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Asymmetric Dihydroxylation of D-Glucose Derived α,β-Unsaturated Ester: Synthesis of Azepane and Nojirimycin Analogues

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The asymmetric dihydroxylation of a D-glucose derived α,β-unsaturated ester **3** afforded syn vicinal diols in good to high diastereoselectivity. The conversion of these vicinal diols to the corresponding cyclic sulfate, regio-, stereoselective nucleophilic ring opening by sodium azide, and LAH reduction afforded amino heptitols **7a**,**b** that were converted to azepane **1c**,**d** and nojirimycin analogues **2c**,**d**.

Introduction

Among the strategies available for the dihydroxylation of olefins,[1] one of the most attractive is the asymmetric dihydroxylation with osmium tetroxide in combination with cinchona alkaloids.[2] Furthermore, the formation of cyclic sulfite or sulfate from diols, followed by regio- and stereoselective nucleophilic ring opening of the latter, makes this approach extremely versatile for organic synthesis.[3] This strategy has been widely exploited in the synthesis of many natural products. However, only limited applications are known for azasugars.[4] In recent years, attention has been increasingly focused on the structure−activity relationship of azasugars, particular in seven-membered hydroxy and tetraoxy azepanes **1a**,**b**[5] and six-membered piperidine alkaloids, namely nojirimycin **2a** and 1-deoxynojirimycin **2b** (Figure 1).[4] These compounds have become important synthetic targets because of their promising glycosidase inhibitory activity in the treatment of various diseases such as diabetes, cancer, and viral infections, including AIDS.[4,6] In addition, azepanes are also potentially useful as DNA minor groove binding ligands (MGBL).[5d] The hydroxyl groups in azepanes adopt different conformations due to the flexibility of the seven-membered ring (compared with five- or six-membered rings) thereby increasing the probability of forming hydrogen bonds with nitrogen base, thus showing the ability to point into the minor

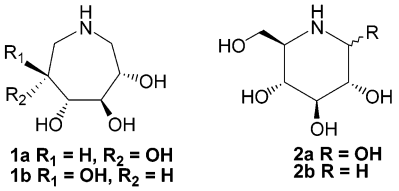

FIGURE 1. Azepane and nojirimycin anlogues.

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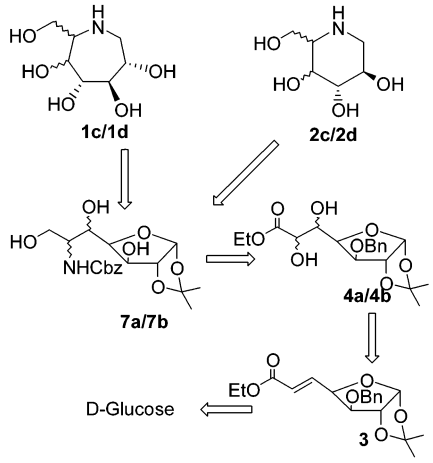
groove of DNA. The high water solubility, allowing them to circumvent the problem of poor bioavailability seen in many other MGBL's, is an additional advantage of these compounds. The development of new azasugars thus opened a dynamic research field at the interface between glycobiology and synthetic organic chemistry. During the course of our investigations in the area of nojirimycin, castanospermine, and azepane analogues,[7] we thought of synthesizing altogether different one-carbon ring homologues of 1-deoxynojirimycin namely azepanes **1c** and **1d**, with $-CH_2OH$ functionality at C5, as well as piperidine alkaloids 1-deoxy-D-altronojirimycin **2c**, a recently reported natural product from the bark extract of *Angylocalyx pynaertii* (Leguminosae),[8] and **2d** (1-deoxy-L-nojirimycin),[9] the enantiomer of 1-deoxynojirimycin **2b**.

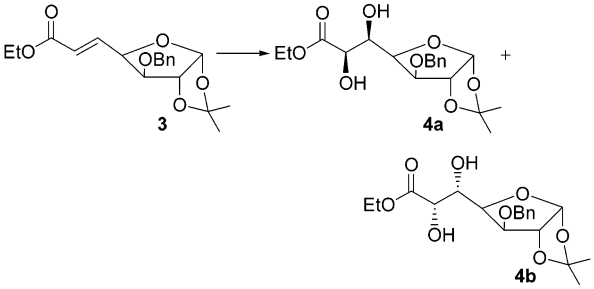
Results and Discussion

Retrosynthetic Analysis. As shown in retrosynthetic analysis (Scheme 1), the key intermediate in our approach, common to both types of target molecules, is the 6-aminoheptulose **7** that could be derived by applying the asymmetric dihydroxylation, cyclic sulfate formation, and nucleophilic azide ring opening protocol to the easily available D-glucose-derived α,β-unsaturated ester **3**. An attractive feature of this strategy lies in its inherent flexibility wherein the stereoselectivity of the vicinal diol formation, at the α,β-unsaturated double bond, could be controlled by making use of the Sharpless asymmetric dihydroxylation. Our efforts in the successful implementation of this method for the formation of azepanes **1c**,**d** and piperidine alkaloids **2c**,**d** are reported herein.

SCHEME 1. Retrosynthetic Analysis



Asymmetric Dihydroxylation of 3. The required (*E*)-ethyl-1,2-*O*-isopropylidene-3-*O*-benzyl-5,6-dideoxy-α-D-*xylo*-5-enoheptofuranuronate (**3**) was prepared from D-glucose as reported earlier.[7f] The dihydroxylation of **3** with potassium osmate (catalytic), potassium ferricyanide, potassium carbonate, and methane sulfonamide in *tert*-butyl alcohol−water (1:1) afforded a diastereomeric mixture of vicinal diols **4a** and **4b** in the ratio 2:1 (eq 1).



