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Synthesis of Azasugars through a Proline-Catalyzed Reaction

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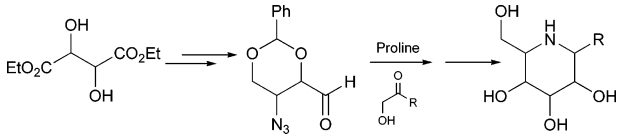

We report an efficient route to obtain azasugars from the enantiomerically pure L- and D-diethyltartrate. The key step is a proline-catalyzed aldol condensation, in which both enantiomers of proline have been used as catalyst, affording complementary *anti*-aldol products.

The use of asymmetric enamine organocatalysis in the formation of new C−C bonds has emerged as an important tool in the synthesis of carbohydrates.[1] Continuing in this field[2] and because of their major interest to medicinal chemistry, we have focused our efforts on the application of this methodology to the synthesis of iminocyclitols. Our interest in these compounds,[3] also called azasugars as the ring oxygen of a carbohydrate is replaced by nitrogen, starts from their ability to act as potent inhibitors of enzymes involved in carbohydrate processing, such as glycosidases and glycosyltransferases.[4] This fact, together with their functional and stereochemical complexities, has stimulated the development of a variety of synthetic routes, and a number of synthetic analogues have been prepared.[5]

Herein we present a novel route to obtain azasugars from diethyl tartrate **4** in which the key step is a proline-catalyzed aldol reaction of aldehyde **3** with either 2,2-dimethyl-1,3-dioxan-5-one[1b] (**1**, dioxanone) or hydroxyacetone (**2**), to afford the corresponding aldol which, after hydrogenation, leads to the final azasugar (Scheme 1). Both enantiomers of diethyl tartrate have been used in combination with D- and L-proline as catalyst, obtaining the complementary *anti*-aldol products and, therefore, broadening the number of compounds that can be obtained.

Aldehyde **3** and its enantiomer *ent*-**3** were readily prepared following the route described in Scheme 2. The azide group was introduced by nucleophilic attack to the cyclic sulfide formed on **4**.[6] Afterward, reduction of the esters with $NaBH_4$/LiCl in ethanol, transketalation with benzaldehyde dimethylacetal and oxidation with TEMPO,[7] afforded the desired aldehyde **3**.

The results of the reaction of **3** and *ent*-**3** with ketones **1** and **2** in the presence of D- and L-proline are shown in Scheme 3. The diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture, and the absolute configuration of the major diastereoisomer was determined on the basis of NMR spectral data.[8]

Reaction of **3** with ketone **1** catalyzed by L-proline at 4 °C gave the *anti*-aldol **9a** in 70% yield and >20:1 diastereoselectivity (Scheme 3). In contrast, D-proline afforded the *anti*-aldol **9b** in similar yield (60%) but lower diastereoselectivity (diastereoselectivity ratio (d.r.) 5:1). Similar pattern of results were observed in reactions between ketone **2** and aldehyde **3**. However, reactions had to be carried out at higher temperature (room temperature), and lower yields of products were obtained. This topicity was confirmed when aldehyde *ent*-**3** was used as an acceptor affording the enantiomeric aldols (Scheme 3). Therefore, the best results for the reaction of **3** with both ketones were found when L-proline was the catalyst, while in the case of *ent*-**3** when D-proline was used. These results show the importance of the choice of the proline enantiomer in the reactions of chiral α-branched aldehydes. We are currently investigating the origin of this *double asymmetric induction* on the basis of the transition states postulated by Houk et al.[9]

Hydrogenation (H_2, 45 psi) of the *anti*-aldols **9a** and **10a** in the presence of HCl afforded unprotected iminocyclitols **11** and **13a** (Scheme 3), respectively, with high stereoselectivity; however, aldols **9b** and **10b** gave a nearly equimolecular mixtures of diastereosiomers **12a**,**b** and **14a**,**b**, respectively. The results obtained seem to indicate that the stereoselectivity of the hydrogenation is rather dependent on the relative orientation of the 3,4-diol of the imine intermediate. Nevertheless, further work is currently underway to control the stereochemistry of the hydrogenation using other reducing agents.

