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Concise and Highly Stereocontrolled Synthesis of 1-Deoxygalactonojirimycin and Its Congeners Using Dioxanylpiperidene, a Promising Chiral Building Block

Hiroki Takahata,*,† Yasunori Banba,‡ Hidekazu Ouchi,† and Hideo Nemoto‡

Faculty of Pharmaceutical Sciences, Tohoku Pharmaceutical University, Sendai 981-8558, Japan, and Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Toyama 930-0194, Japan

takahata@tohoku-pharm.ac.jp

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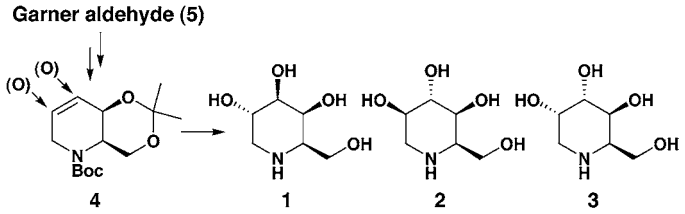
ABSTRACT



A concise and stereoselective synthesis of the chiral building block, dioxanylpiperidene 4 as a precursor for deoxyazasugars, starting from the Garner aldehyde 5 using catalytic ring-closing metathesis (RCM) for the construction of the piperidine ring is described. The asymmetric synthesis of 1-deoxygalactonojirimycin and its congeners 1–3 was carried out via the use of 4 in a highly stereocontrolled mode.

Interest continues to mount in new applications of natural and synthetic glycosidase inhibitors in basic research and medicine.[1] Polyhydroxylated piperidines and their synthetic analogues have attracted a great deal of attention in recent years due to their ability to mimic sugars and competitively and selectively inhibit glycosidases and glycotransferases[2] of carbohydrate processing enzymes. Inhibition of digestive glycosidases by inhibitors leads to the regulation of carbohydrate absorption from the wall of the small intestine, and hence such inhibitors can be used for the treatment of type II diabetes. In addition, since inhibition of glycoprotein processing glycosidases can alter cell−cell or cell−virus recognition processes, such inhibitors are applicable for cancer cell invasion and migration and viral infection.[3] Included among the polyhydroxylated piperidines of recent interest are 1-deoxygalactonojirimycin (**1**) and its derivatives. These compounds are strong inhibitors of α-galactosidase A and are currently in preclinical trials as a potential therapy for Farby's disease, a severe lysosomal storage disorder.[4] Because of the therapeutic importance of these compounds many synthetic efforts have been directed toward their preparation.[5] However, most of the reported methodologies are lengthy and/or lead to low selectivity. In a project devoted to the asymmetric synthesis of glycosidase inhibitors,[6] our

† Tohoku Pharmaceutical University.
‡ Toyama Medical & Pharmaceutical University.

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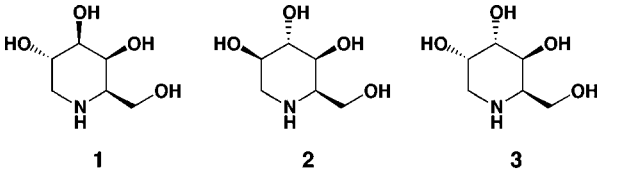
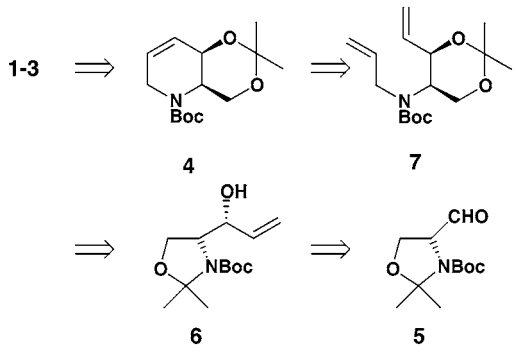


Figure 1. Structure of 1-deoxygalactonojirimycin (**1**) and its congeners (**2** and **3**).

