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Chiron approach strategy to the bicyclic oxazolidinylpiperidine: a building block for preparing mono- and bi-cyclic iminosugars

Navnath B. Kalamkar, Dilip D. Dhavale *

Department of Chemistry, Garware Research Centre, University of Pune, Pune 411 007, India

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ABSTRACT

A chiron approach to the synthesis of bicyclic oxazolidinylpiperidine, a synthetically potential building block for preparing mono- and bi-cyclic iminosugars, is reported from D-glucose using ring closing metathesis as the key step.

The enantiomerically pure bicyclic oxazolidinylpiperidine **1** (Fig. 1) is endowed with unique structural features such as (i) hydroxylated dehydropiperidine skeleton (ii) the presence of amine and primary hydroxyl functionality in the protected cyclic carbamate form and (iii) endocyclic C=C bond prone for *cis*-/*trans*-dihydroxylation. These facts render **1** to act as a versatile building block for the preparation of a variety of mono- and bi-cyclic iminosugars I–IV.[1–4]

Iminosugars, also known as azasugars, are the polyhydroxylated heterocyclic compounds with structural resemblance to carbohydrates wherein the endocyclic ring oxygen is replaced by the basic nitrogen atom.[7] Nojirimycin and its 1-deoxy analog, deoxynojirimycin I, are the earliest two examples of natural iminosugars found to exhibit potent glycosidase inhibitory activity.[7a,8] Since then much attention has been focused to discover their use in clinical applications of carbohydrate-mediated diseases such as diabetes, cancer, lysosomal storage disorders, and viral infections (including HIV).[9] Recently, two derivatives of these structure-based compounds namely *N*-hydroxyethyl deoxynojirimycin (Miglitol™) and *N*-butyl deoxynojirimycin (Zavesca™) have been commercialized for the treatment of type II diabetes and Gaucher's disease, respectively.[9c,d] Although, a number of chiron as well as asymmetric approaches are known for the preparation of iminosugars[10] the development of a simple, efficient, and practical approach is still desirable. In this respect synthesis of oxazolidinylpiperidine **1** or its derivatives and their utility in the synthesis of different iminosugars is well established by different research groups.[1–6] For example, Ciufolini et al.[2] prepared a benzyl ether derivative of **1** from racemic furylglycine and Katsumura[3] and coworkers reported its *O*-TBDMS derivative from (*R*)-4-methoxycarbonyloxazolidinone which, in turn, was prepared from glycidol. Riera and coworkers described an asymmetric approach toward both enantiomers of **1** using the Sharpless asymmetric epoxidation of (*E*)-2,4-pentadienol and regioselective intramolecular epoxide ring opening as key steps[1a,b] while; Sato as well as Lin's group reported chiral pool approach to **1** from D-serine in multistep sequences.[5,6] In continuation of our interest in the syntheses of compounds[11] analogous to **1** as well as iminosugars from

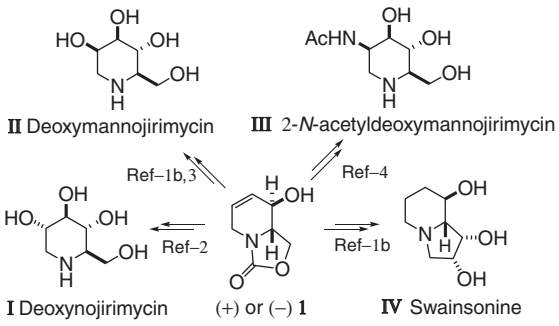

Figure 1. Iminosugars from oxazolidinylpiperidine **1**.

* Corresponding author. Tel.: +91 225691727; fax: +91 20 25691728.
E-mail addresses: ddd@chem.unipune.ac.in, ddd@chem.unipune.ernet.in (D.D. Dhavale).

