Articles

Synthesis and Evaluation of Homoazasugars as Glycosidase Inhibitors†

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In an effort to develop transition-state mimetics of the glycosidase-catalyzed reaction, five- and six-membered azasugars and their homo-analogs were prepared and tested as inhibitors of glycosidases. Inhibition studies indicate that the fucosyl cationlike, five-membered imine **1** and its reduced form **2** are potent inhibitors of α-fucosidase from bovine kidney with respective K_i values of 160 nM and 2 μM. The five-membered homoaminoazasugar **3** is also a potent inhibitor of the enzyme ($K_i = 1.9 \times 10^{-6}$ M), while the glucose and mannose-like six-membered homoaminoazasugars **4** and **5** are less potent than the corresponding 1-deoxyazasugars as inhibitors of α-glucosidase and α-mannosidase, respectively. The primary amino group was placed in an attempt to introduce additional electrostatic interactions in the active site. The inhibitory activities are, however, in the high μM range. Synthesis of homoazasugars structurally related to a disaccharide and a nucleoside is also described.

Introduction

Polyhydroxylated piperidines and pyrrolidines are compounds that have been shown to selectively inhibit the oligosaccharide processing enzymes known as glycosidases. These enzymes modify glycoconjugates by hydrolyzing glycosidic linkages, a process which is essential for normal cell growth, regulation, and development. Azasugars that inhibit these enzymes are potentially useful as antiviral, antiadhesive, antimetastatic, antibacterial, antihyperglycemic, or immunostimulatory agents.[1]

Azasugars are good inhibitors of glycosidase enzymes, presumably by mimicking the developing positive charge on the pyranose-ring of the high-energy intermediate with the heterocyclic nitrogen protonated at physiological pH. Of the several different azasugars developed, the five- and six-membered structures of types A and B (Figure 1) have been synthesized and used as inhibitors of glycosidases and glycosyltransferases.[1b,d] We describe here the synthesis and evaluation of a new type of azasugar (i.e., the homoaminoazasugar) in which an aminomethyl group is attached to position one of the deoxyazasugar (Figure 1, C). The primary amino group may also be used for incorporation of an aglycon moiety to prepare sequence-specific glycosidase inhibitors, as many glycosidases differ only with aglycon specificity.[2] We also describe the synthesis of an azasugar-containing C-linked disaccharide and a nucleoside in an effort to develop specific glycosidase inhibitors, as many glycosidases which recognize the same glycon moiety may differ only with the substrate aglycon portion and the type of glycosidic linkage. The aglycon binding may also affect the catalysis of glycosidases and therefore contributes to transition-state recognition in the enzymatic glycosidic cleavage.[2]

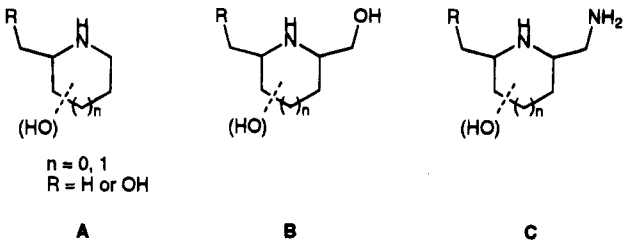

Figure 1. Azasugars, homoazasugars, and homoaminoazasugars.

Results and Discussion

New Homoazasugars as Glycosidase Inhibitors. Primary tosylate **6**, obtained from D-ribose,[3] was stirred with sodium azide in dimethylformamide to afford the primary azide **7** (Scheme 1). The C4 functionality was changed to nitrogen by a reductive ring closure[4] with

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(1) (a) van den Broek, L. A. G. M.; Vermaas, D. J.; Heskamp, B. M.; van Boeckel, C. A. A.; Tan, M. C. A. A.; Bolscher, J. G. M.; Ploegh, H. L.; van Kemenade, F. J.; de Goede, R. E. Y.; Miedema, F. *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 82. (b) Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182. (c) Nishimura, Y. *Stud. Nat. Prod. Chem.* **1992**, *10*, 495. (d) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319. (e) Winchester, B.; Fleet, G. W. *Glycobiology* **1992**, *2*, 199.

