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

Received (in Cambridge, UK) 6th July 1999, Accepted 23rd July 1999

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} Nalkyl nojirimycin^{2c} and N-linked disaccharide units.^{2d} In recent years, preparation and evaluation of homoazasugars with a CH₂ 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 analogues⁴ 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 $\hat{2}$ (Scheme 1) followed by reductive amination

D-Glucose



Scheme 1 Reagents and conditions i, ref 8; ii, PPh₃CHCO₂Et (1.3 equiv.), MeCN, reflux, 2 h; iii, TFA–H₂O (3:2), rt, 2 h; iv, BnNH₂ (1.0 equiv.), NaCNBH₃ (2.0 equiv.), AcOH (0.2 equiv.), MeOH, -78 °C, 2 h, rt, 24 h; v, Ac₂O, pyridine, DMAP, rt, 24 h; vi, LAH (3.0 equiv.), dry THF, 0 °C to rt, 2 h; vii, 10% Pd/C, HCO₂NH₄, MeOH, reflux, 1 h.

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

Our synthetic route involves 2 as the starting compound, which was prepared in high yield from D-glucose. Thus, the Wittig reaction⁷ of α -D-xylo-pentodialdose⁸ 1 with PPh₃CHCO₂Et 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, $\alpha:\beta = 7:3$) 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 NaCNBH₃ 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 domino9 lactonisation to yield diastereoselective formation of 4a in 79% yield. The lactone 4a was acetylated with Ac₂O 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 ${}^{1}C_{4}$ 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 (5S) 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



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 Et₂O, and the primary alcohol **5a** (colorless solid, 84%) thus obtained was peracetylated to afford **5b** (80%).|| In the ¹H NMR spectra of **5a** and **5b**, H-3 showed a double doublet with large coupling constants ($J_{2,3}$ and $J_{3,4} \sim 8.8$ 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 ${}^{1}C_{4}$ to ${}^{4}C_{1}$. Finally, removal of the benzyl groups in **5a** was achieved in one step using HCO₂NH₄ and 10% Pd/C in MeOH to give 1-deoxy-L-*ido*-homonojirimycin **6** (90%). The ¹H and ¹³C NMR spectra and analytical data are in agreement with the proposed structure with the ${}^{4}C_{1}$ 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.

We are thankful to AICTE, New Delhi, for the financial support, TIFR Bombay for high resolution NMR spectra and to UGC, New Delhi, for the JRF to V. N. D. We are grateful to Professor M. S. Wadia for helpful discussions.

Notes and references

[†] As indicated from the ¹H NMR spectrum, the cleavage of the acetonide group either in the isomeric mixture **2** or in **2b** (*Z*-isomer) with TFA–H₂O 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 ¹H 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 (5S) 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 Ac₂O and DMAP in pyridine gave **4b** as the only isolable product in 88% vield.

 \P 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, $[α]_D = +38.45$ (*c* 0.5, CHCl₃); $v_{max}(Nujol)/cm^{-1}$ 3500–3300 (OH), 1770 (C=O); $\delta_H(CDCl_3, 300 MHz)$ 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 D₂O, 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, NCH₂Ph), 3.46 (1H, dd, *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, NCH₂Ph), 3.90 (1H, m, 2-H), 4.54 (1H, d, *J* 11.7, OCH₂Ph), 4.72 (1H, dd, *J* 4.3, 5.3, 4-H), 4.77 (1H, d, *J* 11.7, OCH₂Ph), 7.26–7.37 (10H, m, Ar-H); $\delta_C(CDCl_3, 125 MHz)$ 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 C₂₁H₂₃NO₄: C, 71.37; H, 6.56. Found: C, 71.62; H, 6.77%). For **4b**: white solid, mp 89–90 °C; $[α]_D$ +38.68 (*c* 0.4, CHCl₃); $v_{max}(Nujol)/cm^{-1}$ 1783 (C=O), 1742 (C=O); $\delta_H(CDCl_3, 300 MHz)$ 2.01 (3H, s, CH₃), 2.48 (1H, dd, *J* 6.6, 16.8, 6_a -H), 2.62 (1H, dd, *J* 5.5, 1a, -H), 2.65 (1H, dd, *J* 4.6, 16.8, 6_e -H), 2.80 (1H, dd, *J* 3.7, 12.5, 1_e -H), 3.43 (1H, d, *J* 14.0, NCH₂Ph), 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, NCH₂Ph), 4.52 (1H, dd, J 6.6, 6.9, 4-H), 4.68 (1H, d, J 11.7, OCH₂Ph), 4.76 (1H, d, J 11.7, OCH₂Ph), 4.93 (1H, m, 2-H), 7.24–7.37 (10H, m, Ar-H); $\delta_{\rm C}({\rm CDCl}_3, 125 \text{ MHz})$ 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 C23H25NO5: C, 69.85; H, 6.37. Found: C, 69.72; H, 6.15%). For 5a: white solid, mp 105–107 °C, $[\alpha]_{\rm D}$ = 3.66 (*c* 0.5, CHCl₃); $v_{\rm max}$ (Nujol)/cm⁻ 3500-3050, 3453, 3200 (OH); δ_H(CDCl₃, 300 MHz) 1.87-1.92 (2H, m, 6-H), 2.20-2.55 (3H, br, exchanges with D2O, 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, NCH₂Ph), 3.73-3.77 (1H, m, 7-H), 3.83 (1H, d, J 13.2, NCH₂Ph), 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, OCH2Ph), 4.85 (1H, d, J 11.7, OCH2Ph), 7.25-7.40 (10H, m, Ar-H); δ_C (CDCl₃, 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 C₂₁H₂₇NO₄: C, 70.56; H, 7.61. Found: C, 70.36; H, 7.89%). For **5b**: thick liquid; $[\alpha]_D$ -15.60 (c 0.35, CHCl₃); v_{max} (neat)/cm⁻¹ 1736 (C=O); δ_{H} (CDCl₃, 300 MHz) 1.80-1.88 (2H, m, 6-H), 1.92 (3H, s, CH₃), 1.95 (3H, s, CH₃), 2.01 (3H, s, CH₃), 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, NCH₂Ph), 3.89 (1H, d, J 13.2, NCH₂Ph), 3.95-4.10 (2H, m, 7-H), 4.67 (2H, s, OCH₂Ph), 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 (CDCl₃, 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 C27H33NO7: 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, H₂O); $\nu_{max}(\text{KBr})/\text{cm}^{-1}$ 3336, 3062, 1216, 1094; $\delta_H(D_2O, 300 \text{ MHz})$ 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(D₂O, 125 MHz) 30.9, 46.7, 55.1, 62.1, 73.2, 74.5, 75.3 (Calc. for C7H15NO4: C, 47.44; H, 8.53. Found: C, 47.25; H, 8.74%).