(1)

The appreciable difference in R_f value allowed us to separate the isomers by column chromatography. Fortunately, **4a** was obtained as a colorless solid and the single-crystal X-ray analysis (Figure 2) established the absolute configurations at the newly generated stereocenters as 5*R* and 6*R*. The formation of **4a** as a major product is in accordance with Kishi's empirical rule,[10] wherein the *syn*-hydroxylation from the side opposite to the preexisting furanose alkoxy group is preferred, while the *syn*-hydroxylation from the same side of the preexisting furanose alkoxy group, which is sterically more compressed, afforded the minor product **4b** with absolute configurations 5*S* and 6*S*. The diastereoselectivity in the formation of **4a** and **4b** was improved by using cinchona alkaloids as chiral ligands. Thus, the use of $[(DHQ)_2PHAL]$ in osmylation afforded **4a** with high diastereoselectivity (de 94%), while the use of $[(DHQD)_2PHAL]$ gave **4a**:**4b** in the ratio 32:68 as determined by the ^1H NMR of the crude mixture (Table 1).

The utility of **4a**,**b** was initially demonstrated in the formation of azepane analogues **1c**,**d**, respectively. As shown in Scheme 2, treatment of diol **4a** with thionyl

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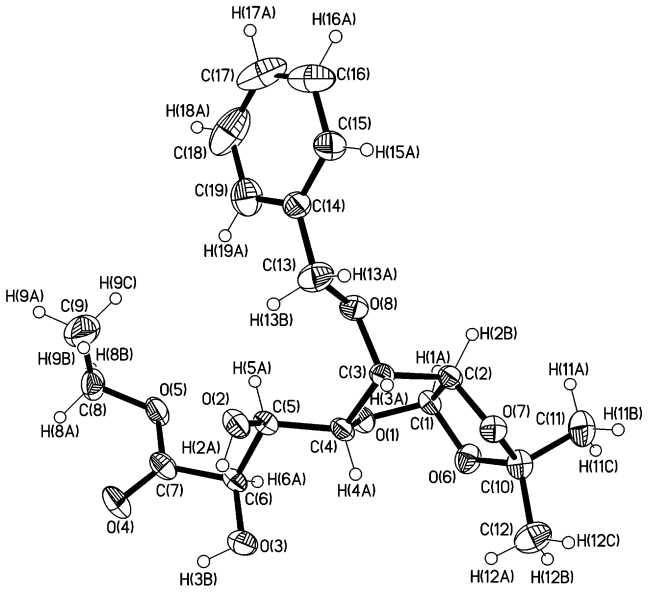
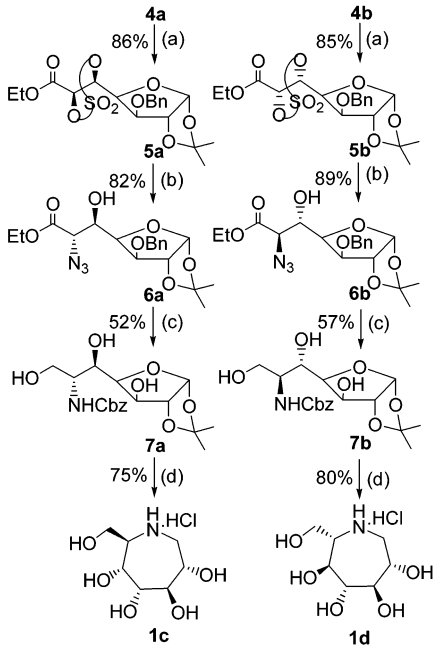


FIGURE 2. ORTEP drawing of compound **4a**.

TABLE 1. Asymmetric Dihydroxylation of 3

entry	ligand	ratio of **4a/4b**	yield, %
1	no ligand	67:33	91
2	$(DHQ)_2PHAL$	97:03	88
3	$(DHQD)_2PHAL$	32:68	82

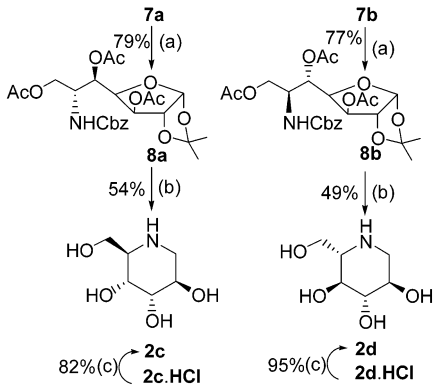
SCHEME 2. Synthesis of 1c,d[a]



[a] Reaction conditions: (a) (i) $SOCl_2$, Py, CH_2Cl_2, 0 °C, 30 min; (ii) $NaIO_4$, $RuCl_3{\cdot}3H_2O$, $CH_3CN{:}H_2O$ (3:1), 0 °C, 10 min. (b) (i) NaN_3, acetone:water (4:1), 0 to 25 °C, 2 h; (ii) 20% H_2SO_4, ether: water (6:1), 25 °C, 6 h. (c) (i) LAH, THF, 0 to 25 °C, 3 h; (ii) $HCOONH_4$, Pd/C, MeOH, 80 °C, 1 h; (iii) CbzCl, MeOH:H_2O (9:1), 0 to 25 °C, 3.5 h; (d) (i) TFA:H_2O (2:1), 0 to 25 °C, 2.5 h; (ii) H_2, Pd/C, MeOH:HCl (9:1), 80 psi, 24 h.

chloride in pyridine afforded the cyclic sulfite that was further oxidized with sodium metaperiodate and a catalytic amount of ruthenium trichloride to furnish the cyclic sulfate **5a** in 86% yield. The regioselective ring opening of cyclic sulfate **5a** with sodium azide, at the α-position to the carboethoxy group in an S_N2 fashion, followed by acid hydrolysis provided the azido ester **6a** in high yield. Reduction of the azido ester **6a** with LAH afforded an amino alcohol that was directly subjected to hydrogenolysis with ammonium formate in the presence of 10% Pd/C followed by reaction with benzyl chloroformate to give *N*-Cbz-protected amino alcohol **7a**. The compound **7a** was reacted with TFA−water to cleave the 1,2-acetonide functionality, and the product thus obtained was subjected to hydrogenation with 10% Pd/C in methanol−HCl (9:1) to give 1,6-dideoxy-1,6-imino-(2*S*,3*R*,4*R*,5*R*,6*R*)-L-glycero-D-gluco-heptitol **1c** as a hydrochloride salt. The same sequence of reactions with **4b** gave the hydrochloride of 1,6-dideoxy-1,6-imino-(2*S*,3*R*,4*R*,5*S*,6*S*)-D-glycero-L-*ido*-heptitol **1d**. The compounds **5b**, **6b**, and **7b** were obtained in good yields and were characterized by spectral and analytical techniques and the data were found to be in agreement with the structures (Scheme 2).

