TFA–H_2O (3:2), rt, 2 h; iv, $BnNH_2$ (1.0 equiv.), $NaCNBH_3$ (2.0 equiv.), AcOH (0.2 equiv.), MeOH, −78 °C, 2 h, rt, 24 h; v, Ac_2O, pyridine, DMAP, rt, 24 h; vi, LAH (3.0 equiv.), dry THF, 0 °C to rt, 2 h; vii, 10% Pd/C, HCO_2NH_4, MeOH, reflux, 1 h.

Our synthetic route involves **2** as the starting compound, which was prepared in high yield from D-glucose. Thus, the Wittig reaction[7] of α-D-*xylo*-pentodialdose[8] **1** with PPh_3CHCO_2Et gave an isomeric mixture of **2** (*E*:*Z* = 73:27) which was separated by chromatography to afford **2a** (*E*, 64%) and **2b** (*Z*, 24%). The cleavage of acetonide group in **2a** afforded hemiacetal **3** (anomeric mixture, α:β = 7:3) with an exclusively *E* geometry at the double bond.† The one pot reaction of **3** with $BnNH_2$ (1.0 equiv.) in the presence of catalytic amounts of AcOH in MeOH followed by treatment with $NaCNBH_3$ afforded a lactone **4a** as the only isolable product (Scheme 1). Thus, the overall three step transformation presumably involves amine as the primary reaction product which undergoes concomitant intramolecular Michael addition and domino[9] lactonisation to yield diastereoselective formation of **4a** in 79% yield. The lactone **4a** was acetylated with Ac_2O in pyridine to give **4b** (78%).‡ The spectroscopic and analytical data obtained for **4a** and **4b** were in full accord with the assigned structures.§ The configuration at C-5 and conformation of **4a** and **4b** were determined from their high field ^1H NMR spectra based on the coupling constant values. The initial geometry ensures that, in the product, the substituents at C-2, C-3 and C-3, C-4 should be *trans*. The low values of $J_{3,2}$ (~6.4 Hz) and $J_{3,4}$ (~4.3 Hz) indicate that the protons at these carbons are equatorial and the substituents are axial. This suggests that the bicyclic lactones have the $^1C_4$ conformation. The small value of $J_{5,4}$ (~5.3 Hz) along with the axial orientation of the C-4 hydroxy group suggests that the C-5 substituent is equatorial with the (5*S*) configuration. This confirms that the six membered piperidine ring is *cis* fused with the lactone ring.

The diastereoselective formation of **4a** can be explained by considering the transition states **A** and **B** (Fig. 1). In general, the stereoelectronic and steric factors often play an integral role in affecting the stereochemical outcome of the intramolecular Michael addition reactions.[10] However we believe that, under the reaction conditions of borohydride reductive amination and *in situ* Michael addition, the complexation of boron with nitrogen and the C-2 and C-4 hydroxy groups determines the

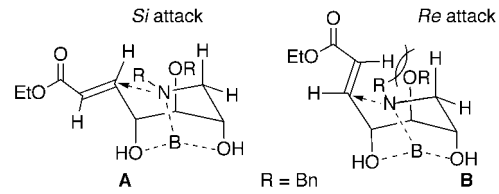


Fig. 1

amine addition.[5] Thus, the complexation of the boron with the C-2,4 hydroxy and amine groups holds the nitrogen atom in such a way that the preferred *Si* face attack at the diastereotopic β-carbon atom, as shown in transition state **A** (Fig. 1), leads to the formation of **4a**.¶ However, transition state **B** (Fig. 1), in which *Re* face attack leads to the formation of the other isomer, is destabilised due to the non-bonded interactions of the α-olefinic hydrogen with the C-1 axial hydrogen and C-3 *O*-benzyl group.

