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A complete asymmetric synthesis of polyhydroxypiperidines

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Abstract—A new general methodology for the asymmetric synthesis of polyhydroxypiperidines is described. The readily available achiral olefin **4** was transformed to 5-des(hydroxymethyl)-1-deoxynojirimycin (**1**) and its mannose analog **10** via regioselective aminohydroxylation (AA), ring-closing metathesis (RCM), and diastereoselective dihydroxylation reactions. Thus, the developed methodology made it possible to install all stereocenters in **1** and **10** in a highly stereocontrolled fashion.

In recent years polyhydroxypiperidines such as 5-des(hydroxymethyl)-1-deoxynojirimycin (**1**), **2**, and isofagomine (**3**) have drawn much attention among (bio)chemists (Fig. 1).[1] Such intense interest stems from the fact that these compounds are potent inhibitors of glycosidases that have been suggested to be implicated in various diseases including diabetes,[2] cancer,[3] and viral infection,[4] and further drugs for treating these diseases can be developed based on polyhydroxypiperidine structures.

Among polyhydroxypiperidines, of particular interest are 5-des(hydroxymethyl)-1-deoxynojirimycin (**1**) and its stereoisomers. Because they are potent glycosidase inhibitors, and moreover, have been used as convenient intermediates for the asymmetric synthesis of **2**, **3**, and their stereoisomers.[5] Since the first synthesis by Ganem, a number of methodologies have been developed for the asymmetric synthesis of **1** and its stereoisomers.[5,6] However, all reported methodologies required chiral starting materials and/or lengthy synthetic routes. Herein we wish to report a complete asymmetric synthesis of **1** and the mannose analog **10** starting from the readily available achiral olefin **4**.

The developed strategy utilizes the regioselective aminohydroxylation (AA) reaction[7] of olefins, which installs the vicinal aminoalcohol functionality in the targets. In addition, the ring-closing metathesis[8] and diastereoselective dihydroxylation reactions[9] will be used to introduce the required six-membered ring and vicinal diol functionality respectively (Fig. 2)

As shown in Scheme 1, the achiral olefin **4** was a starting point of our synthesis. The olefin **4** was designed as a substrate for the regioselective aminohydroxylation reaction from the consideration that aryl-aryl stacking interaction between the *p*-methoxyphenyl group of **4** and the AA catalyst could increase enantioselectivity of the AA reaction,[10] and the AA reaction of terminal olefins has been observed to occur in such a way that a nitrogen atom predominantly adds to the terminal carbon of the olefins.[11] Thus, the osmium

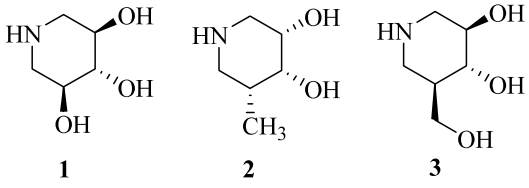

Figure 1.

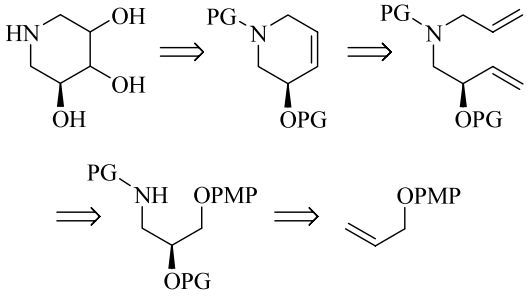

Figure 2. Retrosynthetic analysis.

Keywords: polyhydroxypiperidine; regioselective aminohydroxylation; ring-closing metathesis.

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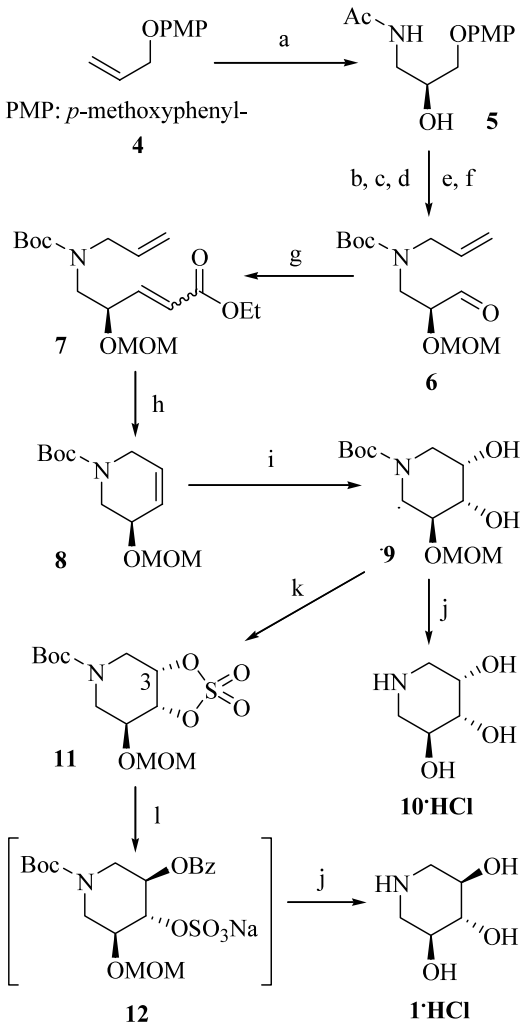