(2) For recent papers related to this approach see: (a) Knapp, S.; Purandare, A.; Rupitz, K.; Withers, S. G. *J. Am. Chem. Soc.* **1994**, *116*, 7461. (b) Liu, P. S. *J. Org. Chem.* **1987**, *52*, 4717. (c) Ogawa, S.; Uchida, C.; Shibata, Y. *Carbohydr. Res.* **1992**, *223*, 279. (c) Briggs, J. C.; Haines, A. H.; Taylor, R. J. K. *J. Chem. Soc. Chem. Commun.* **1993**, 1410. (e) Hoos, R.; Naughton, A. B.; Thiel, W.; Vasella, A.; Rupitz, K.; Withers, S. G. *Helv. Chim. Acta* **1993**, *76*, 2666. (f) Pan, Y.-T.; Kaushel, G. P.; Papandreou, G.; Ganem, B.; Elbein, A. D. *J. Biol. Chem.* **1992**, *267*, 8313.

(3) Yamamoto, H.; Nakamura, Y.; Kawamoto, H.; Inokawa, S.; Yamashita, M.; Armour, M.-A.; Nakashima, T. *Carbohydr. Res.* **1982**, *102*, 185.

(4) Dureault, A.; Carreaux, F.; Depezay, J. C. *Synthesis* **1991**, 153.

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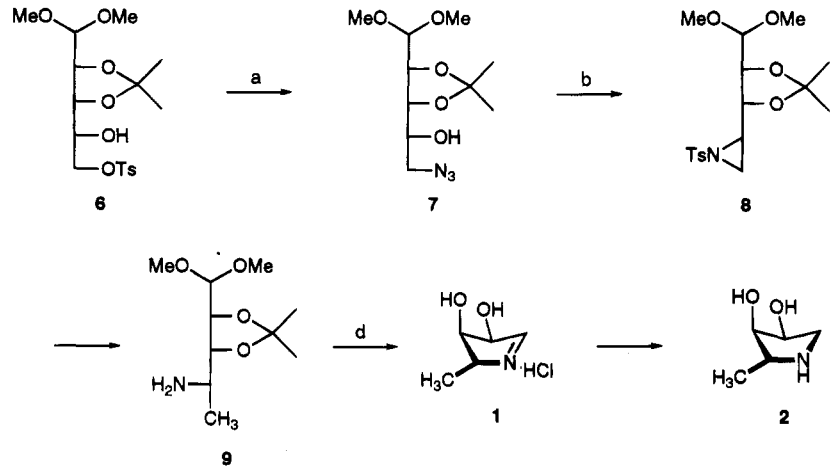
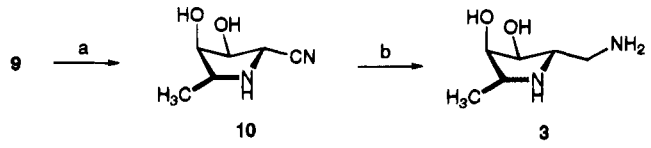
Scheme 1



[a] (a) NaN_3, DMF, 80 °C (86%); (b) (i) PPh_3, $PhCH_3$, reflux; (ii) *p*-TsCl, Et_3N, CH_2Cl_2 (100%); (c) (i) Red-Al, THF; (ii) Na, NH_3, THF (88%); (d) MeOH, 1 N HCl (100%); (e) $NaCNBH_3$, MeOH (12%).

Scheme 2



[a] (a) (i) HCl, H_2O; (ii) KCN, dioxane, H_2O (62%); (b) PtO_2, HCl, EtOH (100%).

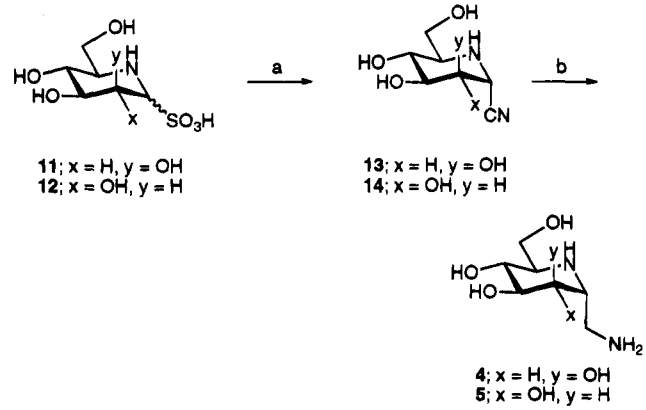
inversion when azide **7** was treated with triphenylphosphine in refluxing toluene. Protection of the resulting aziridine with *p*-toluenesulfonyl chloride afforded activated aziridine **8**, which underwent regioselective ring opening when treated with sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) to afford amine **9** after reductive removal of the tosyl group. Thus the configurations at carbons C3–C6 of fuconojirimycin were established at carbons C2–C5 in intermediate **9**. Acetal removal using 1 N hydrochloric acid produced imine hydrochloride **1**, which was subsequently reduced using sodium cyanoborohydride to give azasugar **2**.