SCHEME 3. Synthesis of 2c,d[a]



[a] Reaction conditions: (a) Ac_2O, py, DMAP. (b) (i) TFA:H_2O (2:1), 0 °C to room temperature, 2.5 h; (ii) $NaIO_4$, acetone:H_2O (5:1), 0 °C, 1.5 h; (iii) H_2, Pd/C, MeOH, 80 psi, 12h; (iv) MeOH:HCl (9:1), 80 °C, 6 h. (c) NH_3, rt, 15 min.

Although the physical and spectral data of **1c**,**d** were found to be consistent with the structures, the configurational assignment at each carbon atom in **1c** was based on the X-ray analysis of **4a** while in the case of **1d** the configurational assignment was tentatively made on the expected *syn*-dihydroxylation from the other face of **3** leading to **4b**. The ^{1}H NMR spectrum of **1c** and **1d** did not give any supportive information on the conformational and configurational assignment due to the flexibility in seven-membered ring systems.[7j,k] As an alternative, we thought of converting **4a**,**b** to the corresponding six-membered piperidine analogues **2c**,**d** wherein the configurational assignment at each carbon atom will be clearly evident from the six-membered cyclic structure, with either $^4C_1$ or $^1C_4$ conformations, and the same configurational assignments would be applicable to azepane analogues. For this, the amino alcohols **7a**,**b** (obtained from **4a**,**b**) were found to be the true intermediates wherein cleavage of the anomeric carbon atom (C1) and reductive aminocyclization would afford the corresponding six-carbon azasugars **2c**,**d**. Thus, peracetylation of **7a** with acetic anhydride in pyridine afforded the peracetylated product **8a** (Scheme 3). In the subsequent

steps, cleavage of the 1,2-acetonide functionality in **8a** by TFA−water, treatment with sodium metaperiodate (to cleave the anomeric carbon atom), and hydrogenation with 10% Pd/C in methanol afforded triacetoxy-1-deoxy-altronojirimycin.[11]

One-pot removal of *O*-acetoxy and -formyl groups with MeOH:HCl (9:1) afforded the hydrochloride salt of 1-deoxy-altronojirimycin **2c** as a sticky solid $[\alpha]_D$ +31.0 (*c* 2.0, MeOH) [lit.[4o] $[\alpha]_{589}$ +33.2 (*c* 0.5, MeOH)], which on treatment with methanolic ammonia and purification by resin column afforded **2c**. The rotational value and spectral data of **2c** were found to be in consonance with that reported.[4o] Similarly, the reaction of **7b** gave 1-deoxy-L-nojirimycin **2d** as a hydrochloride salt. The compounds **5b**, **6b**, **7b**, and **8b** were characterized by spectral and analytical techniques and the data were found to be in agreement with the structures. The compound **2d·HCl** showed the specific rotation value $[\alpha]_D$ −46.0 (*c* 1.26, H_2O) which is identical, but with opposite sign of rotation, to that reported for the hydrochloride salt of 1-deoxy-D-nojirimycin **2b** [lit.[4n] $[\alpha]_D$ +46.9 (*c* 0.17, H_2O)], indicating their enantiomeric relationship. Furthermore, treatment of **2d·HCl** with methanolic ammonia and purification with resin column afforded 1-deoxy-L-nojirimycin **2d** as a free base that showed identical analytical data with that reported.[9]

Conformational Analysis. Azasugars are known to exist in $^4C_1$ or $^1C_4$ conformations.[4] To determine the conformations of **2c** and **2d**, we studied the ^{1}H NMR spectra and the coupling constant information was obtained by decoupling experiments. In the ^{1}H NMR spectrum of **2c**, the appearance of a doublet of doublets corresponding to the H1a proton with one large geminal ($J_{1a,1e}$ = 14.1 Hz) and another small vicinal ($J_{1a,2}$ = 2.1 Hz) coupling indicated the axial−equatorial relation with the H2 proton. The initial geometry in the precursor **8a** ensures that in the product **2c** the substituent at C2/C3 should be trans. Therefore, the proton at H3 should be equatorial. Unfortunately, H2 and H3 appeared as accidentally equivalent protons. However, the appearance of H5 as a doublet of triplets ($J_{4,5}$ = 9.6 and $J_{5,6}$ = 4.5 Hz) proves that C4/C5 are diaxial protons. The coupling constant value between H5 and H4 was evident from the decoupling experiments and was found to be 9.6 Hz. The large value of $J_{4,5}$ clearly requires the trans-diaxial relationship of these protons, thus indicating the $^4C_1$ conformation with 5*R* absolute configuration. In the ^{1}H NMR spectrum of **2d** the appearance of a triplet corresponding to H3 with $J_{2,3} = J_{3,4}$ = 9.0 Hz indicated the axial orientation of this proton with H2 and H4. The triplet corresponding to H4 with $J_{4,5} = J_{3,4}$ = 9.0 Hz requires a trans-diaxial relationship with H3 and H5. Thus, the axial−axial relationship of H2/H3, H3/H4, and H4/H5 clearly requires the $^1C_4$ conformation of **2d** with 5*S* absolute configuration. Thus, the stereochemistry assigned to **2c**,**d** on the basis of the stereochemistry of **7a**,**b** was confirmed by the ^{1}H NMR of **2c,d**. Because the formation of **2c**,**d** involves the loss of the corresponding anomeric carbon of **7a**,**b**, the configurational assignments

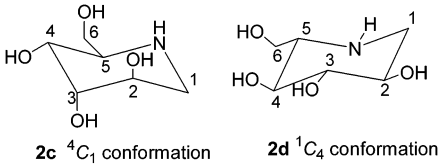


FIGURE 3. Conformations of **2c**,**d**.

at each carbon atom of **2c**,**d** provided proofs for the stereochemistry of azepane analogues **1c**,**d** at four stereocenters.