The NMR spectral data and optical rotation values for **11** and **13a** were in good agreement with previously reported data.[10] The structure of **12a**,**b** and **14a**,**b** was determined by a

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(7) De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett*. **2001**, *3*, 3041−3043.

(8) Final absolute configuration of compounds **9a** and **9b** was determined by a combination of measurement of coupling constants and NOESY spectra. The configuration of compounds **10a** and **10b** was assigned by comparison of the $\Delta\delta^{RS}$ signs of their ^{1}H NMR spectra of the corresponding diesters (*R*)- and (*S*)-methoxyphenylacetic acid (see Supporting Information). The assigned configuration data were reconfirmed in the final cyclized compounds.

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10.1021/jo060568b CCC: $33.50
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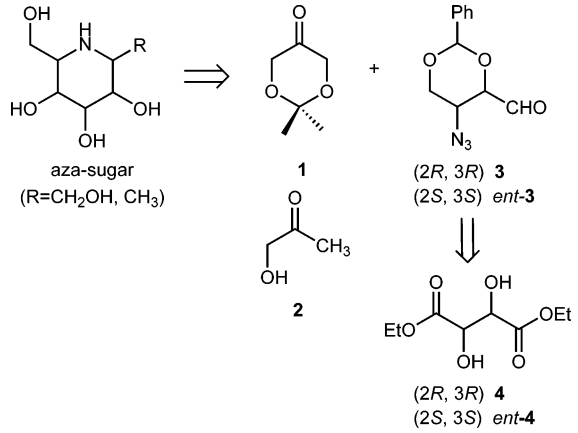
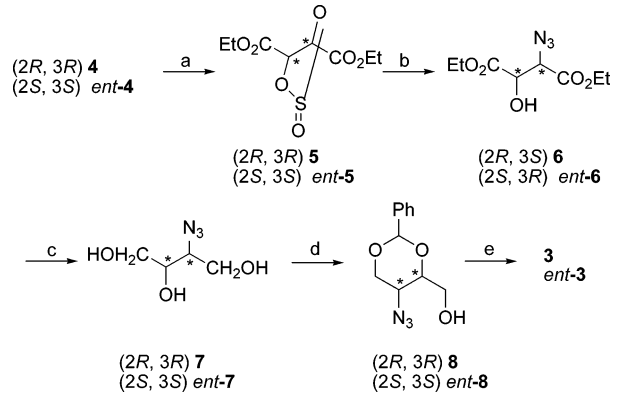
SCHEME 1. Retrosynthetic Path To Obtain Azasugars from 4



SCHEME 2. Synthesis of Aldehyde 3[a]



[a] Reaction conditions: (a) Et_3N, thionyl chloride, 3 h, 100%; (b) NaN_3, DMF, 5 h, 70%; (c) $NaBH_4$, LiCl, EtOH, 4 h, 63%; (d) benzaldehyde dimethylacetal, *p*-TsOH, MeCN, 3 h, 45%; (e) TEMPO, trichloroisocianuric acid, CH_2Cl_2, 30 min, 60%.

combination of the measurement of the coupling constant and NOESY spectra (see Supporting Information).

When the hydrogenation of **9a** and **10a** was performed under milder conditions (H_2, 10 psi) in the absence of HCl, the protected azasugars **15** and **18**/**19** were obtained (Scheme 4), which are useful intermediates for further modifications. Interestingly, when the same conditions were applied to the isomers **9b** and **10b** poor yields of protected azasugars **16**/**17** and **20**/**21** were obtained, owing to the rapid formation of the unprotected **12a**,**b** and **14a**,**b**.

