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Synthesis of novel 1-*N*-iminosugars from chiral nonracemic bicyclic lactams

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Abstract—This communication reported the synthesis of novel C-6 substituted isofagomine analogues from easily accessible chiral nonracemic bicyclic lactams. These azasugars have potentially very interesting structure and are difficult to obtain by other methods.

Polyhydroxylated piperidines such as 1-deoxynojirimycin and isofagomine are strong inhibitors of glycosidases, presumably by mimicking the transition state of enzymatic glycoside cleavage.[1] These compounds are now finding clinical applications as anti-HIV,[2] anticancer,[3] antidiabetic agents[4] or in the treatment of Gaucher disease.[5] The promising therapeutic potential of iminosugars has led to increased interest and demand. Homologues, *N*-substituted, deoxygenated, and a number of other 1-deoxynojirimycin and isofagomine derivatives have been synthesized during the last few years.[6] Most of the syntheses start from carbohydrates and in general require numerous steps to reach a specific target. The development of efficient and general procedures for their synthesis is still an area of great interest, not only for the synthesis of natural products, but also for that of chemically modified analogues.

Recently, chiral nonracemic bicyclic lactams derived from homochiral β-aminoalcohols have found wide applications in the asymmetrical synthesis of substituted heterocycles.[7] Several iminosugars have been prepared in a rapid and efficient way by employing the appropriate bicyclic lactam template.[8] However, to the best of our knowledge, no isofagomine analogue has ever been prepared from chiral bicyclic lactam.[1,9] Subsequent to our preceding stereocontrolled synthesis of new bicyclic lactams,[10] we envisaged the preparation of 1-*N*-iminosugars **A** (Fig. 1) as stereoisomers or derivatives of isofagomine from chiral bicyclic lactam **1**. As shown in the retrosynthesis (Scheme 1), the target molecule **A** is accessible from the dihydroxylated lactam **B**, which could be obtained from **1**, via unsaturated compound **C**. In this paper, we report the development of this strategy with methyl substituted lactam **1** (R = Me).

We started the synthesis from the bicyclic lactam **1a**, obtained stereoselectively from (*S*)-phenylglycinol **6**,[10c] by introducing an unsaturation using the mild selenoxide *syn*-elimination method (Scheme 2). Treatment of the anion of **1a** with PhSeBr led to a mixture of monoselenide **2** and di-selenide **3**. The ratio **2/3** was dependant

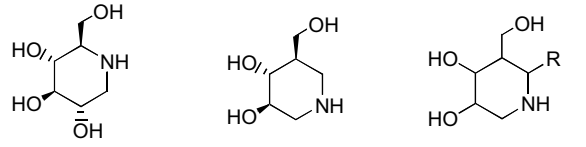

Figure 1. Structure of natural and target iminosugars.

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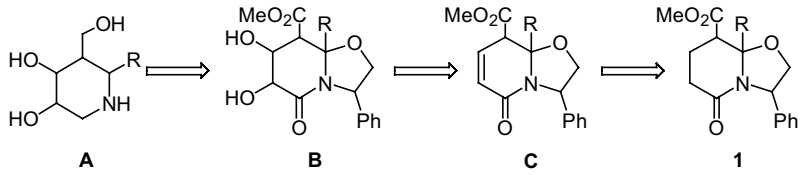
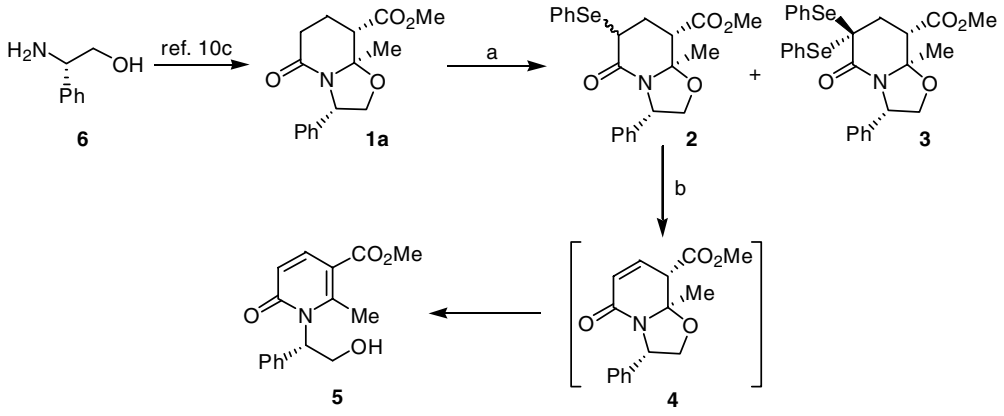


Scheme 1. Retrosynthesis of iminosugars **A**.