Conclusions

We have demonstrated the utility of D-glucose-derived α,β-unsaturated ester **3** in the synthesis of new nojirimycin and azepane analogues using an asymmetric dihydroxylation, cyclic sulfate formation, and nucleophilic ring-opening protocol. The easy availability of reagents, high yielding steps, and good regio- and stereoselectivity in the process would give easy access for the synthesis of different types of otherwise difficult azasugars required for structure−activity relationship studies, as a number of α,β-unsaturated esters could be readily prepared from the pool of chiral compounds. Another interesting aspect of the present route is that we have converted D-glucose to **2d**, the enantiomer of **2b**, and **2b** has been prepared earlier from D-glucose.[4a] Thus a single starting compound D-glucose has been used to synthesize two enantiomers having several stereocenters.

Experimental Section

Ethyl 3-*O*-Benzyl-1,2-*O*-isopropylidene-*β*-L-*glycero*-D-*gluco*-heptofuranuronate (4a) and Ethyl 3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-*glycero*-L-*ido*-heptofuranuronate (4b). To a mixture of $K_3Fe(CN)_6$ (8.51 g, 25.86 mmol), K_2CO_3 (3.57 g, 25.86 mmol), and $(DHQD)_2$PHAL or $(DHQ)_2$PHAL (0.067 g, 0.0862 mmol, 1 mol %) or without ligand in *t*-BuOH/H_2O (1:1, 80 mL) at 0 °C was added a catalytic amount of potassium osmate (0.189 g, 0.516 mmol) followed by methanesulfonamide (0.82 g, 8.62 mmol). After the solution was stirred for 5 min at 0 °C, the compound **3** (3.0 g, 8.62 mmol) in *t*-BuOH/H_2O (1:1, 20 mL) was added over a period of 5 min. The reaction mixture was stirred at 0 °C for 24 h and quenched with solid sodium sulfite (6 g). The stirring was continued for another 45 min and the reaction mixture was extracted with ethyl acetate (5 × 40 mL). The combined organic phase was washed with 10% KOH and worked up to afford a diastereomeric mixture of diols **4a** and **4b**. Purification by column chromatography and elution first with *n*-hexane/ethyl acetate (9/1) gave **4a** as a white solid (2.0 g, 61%). Mp 91−93 °C; R_f 0.60 (*n*-hexane/ethyl acetate = 5/5); $[\alpha]_D$ −27.2 (*c* 0.52, $CHCl_3$); IR (Nujol) 3200−3600 (broad band), 1742, 1456, 1379, 1076, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J* = 7.2 Hz, 3H), 1.33 (s, 3H), 1.51 (s, 3H), 2.69 (d, *J* = 9.0 Hz, exchanges with D_2O, 1H), 3.15 (d, *J* = 4.9 Hz, exchanges with D_2O, 1H), 4.15 (d, *J* = 3.0 Hz, 1H), 4.23−4.37 (m, 4H), 4.39 (dd, *J* = 4.9, 1.4 Hz, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.62 (d, *J* = 3.9 Hz, 1H), 4.71 (d, *J* = 11.7 Hz, 1H), 5.94 (d, *J* = 3.9 Hz, 1H), 7.25−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 26.3, 26.8, 62.0, 69.8, 71.0, 72.3, 79.1, 81.9, 82.4, 104.9, 111.8, 127.7 (s), 127.9, 128.4 (s), 137.2, 173.1. Anal. Calcd for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85. Found: C, 59.62; H, 6.75. Further elution with *n*-hexane/ethyl acetate (8/2) afforded **4b** as a thick liquid (1.0 g, 30%). R_f 0.54 (*n*-hexane/ethyl acetate 5/5); $[\alpha]_D$ −16.5 (*c* 0.48, $CHCl_3$); IR (neat) 3200−3600 (broad band), 1741, 1624 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.32 (t, *J* = 7.2 Hz, 3H),

(11) In these particular experiments, triacetylated products were obtained as a mixture of two compounds one with free C3−OH and other with C3−OCHO. Our attempts to separate the mixture were unsuccessful. Therefore, we directly converted the triacetylated products to corresponding hydrochlorides.

1.38 (s, 3H), 1.52 (s, 3H), 4.03 (broad s, 1H), 4.09 (d, J = 2.4 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 4.37−4.41 (m, 2H), 4.51 (d, J = 12.0 Hz, 1H), 4.71 (d, J = 3.9, Hz 1H), 4.76 (d, J = 12.0 Hz, 1H), 6.01 (d, J = 3.9 Hz, 1H), 7.38 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 26.3, 26.7, 61.9, 70.7, 70.9, 71.7, 80.8, 81.5, 82.2, 104.9, 112.0, 127.8 (s), 128.1, 128.5 (s), 136.8, 172.5. Anal. Cald for $C_{19}H_{26}O_8$: C, 59.68; H, 6.85. Found: C, 59.58; H, 6.97.