We hypothesized that the favorable disposition of the axially oriented hydroxyl goup in **16** and **20**, to form a hydrogen bond with the adjacent oxygen of the benzylidene acetal, can catalyze the cleavage of this protecting group. This was confirmed when the same reductive conditions were applied to the acetylated **22**, which gave the protected **23** in high yield (80%, Scheme 4).

In conclusion, we have described a novel asymmetric route to obtain a diversity of azasugars in seven steps from diethyl tartrate, where the key step is a proline-catalyzed aldol reaction. The best results in terms of yield and stereoselectivity were obtained with matched substrate/catalyst pairs **3**/L-proline and *ent*-**3**/D-proline, providing efficient access to known glycosidase inhibitors, such as β-homomannojirimycin **(11)** and β-homofuconojirimycin **(13a)**.

Experimental Section

General Procedure for the Catalytic Asymmetric Aldol Reaction of Ketone 1 and Aldehyde 3 Using (*R*)- or (*S*)-Proline. To a solution of ketone **1** (0.26 g, 2 mmol) in DMF (0.5 mL), aldehyde **3** (0.23 g, 1 mmol) and proline (30% mol) were added. The suspension was stirred at 4 °C for 96 h. After this time, the suspension was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 2 mL). The combined organic layers were concentrated and purified by flash chromatography (hexane/AcOEt, 4:1). Yields, reaction conditions, and dr are reported in Scheme 3.

6-Azido-5,7-*O*-benzylidene-6-deoxy-1,3-isopropylidene-D-*manno*-hept-2-ulose (9a). $[\alpha]^{25}_D$ −92.3 (c 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5−7.3 (m, 5H), 5.45 (s, 1H), 4.58 (d, J = 9 Hz, 1H), 4.45 (dd, J = 5.1, 10.8 Hz, 1H), 4.30 (d, J = 15.7 Hz, 1H), 4.2−4.1 (ddd, 1H), 4.1−4.0 (m, 2H), 3.83 (dd, J = 12.4 Hz, 1H), 3.68 (dd, 1H), 3.38 (s, 1H), 1.43 (s, 3H), 1.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 212.6, 137.3, 129.3, 128.5, 126.2, 101.7, 101.6, 78.1, 70.7, 69.2, 68.2, 66.7, 52.2, 23.9, 23.6. MS(EI): *m*/*z* 364.1 (M + 1). Anal. Calcd for $C_{17}H_{21}N_3O_6$: C, 56.1; H, 5.8; N, 11.5. Found: C, 56.0; H, 6.3; N, 11.2.

6-Azido-5,7-*O*-benzylidene-6-deoxy-1,3-isopropylidene-D-*allo*-hept-2-ulose (9b). $[\alpha]^{25}_D$ +20.5 (*c* 0.7, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5−7.2 (m, 5H), 5.49 (s, 1H), 4.58 (dd, J = 9, 3.0 Hz, 1H), 4.38 (dd, J = 12.0, 6.2 Hz, 1H), 4.25 (m, 1H), 4.20 (dd, J = 18, 1.2 Hz, 1H), 4.0−3.8 (m, 3H), 3.66.(dd, J = 12.0, 1H), 3.48 (s, 1H), 1.51 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.9, 137.4, 129.6, 128.7, 126.6, 102.1, 101.1, 80.6, 73.2, 71.4, 69.7, 66.9, 54.9, 24.3, 24.0. MS(EI): *m*/*z* 364.1 (M + 1). Anal. Calcd for $C_{17}H_{21}N_3O_6$: C, 56.1; H, 5.8; N, 11.5. Found: C, 56.1; H, 5.4; N, 11.2.

General Procedure for the Catalytic Asymmetric Aldol Reaction of Hydroxyacetone (2) and Aldehyde 3 Using (*R*)- or (*S*)-Proline. To a solution of **2** (2.2 g, 30 mmol) in DMF (0.5 mL), aldehyde **3** (0.23 g, 1 mmol) and proline (30% mol) were added. The suspension was stirred at room temperature for 48 h. After this time the suspension was quenched with saturated aqueous ammonium chloride solution and extracted with ethyl acetate (3 × 2 mL). The combined organic layers were concentrated and purified by flash chromatography (hexane/AcOEt, 3:1). Yields, reaction conditions, and d.r. are reported in Scheme 3.