goal involved the preparation of a new common chiral building block, dioxanylpiperidene **4**, which represents an ideal precursor for the synthesis of 1-deoxygalactonojirimycin (**1**) and its congeners (Figure 1). Herein we describe a straightforward and stereoselective synthesis of 1-deoxygalactonojirimycin and its congeners **1**−**3** via **4** starting from the Garner aldehyde **5**[7] using catalytic ring-closing metathesis (RCM) for the construction of the piperidine ring.[8]

Our retrosynthetic analysis of 1-deoxyazasugars **1**−**3** is outlined in Scheme 1. The common intermediate **4** can be

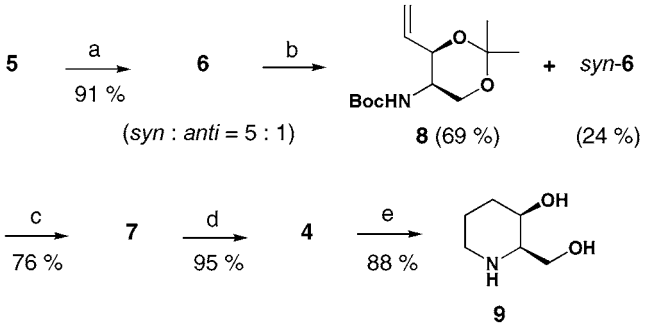
Scheme 1



prepared by the RCM of diolefin **7**, produced by the stereoselective coupling of **5** with vinyl metals.

The D-serine-derived Garner aldehyde **5** provided an attractive starting point for the synthesis because it reacts with organometallic reagents with a high degree of diastereoselectivity and little racemization.[9] The diastereoselective addition of vinyl metals to **5** may furnish the *syn* vinyl alcohol, depending on the reaction conditions.[10] The reagent formed from in situ prepared vinyllithium and anhydrous zinc dibromide in diethyl ether was found to provide the *syn* alcohol as a solid with a 5:1 diastereoselectivity (*syn*:*anti*) in 91% yield.[11] The diastereoselectivity can be rationalized by considering the preferred transition state in each reaction. The vinyl zinc bromide complex coordinated with the carbamate carbonyl in the transition state is delivered to the *re* face of the aldehyde carbonyl to afford the vinyl alcohol *syn*-**6**. The chromatographic separation of a diastereomeric mixture of alcohols **6** was incomplete. However, the 67% de of the *syn*-preferred **6** was improved to 92% de (72%) by one recrystallization. When the recrystallized **6** was treated with HCl gas in chloroform, it was converted to the 1,3-acetonide **8** (69%) together with the recovery of *syn*-**6** (24%) (Scheme 2).

Scheme 2 [a]



[a] Reagents and conditions: (a) vinyl zinc bromide, ether, −78 °C to rt; (b) (i) recrystallization from *n*-hexanes−ethyl acetate (5:1), (ii) HCl gas, $CHCl_3$, rt; (c) allyl iodide, NaH, THF, 0 °C; (d) Grubbs' catalyst, CH_2Cl_2, rt; (e) (i) H_2, cat. 10% Pd−C, MeOH, rt, (ii) 5 N HCl, MeOH, 60 °C; (iii) 30% NaOH, 0 °C.

N-Allylation of **8** with allyl iodide using NaH as a base gave the diolefin product **7** in 76%. Finally, **7** was subjected to RCM in the presence of Grubbs' catalyst, (benzylidine)-bis(tricyclohexylphosphine)ruthenium(IV) dichloride, in dichloromethane to provide the desired piperidene **4** in excellent yield. In addition, the stereochemistry of **4** was unambiguously confirmed by its transformation to the known *cis*-3-hydroxy-2-hydroxymethyl piperidine **9**[5p] (Scheme 2).