Ethyl 3-*O*-Benzyl-5,6-cyclic sulfate-1,2-*O*-isopropylidene-*β*-L-*glycero*-D-*gluco*-heptofuranuronate (5a). To an ice-cooled solution of **4a** (2.0 g, 5.26 mmol) and pyridine (1.15 g, 14.58 mmol) in dry dichloromethane (20 mL) was added thionyl chloride (0.53 mL, 7.21 mmol) dropwise over a period of 10 min. After 20 min at 0 °C, the reaction was quenched with cold water and extracted with dichloromethane (3 × 30 mL). Usual workup afforded crude cyclic sulfite that was dissolved in acetonitrile:water (30 mL, 5:1), cooled at 0 °C. Sodium metaperiodate (1.54 g, 7.21 mmol) followed by $RuCl_3$·$3H_2O$ (5 mg) were added and the solution was vigorously stirred for 10 min. The reaction mixture was diluted with diethyl ether and the organic layer was filtered through a pad of Celite. The filtered organic layer was washed with water and sodium bicarbonate solution and worked up to afford a thick liquid that on purification by column chromatography (n-hexane/ethyl acetate = 9/1) gave **5a** as a white solid (2.0 g, 86.0%). Mp 99−101 °C; R_f 0.46 (n-hexane/ethyl acetate = 8/2); $[\alpha]_D$ −79.1 (c 0.86, $CHCl_3$); IR (Nujol) 1747, 1460, 1375, 1221, 1080, 1022 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H), 1.32 (3H, s), 1.49 (3H, s), 4.10 (d, J = 3.3 Hz, 1H), 4.12 (dq, J = 10.8, 7.2 Hz, 1H), 4.26 (dq, J = 10.8, 7.2 Hz, 1H), 4.52 (d, J = 11.4 Hz, 1H), 4.58 (dd, J = 3.6, 3.3 Hz, 1H), 4.64 (d, J = 11.4 Hz, 1H), 4.65 (d, J = 3.6 Hz, 1H), 5.34 (d, J = 3.9 Hz, 1H), 5.48 (dd, J = 6.3, 3.9 Hz, 1H), 5.97 (d, J = 3.6 Hz, 1H), 7.24−7.38 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 26.3, 26.9, 63.1, 72.3, 77.6, 78.1, 79.5, 80.9, 81.9, 105.5, 112.6, 127.8 (s), 128.3, 128.6 (s), 136.0, 164.8. Anal. Calcd for $C_{19}H_{24}O_{10}S$: C, 51.34; H, 5.44. Found: C, 51.42; H, 5.52.

Ethyl 3-*O*-Benzyl-5,6-(cyclic sulfate)-1,2-*O*-isopropylidene-α-D-*glycero*-L-*ido*-heptofuranuronate (5b). The reaction of **4b** (1.8 g, 4.71 mmol) with pyridine (0.98 mL, 13.03 mmol) and thionyl chloride (0.45 mL, 6.45 mmol) followed by oxidation with sodium metaperiodate (1.34 g, 6.45 mmol) and ruthenium trichloride trihydrate (4 mg) as described in the preparation of **5a** and purification by column chromatography (n-hexane/ethyl acetate = 8.5/1.5) afforded **5b** as a white solid (1.8 g, 85.0%). Mp 101−103 °C; R_f 0.63 (n-hexane/ethyl acetate = 7/3); $[\alpha]_D$ +23.0 (c 0.69, $CHCl_3$); IR (Nujol) 1749, 1620, 1400, 1213, 1080, 1026 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3H), 1.34 (s, 3H), 1.49 (s, 3H), 4.15 (dq, J = 11.1, 7.2 Hz, 2H), 4.22 (d, J = 4.8 Hz, 1H), 4.53 (d, J = 11.7 Hz, 1H), 4.65 (t, J = 5.4 Hz, 1H), 4.67 (d, J = 11.7 Hz, 1H), 4.69 (d, J = 3.9 Hz, 1H), 5.15 (d, J = 6.3 Hz, 1H), 5.29 (dd, J = 6.3, 5.8 Hz, 1H), 6.03 (d, J = 3.9 Hz, 1H), 7.22−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.9, 26.6, 27.2, 63.3, 71.9, 77.0, 78.1, 81.4, 81.8, 82.3, 105.5, 113.1, 127.5 (s), 128.1, 128.5 (s), 136.3, 164.5. Anal. Calcd for $C_{19}H_{24}O_{10}S$: C, 51.34; H, 5.44. Found: C, 51.38; H, 5.50.

Ethyl 6-Azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranuronate (6a). To a stirred solution of cyclic sulfate **5a** (2.0 g, 4.52 mmol) in acetone:water (25 mL, 4:1) at 0 °C was added sodium azide (1.76 g, 27.15 mmol) and the reaction mixture was allowed to attain room temperature and then stirred for 2 h. The mixture was concentrated under reduced pressure and diethyl ether (40 mL) and water (6 mL) were added. After dropwise addition of 20% H_2SO_4 (4 mL) the resulting solution was stirred at room temperature for 6 h. The solution was neutralized by adding saturated potassium carbonate solution (10 mL) and the reaction mixture was extracted with diethyl ether (3 × 30 mL), which on usual workup and purification by column chromatography with (n-hexane/ethyl acetate = 8/2) afforded **6a** as a thick liquid (1.5 g, 81.7%). R_f 0.55 (n-hexane/ethyl acetate = 7/3); $[\alpha]_D$ −55.8 (c 0.82, $CHCl_3$); IR (neat) 3400−3600 (broad band), 2114, 1742, 1456, 1377, 1211, 1026, 856 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 1.33 (s, 3H), 1.49 (s, 3H), 2.79 (d, J = 7.2 Hz, 1H, exchanges with D_2O), 4.12 (d, J = 3.3 Hz, 1H), 4.20 (d, J = 3.0 Hz, 1H), 4.24−4.39 (m, 3H), 4.36 (dt, J = 7.8, 7.2, 3.3 Hz, 1H, became dd J = 7.8, 3.3 Hz on D_2O exchange), 5.54 (d, J = 11.4 Hz, 1H), 4.62 (d, J = 3.6 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 5.91 (d, J = 3.6 Hz, 1H), 7.32−7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 26.2, 26.7, 61.8, 64.0, 70.1, 71.9, 78.6, 81.4, 81.8, 104.8, 111.8, 127.5 (s), 127.9, 128.4 (s), 136.7, 167.7. Anal. Calcd for $C_{19}H_{25}N_3O_7$: C, 56.01; H, 6.18. Found: C, 56.22; H, 6.28.