Treatment of imine hydrochloride **1** with potassium cyanide afforded the nitrile-azasugar as a separable mixture of β (**10**) and α isomers (3:1) (Scheme 2). It is interesting to note that the α isomer equilibrated back to the 3:1 ratio after being dissolved in deuterium oxide and allowed to stand for several days. The β-nitrile **10** was reduced by a platinum oxide-catalyzed hydrogenation to produce homoaminoazasugar **3**. The selectivity of the nitrile addition was determined by NOE studies on **10** and further confirmed by the H2–H3 coupling constant being 9.2 Hz, and the cis H3–H4 and the cis H4–H5 coupling constants being 3.7 and 2.7 Hz, respectively, in homoaminoazasugar **3**.

The homoaminoazasugars **4** and **5** were synthesized from commercially available nojirimycin bisulfite and mannojirimycin bisulfite, respectively. Reaction of bisulfite adducts **11** and **12** with potassium cyanide in the presence of $Ba(OH)_2$ and ethanolic HCl[5] afforded the corresponding α-nitriles **13** and **14**, which were converted to the homoaminoazasugars **4** and **5** by a palladium-catalyzed reduction under acidic conditions (Scheme 3).

Interestingly, of the inhibitors tested against α-fucosidase (Table 1), the intermediate imine **1**, which also

Scheme 3

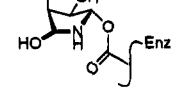


[a] (a) $Ba(OH)_2$, KCN, HCl (**12** → **14**; 78%); (b) H_2, Pd/C, HCl (**13** → **4**, 100%; **14** → **5**, 78%).

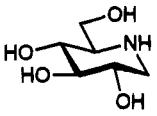
exists as a dimer and as the 1-hydroxy form,[6] proved to be the most powerful inhibitor with K_i = 0.16 μM, and exhibited time dependent inhibition indicating the possibility of a covalent attachment to the enzyme.[6e,7] The inhibition of homoaminoazasugar **3** (K_i = 1.9 μM) is only slightly better than azasugar **2** (K_i = 2.0 μM) and is comparable to the analogous homoazasugar having the amino group replaced by a hydroxyl group.[1b] This indicates that the additional electrostatic interaction of the primary amino group does not lead to increased binding, and the transition state of the leaving group may not be positively charged. Homoaminoazasugar **5** and 1-deoxynojirimycin exhibited similar inhibition (K_i = 31 and 25 μM, respectively) to α-glucosidase;[8] however,

(5) Böshagen, H.; Geiger, W.; Junge, B. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 806.

(6) (a) Kayakiri, H.; Takase, S.; Setoi, H.; Uchida, I.; Terano, H.; Hashimoto, M. *Tetrahedron Lett.* **1988**, *29*, 1725. (b) Witte, J. F.; McClard, R. W. *Tetrahedron Lett.* **1991**, *32*, 3927. (c) Shibata, T.; Nakayama, O.; Tsurumi, Y.; Okuhara, M.; Terano, H.; Kohsaka, M. *J. Antibio.* **1988**, *41*, 296. (d) Paulsen, H.; Koebernick, H.; Schönherr, H. *Chem. Ber.* **1972**, *105*, 1515. (e) Provencher, L.; Steensma, D. H.; Wong, C.-H. *Bioorg. Med. Chem.* **1994**, *2*, 1179. The 3-epimer of **1** is a potent time-dependent inactivator (K_i = 0.12 μM) of α-rhamnosidase. The time dependent inactivation rate was not determined as the kinetics were not first order. The imine may form a covalent adduct with the active-site carboxylate group.



homoaminoazasugar **4** (K_i = 500 μM) is a weaker inhibitor than 1-deoxymannojirimycin (K_i = 68 μM) of α-mannosidase.[9] Compounds **4** and **5** likely adopt a chairlike conformation. Since both chair- and half-chairlike aza-



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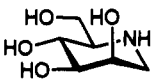
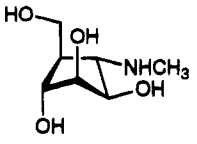


