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A general methodology for the asymmetric synthesis of 1-deoxyiminosugars

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Abstract—A general methodology for the stereoselective synthesis of 1-deoxymannojirimycin and its three other stereoisomers is described. The achiral olefin **6** was converted through the common olefin intermediate **12** to the target compounds in a highly stereocontrolled manner. The *regioselective* asymmetric aminohydroxylation (AA) and diastereoselective dihydroxylation reactions were used for the introduction of all four stereocenters in the targets, and the ring-closing metathesis (RCM) reaction was utilized for the construction of the required six-membered ring.

Glycosidases catalyze cleavage/formation of the glycosidic bonds in carbohydrates and related molecules.[1] 1-Deoxyiminosugars such as **1**, **2**, **3**, **4**, and **5** are potent glycosidase inhibitors (Fig. 1).[2] When protonated, they mimic charge and shape of the cationic intermediates generated in the glycosidase catalyzed reactions.

Glycosidases are implicated in various diseases such as diabetes,[3] metastatic cancer,[4] malaria,[5] and viral infection,[6] making glycosidases good targets for drug development. *N*-Butyl-1-deoxynojirimycin, for example, is an inhibitor of glucosidase **I**[7] and ceramide glucosyltransferase[8] and currently in clinical trials as a potential therapy for Gaucher disease. As such, much effort has been put forth in developing methodologies for the asymmetric synthesis of 1-deoxyiminosugars. However, most syntheses reported so far relied on chiral pools such as carbohydrates and amino acid derivatives, and/or required chiral auxiliaries for the asymmetric induction.[2,9] Truly asymmetric methodologies, which are amenable to stereochemical manipulation and derivatization, have been scarcely reported.[10]

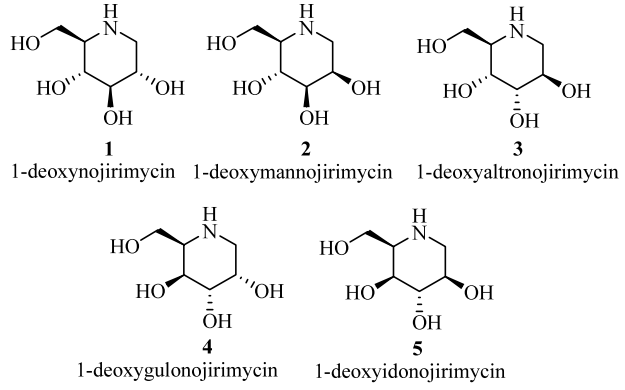

Figure 1.

We recently developed a substrate-based methodology that allowed the regioselective control of the Sharpless asymmetric aminohydroxylation (AA) reaction of olefins.[11] In this approach, steric, electronic, and aryl–aryl stacking interactions between olefins and the AA catalyst were utilized to control regioselectivity. We have been interested in applying this methodology to the asymmetric synthesis of biologically important compounds.[12] As depicted in Scheme 1, it is envisioned that 1-deoxyimino-sugars can be prepared from the achiral olefin **V** in a highly stereoselective fashion. The regioselective asymmetric aminohydroxylation[11,13] (**V** to **IV**) and diastereoselective dihydroxylation[14] (**II** to **I**) reactions will respectively install the vicinal aminoalcohol and diol functionalities in the targets, and the ring-closing metathesis[15] (**III** to **II**) will furnish the required six-membered ring. Herein, we report a successful implementation of this strategy to the asymmetric synthesis of 1-deoxymannojirimycin (**2**) and its three other stereoisomers **3**, **4**, and **5**.

As shown in Scheme 2, our synthesis started with the olefin **6**, which was readily prepared from ethyl 4-bro-

Keywords: 1-deoxyiminosugar; regioselective aminohydroxylation; ring-closing metathesis.