6-Azido-5,7-*O*-benzylidene-1,6-dideoxy-D-*manno*-hept-2-ulose (10a). $[\alpha]^{25}_D$ +4.5 (*c* 0.14, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5−7.3 (m, 5H), 5.59 (s, 1H), 4.50 (dd, J = 12.9, 6.6, 1H), 4.26 (d, J = 12.9, 1H), 4.0−3.7 (m, 4H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 210.2, 137.1, 129.8, 128.8, 126.4, 101.4, 78.7, 76.4, 70.8, 69.3, 52.6, 29.7. MS(EI): *m*/*z* 330.1 (M + 23). Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.7; H, 5.5; N, 13.6. Found: C, 55.0; H, 5.2; N, 13.5.

6-Azido-5,7-*O*-benzylidene-1,6-dideoxy-D-*allo*-hept-2-ulose (10b). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.6−7.4 (m, 5H), 5.50 (s, 1H), 4.50−3.4 (m, 6H), 2.22 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 208.6, 136.7, 129.6, 128.6, 126.2, 101.4, 79.5, 77.7, 71.0, 69.1, 53.1, 26.7. MS(EI): *m*/*z* 308.1 (M + 1). Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.7; H, 5.5; N, 13.6. Found: C, 54.1; H, 5.4; N, 13.6.

General Procedure for Hydrogenation. To a solution of aldol product (0.055 mmol) in MeOH/HCl (2.6/ 0.5 mL), 10% Pd/C was added (20 mg). The suspension was stirred under H_2 (45 psi) during 48 h atroom temperature. After this time, the reaction mixture was filtered through Celite, and the solvent was evaporated affording the final azasugar.

β-Homomannojirimycin (11). $[\alpha]^{25}_D$ +16.4 (c 1, H_2O) {lit.[10] $[\alpha]^{25}_D$ +12.0 (c 0.27, H_2O)}. ^{1}H NMR (300 MHz, D_2O, Ph = 9):

(10) Asano, N.; Nishida, M.; Kato, A.; Kizu, H.; Matsui, K.; Shimada, Y.; Itoh, T.; Baba, M.; Watson, A. A.; Nash, R. J.; de Q. Lilley, P. M.; Watkin, D. J.; G. Fleet, G. W. J. *J. Med. Chem.* **1998**, *41*, 2565−2571.