5a

sugars are good inhibitors (K_i values in the low micromolar range) of α- and β-glucosidases,[1b] azasugars which mimic either the chair structure A or the half-chair structure B (Figure 2) probably are good mimics of the glucopyranosyl cation. Mannopyranosyl cation, however, exists, based on modeling,[10] preferentially in the "triaxial conformation" C (Figure 2), and compounds that contain hydroxyl groups which mimic the unique position of the hydroxyl groups (especially the C2-OH) are good inhibitors of α-mannosidase, as exemplified by the inhibitory activity of compound **15** (IC_{50} = 62 nM).[11] Although the protonated forms of inhibitors **1**–**3** are considered to be effective by mimicking the developing positive charge and the half-chair conformation of the fucosidic cleavage reaction, they are much less active than the chairlike 1-deoxyfuconojirimycin (**16**) as inhibitors of α-fucosidase.[12] The half-chairlike L-fucoamidrazone (**17**)[13] is also less active than **16**. One possible explanation is that the



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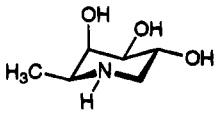

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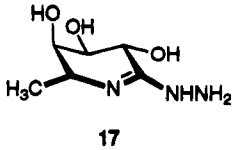

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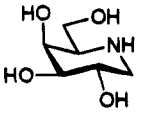

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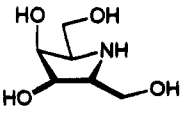

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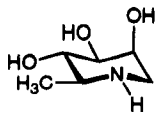

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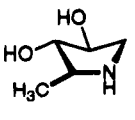

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Table 1. Comparison of Inhibitory Activities

compound	enzyme	K_i (μM)
1	α-L-fucosidase	0.16
2	α-L-fucosidase	2.0
3	α-L-fucosidase	1.9
4	α-D-glucosidase	31
4a	α-D-glucosidase	25
5	α-D-mannosidase	500
5a	α-D-mannosidase	68
15	α-D-mannosidase	0.062 (IC_{50})
16	α-L-fucosidase	0.005
17	α-D-fucosidase	0.82
18	α-galactosidase	0.0016
19	α-galactosidase	0.05
20	α-L-rhamnosidase	490
21	α-L-rhamnosidase	5.5

α-fucosidase-catalyzed reaction may proceed through a transition state which has a high degree of chairlike character (Figure 3, A). Whether protonation of the leaving oxygen (nitrophenoxide) occurs or not, the α-glycoside may provide a favorable stereoelectronic effect (the anomeric effect) for the glycosidic cleavage without prior distortion to a half-chair conformation, which may exist in the late transition state.[14] Similarly, the chairlike six-membered 1-deoxygalactojirimycin (**18**) is a better inhibitor (K_i = 1.6 nM)[15] of α-galactosidase than any other half-chairlike azasugar, including the five-membered homoazasugar **19** (K_i = 50 nM).[16] Another explanation is that the half-chairlike azasugars prepared so far do not perfectly mimic the half-chair transition state, especially with regard to the charge distribution and the hydroxyl group orientation. 1-deoxyrhamnojirimycin (**20**) is, however, a weaker inhibitor (K_i = 490 μM) of α-L-rhamnosidase than the five-membered azasugar **21** (K_i = 5.5 μM)[6e] suggesting the likelihood of a half-chair transition state for this enzymatic reaction.

This study provides some new information regarding the mode of inhibition of several glycosidases. Although many azasugars that resemble glycopyranosyl cation species are considered to be transition-state analog inhibitors of glycosidases, the conformation of the transition state and the timing of bond breaking and forming in the enzymatic reaction, including the protonation step, remain subjects for investigation. The ^{18}O effects on the acid-catalyzed hydrolysis of oxygen glycosides indicate that the glycosidic bond is largely broken at the transition state and the leaving-group oxygen may be protonated in a general-acid catalysis step or in a preequilbrium step.[17a-c] The β_{lg} values obtained with different leaving groups and catalysts are always negative or zero, indicating that the charge on the leaving group oxygen either becomes more negative or remains uncharged.[17d] Comparison to the hydrolysis of α- and β-glycosyl fluorides shows a more pronounced double bond character between O5 and C1 in the case of the glycosyl fluorides and a significant difference in the transition-state conformation,[18] thus indicating the importance of considering the leaving-group moiety in the design of a selective inhibitor. Due to the importance of sialyl Lewis x as a ligand for