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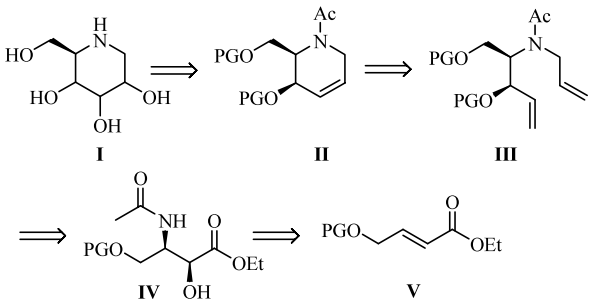
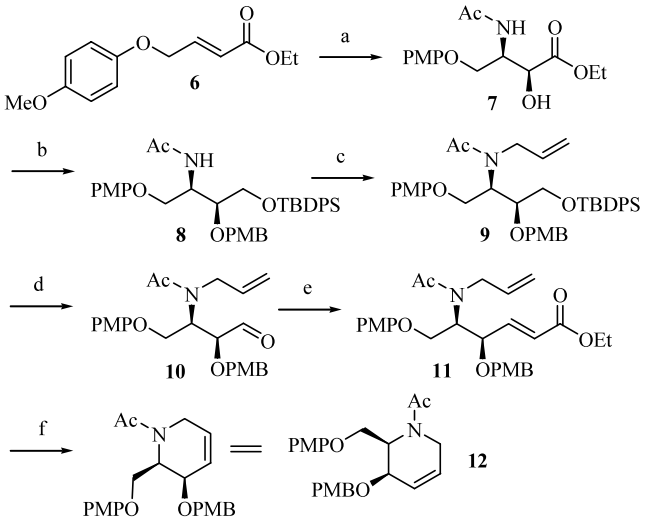


Scheme 1.

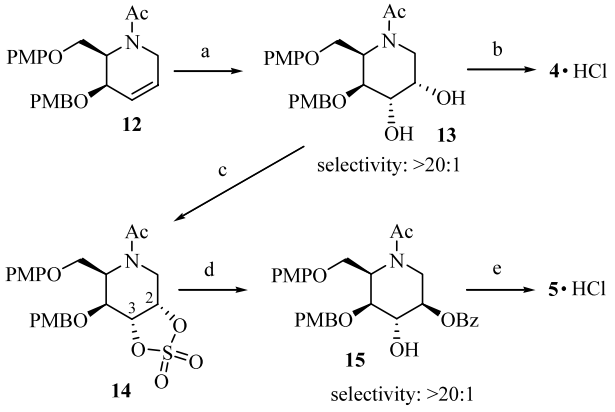


Scheme 2. *Reagents and conditions*: (a) $K_2OsO_4{\cdot}2H_2O$ (5 mol%), $(DHQD)_2PHAL$ (6 mol%), LiOH, *N*-bromoacetamide, *t*-BuOH–H_2O 3:2, 4°C, 8 h, 70%; (b) (i) NaH, PMBCl, DMF, 0°C, 8 h, 80%, (ii) $LiBH_4$, ether, 15 min, quantitative, (iii) TBDPSCl, TEA, DMAP, CH_2Cl_2, 25°C, 4 h, quantitative; (c) KH, 18-crown-6-ether, allyl bromide, THF, 25°C, 5 h, 95%; (d) (i) TBAF, THF, 25°C, 1 h, quantitative, (ii) periodinane, CH_2Cl_2, 25°C, 1 h, 90%; (e) triethyl phosphonoacetate, LiBr, DBU, THF, 25°C, 2 h, 94%; (f) Grubbs' catalyst (10 mol%), toluene, 90°C, 2 h, 80%.

mocrotonate and *p*-methoxyphenol. The olefin **6** was designed in such a way that electronic and aryl–aryl stacking interactions between **6** and the AA catalyst could reinforce each other to increase regioselectivity in the AA reaction of **6**.[16] Thus, the osmium catalyzed regioselective AA reaction of **6** afforded the aminoalcohol **7** in an excellent regioselectivity (>20:1),[17] and a single recrystallization of the column purified product from ethyl acetate–hexane gave analytically pure **7** in 70% yield and >99% ee. A reaction sequence of protection of the hydroxyl group with *p*-methoxybenzyl chloride,[18] reduction of the resulting ester with $LiBH_4$ in the ether solution containing a trace amount of methanol,[19] and TBDPS protection[20] of the alcohol furnished **8**.