Ethyl 6-Azido-6-deoxy-3-*O*-benzyl-1,2-*O*-isopropylidene-*β*-L-*glycero*-L-*ido*-heptofuranuronate (6b). The reaction of cyclic sulfate **5b** (1.78 g, 4.03 mmol) with sodium azide (1.57 g, 24.17 mmol) followed by hydrolysis with 20% H_2SO_4 (3 mL) as described in the preparation of **6a**, and column purification (n-hexane/ethyl acetate = 8.5/1.5), afforded **6b** as a thick liquid (1.46 g of 89%); R_f 0.56 (n-hexane/ethyl acetate = 7/3); $[\alpha]_D$ −40.7 (c 0.59, $CHCl_3$); IR (neat) 3200−3600 (broad band), 2106, 1743, 1454, 1379, 1179, 1024 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 1.34 (s, 3H), 1.49 (s, 3H), 3.38 (d, J = 2.1 Hz, 1H, exchanges with D_2O), 3.86 (d, J = 6.3 Hz, 1H), 4.12 (d, J = 3.6 Hz, 1H), 4.18−4.28 (m, 3H), 4.35 (dd, J = 3.9, 3.6 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 3.9 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 5.98 (d, J = 3.9 Hz, 1H), 7.33−7.30 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 26.4, 26.9, 61.9, 62.6, 70.8, 74.7, 78.4, 82.2, 82.9, 104.7, 112.1, 127.7 (s), 128.2, 128.5 (s), 136.2, 168.9. Anal. Calcd for $C_{19}H_{25}N_3O_7$: C, 56.01; H, 6.18. Found: C, 56.18; H, 6.25.

6-(*N*-Benzoxycarbonylamino)-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranose (7a). To an ice cooled suspension of LAH (0.486 g, 14.74 mmol) in dry THF (4 mL) was added azido ester **6a** (1.0 g, 2.46 mmol) in dry THF (10 mL) at 0 °C and the solution was stirred for 10 min. The reaction mixture was slowly warmed to room temperature and stirred for an additional 2 h. Reaction was quenched by adding ethyl acetate (30 mL), followed by an aqueous solution of ammonium chloride (3 mL). The reaction mixture was filtered through Celite and the filtrate was concentrated under vacuum. The solution of crude amino alcohol (0.833 g, 2.46 mmol), 10% Pd/C (0.200 g), and ammonium formate (1.24 g, 19.66 mmol) in methanol (10 mL) was refluxed for 1 h. The reaction mixture was filtered through Celite and the filtrate was evaporated to give a thick oil. To a cooled solution of amino alcohol (0.565 g, 2.46 mmol) in methanol−water (10 mL, 9:1) was added benzylchloroformate (0.503 g, 2.92 mmol) and sodium bicarbonate (0.500 g, 5.95 mmol) at 0 °C and the solution was stirred for 2.5 h. Methanol was evaporated under reduced pressure and the residue was extracted with chloroform (3 × 20 mL). Usual workup and purification by column chromatography (n-hexane/ethyl acetate = 1/1) gave **7a** as a white solid (0.47 g, 52.0% overall). Mp 135−137 °C; R_f 0.41 (ethyl acetate); $[\alpha]_D$ +11.7 (c 0.51, $CHCl_3$); IR (Nujol) 3200−3600 (broad band), 1687.6, 1560.3, 1456.2, 1375.2 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.30 (s, 3H), 1.44 (s, 3H), 3.72 (dd, J = 12.3, 4.8 Hz, 1H), 3.92−3.99 (m, 2H), 4.01 (dd, J = 8.1, 3.9 Hz, 1H), 4.16 (dd, J = 8.1, 2.4 Hz, 1H), 4.39 (d, J = 2.4 Hz, 1H), 4.51 (d, J = 3.6 Hz, 1H), 5.10 (s, 2H), 5.92 (d, J = 3.6 Hz, 1H), 7.24−7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 27.0, 53.4, 61.6, 70.8, 72.6, 77.2, 79.3, 82.0, 105.2, 112.1, 127.8 (s), 128.0, 128.5 (s), 137.1, 162.3. Anal. Calcd for $C_{18}H_{25}NO_8$: C, 56.39; H, 6.57. Found: C, 56.48; H, 6.74.

6-(*N*-Benzoxycarbonylamino)-6-deoxy-1,2-*O*-isopropylidene-*β*-L-*glycero*-L-*ido*-heptofuranose (7b). The reaction of **6b** (1.4 g, 3.43 mmol) with LAH (0.68 g, 20.6 mmol) followed by hydrogenolysis and N-Cbz protection as described for **7a** and purification by column chromatography (n-hexane/ethyl acetate = 4/6) afforded **7b** as a white solid (0.75 g, 57%). Mp 119−121 °C; R_f 0.50 (ethyl acetate); $[\alpha]_D$ −10.6 (c 0.56, $CHCl_3$); IR (KBr) 3200−3600 (broad band), 1711, 1537, 1227, 1076 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + D_2O) δ 1.30 (s, 3H), 1.46

(s, 3H), 3 0.72 (dd, J = 11.4, 4.5 Hz, 1H), 3.77−3.79 (m, 1H), 3.98 (dd, J = 11.7, 2.7 Hz, 1H), 4.19−4.24 (m, 2H), 4.30 (d, J = 2.0 Hz, 1H), 4.53 (d, J = 3.6 Hz, 1H), 5.11 (ABq, J = 11.0 Hz, 2H), 5.98 (d, J = 3.9 Hz, 1H), 7.32 (broad s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.3, 26.9, 53.9, 61.8, 67.2, 72.1, 76.0, 79.6, 85.2, 104.8, 111.9, 128.0 (s), 128.2, 128.4 (s), 135.8, 156.8. Anal. Calcd for $C_{18}H_{25}NO_8$: C, 56.57; H, 6.18. Found: C, 56.48; H, 6.25.