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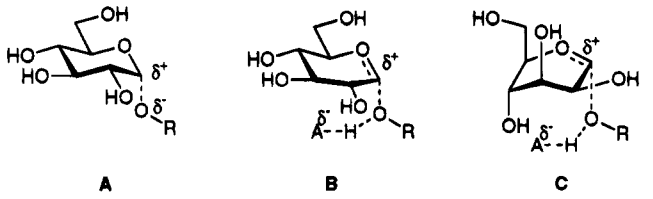

Figure 2. Possible transition-state structures for the acid-catalyzed hydrolysis of α-glucosides (**A**, **B**) and α-mannosides.

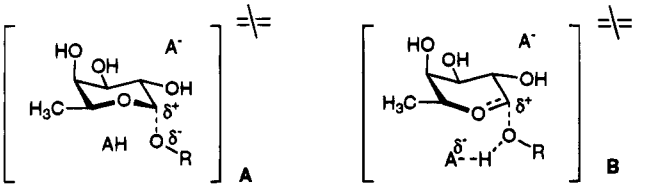

Figure 3. Putative chairlike (**A**) and half-chairlike (**B**) transition-state structures of α-fucosidase-catalyzed reactions.

the cell adhesion molecule E-selectin,[19] we are continuing to refine the structures of azasugars to develop effective and selective inhibitors of L-fucosidase and L-fucosyltransferase, which are involved in the processing of sialyl Lewis x.

Synthesis of C-Linked Azadisaccharide and Azanucleoside. Several natural products and synthetic analogs[2,20] that act as sequence selective glycosidase inhibitors contain an aglycon moiety attached to an appropriate glycosyl cation mimetics.

As described in this and previous studies[1,21] that five-membered azasugars and their homoanalogs are effective inhibitors of glycosidases, incorporation of a leaving grouplike aglycon moiety into a five-membered azasugar (Schemes 4, 5, 7) may be useful for the development of selective glycosidase inhibitors.

For the synthesis of the protected pseudoazadisaccharide **36**, a reductive amination was used to link the glycon and the aglycon moieties, while in the synthesis of the pseudoazanucleoside (**43**), a displacement reaction was used.

The homoazasugar **22** prepared previously based on an aldolase reaction[22] was shown to be an effective inhibitor of α- and β-glucosidases with K_i at the low micromolar range. The X-ray crystal structure of **22** indicates a half-chairlike structure (Figure 4), supporting the argument that five-membered azasugars can be effective inhibitors of glycosidases. Further straightforward manipulation of **22** leads to a key intermediate ready for the aglycon coupling. As shown in Scheme 4, regioselective protection of **22** with triphosgene gave **23** in 91% yield. A minor contamination (~8%) of the regioisomer **23a** was removed by flash chromatography. In addition to NMR analysis, the structures of **23** and **23a** were further confirmed by comparison with an authentic sample of **23a** prepared from **38** (Scheme 6)

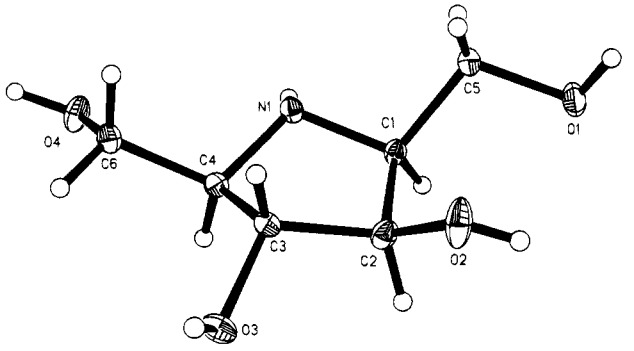

Figure 4. X-ray structure of **22**.

which was prepared from **37**[23] and structurally verified by NMR and X-ray structural analysis (Figure 5).

Compound **23** was then converted to aldehyde **27** which was coupled to **35** via reductive amination to give **36** in 60% yield (Scheme 5). Debenzylation of **36** should give the desired pseudodisaccharide. This strategy should be applicable to the synthesis of other pseudoazasaccharides with different aglycon groups.