- A. B. Hughes and A. J. Rudge, *Nat. Prod. Rep.*, 1994, **11**, 135; P. Sears and C.-H. Wong, *Chem. Commun.*, 1998, 1161;
- (a) A. Defoin, H. Sarazin and J. Streith, *Helv. Chim. Acta*, 1996, **79**, 560 and references therein; (b) U. M. Lindstrom and P. Somfai, *Tetrahedron Lett.*, 1998, **39**, 7173; A. J. Rudge, I. Collins, A. B. Holmes and R. Baker, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2320; (c) C. R. R. Matos, R. S. C. Lopes and C. C. Lopes, *Synthesis*, 1999, 571; Y. Yoshikuni, *Agric. Biol. Chem.*, 1988, **52**, 121; (d) L. Sun, P. Li, N. Amankulor, W. Tang, D. W. Landry and K. Zhao, *J. Org. Chem.*, 1998, **63**, 6472.
- 3 Y. Suhara and K. Achiwa, *Chem. Pharm. Bull.*, 1995, **43**, 414; C. Herdeis and T. Schiffer, *Tetrahedron*, 1996, **52**, 14745; C.-H. Wong, L. Provencher, J. A. Porco Jr., S.-H. Jung, Y.-F. Wang, L. Chen, R. Wang and D. H. Steensma, *J. Org. Chem.*, 1995, **60**, 1492; A. Defoin, H. Sarazin and J. Streith, *Tetrahedron*, 1997, **53**, 13769; 1997, **53**, 13783.
- 4 D. D. Dhavale, V. N. Desai, M. D. Sindkhedkar, R. S. Mali, C. Castellari and C. Trombini, *Tetrahedron: Asymmetry*, 1997, 8, 1475; D. D. Dhavale, N. N. Saha and V. N. Desai, *J. Org. Chem.*, 1997, 62, 7482.
- 5 S. Saito, S. Matsumoto, S. Sato, M. Inaba and T. Moriwake, *Heterocycles*, 1986, 24, 2785; K. Shishido, Y. Sukegawa and K. Fukumoto, J. Chem. Soc., Perkin Trans. 1, 1987, 993; T. Wakabayashi and M. Saito, Tetrahedron Lett., 1977, 93; C. Schneider and C. Borner, Synlett, 1998, 652; M. G. Banwell, C. T. Bui, H. T. T. Pham and G. W. Simpson, J. Chem. Soc., Perkin Trans. 1, 1996, 967; R. A. Bunce, C. J. Peeples and P. B. Jones, J. Org. Chem., 1992, 57, 1727; M. Hirama, T. Shigemoto, Y. Yamazaki and S. Ito, J. Am. Chem. Soc., 1985, 107, 1797.
- 6 F. Compernolle, G. Joly, K. Peeters, S. Toppet, G. Hoornaert, A. Kilonda and B. Bila, *Tetrahedron*, 1997, **53**, 12739; A. Kilonda, F. Compernolle, S. Toppet and G. J. Hoornaert, *Tetrahedron Lett.*, 1994, **35**, 9047;
- 7 D. Tulshian, R. J. Doll, M. F. Stansberry and A. T. McPhail, J. Org. Chem., 1991, 56, 6819.
- 8 M. L. Wolfrom and S. Hanessian, J. Org. Chem., 1962, 27, 1800.
- 9 L. F. Tietze, Chem. Rev., 1996, 96, 115; L. F. Tietze and U. Beifuss, Angew. Chem., Int. Ed. Engl., 1993, 32, 131.
- 10 R. D. Little, M. R. Masjedizadeh, O. Wallquist and J. I. McLoughlin, Org. React., 1995, 47, 315.
- 11 Stereochemistry of alkenes, in Stereochemistry of Organic Compounds, ed. E. L. Eliel, S. H. Wilen and L. N. Mander, Wiley, New York, 1994, p. 579.

Communication 9/05440E