1,6-Dideoxy-1,6-imino-(2*S*,3*R*,4*R*,5*R*,6*R*)-L-*glycero*-D-*gluco*-heptitol (1c) Hydrochloride. A solution of **7a** (0.10 g, 0.269 mmol) in TFA−H_2O (3 mL, 2:1) was stirred at 25 °C for 2.5 h. Trifluroacetic acid was coevaporated with benzene to furnish a thick liquid. To a solution of the above product in methanolic hydrochloric acid (5 mL, 9:1) was added 10% Pd/C (0.05 g). The solution was hydrogenated at 80 psi for 24 h. The catalyst was filtered through Celite and washed with methanol. The filtrate was concentrated to obtain a semisolid of **1c** (0.045 g, 75%). R_f 0.20 (chloroform/methanol 8/2); $[\alpha]_D$ +15.9 (c 1.26, MeOH); IR (Nujol) 3200−3600 (broad band) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.19 (broad dd, J = 12.6, 7.2 Hz, 1H), 3.26−3.35 (m, 1H), 3.38−3.48 (m, 1H), 3.72 (dd, J = 12.4, 6.0 Hz, 1H), 3.80−3.92 (m, 4H), 4.02 (broad d, J = 7.2 Hz, 1H); ^{13}C NMR (75 MHz, D_2O) δ 45.3, 59.7, 60.2, 67.6, 70.5, 72.3, 75.1. Anal. Calcd for $C_7H_{16}ClNO_5$: C, 36.61; H, 7.02. Found: C, 36.68; H, 7.25.

1,6-Dideoxy-1,6-imino-(2*S*,3*R*,4*R*,5*S*,6*S*)-D-*glycero*-L-*ido*-heptitol (1d) Hydrochloride. A solution of **7b** (0.10 g, 0.269 mmol) in TFA−H_2O (3 mL, 2:1) was stirred at 25 °C for 2.5 h, and following the procedure described in the synthesis of **1c** afforded **1d** as a sticky gum (0.040 g, 80%). R_f 0.18 (chloroform/methanol 8/2); $[\alpha]_D$ −4.8 (c 3.35, MeOH); IR (neat) 3200−3600 (broad band) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.27−3.36 (m, 2H), 3.56−3.74 (m, 2H), 3.76−3.87 (m, 2H), 3.88−3.96 (m, 1H), 3.98−4.16 (m, 2H); ^{13}C NMR (75 MHz, D_2O) δ 45.9, 58.9, 60.5, 67.5, 68.4, 75.1, 75.6. Anal. Calcd for $C_7H_{16}ClNO_5$: C, 36.61; H, 7.02. Found: C, 36.63; H, 7.10.

3,5,7-Tri-*O*-acetyl-6-(*N*-benzoxycarbonylamino)-6-deoxy-1,2-*O*-isopropylidene-α-D-*glycero*-D-*gluco*-heptofuranose (8a). To an ice-cooled solution of **7a** (0.50 g, 1.30 mmol) in dry pyridine (1.5 mL) was added acetic anhydride (2.65 g, 26.11 mmol). After the mixture was stirred for 8 h at room temperature, ice water was added and extracted with chloroform (3 × 15 mL). Usual workup and chromatographic purification (n-hexane/ethyl acetate = 9/1) afforded triacetate **8a** as a thick liquid (0.524 g, 79%). R_f 0.54 (n-hexane/ethyl acetate 7/3); $[\alpha]_D$ +2.0 (c 1.0, $CHCl_3$); IR (Nujol) 3346, 1747 (broad), 1668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.55 (s, 3H), 2.04 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 4.10−4.21 (m, 1H), 4.30−4.46 (m, 2H), 4.43 (dd, J = 9.6 and 2.7 Hz, 1H), 4.49 (d, J = 3.6 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 5.17 (dd, J = 9.6 and 2.7 Hz, 1H), 5.18 (d, J = 12.0 Hz, 1H), 5.28 (bd, J = 8.7 Hz, 1H, exchanges with D_2O), 5.33 (d, J = 2.7 Hz, 1H), 5.94 (d, J = 3.6 Hz, 1H), 7.39 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7, 20.8 (s), 26.2, 26.7, 51.8, 62.6, 66.9, 69.6, 74.9, 82.9 (s), 105.1, 112.5, 128.1 (s), 128.5 (s), 136.3, 156.0, 169.6, 169.9, 170.8 (s). Anal. Calcd for $C_{24}H_{31}NO_{11}$: C, 56.58; H, 6.13. Found: C, 56.45; H, 6.25.

3,5,7-Tri-*O*-acetyl-6-(*N*-benzoxycarbonylamino)-6-deoxy-1,2-*O*-isopropylidene-*β*-L-*glycero*-L-*ido*-heptofuranose (8b). The reaction of **7b** (0.55 g, 1.44 mmol) with acetic anhydride (2.93 g, 28.72 mmol) and dry pyridine (1.6 mL) under the same conditions used for **7a** followed by column chromatography (n-hexane:ethyl acetate = 8/2) afforded **8b** as a white solid (0.56 g, 77%). Mp 141−143 °C; R_f 0.48 (n-hexane/ethyl acetate = 7/3); $[\alpha]_D$ −3.9 (c 1.03, $CHCl_3$); IR (Nujol) 3375, 1738 (broad), 1689, 1524, 1460, 1377 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 3H), 1.53 (s, 3H), 2.08 (s, 3H), 2.12 (s, 3H), 2.13 (s, 3H), 4.10−4.22 (m, 3H), 4.50 (dd, J = 7.2, 3.3 1H), 4.56 (d, J = 3.9 Hz, 1H), 5.12 (ABq, J = 12.0 Hz, 2H), 5.26 (d, J = 3.3 Hz, 1H), 5.33 (broad s, exchanges with D_2O, 1H), 5.36 (dd, J = 7.2, 3.3 Hz, 1H), 5.94 (d, J = 3.9 Hz, 1H), 7.32−7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (s), 21.0, 26.2, 26.7, 50.6, 62.2, 67.1, 70.9, 77.5, 83.7, 104.3, 112.4, 128.1 (s), 128.2, 128.5 (s), 136.1, 155.6, 170.2 (s), 170.5 (s). Anal. Calcd for $C_{24}H_{31}NO_{11}$: C, 56.58; H, 6.13. Found: C, 56.65; H, 6.20.