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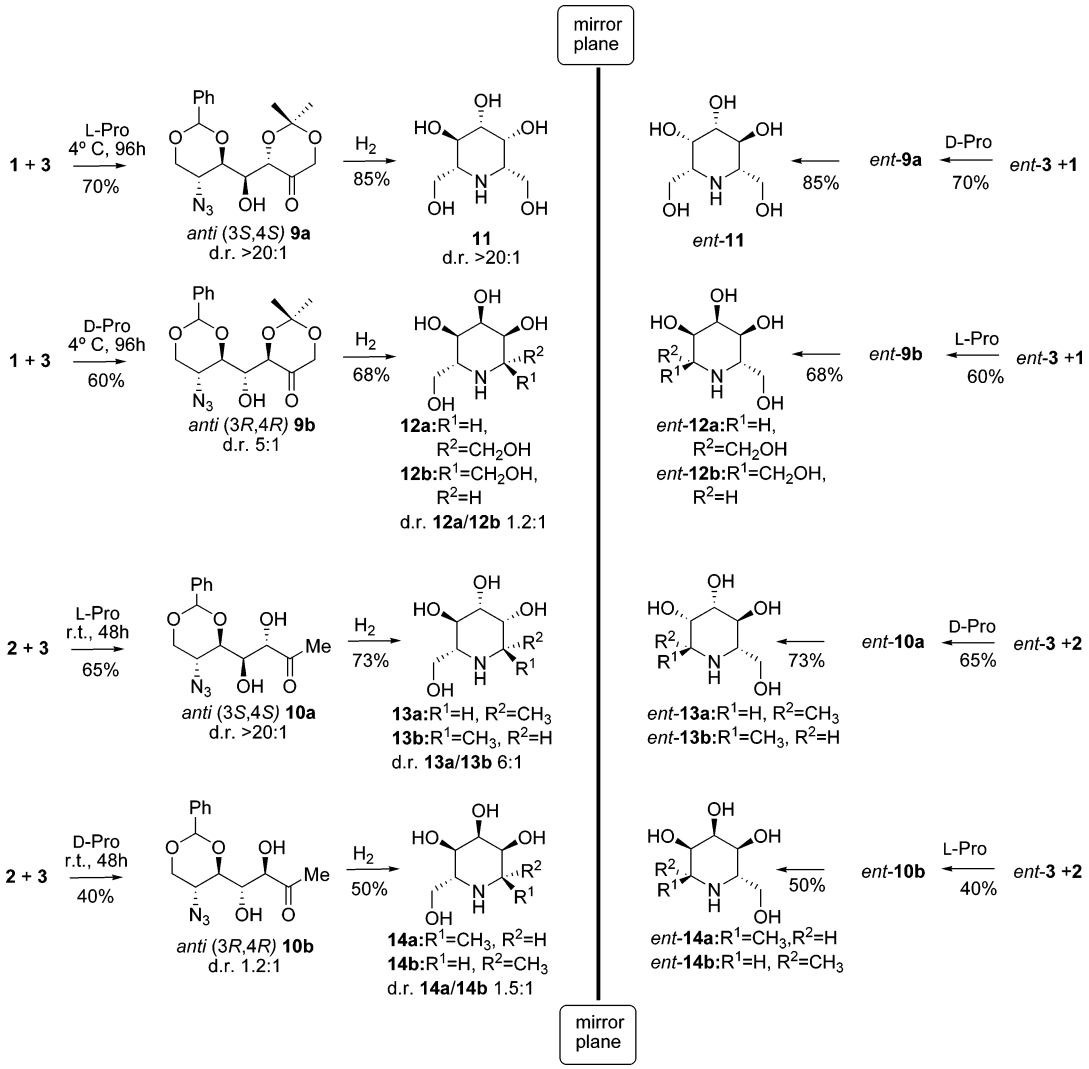
SCHEME 3. Two-Step Synthesis of Iminociclitols from Aldehyde 3



δ 4.05 (dd, 1H), 3.9.3.6 (m, 5H), 3.51 (dd, J = 2.7, 9.6 Hz, 1H), 3.31 (dt, J = 6.3 Hz, 1H), 2.9 (m, 1H). ^{13}C NMR (75 MHz, D_2O, Ph = 9): δ 76.8, 70.5, 69.2, 64.0, 63.4, 62.5, 61.5. MS (EI): *m*/*z* 194.1 (M + 1), 217.3 (M + 23). Anal. Calcd for $C_7H_{15}NO_5$: C, 43.5; H, 7.8; N, 7.25. Found: C, 44.0; H, 7.8; N, 7.2.

Compound 12 (Obtained as a Mixture of Diastereoisomers 12a and 12b). ^{1}H NMR (300 MHz, D_2O, Ph = 9): δ 4.0−3.6 (m, 4H), 3.5.3.2 (m, 5H). ^{13}C NMR (75 MHz, D_2O, Ph = 9): δ 72.2, 72.1, 72.0, 71.2, 71.0, 65.8, 65.4, 63.5, 62.7, 58.1, 57.2. MS (EI): *m*/*z* 194.1 (M + 1), 217.3 (M + 23). Anal. Calcd for $C_7H_{15}NO_5$: C, 43.5; H, 7.8; N, 7.25. Found: C, 43.4; H, 7.2; N, 7.8.