(5) 1-Deoxygalactonojirimycin: (a) Liguchi, T.; Tajiri, K.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 5819−5833. (b) Mehta, G.; Mohal, N. *Tetrahedron Lett*. **2000**, *41*, 5741−5745. (c) Asano, K.; Hakogi, T.; Iwama, S.; Katsumura, S. *Chem. Commun*. **1999**, 41−42. (d) Johnson, C. R.; Golebiowsky, A.; Sundram, H.; Miller, M. W.; Dwaihy, R. L. *Tetraherdon Lett*. **1995**, *36*, 653−654. (e) Uriel, C.; Santoyo-Gonzalez, F. *Synlett* **1999**, 593−595. (f) Ruiz, M.; Ruanova, T. M.; Ojea, V.; Quintela, J. M. *Tetrahedron Lett*. **1999**, *40*, 2021−2024. (g) Shilvock, J. P.; Fleet, G. W. J. *Synlett* **1998**, 554−556. (h) Chida, N.; Tanikawa, T.; Tobe, T.; Ogawa, S. *J. Chem. Soc., Chem. Commun*. **1994**, 1247−1248. (i) Aoyagi, S.; Fujimaki, S.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1991**, *56*, 815−819. (j) Kajimoto, T.; Chen, L.; Liu, K. K. C.; Wong, C. H. *J. Am. Chem. Soc*. **1991**, *113*, 6678−6680. (k) Bernotas, R. C.; Pezzone, M. A.; Ganem, B. *Carbohydr. Res*. **1987**, *167*, 305−311. 1-Deoxyidonojirimycin: (l) Singh, O. V.; Han, H. *Tetrahedron Lett.* **2003**, *44*, 2387−2391. (m) Schaller, C.; Vogel, P.; Jager, V. *Carbohydr. Res*. **1998**, *314*, 25−35. (n) Fowler, P. A.; Haines, A. H.; Taylor, R. J. K.; Chrystal, E. J. T.; Gravestock, M. B. *Carbohydr. Res*. **1993**, *246* 377−381. (o) Liu, K. K. C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C. H. *J. Org. Chem*. **1991**, *56*, 6280−6289. 1-Deoxygulonojirimycin: ref 5l. (p) Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2001**, *3*, 401−404. (q) Ruiz, M.; Ojea, V.; Ruanova, T. M.; Quintela, J. M. *Tetrahedron: Asymmetry* **2002**, *13*, 795−799. (r) Liao, L.-X.; Wang, Z.-M.; Zhang, H.-X.; Zhou, W.-S. *Tetrahedron: Asymmetry* **1999**, *10*, 3649−3657.

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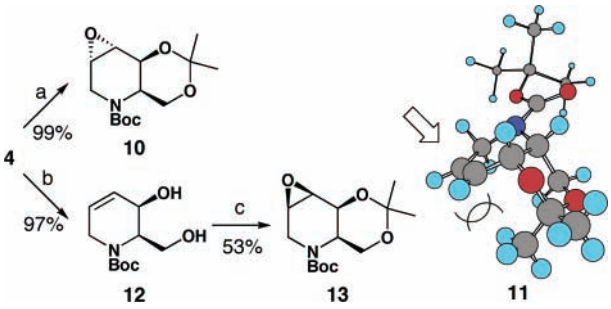
(11) On the other hand, the use of HMPA as an additive in place of $ZnBr_2$ showed an *anti*-diastereoselectivity (68% de) in 91% yield.

With the promising educt **4** in hand, our interest was directed to the stereoselective synthesis of compounds **1**−**3**. We first introduced an epoxy functionality into the double bond to obtain both **1** and **2** containing a *trans* diol in the 3 and 4 positions. The dioxirane, generated in situ from Oxone with 1,1,1-trifluoroacetone, was reacted with **4** to give the *anti* epoxide **10** as a single diastereomer in 99% yield. The Chem 3D MOPAC calculation[12] indicated that the most stable conformer of **4** was **11** (Scheme 3). This indicates

Scheme 3 [a]



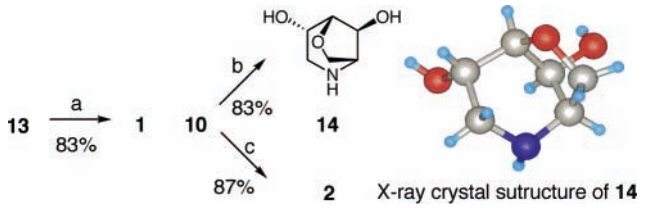
[a] Reagents and conditions: (a) Oxone, CF_3COCH_3, $NaHCO_3$, aqueous Na_2·EDTA, CH_3CN, 0 °C; (b) *p*-TsOH·H_2O, MeOH, rt; (c) (i) *m*-CPBA, NaH_2PO_4, CH_2Cl_2, 0 °C to room temperature, (ii) 2,2-dimethoxypropane, cat. PPTS, acetone, rt.