For the synthesis of the pseudo-azanucleoside **43**, compound **25** prepared above was converted to **40** which was then subjected to a nucleophilic displacement with a purine base, 2-amino-6-chloropurine,[24] to give **41** in 50% yield (Scheme 7). Refluxing **41** with mercaptoethanol and sodium methoxide in ethanol[25] gave **42** in 49% isolated yield. In an attempt to remove the protecting groups of **42**, hydrogenolysis (50 psi) in the presence of Pd–C in methanol was conducted for 24 h; however, no reaction was observed, and the starting material was recovered. Boron trichloride[26] was therefore used for the deprotection to give **43** in 37% yield. The synthesis of **43** from **22** takes eight steps with an overall yield of 15%.

These two procedures appear to be quite general, and work is in progress to use this strategy to prepare some other azaglycosides for evaluation as sequence-specific glycosidase inhibitors.

Experimental Section

General. All chemicals were purchased from commercial sources as reagent grade. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Melting points are uncorrected. Optical rotations were recorded on a Perkin-Elmer 141 or an Autopol III polarimeter.

5-Azido-5-deoxy-2,3-*O*-isopropylidine-D-ribose-dimethylacetal (7). To a stirred solution of **6** (2.83 g, 7.25 mmol) in dry dimethylformamide (40 mL) was added sodium azide (2.35 g, 36.24 mmol), and the reaction mixture was stirred at 80 °C for 19 h. The solvent was then evaporated, the residue dissolved in EtOAc (100 mL), and the organic phase washed with water (3 × 15 mL) and brine (1 × 15 mL), dried over magnesium sulfate, filtered, and evaporated. The residue was chromatographed on silica gel using 2:1 EtOAc/hexanes to afford **7** (1.63 g, 6.22 mmol, 86%) as a clear oil; $[\alpha]^{24}_D$ +4.2 (c = 1.42, $CHCl_3$); IR 3483, 2988, 2938, 2836, 2102, 1736, 1672, 1446, 1382, 1306, 121, 1169, 1081, 973, 923, 869,

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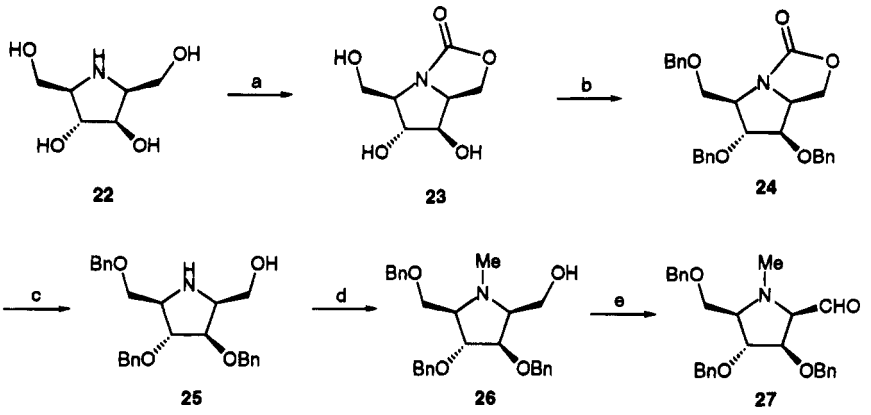
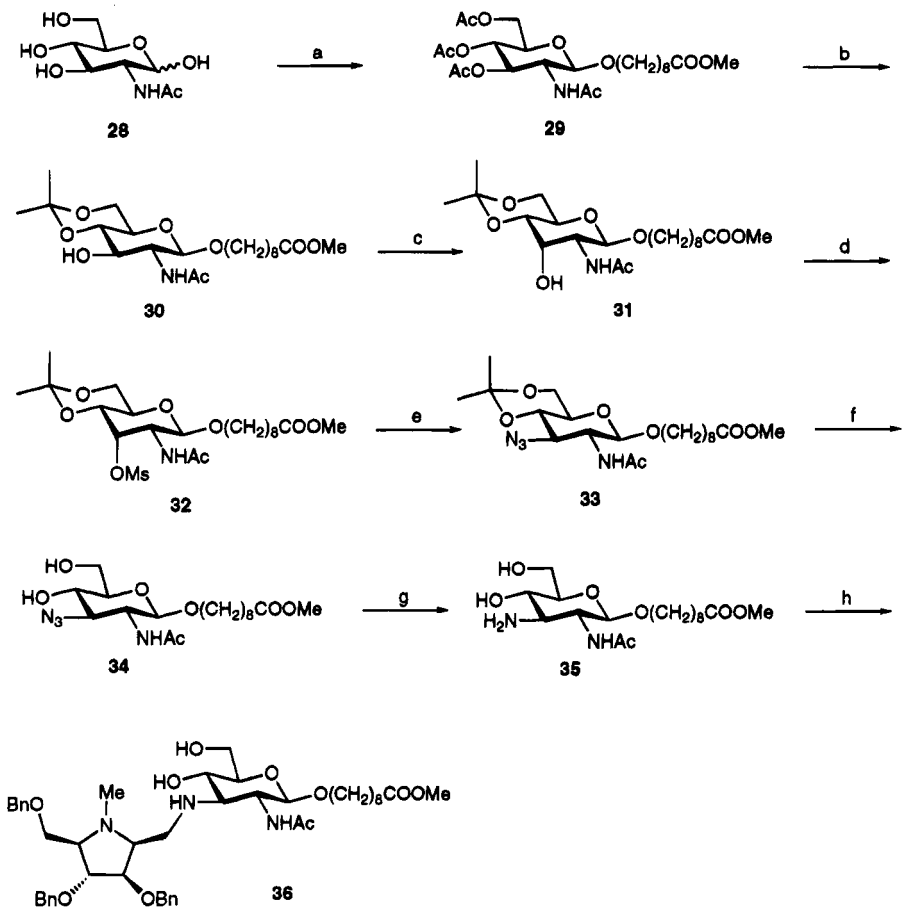
Scheme 4