Allylation of **8** with allyl bromide and KH in THF proceeded to give **9** in a good yield only when a catalytic amount of crown ether was present in the reaction mixture.[21] In all initial attempts using NaH, KH, and potassium *t*-butoxide as a base, the starting material **8** was recovered unchanged. Deprotection of the TBDPS group by tetrabutyl ammonium fluoride (TBAF) and the subsequent oxidation of the alcohol under the Des–Martin conditions[22] yielded the aldehyde **10**. Terminal olefination reaction of **10** with the Wittig reagent[23] suffered from a poor reaction yield (~30%), and thus the modified Horner–Wadsworth–Emmones olefination[24] was attempted. Olefination of the aldehyde **10** with triethyl phosphonoacetate and DBU in the presence of lithium bromide produced the α,β-unsaturated ester **11** in 94% yield. The RCM reaction of **11** using the Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidineruthenium(IV)dichloride] required elevated temperature (90°C) to generate the key olefin intermediate **12** in 80% yield.

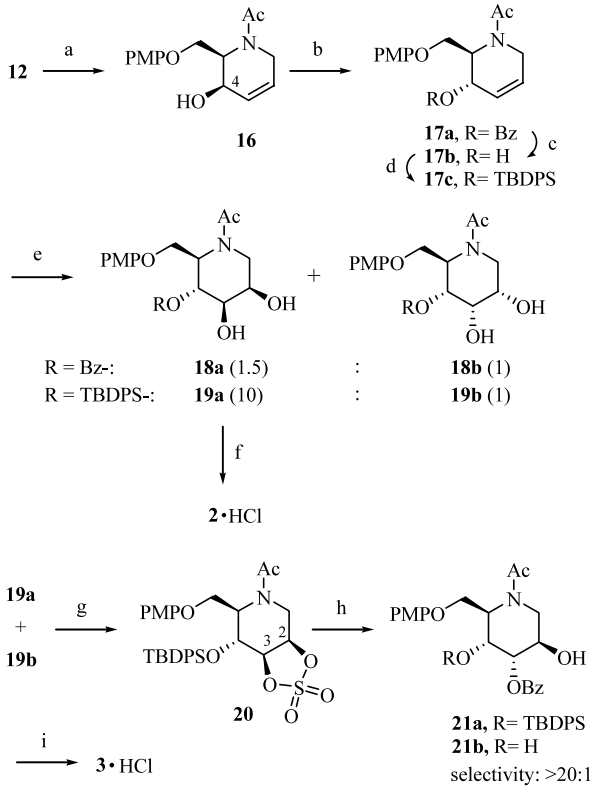
Scheme 3 shows how the key olefin intermediate **12** was utilized to generate 1-deoxygulonojirimycin (**4**) and 1-deoxyidonojirimycin (**5**). Dihydroxylation reaction of **12** by OsO_4 gave **13** as a sole diol product, since steric congestion at the top face of **12** preferred approach of OsO_4 from the bottom face of the molecule. The diol **13** was isolated as an acetonide from the reaction mixture,[25] which upon two successive deprotection reactions by cerric ammonium nitrate (CAN)[26] and then 6N HCl converted to the HCl salt of 1-deoxygulonojirimycin (**4**).[27] Contrary to the literature,[28] the *p*-methoxybenzyl group remained intact under the CAN deprotection conditions. *trans*-Diol stereochemistry at C2 and C3 for 1-deoxyidonojirimycin (**5**) was introduced by applying cyclic sulfate chemistry[29] to the *cis*-diol **13**. Thus, treatment of **13** with thionyl chloride followed by oxidation of the resulting cyclic sulfite using $RuCl_3$ and $NaIO_4$ produced the cyclic sulfate **14**. Ring opening reaction of the cyclic sulfate **14** by sodium benzoate took place almost exclusively at C2,