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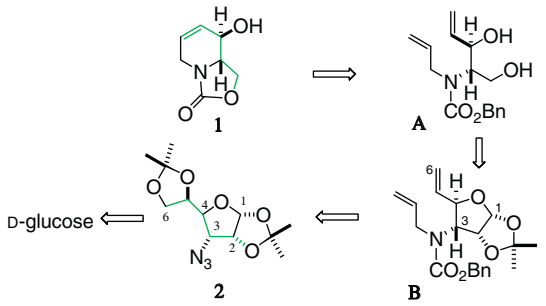
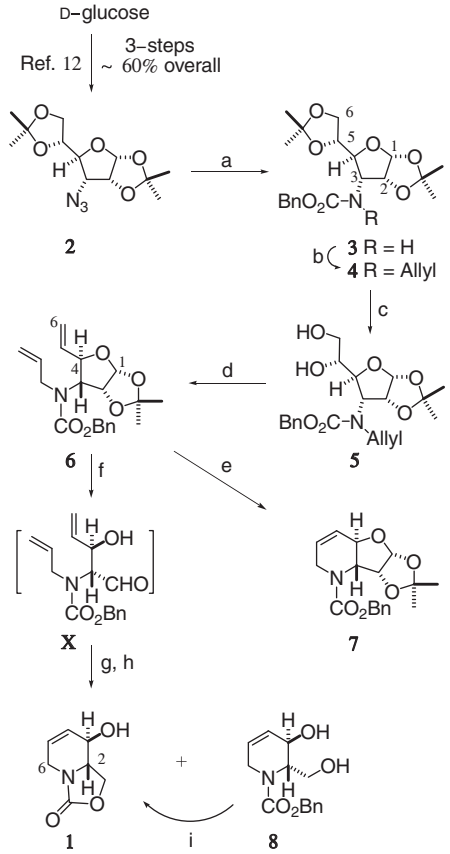


Scheme 1. Retrosynthetic analysis of **1**.

carbohydrates, we describe herein a new and efficient synthesis of (+)-**1** from D-glucose.

We envisioned that, the bicyclic ring skeleton of **1** could be constructed from bisalkenyl diol **A** by ring closing metathesis (RCM) and intramolecular carbamate formation (Scheme 1). The diol functionality in **A** could be prepared from sugar-derived bisalkene **B** by the sequential reaction path of 1,2-acetonide opening, cleavage of anomeric carbon (C1), and reduction of aldehyde. The sugar appended bisalkene **B** could be synthesized from 3-azido-D-allose derivative **2**, obtained from D-glucose, by usual functional group manipulations.



Scheme 2. Synthesis of **1**. Reagents and conditions: (a) Ph_3P, THF/H_2O, rt, 30 h then aq $NaHCO_3$, CbzCl, rt, 5 h, 90%; (b) allyl-Br, NaH, cat TBAI, THF, 0 °C to rt, 3 h, 96%; (c) 1% aq H_2SO_4, MeOH, rt, 10 h, 90%; (d) PPh_3, I_2, Imidazole, toluene, 70 °C, 3 h, 88%; (e) Grubbs first generation cat (10 mol %), CH_2Cl_2, reflux, 10 h, 70%; (f) (i) TFA/H_2O (3:2), rt, 4 h; (ii) $NaIO_4$, acetone/H_2O, rt, 1 h; (g) $NaBH_4$, MeOH/H_2O (4:1), 0 °C to rt, 1 h; (h) Grubbs first generation cat (10 mol %), CH_2Cl_2, 40 °C, 5 h; (i) NaH, THF, 0 °C to rt, 45 min, overall 61% (from **6**).

The requisite C3 azido derivative **2** was prepared in three steps from D-glucose as reported earlier by us and others (Scheme 2).[12] The one pot Staudinger reduction of the azide functionality in **2** with PPh_3 in THF/water followed by *N*-Cbz protection using benzylchloroformate and $NaHCO_3$ furnished **3**[13] in 90% yield. The N-allylation of **3** using allyl bromide and sodium hydride in the presence of catalytic TBAI in THF gave N-allylated compound **4** in 96% yield. The regioselective hydrolysis of 5,6-acetonide in **4** using 1% H_2SO_4 in methanol afforded diol **5** that on reaction with PPh_3, I_2, and imidazole in toluene at 70 °C provided bisalkenyl sugar derivative **6** in 80% yield (over two steps). The RCM[14] of **6** with the Grubbs catalyst (first generation) afforded the requisite dehydropiperidine ring skeleton **7**.[15]