[a] (a) Triphosgene, toluene, 10% $NaHCO_3$ (91%); (b) BnBr, NaH, KI, DMF (88%); (c) aqueous KOH, ethylene glycol, 110 °C (99%); (d) (i) $(CH_2O)_n$, MeOH, reflux; (ii) $NaCNBH_3$, 0 °C, Na_2CO_3, THF–MeOH (88%); (e) DMSO, $(CO)_2Cl_2$, CH_2Cl_2, Et_3N, −78 °C.

Scheme 5

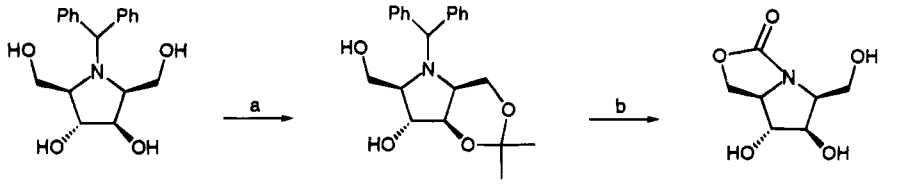


[a] (a) (i) AcCl; (ii) $HO(CH_2)_8COOMe$, $Hg(CN)_2$, $CaSO_4$ (92%); (b) (i) NaOMe, MeOH; (ii) 2,2-dimethoxypropane, TsOH, DMF (94%); (c) (i) MsCl, pyridine; (ii) NaOAc, 2-methoxyethanol–H_2O (95:5), 100 °C; (iii) NaOMe, MeOH (95%); (d) MsCl, pyridine; (e) NaN_3, DMF; (f) 80% AcOH, 95 °C, 2 h (90%); (g) H_2, Lindlar (99%); (h) (i) **27**, $MgSO_4$, MeOH; (ii) $NaBH_4$, MeOH (60%).

800 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.48 (d, J = 6.84 Hz, 1H), 4.23 (dd, $J_1 = J_2$ = 6.0 Hz, 1H), 4.14 (dd, J_1 = 9.5 Hz, J_2 = 5.9 Hz, 1H), 3.96 (ddd, J_1 = 12.04 Hz, J_2 = 5.92 Hz, J_3 = 2.84 Hz, 1H), 3.84 (d, J = 3.0 Hz, 1H), 3.54 (ddd, J = 12.76 Hz, J_2 = 2.52 Hz, J_3 = 0.92 Hz, 1H), 3.50 (s, 3H), 3.49 (s, 3H), 3.40 (ddd, J_1 = 12.88 Hz, J_2 = 6.16 Hz, J_3 = 0.48 Hz, 1H), 1.44 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 109.29, 102.71, 77.07, 75.89, 68.69, 55.48, 54.15, 53.82, 27.48, 25.26; HRMS calcd for $C_{10}H_{19}N_3O_5$ (M + Na^+) 284.1222, found 284.1222.