In the subsequent steps, lactone **4a** was reduced with LAH in Et_2O, and the primary alcohol **5a** (colorless solid, 84%) thus obtained was peracetylated to afford **5b** (80%).‖ In the ^{1}H NMR spectra of **5a** and **5b**, H-3 showed a double doublet with large coupling constants ($J_{2,3}$ and $J_{3,4}$ ~ 8.8 Hz).§ This indicated the axial–axial relationship of H-3 with H-2 and H-4, confirming the change in conformation of piperidine ring from $^1C_4$ to $^4C_1$. Finally, removal of the benzyl groups in **5a** was achieved in one step using HCO_2NH_4 and 10% Pd/C in MeOH to give 1-deoxy-L-*ido*-homonojirimycin **6** (90%). The ^{1}H and ^{13}C NMR spectra and analytical data are in agreement with the proposed structure with the $^4C_1$ conformation.§

In conclusion, the one pot reaction sequence of introduction of amine functionality and concomitant intramolecular conjugate addition to D-glucose derived α,β-unsaturated ester provides a unique strategy for the synthesis of homoazasugars. Easy availability of starting materials, mild reaction conditions, high diastereoselectivity and good yields make the route attractive and indicate that it could operate on a gram scale. Work is in progress to study the intermolecular Michael addition of amines to **2** and its applications to the synthesis of homoazasugars and indolizidine alkaloids.

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Notes and references

† As indicated from the ^{1}H NMR spectrum, the cleavage of the acetonide group either in the isomeric mixture **2** or in **2b** (*Z*-isomer) with TFA–H_2O afforded hemiacetal **3** (α:β = 7:3) with exclusively *E* geometry. Acid catalysed $Z \rightarrow E$ isomerisation has been reported (ref. 11).

‡ Our attempts to isolate either the diastereomer or other products in pure form were unsuccessful. The ^{1}H NMR spectrum of the crude mixture indicated the presence of signals (< 10%) corresponding to an ethyl group. This could be the uncyclised open ester with (5*S*) configuration. Lactone **4a** was easily removed from the mixture by column chromatography followed by recrystallisation. The other diastereomer could not be detected even though the subsequent transformations were conducted without separation of **4a**. For example the direct acetylation of crude mixture of **4a** with Ac_2O and DMAP in pyridine gave **4b** as the only isolable product in 88% yield.

¶ This argument would be valid even if lactonisation precedes Michael addition.

‖ The direct reduction of crude mixture **4a** with LAH followed by peracetylation afforded **5b** in 68% yield.