Scheme 1. *Reagents and conditions*: (a) $(DHQD)_2PHAL$ (6 mol%), potassium osmate (5 mol%), LiOH, AcNHBr, *tert*-BuOH–H_2O 1:1, 4°C, 63%; (b) MOMBr, DIPEA, CH_2Cl_2, 86%; (c) $(Boc)_2O$, THF, reflux then LiOH, 85%; (d) allyl bromide, KH, THF, 97%; (e) CAN, MeCN–H_2O 4:1, 0°C, 73%; (f) oxalyl chloride, DMSO, CH_2Cl_2, −50°C, then TEA, 73%; (g) triethyl phosphonoacetate, LiBr, DBU, THF, 88%; (h) second generation Grubbs' catalyst, CH_2Cl_2, 89%; (i) OsO_4, NMO, MeCN–H_2O 1:1, 98%; (j) 6N HCl, 80°C, 94%; (k) $SOCl_2$, Et_3N then $NaIO_4$, $RuCl_3$, MeCN–CH_2Cl_2–H_2O 1:1:1, 88%; (l) NaOBz, DMF, 105°C then (j), 90%.

catalyzed AA reaction of **4** gave the aminoalcohol **5** in 9:1 regioselectivity as determined by the ^1H NMR spectrum of the crude products. Analytically pure **5** was obtained by a single recrystallization of the column purified mixture of two regioisomers from ethyl acetate. After a MOM protection reaction, the *N*-acetyl group of **5** was converted to the Boc group,[12] because the *N*-acetyl group not only complicated the NMR spectrum of the subsequent reaction products due to the amide resonance, but also caused a poor reaction yield in the dihydroxylation reaction of *N*-acetylated **8**.[13] Then, a reaction sequence of *N*-allylation, deprotection of the PMP group by cerric ammonium nitrate (CAN),[14] and Swern oxidation[15] of the resulting alcohol transformed **5** to **6**. Initial terminal olefination reactions of the aldehyde **6** with methyltriphenylphosphonium bromide under the various reaction conditions suffered from a poor reaction yield, and thus the modified Horner–Wadsworth–Emmons olefination[16] was used to produce the RCM precursor **7** in 89% yield. The RCM reaction of the diene **7** required using the second generation Grubbs' catalyst.[17] Several attempts using the Grubbs' catalyst proved unsuccessful generating a complex reaction mixture and/or an unidentifiable product. Dihydroxylation of the cyclic olefin **8** under the Upjohn conditions cleanly proceeded to furnish **9** in a highly diastereoselective manner (exclusive *anti*-addition), which upon acidic hydrolysis turned into the mannose analog **10·HCl**.[18]

5-Des(hydroxymethyl)-1-deoxynojirimycin (**1**) was synthesized by applying cyclic sulfate chemistry[19] to the diol **9**. Thus, treatment of **9** with thionyl chloride followed by oxidation of the resulting cyclic sulfite using $RuCl_3$ and $NaIO_4$ secured the cyclic sulfate **11**. Ring opening reaction of **11** by sodium benzoate and a final acidic hydrolysis were performed in one pot without the isolation of the intermediate **12** to generate 5-des(hydroxymethyl)-1-deoxynojirimycin (**1**) as a HCl salt.[18] Ring opening reaction of the cyclic sulfate took place predominantly (in 9:1 ratio) at C-3, since both *trans*-diaxial ring opening rule[20] and steric congestion at C-4 favored ring opening at C-3.

In summary, 5-des(hydroxymethyl)-1-deoxynojirimycin (**1**) and the mannose analog **10** were synthesized as HCl salts from the common olefin **4** via regioselective aminohydroxylation, ring-closing metathesis, and dihydroxylation reactions in a highly stereoselective manner. Extension of this methodology to the asymmetric synthesis of the remaining other isomers as well as isofagomine and its stereoisomers is currently under investigation. Furthermore, the developed strategy should provide a general solution for the asymmetric synthesis of these classes of iminosugars.

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18. The NMR data of **1·HCl** and **10·HCl** are consistent with those in the literature (Ref. 6a). For **10·HCl**, ^{1}H NMR (500 MHz, D_2O) δ 4.25 (m, 1H), 4.11 (ddd, 1H, $J=8.1$, 7.8, and 4.0 Hz), 3.79 (dd, 1H, $J=7.8$ and 2.8 Hz), 3.43 (dd, 1H, $J=12.8$ and 4.0 Hz), 3.31 (dd, 1H, $J=13.0$ and 6.0 Hz), 3.23 (dd, 1H, $J=13.3$ and 2.8 Hz), 2.98 (dd, 1H, $J=12.7$ and 8.2 Hz). For **1·HCl**, ^{1}H NMR (500 MHz, D_2O) δ 3.82 (m, 2H, H-3 and H-5), 3.54 (t, 1H, $J=8.5$ Hz, H-4), 3.49 (dd, 2H, $J=13.0$ and 4.0 Hz, H-2_{eq} and H-6_{eq}), 2.97 (dd, 2H, $J=13.0$ and 10.0 Hz, H-2_{ax} and H-6_{ax}).
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