1,5-Dideoxy-1,5-imino-(2*R*,3*S*,4*R*,5*R*)-D-altritol (1-Deoxy-altronojirimycin) Hydrochloride (2c·HCl) and 2c. A solution of **8a** (0.20 g, 0.393 mmol) in TFA−H_2O (2:1, 3 mL) was stirred at 25 °C for 2.5 h. Trifluroacetic acid was coevaporated with benzene to furnish a thick liquid. To a cooled solution of hemiacetal (0.162 g, 0.38 mmol) in acetone: water (10 mL, 5:1) was added sodium metaperiodate (0.099 g, 0.46 mmol). After the reaction was stirred for 1.5 h ethylene glycol (0.2 mL) was added and the reaction mixture was concentrated and residue extracted with chloroform (3 × 15 mL). Workup and column purification (n-hexane/ethyl acetate = 8/2) afforded an aldehyde that was directly subjected to hydrogenation in methanol (8 mL) and 10% Pd/C (0.10 g) under 80 psi for 12 h. The catalyst was filtered and washed with methanol and the filtrate was concentrated to get a gummy solid that was directly subjected to deacetylation by MeOH:HCl (3 mL, 9:1) under reflux for 6 h. Then reaction mixture was cooled to room temperature,and on freeze-drying afforded a semisolid of **2c** as hydrochloride (0.042 g, 54% overall). R_f 0.24 (chloroform/methanol = 5/5); $[\alpha]_D$ +31.0 (c 2.0, MeOH) [lit.[4o] $[\alpha]_{589}$ +33.2 (c 0.5, MeOH)]; IR (neat) 3200−3600 (broad band) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 3.09 (dd, J = 13.5, 2.7 Hz, 1H), 3.19−3.30 (m, 2H), 3.70 (dd, J = 12.6, 6.7 Hz, 1H), 3.84 (dd, J = 12.6, 3.6 Hz, 1H), 3.87−3.92 (m, 2H), 3.99−4.24 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 55.8, 58.1, 63.5, 66.1, 68.3. Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07. Found: C, 35.95; H, 7.25.

A solution of **2c·HCl** (0.042 g, 0.21 mmol) in methanol and 25% aqueous ammonia (2:1, 3 mL) was stirred at room temperature for 15 min. The solvent was evaporated on a rotary evaporator and the crude mixture was loaded on Dowex 50W × 8 (100−200 mesh) resin. Elution with methanol−25% aq ammonia (19:1) afforded **2c** (0.028 g, 82%) as a semisolid. R_f 0.30 (chloroform/methanol = 5/5); $[\alpha]_D$ +21.0 (c 0.92, H_2O) [lit.[8a] $[\alpha]_D$ +19.1 (c 0.74, H_2O)]; IR (neat) 3200−3600 (broad band) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 2.68 (dd, J = 14.1, 2.1 Hz, 1H), 2.75 (dt, J = 9.6, 4.5 Hz, 1H), 2.87 (dd, J = 13.8, 2.1 Hz, 1H), 3.62 (d, J = 4.5 Hz, 2H), 3.69 (dd, J = 9.6, 2.7 Hz, 1H), 3.75−3.82 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 44.3, 55.6, 60.3, 65.7, 68.8, 70.3. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03. Found: C, 44.35; H, 8.25.

1,5-Dideoxy-1,5-imino-(2*R*,3*S*,4*S*,5*S*)-L-glucitol (1-Deoxy-L-nojirimycin) Hydrochloride (2d·HCl) and 2d. The reaction of **8b** (0.19 g, 0.373 mmol) with TFA:H_2O (2:1, 3 mL), then with $NaIO_4$ (0.094 g, 0.44 mmol) and hydrogenolysis in the presence of 10% Pd/C (0.10 g), followed by deacetylation in methanolic hydrochloric acid (3 mL, 9:1) with the same reaction conditions as used for **8a** afforded **2d·HCl** as a semisolid (0.070 g, 48.6% overall). R_f 0.20 (chloroform/methanol = 5/5); $[\alpha]_D$ −46.0 (c 1.26, H_2O); IR (neat) 3200−3600 (broad band) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 2.84 (dd, J = 12.3, 12.0 Hz, 1H), 3.08 (ddd, J = 10.2, 5.2, 3.4 Hz, 1H), 3.38 (dd, J = 12.3, 5.4 Hz, 1H), 3.41 (t, J = 9.3 Hz, 1H), 3.47 (dd, J = 10.2, 9.3 Hz, 1H), 3.66 (ddd, J = 12.0, 9.3, 5.4 Hz, 1H), 3.74 (dd, J = 12.6, 5.2 Hz, 1H), 3.81 (dd, J = 12.6, 3.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 43.8, 55.8, 58.1, 63.5, 66.1, 68.3. Anal. Calcd for $C_6H_{14}ClNO_4$: C, 36.10; H, 7.07. Found: C, 36.05; H, 7.18.

The reaction of **2d·HCl** (0.058 g, 0.29 mmol) in methanol and 25% aqueous ammonia as described for **2c** and resin column purification afforded **2d** as a solid (0.045 g, 95%). Mp 192−194 °C (lit.[9b] mp 193−195 °C); R_f 0.10 (chloroform/methanol = 5/5); $[\alpha]_D$ −45.5 (c 0.81, H_2O) [lit.[9b] $[\alpha]^{25}_{589}$ −46° (c 0.3 H_2O)]; IR (neat) 3200−3600 (broad band) cm^{-1}; ^{1}H NMR (300 MHz, D_2O) δ 2.46 (dd, J = 12.0, 11.0 Hz, 1H), 2.56 (ddd, J = 9.0, 6.3, 3.0 Hz, 1H), 3.11 (dd, J = 12.0, 5.4 Hz, 1H), 3.21 (t, J = 9.0 Hz, 1H), 3.29 (t, J = 9.0 Hz, 1H), 3.47 (ddd, J = 11.0, 9.0, 5.4 Hz, 1H), 3.60 (dd, J = 11.7, 6.3 Hz, 1H), 3.79 (dd, J = 11.7, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.3,

60.3, 60.9, 70.4, 71.0, 78.0. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03. Found: C, 44.05; H, 7.95.

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Supporting Information Available: General experimental methods, crystallographic data for **4a**, and copies of ^{1}H and ^{13}C NMR spectra of compounds **1c·HCl**, **1d·HCl**, **2c·HCl**, **2d·HCl**, **2c**, **2d**, **4a**, **4b**, **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **8a**, and **8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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