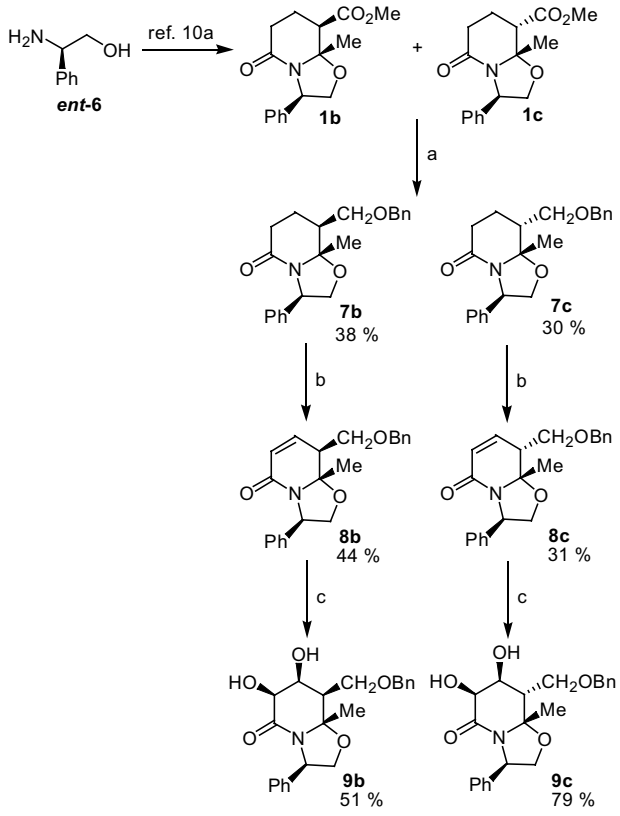


Scheme 2. Reagents and conditions: (a) (i) LiHMDS (1.2 equiv), THF, −78 °C, 1 h; (ii) PhSeBr (1.5 equiv), −78 to −50 °C, 0.5 h; **2**: 40%, **3**: 29%; (b) *m*CPBA (2.3 equiv), THF, −15 °C, 0.5 h or 3 equiv $NaIO_4$, THF, rt, 15 h, 50%.

on the quantity of base and PhSeBr: the best result (**2**/**3** = 40/29) was obtained using 1.2 equiv LiHMDS and 1.5 equiv PhSeBr. Subsequent periodate or *m*CPBA oxidation of **2** followed by benzeneselenenic acid elimination, produced however the pyridone **5**, instead of the desired α,β-unsaturated molecule **4**. The instability of α,β-unsaturated bicyclic lactams with similar structures and their spontaneous transformation into the corresponding pyridone as a minor product has recently been observed.[11]

To avoid this side reaction, we decided to reduce first the ester function, which could be the cause of this elimination reaction. Furthermore, in order to obtain several stereoisomers of 1-*N*-iminosugars **A**, the synthesis was started with **1b**,**c** (stereoisomers of **1a**), which are readily accessible from (*R*)-phenylglycinol *ent*-**6** as a mixture of *cis* and *trans* diastereomers (**1b**/**1c** = 55/45).[10a] Reduction of the ester function with $LiAlH_4$ gave primary alcohols, which were protected as benzyl ethers **7b**,**c**. At this stage, the two diastereomers **7b** and **7c** were easily separated by silica gel chromatography. The required unsaturated lactams **8b** and **8c** were prepared separately by phenylselenenylation followed by oxidative elimination with *m*CPBA (Scheme 3).