β-Homofuconojirimycin (13a) (Major Product). ^{1}H NMR (300 MHz, D_2O): δ 4.8 (m, 1H), 3.9−3.7 (m, 2H), 3.69 (m, 1H), 3.54 (dd, J = 2.7, 9.6, 1H), 3.3−3.2 (m, 1H), 3.1−3.0 (m, 1H), 1.21 (d, 3H, J = 6.3). ^{13}C NMR (75 MHz, D_2O): δ 74.1, 70.8, 66.5, 61.1, 59.2, 55.5, 14.9. MS (EI): *m*/*z* 178.1 (M + 1). Anal. Calcd for $C_7H_{15}NO_4$: C, 47.4; H, 8.5; N, 7.9. Found: C, 47.4; H, 8.4; N, 7.8.

Compound 14 (Obtained as a Mixture of Diastereoisomers 14a and 14b). ^{1}H NMR (300 MHz, D_2O): δ 4.2−3.0 (m, 7H), 1.4 (d, J = 6.3, 3H). ^{13}C NMR (75 MHz, D_2O): δ 79.1, 77.3, 77.0, 68.2, 56.8, 53.5, 18.1. MS (EI): *m*/*z* 178.1 (M + 1). Anal. Calcd for $C_7H_{15}NO_4$: C, 47.4; H, 8.5; N, 7.9. Found: C, 47.2; H, 8.2; N, 7.9.

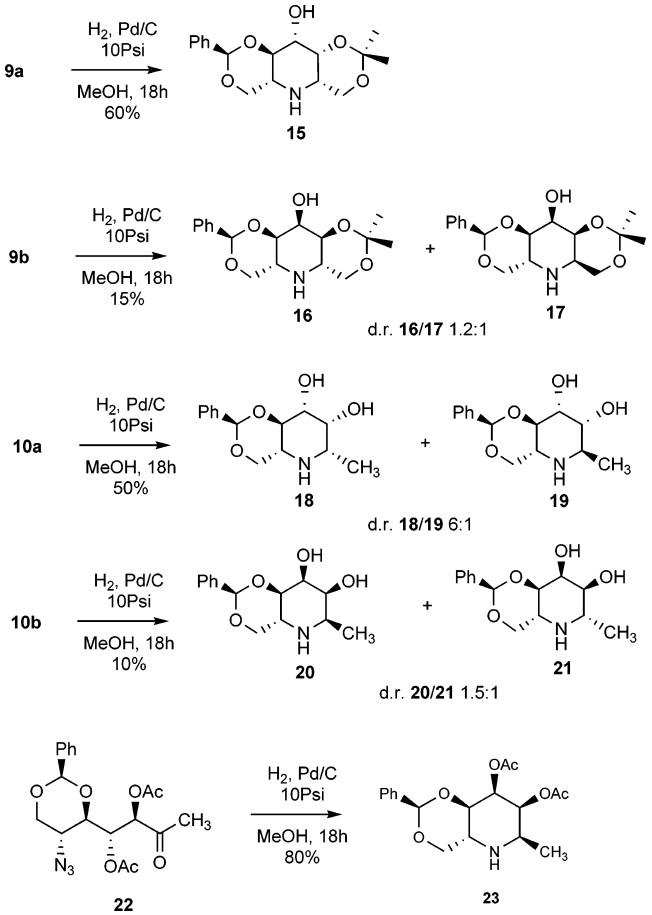
General Procedure for Partial Hydrogenation (Preparation of 15−21). To a solution of aldol product (0.055 mmol) in MeOH (3.0 mL), 10% Pd/C was added (20 mg). The suspension was stirred under H_2 (10 Psi) during 18 h at room temperature. After this time, the reaction mixture was filtered through Celite, and the solvent was evaporated affording final azasugar.