that the epoxidation occurred exclusively from the less hindered convex face, because the concave face is shielded by a methyl substituent. On the other hand, the *syn* epoxide was obtained by the hydroxy-directed epoxidation of the diol **12**, prepared by hydrolysis of the acetonide of **4** with *p*-TsOH in methanol. The epoxidation of the diol with *m*-CPBA followed by acetonization afforded the *syn* epoxide **13** in 53% overall yield (Scheme 3).

Acid hydrolysis of the epoxy ring of the *syn* epoxide **13** was accomplished by using a mixture of H_2SO_4/1.4-dioxane/H_2O in a ratio of 0.2/3/2, and further treatment with an ion-exchange resin (DOWEX 1x2, OH^- form) gave only **1**[13] in 83% yield.[14] Surprisingly, a similar treatment of *anti* epoxide **10** provided the abnormal bicyclic product **14** in 83% yield. The structure of **14** was confirmed by X-ray crystallographic analysis (Scheme 4). Presumably, the hydroxymethyl group generated by acid hydrolysis of the acetonide would intramolecularly attack the epoxide ring to form a bicyclo-[3.2.1]ring. Fortunately, basic cleavage of the epoxide with a mixture of KOH/1,4-dioxane/H_2O followed by a sequence of deprotection and desalting gave 1-deoxyidonojirimycin (**2**)[13] exclusively in 87% combined yield.

The stereoselective dihydroxylation of the double bond was also examined. Under modified Upjohn condition,[15]

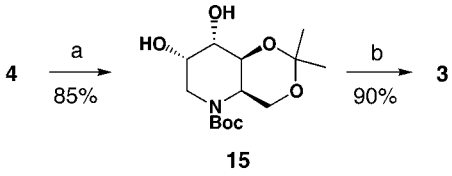
Scheme 4 [a]



[a] Reagents and conditions: (a) (i) H_2SO_4, 1,4-dioxane, H_2O, reflux, (ii) Amberlite IRA-410 (OH^- form), (iii) DOWEX 1x2 (OH^- form); (b) (i) H_2SO_4, 1,4-dioxane, H_2O, reflux, (ii) Amberlite IRA-410 (OH^- form); (c) (i) 0.3 M KOH,1,4-dioxane, H_2O, reflux, (ii) 6 N HCl, MeOH, rt, (iii) Amberlite IRA-410 (OH^- form).

treatment of **4** with a catalytic amount of K_2OsO_4·$2H_2O$ (5 mol %) and 4-methylmorphorine *N*-oxide as a cooxidant gave the diol **15** as a single diastereomer in 85% yield. This remarkably high diastereoselectivity of the dihydroxylation would arise from the same steric blocking of the concave face as explained for the epoxidation of **4**. Deprotection of **15** with HCl in methanol followed by treatment with an ion-exchange (DOWEX 50Wx8 H^+ form) afforded 1-deoxy-gulonojirimycin (**3**)[13] in 90% combined yield.

Scheme 5 [a]



[a] Reagents and conditions: (a) K_2OsO_4·$2H_2O$, NMO, acetone, H_2O, rt; (b) (i) 6 N HCl, MeOH, rt, (ii) DOWEX 50Wx8 (H^+ form).

In summary, the newly promising chiral building block **4** in the synthesis of 1-deoxyazasugars was prepared in only four steps from the Garner aldehyde **5**. In practice, a straightforward synthesis of **1**−**3** using **4** has been demonstrated in a highly stereocontrolled fashion. This developed method provides stereoisomeric diversity for the synthesis of deoxyazasugars[11] suitable for further studies of their abilities as glycosidase inhibitors.

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Supporting Information Available: Experimental details and characterization data for all new compounds, including crystallographic details for **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The optimal configuration for **11** was simulated using the semiempirical method PM3 (software package Chemdraw ultra 6.0/Chem 3D Pro 5.0).

(13) The specific rotations and spectral data of these compounds were consistent with the reported values; see Supporting Information.

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