Dihydroxylation with OsO_4 cat./$Ba(ClO_3)_2$[12] furnished **9b**[13] and **9c**[13] as single stereoisomers in 51% and 79% yields, respectively. Consequently, the same *exo*-facial diastereoselectivity was obtained with the two diastereoisomers **8b** and **8c**. This stereoselectivity has already been observed in the dihydroxylation of analogous unsaturated lactams.[8a,9g] These results suggest that the

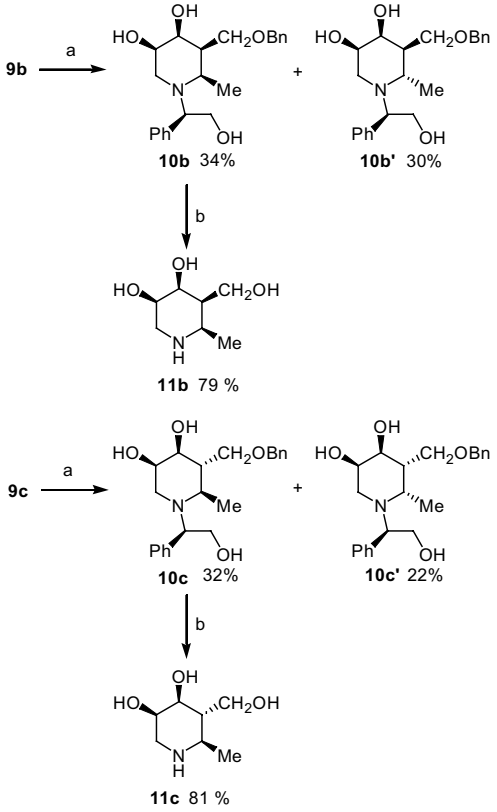


Scheme 3. Reagents and conditions: (a) (i) $LiAlH_4$ (1 equiv), THF, 0 °C to rt, 5 h; (ii) NaH (1.4 equiv), THF, 0 °C, BnBr (1.5 equiv), 24 h; (b) (i) LiHMDS (1.4 equiv), PhSeBr (1.5 equiv), THF, −78 °C; (ii) *m*CPBA (3 equiv), CH_2Cl_2, rt, 1 h 30; (c) OsO_4 (0.28 equiv), $Ba(ClO_3)_2$ (1.5–3 equiv), THF/H_2O (2:1), 4 d.

stereoselectivity is not governed by the stereogenic center bearing the methylenebenzyloxy group but by the more remote phenyl- and methyl-bearing stereocenters (stereocenters which define the *exo* and *endo* faces).

The reduction of lactams **9b** and **9c** with $BH_3{\cdot}Me_2S$ furnished the easily separable piperidines **10b**,**b′** and **10c**,**c′**, but with low diastereoselectivities (de <10% in the two cases as determined by ^1H NMR of the crude mixtures) (Scheme 4). These results contrast with the high facial selectivity (retention of configuration at C-6) generally observed during the reduction of analogous bicyclic lactams.[8a,c,d,10b] The lack of stereoselectivity in the reduction of the hydroxylated bicyclic lactams **9b** and **9c** could be explained by a competitive precomplexation[14] of the borane by one of the two hydroxyl groups. Finally, hydrogenolysis of piperidines **10b** and **10c** with $Pd(OH)_2$ in methanol led to the expected analogues of isofagomine **11b**[13] and **11c**[13] in good yields.

In summary, synthesis of novel 1-*N*-iminosugars has been developed from the easily available bicyclic lactams **1**. These compounds constitute the first examples of analogues of isofagomine substituted on the C-6 position, which are difficult to obtain by other methods so far reported. The methodology reported therein should provide access to other new C-6 substituted 1-*N*-iminosugars as potential glycosidase inhibitors.



Scheme 4. Reagents and conditions: (a) $BH_3{\cdot}DMS$ (6–10 equiv), THF, 0 °C to rt, 1 d; (b) $Pd(OH)_2$ (0.6 equiv), MeOH, rt, 4–6 d.