Hydrolysis of 1,2-acetonide group in **7** under a variety of reaction conditions (60% TFA/H_2O, Dowex–H^+, 2 N H_2SO_4, 30% aq $HClO_4$) gave a complex mixture. Therefore, we thought of an alternative pathway. Thus, compound **6** on hydrolysis of the 1,2-acetonide functionality using 60% TFA/H_2O followed by oxidative cleavage with $NaIO_4$ in acetone/water gave aldehyde **X** which was found to be relatively unstable, and therefore immediately reacted with $NaBH_4$ in methanol/H_2O to afford an inseparable mixture of compounds.[16] This mixture was directly reacted with the Grubbs catalyst (first generation) in CH_2Cl_2 at 40 °C for 5 h to give a separable mixture of RCM products **1** and **8** in 5:2 ratio. The spectral and analytical data of compound **1** were found to be in good agreement with that reported; $[\alpha]_D^{25}$ +18.2 (*c* 1.2, CH_2Cl_2) [lit[1b] for the antipode $[\alpha]_D^{20}$ −16.7 (*c* 1.2, CH_2Cl_2)]. The minor product **8** was characterized by spectral data[13] and the structure was confirmed by converting it into **1** using sodium hydride in THF at 0 °C. The combined yield of **1**, from **6**, was found to be 61% in overall four steps.

In summary, we have developed an efficient strategy for the preparation of synthetically useful chiral bicyclic oxazolidinylpiperidine (+)-**1**. The overall synthesis is straightforward and makes use of cheap starting material/reagents under mild reaction conditions. Utility of **1** in the syntheses of deoxyazasugars and anticancer swainsonine is known in the literature[1–4] however, exploration of **1** to the synthesis of new iminosugars and their biological evaluation is in progress and will be reported separately.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and copies of ^1H and ^{13}C NMR spectra of compounds **3**–**8** and **1**) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.039.