Compound 15. $[\alpha]^{25}_D$ +34.4 (c 0.7, MeOH). ^{1}H NMR (300 MHz, C_6D_6): δ 7.7−7.1 (m, 5H), 5.28 (s, 1H), 4.15 (dd, J = 5.1, 12.1 Hz, 1H), 3.63−3.41 (m, J = 10.8, 8.7, 3.0 Hz, 5H), 3.07 (dd, J = 10.5, 12.1 Hz, 1H), 2.53 (m, J = 10.8, 8.7, 5.1 Hz, 1H), 1.74 (ddd, J = 8.7, 4.8, 3.0 Hz, 1H), 1.36 (s, 3H), 1.08 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 139.0, 129.8, 128.8, 126.8, 101.8, 99.0, 81.6, 71.9, 70.7, 69.8, 63.7, 53.3, 51.4, 29.7, 18.0. MS (EI): *m*/*z* 322.2 (M + 1). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.2; N, 4.3. Found: C, 63.1; H, 7.2; N, 4.4.

Compound 16 (Major Product). ^{1}H NMR (300 MHz, C_6D_6): δ 7.4−7.2 (m, 5H), 5.49 (s, 1H), 4.58 (dd, J = 12.2, 1H), 4.5−4.3 (m, 2H), 4.3−4.2 (m, 1H), 4.15 (dd, J = 14, 1H), 4.0−3.9 (m, 2H), 3.8−3.5 (m,2H), 1.51 (s, 3H), 1.46 (s, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 139.2, 129.4, 128.2, 127.2, 101.3, 100.1, 76.1, 72.4, 69.2, 67.3, 64.2, 57.2, 56.1, 26.2, 19.2. MS (EI): *m*/*z* = 322.2 (M + 1).

Compound 18 (Major Product). ^{1}H NMR (300 MHz, MeOD): δ 7.5−7.3 (m, 5H), 5.57 (s, 1H), 4.16 (dd, J = 11.4, 4.2 Hz, 1H), 3.7−3.6 (m, 5H), 2.89 (dd, J = 6.6, 1.3 Hz, 1H), 2.68 (ddd, J = 10.3, 10.5, 4.2 Hz, 1H), 1.17 (d, J = 6.6, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 139.5, 129.8, 129.0, 127.4, 103.2, 81.4, 74.3, 73.9, 70.3,

SCHEME 4. Partial Hydrogenation of Aldol Products



54.9, 54.7, 17.6. MS (EI): $m/z = 266.1$ (M + 1). Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.8; H, 7.2; N, 5.2. Found: C, 63.9; H, 7.0; N, 5.6.

Compound 20 (Major Product). ^{1}H NMR (300 MHz, C_6D_6): δ 7.5−7.3 (m, 5H), 5.57 (s, 1H), 4.23 (dd, $J = 3.0$, 12.2 Hz, 1H), 3.8−3.4 (m, 4H), 3.05 (m, $J = 3.0$, 9.0, 1H), 2.87 (m, 1H), 1.08 (d, $J = 6.2$, 3H). MS (EI): $m/z = 266.1$ (M + 1).

Compound 23. To a solution of **22** (24 mg, 0.06 mmol) in MeOH (3.0 mL), 10% Pd/C was added (20 mg). The suspension was stirred under H_2 (10 psi) during 18 h at room temperature. After this time, the reaction mixture was filtered through Celite, and the solvent was evaporated. The crude reaction was chromatographed (hexane/AcOEt, 4:1) yielding **23** (13.9 mg, 80%) as a palid oil. $[\alpha]^{25}_D$ −72.3 (c 0.1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.8−7.2 (m, 5H), 5.42 (s, 1H), 4.8 (m, 1H), 3.96 (dd, $J = 4.5$, 10.8 Hz, 1H), 3.56 (dd, $J = 4.2$, 9.0 Hz, 1H), 3.25 (dd, $J = 10.5$ Hz, 1H), 2.53 (ddd, $J = 4.5$, 9.8,0.13.8 Hz, 1H), 2.3 (m, $J = 6.6$, 2.1 Hz, 1H), 2.24 (m, $J = 4.2$, 3.8 Hz, 1H), 1.68 (s, 3H), 1.66 (s, 3H), 0.78 (d, $J = 6.6$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.9, 169.8, 139.8, 129.2, 128.6, 127.0, 102.4, 80.6, 76.9, 72.3, 57.3, 54.2, 33.7, 23.9, 22.2, 18.6. MS (EI): $m/z = 350.7$ (M + 1). Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.8; H, 6.6; N, 4.0. Found: C, 61.9; H, 6.2; N, 3.9.