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13. Selected physical data. Compound **9b**: ^1H NMR ($CDCl_3$, 400 MHz): 1.32 (s, 3H, H-9), 2.21 (ddd, 1H, $J = 1.2$, 4.8, 8.6 Hz, H-8), 2.84 (s, 1H, OH), 3.74 (dd, 1H, $J = 5.1$, 9.1 Hz, H-10), 3.82 (t, 1H, $J = 8.8$ Hz, H-10), 3.93 (dd, 1H, $J = 7.3$, 8.8 Hz, H-2), 4.00 (d, 1H, $J = 3.8$ Hz, H-6), 4.49 (dd, 1H, $J = 1.5$, 3.8 Hz, H-7), 4.55 (t, 1H, $J = 9.1$ Hz, H-2), 5.27 (t, 1H, $J = 8.1$ Hz, H-3), 7.08–7.25 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$): 21.5 (C-9), 46.2 (C-8), 58.4 (C-3), 66.0 (C-7), 66.6 (C-10), 69.8 (C-2), 70.7 (C-6), 73.3 (C-11), 94.6 (C-8a), 125.2, 127.0, 127.6, 128.3, 128.4 (Ph); 137.4, 139.9 (*Cipso*); 170.0 (CO). Compound **9c**: ^1H NMR ($CDCl_3$): 1.52 (s, 3H, H-9), 2.80 (dt, 1H, $J = 4.8$, 8.3 Hz, H-8), 3.25 (s, 1H, OH), 3.51 (dd, 1H, $J = 8.6$, 9.8 Hz, H-10), 3.74 (dd, 1H, $J = 4.6$, 9.8 Hz, H-10), 3.90 (dd, 1H, $J = 7.4$, 8.6 Hz,

H-2), 4.25 (d, 1H, $J = 3.8$ Hz, H-6), 4.40–4.49 (m, 4H, H-2,7,11), 5.19 (t, 1H, $J = 8.1$ Hz, H-3), 7.09–7.29 (m, 10H, Ph); ^{13}C NMR ($CDCl_3$): 27.4 (C-9), 45.5 (C-8), 58.2 (C-3), 67.3 (C-10), 68.7, 68.8 (C-6,7); 69.7 (C-2), 73.5 (C-11), 94.1 (C-8a), 125.2, 127.3, 127.5, 127.8, 128.5, 128.6 (Ph); 137.7, 139.7 (C*ipso*); 169.4 (CO). Compound **11b**: ^{1}H NMR (CD_3OD, 400 MHz): 1.22 (d, 3H, $J = 6.8$ Hz, H-7), 1.67 (m, 1H, H-5), 2.26 (dd, 1H, $J = 3$, 13.1 Hz, H-2), 2.30 (m, 1H, H-6), 3.02 (dd, 1H, $J = 1.8$, 13.1 Hz, H-2), 3.70 (m, 2H, H-3,4), 3.83 (dt, 1H, $J = 1.3$, 12.1 Hz, H-8), 3.90 (dd, 1H, $J = 3.5$, 11.8 Hz, H-8); ^{13}C NMR (CD_3OD): 17.7 (C-7), 44.3 (C-5), 56.5 (C-8), 60.4 (C-2), 62.6 (C-6), 67.4, 70.3 (C-3,4). Compound **11c**: ^{1}H NMR (CD_3OD, 400 MHz): 1.19 (d, 3H, $J = 6.5$ Hz, H-7), 1.45 (tt, 1H, $J = 3$, 10.5 Hz, H-5), 2.65 (m, 1H, H-6), 2.71 (dd, 1H, $J = 1.5$, 14 Hz, H-2), 2.99 (dd, 1H, $J = 2.7$, 13.7 Hz, H-2), 3.65 (dd, 1H, $J = 3.2$, 5.2 Hz, H-8), 3.70 (dd, 1H, $J = 3.7$, 6.5 Hz, H-8), 3.82 (m, 1H, H-3), 3.92 (dd, 1H, $J = 2.7$, 11.2 Hz, H-4); ^{13}C NMR (CD_3OD): 20.1 (C-7), 49.8 (C-5), 51.4 (C-2), 53.3 (C-6), 60.8 (C-8), 70.0, 71.8 (C-3,4).

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