§ *Selected data* for **4a**: white solid, mp 95 °C, $[\alpha]_D$ = +38.45 (*c* 0.5, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3500–3300 (OH), 1770 (C=O); δ_H($CDCl_3$, 300 MHz) 2.33 (1H, dd, *J* 6.9, 11.9, 1_a-H), 2.42 (1H, dd, *J* 6.4, 16.7, 6_a-H), 2.53 (1H, brd, exchanges with D_2O, OH), 2.81 (1H, dd, *J* 6.0, 16.7, 6_e-H), 2.98 (1H, dd, *J* 2.9, 11.9, 1_e-H), 3.44 (1H, d, *J* 13.4, NC*H*$_2$Ph), 3.46 (1H, ddd, *J* 5.3, 6.0, 6.4, 5-H), 3.63 (1H, dd, *J* 4.3, 6.8, 3-H), 3.73 (1H, d, *J* 13.4, NC*H*$_2$Ph), 3.90 (1H, m, 2-H), 4.54 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.72 (1H, dd, *J* 4.3, 5.3, 4-H), 4.77 (1H, d, *J* 11.7, OC*H*$_2$Ph), 7.26–7.37 (10H, m, Ar-H); δ_C($CDCl_3$, 125 MHz) 31.6, 49.9, 58.2, 58.7, 66.5, 72.9, 76.1, 76.9, 127.6, 127.8, 127.9, 128.4, 128.5, 128.6, 136.7, 137.3, 175.2 (Calc). for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56. Found: C, 71.62; H, 6.77%). For **4b**: white solid, mp 89–90 °C; $[\alpha]_D$ +38.68 (*c* 0.4, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 1783 (C=O), 1742 (C=O); δ_H($CDCl_3$, 300 MHz) 2.01 (3H, s, C*H*$_3$), 2.48 (1H, dd, *J* 6.6, 16.8, 6_a-H), 2.62 (1H, dd, *J* 5.9, 12.5, 1_a-H), 2.65 (1H, dd, *J* 6.6, 16.8, 6_e-H), 2.80 (1H, dd, *J* 3.7, 12.5, 1_e-H), 3.43 (1H, d, *J* 14.0, NC*H*$_2$Ph), 3.58 (1H, q, *J* 6.6, 5-H), 3.74 (1H, dd, *J* 6.2, 6.9, 3-H), 3.78 (1H, d, *J* 14.0, NC*H*$_2$Ph), 4.52 (1H, dd, *J* 6.6, 6.9, 4-H), 4.68 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.76 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.93 (1H, m, 2-H), 7.24–7.37 (10H, m, Ar-H); δ_C($CDCl_3$, 125 MHz) 21.0, 31.0, 48.4, 57.4, 58.6, 69.4, 73.2, 75.7, 80.1, 127.7, 127.8, 128.0, 128.41, 128.5, 128.6, 137.0, 137.6, 170.3, 174.6 (Calc. for $C_{23}H_{25}NO_5$: C, 69.85; H, 6.37. Found: C, 69.72; H, 6.15%). For **5a**: white solid, mp 105–107 °C, $[\alpha]_D$ −3.66 (*c* 0.5, $CHCl_3$); ν_{max}(Nujol)/cm^{-1} 3500–3050, 3453, 3200 (OH); δ_H($CDCl_3$, 300 MHz) 1.87–1.92 (2H, m, 6-H), 2.20–2.55 (3H, br, exchanges with D_2O, OH), 2.68–2.77 (2H, m, 1-H), 3.10 (1H, ddd, *J* 6.11, 4.8, 5.9, 5-H), 3.49 (1H, t, *J* 8.8, 3-H), 3.65–3.70 (2H, m, 7-H, NC*H*$_2$Ph), 3.73–3.77 (1H, m, 7-H), 3.83 (1H, d, *J* 13.2, NC*H*$_2$Ph), 3.84–3.90 (1H, m, 2-H), 3.92 (1H, dd, *J* 4.8, 8.8, 4-H), 4.78 (1H, d, *J* 11.7, OC*H*$_2$Ph), 4.85 (1H, d, *J* 11.7, OC*H*$_2$Ph), 7.25–7.40 (10H, m, Ar-H); δ_C ($CDCl_3$, 125 MHz) 26.6, 50.7, 58.2, 61.2, 62.0, 69.1, 69.9, 74.4, 82.8, 127.4, 127.7, 127.9, 128.5, 128.6, 138.3, 138.5 (Calc. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61. Found: C, 70.36; H, 7.89%). For **5b**: thick liquid; $[\alpha]_D$ −15.60 (*c* 0.35, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1736 (C=O); δ_H($CDCl_3$, 300 MHz) 1.80–1.88 (2H, m, 6-H), 1.92 (3H, s, C*H*$_3$), 1.95 (3H, s, C*H*$_3$), 2.01 (3H, s, C*H*$_3$), 2.61 (1H, dd, *J* 10.6, 13.5, 1_a-H), 2.93 (1H, dd, *J* 5.5, 13.5, 1_e-H), 3.20–3.24 (1H, m, 5-H), 3.71 (1H, t, *J* 9.9, 3-H), 3.82 (1H, d, *J* 13.2, NCH_2Ph), 3.89 (1H, d, *J* 13.2, NCH_2Ph), 3.95–4.10 (2H, m, 7-H), 4.67 (2H, s, OCH_2Ph), 5.06–5.14 (1H, m, 2-H), 5.23 (1H, dd, *J* 5.5, 9.9, 4-H), 7.21–7.36 (10H, m, Ar-H); δ_C ($CDCl_3$, 125 MHz) 21.0(s), 23.7, 46.9, 55.0, 58.4, 62.2, 71.0, 71.8, 74.6, 78.6, 127.5, 128.4, 128.7, 138.5, 169.9(s), 171.0 (Calc. for $C_{27}H_{33}NO_7$: C, 67.06; H, 6.88. Found: C, 66.83; H, 6.84%. For **6**: foamy solid, mp 132–135 °C; $[\alpha]_D$ −13.85 (*c* 0.8, H_2O); ν_{max}(KBr)/cm^{-1} 3336, 3062, 1216, 1094; δ_H(D_2O, 300 MHz) 1.62–1.78 (2H, m, 6-H), 2.62 (1H, dd *J* 8.2, 13.6, 1_a-H), 2.88 (1H, dd *J* 4.2, 13.6, 1_e-H), 3.04–3.18 (1H, m, 5-H), 3.40–3.76 (5H, m, 2-H, 3-H, 4-H, 7-H); δ_C(D_2O, 125 MHz) 30.9, 46.7, 55.1, 62.1, 73.2, 74.5, 75.3 (Calc. for $C_7H_{15}NO_4$: C, 47.44; H, 8.53. Found: C, 47.25; H, 8.74%).

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