Scheme 3. *Reagents and conditions*: (a) OsO_4, NMO, *t*-BuOH–H_2O 1:1, 12 h, 96%; (b) (i) DMP, PPTS, CH_2Cl_2, 25°C, 12 h, 94%, (ii) CAN, MeCN–H_2O 4:1, 0°C, 10 min, 92%, (iii) 6N HCl, 120°C, 12 h, 98%; (c) (i) $SOCl_2$, TEA, CH_2Cl_2, −15°C, 30 min, (ii) $RuCl_3$, $NaIO_4$, MeCN–CH_2Cl_2–H_2O 1:1:1, 25°C, 1 h, 85% for two steps; (d) (i) NaOBz, DMF, 105°C, 3 h, (ii) 20% aq. H_2SO_4–CH_2Cl_2 1:1, 25°C, 12 h, 85% for two steps; (e) b-(ii) and then b-(iii), 90% for two steps.

since both *trans*-diaxial ring opening rule[30] and steric congestion at C3 favored ring opening at that carbon. Deprotection of *p*-methoxyphenyl group of the alcohol **15** by CAN and a final exhaustive acidic hydrolysis gave 1-deoxyidonojirimycin (**5**) as HCl salt.[27]

The olefin **12** was also used as an intermediate for the synthesis of 1-deoxymannojirimycin (**2**) and 1-deoxyaltronojirimycin (**3**) (Scheme 4). *p*-Methoxybenzyl group of **12** was deprotected by 5% trifluoroacetic acid/CH_2Cl_2.[31] Configuration at C4 of the alcohol **16** was inverted by Mitsunobu reaction.[32] Dihydroxylation of the resulting benzoate ester **17a** under the Sharpless–Upjohn conditions[14d,e] generated an inseparable mixture of the diols **18a** and **18b** in 3:2 ratio as determined by ^1H NMR of the reaction mixture. It was reasoned that a low selectivity in the above dihyroxylation reaction might be attributed to the fact that the *p*-methoxyphenyl and benzoate groups in **17a** were similar in size and thus both faces of the molecule were almost equally hindered. Hoping that increasing steric unbalance might improve selectivity in the dihydroxylation reaction, the benzoyl group of **17a** was converted to the much bigger TBDPS group. Gratifyingly, dihydroxylation reaction of **17c** produced two inseparable diastereomers **19a** and **19b** in a good selectivity (10:1). After acetylation reaction, **19a** and **19b** were separated as the corresponding triacetates by column chromatography. Deprotection of the PMP group by CAN and acidic deprotection of the acetyl and TBDPS groups transformed the triacetate of **19a** to 1-deoxymannojirimycin (**2**).[27] In order to synthesize 1-deoxyaltronojirimycin (**3**), the mixture of the diols **19a** and **19b** was converted to the corresponding cyclic sulfates, which were separated by column chromatography. The major cyclic sulfate **20** was subjected to ring opening reaction by sodium benzoate in DMF to generate **21a** as well as **21b** that formed from the partial deprotection of the TBDPS group under the reaction conditions. Deprotection of the *p*-methoxyphenyl group of **21a** and **21b** by CAN followed by acid hydrolysis finished the asymmetric synthesis of 1-deoxyaltronojirimycin (**3**).[27]



Scheme 4. *Reagents and conditions*: (a) 5% TFA in CH_2Cl_2, 25°C, 30 min, 85%; (b) DIPAD, Ph_3P, benzoic acid, THF, 0°C, 2 h, 80%; (c) K_2CO_3, MeOH, 25°C, 5 h, quantitative; (d) TBDPSCl, imidazole, TEA, DMF, 60°C, 12 h, 93%; (e) $K_2OsO_4{\cdot}2H_2O$ or OsO_4, NMO, *t*-BuOH–H_2O 1:1, 16 h, 94%; (f) (i) Ac_2O, DMAP, TEA, CH_2Cl_2, 25°C, 80%, (ii) CAN, MeCN–H_2O 4:1, 0°C, 10 min, (iii) 6N HCl, 120°C, 12 h, 92% for two steps; (g) $SOCl_2$, TEA, CH_2Cl_2, −15°C, 30 min, then $RuCl_3$, $NaIO_4$, MeCN–CH_2Cl_2–H_2O 1:1:1, 25°C, 1 h, 66%; (h) BzONa, DMF, 105°C, 5 h, then 20% aq. H_2SO_4–CH_2Cl_2 1:1, 12 h, 25°C, 80%; (i) (i) CAN, MeCN–H_2O 4:1, 0°C, 10 min, 90%, (ii) 6N HCl, 120°C, 12 h, 98%.