6-Azido-5,7-*O*-benzylidene-6-deoxy-1,3-isopropylidene-L-*gulo*-hept-2-ulose (*ent*-9a). $[\alpha]^{25}_D$ +89.3 (c 0.6, CH_2Cl_2). MS(EI): m/z 364.1 (M + 1); Anal. Calcd for $C_{17}H_{21}N_3O_6$: C, 56.1; H, 5.8; N, 11.5. Found: C, 56.3; H, 6.3; N, 11.8.

6-Azido-5,7-*O*-benzylidene-6-deoxy-1,3-isopropylidene-L-*talo*-hept-2-ulose (*ent*-9b). $[\alpha]^{25}_D$ −23.2 (*c* 0.3, CH_2Cl_2). MS(EI): m/z 364.1 (M + 1). Anal. Calcd for $C_{17}H_{21}N_3O_6$: C, 56.1; H, 5.8; N, 11.5. Found: C, 55.9; H, 5.8; N, 11.8.

6-Azido-5,7-*O*-benzylidene-1,6-dideoxy-L-*gulo*-hept-2-ulose (*ent*-10a). $[\alpha]^{25}_D$ −5.1 (*c* 1.3, CH_2Cl_2). MS (EI): m/z 330.1 (M + 23). Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.7; H, 5.5; N, 13.6. Found: C, 54.2; H, 5.5; N, 13.2.

6-Azido-5,7-*O*-benzylidene-1,6-dideoxy-D-talo-hept-2-ulose (*ent*-10b). MS(EI): m/z 308.1 (M + 1); Anal. Calcd for $C_{14}H_{17}N_3O_5$: C, 54.7; H, 5.5; N, 13.6. Found: C, 54.8; H, 5.7; N, 13.8.

α-Homogulojirimycin (*ent*-11). $[\alpha]^{25}_D$ −21.6 (*c* 0.3, H_2O). MS (EI): m/z 194.1 (M + 1), 217.3 (M + 23). Anal. Calcd for $C_7H_{15}NO_5$: C, 43.5; H, 7.8; N, 7.2. Found: C, 43.0; H, 7.8; N, 7.3.

Compound *ent*-12 (Obtained as a Mixture of Diastereoisomers *ent*-12a + *ent*-12b). MS (EI): m/z 194.1 (M + 1), 217.3 (M + 23). Anal. Calcd for $C_7H_{15}NO_5$: C, 43.5; H, 7.8; N, 7.25. Found: C, 43.0; H, 7.6; N, 7.3.

Compound *ent*-13a (Major Product). MS (EI): m/z 178.1 (M + 1). Anal. Calcd for $C_7H_{15}NO_4$: C, 47.4; H, 8.5; N, 7.9. Found: C, 47.7; H, 8.0; N, 7.6.

Compound *ent*-14a (Obtained as a Mixture of Diastereoisomers *ent*-14a + *ent*-14b). MS (EI): m/z 178.1 (M + 1). Anal. Calcd for $C_7H_{15}NO_4$: C, 47.4; H, 8.5; N, 7.9. Found: C, 47.4; H, 8.6; N, 7.9.

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Supporting Information Available: Structural data and copies of ^{1}H and ^{13}C NMR and experimental procedures for compounds **5**−**8**, **3**, *ent*-**5**, *ent*-**6**, *ent*-**7**, *ent*-**8**, and *ent*-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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