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13. All compounds were characterized by IR, NMR (^{1}H and ^{13}C) and CHN microanalysis; data for compound (**3**): white solid; mp = 72–73 °C; R_f 0.5 (*n*-hexane/ethyl acetate = 3:2); $[\alpha]_D^{25}$ +58.3 (*c* 1.5, $CHCl_3$); IR (neat); 1685 and 3200–3500 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.30 (6H, s, $2CH_3$), 1.38 (3H, s, CH_3), 1.52 (3H, s, CH_3), 3.85 (1H, dd, *J* = 9.3 and 4.0, H-3), 3.92 (1H, dd, *J* = 12.0 and 6.1, H-6a), 3.99–4.14 (2H, m, H-5/H-4), 4.26 (1H, dd, *J* = 11.5 and 6.1, H-6b), 4.60 (1H, t, *J* = 4.0, H-2), 5.12 (2H, AB quartet, *J* = 12.0, OCH_2Ph), 5.21 (1H, d, *J* = 9.1, exchangeable with D_2O, NH), 5.80 (1H, d, *J* = 3.6, H-1), 7.20–7.42 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 25.3 (CH_3), 26.3 (strong, $2CH_3$), 26.4 (CH_3), 55.0 (C3), 65.2 (C6) 67.1 (OCH_2Ph), 75.5 (C5), 78.5 (C4) 78.9 (C2), 103.9 (C1), 109.5 (5,6-*O*-isopropylidene), 112.4 (1,2-*O*-isopropylidene) 128.0, 128.1, 128.4, 135.9 (Ar), 155.5 (NCOO). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 61.15; H, 7.0; N, 3.76. Data for compound (**4**): R_f 0.5 (*n*-hexane/ethyl acetate = 3:2); $[\alpha]_D^{25}$ +140.0 (*c* 1.5, $CHCl_3$); IR (neat); 1630 and 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.30 (6H, s, $2CH_3$), 1.38 (3H, s, CH_3), 1.59 (3H, s, CH_3), 3.50–3.98 (2H, m, H-7), 3.99–4.20 (3H, m, H-3/H-6), 4.21–4.38 (1H, m, H-5), 4.39–4.52 (2H, m, H-2/H-4), 4.95–5.30 (4H, m, OCH_2Ph/H-9), 5.72 (1H, br s, H-1), 5.80–6.06 (1H, m, H-8), 7.20–7.45 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 25.3 (CH_3), 26.3 (CH_3), 26.8 (CH_3), 31.0 (CH_3) 48.0 (C7) 59.5 (C3), 66.5 (C6) 67.6 (OCH_2Ph), 75.0 (C5), 76.2 (C4), 79.8 (C2), 103.8 (C1), 109.4 (5,6-*O*-isopropylidene), 112.9 (1,2-*O*-isopropylidene) 116.1 (C9) 127.7, 127.8, 128.0, 128.3 (Ar) 135.2, 135.5 (C8/Ar-C), 156.7 (NCOO). Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.80; H, 7.25; N, 3.50. Data for compound (**5**): R_f 0.5 (*n*-hexane/ethyl acetate = 4:1)$[\alpha]_D^{25}$ +41 (*c* 1.0, $CHCl_3$); IR (neat): 1632, 3000–3600 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.30 (3H, s, CH_3), 1.80 (3H, s, CH_3), 2.45 (2H, br s, exchangeable with D_2O, OH) 3.65 (2H, br s, H-7), 3.66–4.0 (1H, m, H-3) 4.10 (2H, dd, *J* = 13.5 and 6.4, H-6), 4.35 (1H, dd, *J* = 10.2 and 4.0, H-5), 4.42–4.58 (1H, m, H-4), 4.65 (1H, br s, H-2), 5.0–5.30 (4H, m, OCH_2Ph/H-9), 5.74 (1H, d, *J* = 2.2, H-1), 5.80–6.0 (1H, m, H-8), 7.20–7.42 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 26.2 (CH_3), 26.3 (CH_3), 46.0 (C7), 61.2 (strong, C3/C6), 67.6 (OCH_2Ph), 73.0 (C5) 77.2 (C4), 79.0 (C2), 105.4 (C1), 112.4 (1,2-*O*-isopropylidene) 123.6 (C9) 127.7, 128.0 strong, 128.3 strong (Ar), 128.5 (C8), 136.1, (Ar-C), 155.5 (NCOO). Anal. Calcd for $C_{20}H_{27}NO_7$: C, 61.06; H, 6.92; N, 3.56. Found: C, 59.95; H, 7.02; N, 3.65. Data for compound (**6**): R_f 0.5 (*n*-hexane/ethyl acetate = 7:3); $[\alpha]_D^{25}$ +167 (*c* 1.0, $CHCl_3$); IR (neat): 1630–1640 and 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.32 (3H, s, CH_3), 1.60 (3H, s, CH_3), 4.13 (2H, br s, H-7), 4.30–4.46 (1H, m, H-3) 4.63 (1H, dd, *J* = 10.1 and 6.8, H-2), 4.67–4.78 (1H, m, H-4), 4.98–5.12 (2H, m, H-9a/b), 5.14 (2H, s, OCH_2Ph), 5.28 (1H, d, *J* = 10.2, H-6a), 5.38 (1H, br d, *J* = 17.3, H-6b), 5.64–5.98 (3H, m, H-1/H-5/H-8), 7.22–7.42 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 26.2 (CH_3), 26.5 (CH_3), 48.0 (C7), 61.9 (C3), 67.6 (OCH_2Ph), 76.1 (C2), 79.5 (C4), 103.6 (C1), 112.5 (1,2-*O*-isopropylidene) 116.2, 120.0 (C6/C9), 127.9 strong, 128.3 strong (Ar), 134.1 (C5), 135.6, 136.1 (C8/Ar-C), 156.6 (NCOO). Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.92; H, 6.95; N, 4.02. Data for compound (**7**): white solid; mp = 130–131 °C; R_f 0.4 (*n*-hexane/ethyl acetate = 7:3); $[\alpha]_D^{25}$ +110 (*c* 0.7, $CHCl_3$); IR (neat): 1612 and 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.25 (3H, s, CH_3), 1.56 (3H, s, CH_3), 2.86 (1H, dd, *J* = 9.3 and 3.6, H-7a), 3.904.15 (2H, m, H-2/H-3), 4.42–4.52 (1H, m, H-7b) 4.95–5.20 (1H, m, H-4), 5.07 (1H, d, *J* = 12.1, OCH_2Ph), 5.30 (1H, d, *J* = 12.1, OCH_2Ph), 5.67–5.78 (1H, m, H-6), 5.82 (1H, d, *J* = 2.5, H-1), 6.24 (1H, dd, *J* = 8.2 and 1.9, H-5), 7.22–7.44 (5H, m, ArH); ^{13}C NMR ($CDCl_3$) 26.2 (CH_3), 26.3 (CH_3), 46.0 (C7), 61.2 (C3), 67.7 (OCH_2Ph), 73.0 (C2), 78.9 (C4), 105.4 (C1), 112.4 (1,2-*O*-isopropylidene) 123.6 (C5), 127.7 (C6), 128.0 strong, 128.3 strong, 136.1 (Ar), 155.6 (NCOO). Data for compound (**8**): R_f 0.4 (*n*-hexane/ethyl acetate = 1:1); $[\alpha]_D^{25}$ −7.0 (*c* 0.5, $CHCl_3$); IR (neat): 3100–3500, 1690 and 1625–1640 cm^{-1}. The interpretation of ^{1}H NMR spectrum of this compound was found to be difficult because of broadening and additional signals due to presence of rotamers (due to *N*-Cbz group). However, ^{13}C NMR spectrum showed single isomer; ^{13}C NMR ($CDCl_3$) 41.2 (C6), 57.5 (C2), 62.6 (C1), 68.2 (OCH_2Ph), 69.4 (C3), 125.0, 126.1 (C4/C5), 128.0 strong, 128.4, 128.6 strong, 135.8 (Ar), 157.8 (NCOO). Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.97; H, 6.41; N, 5.52. Data for compound (**1**): white solid; mp 85 °C; [lit.[1b] 86.5 °C]; R_f 0.4 (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D^{25}$ +18.2 (*c* 1.2, CH_2Cl_2) [lit.[1b] for the antipode $[\alpha]_D^{20}$ −16.7 (*c* 1.2, CH_2Cl_2)]; IR (KBr): 2900–3100, 1630 and 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$); 1.98–2.10 (1H, br s, exchangeable with D_2O, OH), 3.49 (1H, dt, *J* = 8.2 and 4.1, H-2), 3.63 (1H, dd, *J* = 18.1 and 2.6, H-6a), 4.05 (1H, dd, *J* = 18.1 and 2.6, H-6b), 4.13–4.20 (1H, m, H-1a) 4.34 (1H, dd, *J* = 9.1 and 4.1, H-1b) 4.54 (1H, dd, *J* = 9.0 and 8.0, H-3) 5.735.81 (2H, br s, H-4/H-5); ^{13}C NMR ($CDCl_3$) 40.8(C6), 56.4 (C2), 67.3, 67.6 (C1/C3), 124.8, 130.0 (C4/C5), 157.9 (carbamate CO). Anal. Calcd for $C_7H_9NO_3$: C, 54.19; H, 5.85; N, 9.03. Found: C, 54.25; H, 5.90; N, 8.95. The ^{1}H NMR spectra of compounds **4**, **5**, **6** and **8** showed broadening of signals while, ^{13}C NMR spectrum of compound **4** and **6** showed doubling of signals due to presence of *N*-Cbz group. In NMR data of these compounds only high intensity signals are mentioned. For the doubling/broadening of signals in NMR spectra due the isomerisation by restricted rotation around C–N bond, see: In *Applications of NMR Spectroscopy in Organic Chemistry*; Jackman, L. M., Sternhell, S., Eds.; Pergamon: Elmsford, NY, 1978; p 361.
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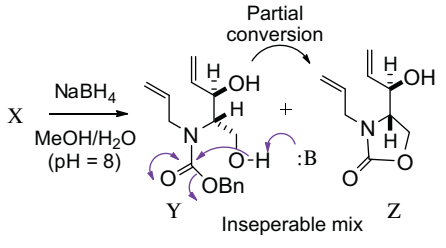
15. Compound **7** was found to be highly unstable and decomposed on standing. We characterised it by spectral methods within 1 h of its preparation as it showed developing multiple spots on TLC after 1 h. Compound **7** is known; however, no (spectral/analytical) data is reported for the same. See: Ghosh, S.; Shashidhar, J.; Dutta, S. K. *Tetrahedron Lett.* **2006**, *47*, 6041. We have prepared it by different methods and characterized independently. For data see Ref. 13.
16. In this reaction, an inseparable mixture (as evident from ^{1}H MNR) would be due to the formation of compounds **Y** and **Z** which can be probably explained as follows (Scheme 3). We believe that $NaBH_4$ reduction of an aldehyde **X** first results in the formation of compound **Y** that concomitantly undergoes partial conversion to the 5-membered carbamate ester **Z** *via* cyclization (of primary alcohol and *N*-Cbz group) initiated by in situ-generated base $NaB(OMe)_4$ (observed reaction pH = 8) by reaction of $NaBH_4$ and aq MeOH. On RCM reaction of this mixture the resulted products were found to be separated by column chromatography. For preparation of $NaB(OMe)_4$, its basic nature and applications as a base, see: Campana, A. G.; Fuentes, N.; GomezBengoa, E.; Mateo, C.; Oltra, J. E.; Echavarren, A. M.; Cuerva, J. M. *J. Org. Chem.* **2007**, *72*, 8127.



Scheme 3. Mechanism for the formation of **Y** and **Z**.