In summary 1-deoxymannojirimycin and its three other stereoisomers were synthesized from the readily available olefin **6** via the regioselective AA, ring closing metathesis, and diastereoselective dihydroxylation reactions in a highly stereoselective manner. The methodology developed (vide supra) is extremely divergent and flexible to stereochemical manipulation and synthetic modification. Extension of this methodology to the asymmetric synthesis of the remaining other stereoisomers and related azasugars is currently under investigation.

Acknowledgements

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27. Spectroscopic data of **4**·HCl: $[\alpha]_{589}=+2.6$ (*c* 1.6, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 4.27 (ddd, 1H, $J=5.0$, 3.0, and 11.5 Hz, *H*-2), 4.14 (dd, 1H, $J=1.5$ and 4.0 Hz, *H*-4), 4.07 (t, 1H, $J=3.5$ and 4.0 Hz, *H*-3), 3.92 (dd, 1H, $J=5.0$ and 12.5 Hz, *H*-6), 3.83 (dd, 1H, $J=9.0$ and 12.5 Hz, *H*-6′), 3.57–3.55 (m, 1H, *H*-5), 3.33 (dd, 1H, $J=5.0$ and 12.0 Hz, *H*-1), 3.15 (t, 1H, $J=11.5$ and 12.5 Hz, *H*-1′); ^{13}C NMR (75 MHz, D_2O): δ 68.69, 67.38, 62.81, 59.01, 55.65, 42.64.
5·HCl: $[\alpha]_{589}=+3.5$ (*c* 1.7, MeOH:H_2O 1:2); ^{1}H NMR (500 MHz, D_2O): δ 4.14–4.12 (m, 1H, *H*-2), 4.10–4.07 (m, 2H, *H*-3, *H*-4), 4.01–3.92 (m, 2H, *H*-6 and *H*-6′), 3.69–3.66 (m, 1H, *H*-5), 3.51 (dd, 1H, $J=3.0$ and 13.75 Hz, *H*-1), 3.43 (dd, 1H, $J=3.5$ and 13.5 Hz, *H*-1′); ^{13}C NMR (75 MHz, $CDCl_3$): δ 67.81, 67.62, 66.59, 58.99, 56.80, 45.47.
2·HCl: $[\alpha]_{589}=-9.9$ (*c* 1.5, MeOH), ^{1}H NMR (500 MHz, D_2O): δ 4.30–4.29 (m, 1H, *H*-2), 4.04 (dd, 1H, $J=3.0$ and 12.5 Hz, *H*-6), 3.93–3.87 (m, 2H, *H*-6′ and *H*-4), 3.75 (dd, 1H, $J=3.5$ and 9.5 Hz, *H*-3), 3.47 (dd, 1H, $J=2.5$ and 13.7 Hz, *H*-1), 3.30 (dd, 1H, $J=1.0$ and 13.5 Hz),

3.24–3.13 (m, 1H, *H*-5); ^{13}C NMR (75 MHz, D_2O): δ 72.24, 65.73, 65.57, 60.18, 57.95, 47.40.
3·HCl: $[\alpha]_{589}=+33.2$ (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, D_2O): δ 4.20 (m, 1H, *H*-2), 4.08 (dd, 1H, $J=3.0$ and 15.7 Hz, *H*-3), 4.07 (br s, 1H, *H*-4), 4.02 (dd, 1H, $J=3.5$ and 12.8 Hz, *H*-6), 3.88 (dd, 1H, $J=6.5$ and 12.8 Hz, *H*-6′), 3.45–3.39 (m, 2H, *H*-5 and *H*-1), 3.273 (dd, 1H, $J=3.0$ and 17.2 Hz, *H*-1′); ^{13}C NMR (75 MHz, D_2O): δ 68.26, 66.00, 63.40, 57.96, 55.67, 43.71.

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