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

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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.

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. Nojirimycin and its 1-deoxy analog, deoxynojirimycin I, are the earliest two examples of natural iminosugars found to exhibit potent glycosidase inhibitory activity. 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). 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. Although, a number of chiron as well as asymmetric approaches are known for the preparation of iminosugars 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. For example, Ciufolini et al. prepared a benzyl ether derivative of 1 from racemic furylglycine and Katsumura and coworkers reported its O-TBDMS derivative from (R)-4-methoxycarbonyloxazolidinone which, in turn, was prepared from glycitol. 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 while; Sato as well as Lin’s group reported chiral pool approach to 1 from o-serine in multistep sequences. In continuation of our interest in the syntheses of compounds analogous to 1 as well as iminosugars from D-glucose using ring closing metathesis as the key step.

Figure 1. Iminosugars from oxazolidinylpiperidine 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.

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 PPh3 in THF/water followed by N-Cbz protection using benzylchloroformate and NaHCO3 furnished 3 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% H2SO4 in methanol afforded diol 5 that on reaction with PPh3, I2, and imidazole in toluene at 70 °C provided bisalkenyl sugar derivative 6 in 80% yield (over two steps). The RCM14 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/H2O, Dowex-H+, 2 N H2SO4, 30% aq HClO4) 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/H2O followed by oxidative cleavage with NaIO4 in acetonitrile/water gave aldehyde X which was found to be relatively unstable, and therefore immediately reacted with NaBH4 in methanol/H2O to afford an inseparable mixture of compounds.16 This mixture was directly reacted with the Grubbs catalyst (first generation) in CH2Cl2 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; [α]D25 +18.2 (c 1.2, CH2Cl2) [lit19 for the antipode [α]D20 −16.7 (c 1.2, CH2Cl2)]. The minor product 8 was characterized by spectral data19 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 deoxyzasugars and anticancer swainsonine is known in the literature1–4 however, exploration of 1 to the synthesis of new iminosugars and their biological evaluation is in progress and will be reported separately.

Acknowledgments

We are grateful to Professor M. S. Wadia for helpful discussions. We thank the Council of Scientific and Industrial Research, New Delhi, for financial support (Project code CSIR01(2343)/09/EMR-II) and Senior Research Fellowship to N.B.K. (CSIR award No. 09/137(0432)/2006-EMR-I).

Supplementary data

Supplementary data (experimental procedures and copies of 1H and 13C 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.

References and notes

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10. For reviews and recent advances on syntheses of iminosugars, see: (a) Davis, B.

8. (a) Inouye, S.; Tsuruoka, T.; Ito, T.; Niida, T.

7. (b) Aoki, T.; Liang, X.; Bols, M.

6. Martin, O. R.

5. 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, H-9c/d).

4.65; (d) Nash, R. J.

3.85; (c) Winchester, B. G.

2.45 (2H, br s, exchangeable with D2O, NH), 5.80 (1H, d, J = 10.2 and 6.1, H-1), 7.20–7.42 (5H, m, ArH); 13C NMR (CDCl3) 26.2 (CH3), 26.3 (CH3), 76.2 (C4), 79.8 (C2), 103.8 (C1), 109.4 (5,6-C6).

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16. (c) Asano, N.


13. Compound 7 was found to be 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.


11. All compounds were characterized by IR, 1H (and 13C) and CHN microanalysis; data for compound (3): white solid; mp = 72–73 °C; [α]D 0.5 (n-hexane/ethyl acetate = 1:2); [α]D +53.8 (c 1.5, CHCl3); IR (neat): 1685 and 3200–3500 cm–1; 1H NMR (CDCl3) 1.30 (6H, s, 2CH3), 1.38 (3H, s, CH3), 1.52 (3H, s, CH3), 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-4a), 4.26 (1H, dd, J = 11.5 and 6.1, H-6b), 4.60 (1H, J = 10.2 and 4, H-2), 5.12 (2H, AB quartet, J = 12.0, OCH2), 5.21 (1H, d, J = 1.9, exchangeable with D2O, NH), 5.80 (1H, d, J = 3.6, H-1), 7.20–7.42 (5H, m, ArH); 13C NMR (CDCl3) 25.3 (CH3), 26.3 (strong, 2CH3), 26.4 (CH3), 35.0 (C3), 65.2 (C6)

67.1 (OCH2), 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).


13. Compound 7 was found to be 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.

12. In this reaction, an inseparable mixture (as evident from 1H NMR) would be due to the formation of compounds Y and Z which can be probably explained as follows (Scheme 3). We believe that NaBH4 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-chz group) initiated by in-situ-generated base NaOme (observed reaction pH = 8) by reaction of NaBH4 and am MeOH. On RCM reaction of this mixture the resulted products were found to be separated by column chromatography. For preparation of NaOme, its basic nature and applications as a base, see: Campana, A. G.; Fuentes, N.; GomezBengoza, E.; Mateo, C.; Ofra, J. E.; Echavarren, A. M.; Cuerva, J. M. I. Org. Chem. 2007, 72, 8127.

X

NaBH4

MeOH/H2O

(pH = 8)

Partial conversion

Inseparable mix

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