4,5-Dideoxy-2,3-isopropylidine-4,5-(tosyl)imino-L-lyxose Dimethyl Acetal (8). To a solution of PPh_3 (1.30 g, 5.0 mmol) in dry toluene (18 mL) was added dropwise **7** (1.31 g, 5.0 mmol) (previously dried by azeotropic removal of water with benzene) in dry toluene (18 mL) at room temperature. The reaction mixture was stirred at 40 °C for 30 min during which time there was an evolution of gas. The reaction mixture was then refluxed for 6 h, the toluene evaporated, and the residue taken up in ether. The precipitated white solid was filtered and the filtrate evaporated. The residue was purified using silica gel chromatography eluting with 5% methanol in chloroform to afford 4,5-dideoxy-4,5-imino-2,3-isopropylidine-L-lyxose dimethyl acetal as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (d, J = 7.76 Hz, 1H), 4.23 (dd,

Scheme 6



[a] (a) 2-Methoxypropene, TsOH (65%); (b) (i) H_2, $Pd(OH)_2$; (ii) triphosgene, toluene, 5% $NaHCO_3$; (iii) TsOH, MeOH (36%).

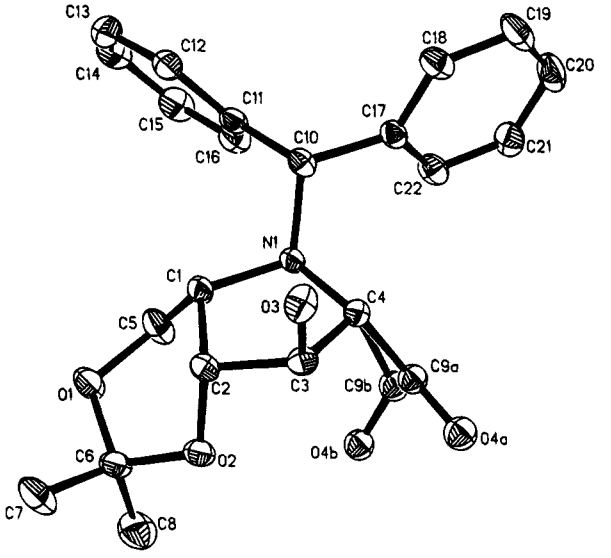


Figure 5. X-ray structure of **38**.

J_1 = 7.76 Hz, J_2 = 6.68 Hz, 1H), 3.93 (dd, $J_1 = J_2$ = 6.04 Hz, 1H), 3.47 (s, 3H), 3.44 (s, 3H), 2.16 (ddd, $J_1 = J_2$ = 5.68 Hz, J_3 = 3.6 Hz, 1H), 1.72 (d, J = 5.80 Hz, 1H), 1.60 (d, J = 3.60 Hz, 1H), 1.50 (s, 3H), 1.36 (s, 3H), 1.08 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 108.74, 102.12, 77.82, 75.84, 54.60, 52.95, 29.03, 27.21, 24.77, 21.59. The above aziridine was dissolved in dichloromethane (65 mL); triethylamine (2.1 mL, 15.0 mmol) and TsCl (1.91 g, 10.0 mmol) were added, and the reaction mixture was stirred overnight. Methanol (5 mL) was added, and the volatiles were removed *in vacuo*. The residue was purified by silica gel chromatography using 2:1 hexanes/EtOAc to afford sulfonamide **8** (1.88 g, 100%) as a colorless oil. $[\alpha]^{24}_D$ +40.4 (*c* 1.73, $CHCl_3$); IR 2987, 2937, 1598, 1455, 1324, 1220, 926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.32 Hz, 2H), 7.33 (d, J = 8.16 Hz, 2H), 4.72 (d, J = 7.68 Hz, 1H), 4.24 (dd, $J_1 = J_2$ = 6.52 Hz, 1H), 3.88 (dd, $J_1 = J_2$ = 6.28 Hz, 1H), 3.46 (s, 3H), 3.43 (s, 3H), 2.97 (dd, J_1 = 10.80 Hz, J_2 = 6.24 Hz, 1H), 2.59 (d, J = 7.12 Hz, 1H), 2.44 (s, 3H), 2.20 (d, J = 4.56 Hz, 1H), 1.39 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 144.41, 135.03, 129.49, 127.95, 109.86, 101.86, 76.19, 76.03, 54.39, 53.93, 39.10, 29.88, 26.94, 25.29, 21.54; HRMS calcd for $C_{17}H_{25}NO_6S$ (M + H^+) 372.1481, found 372.1481.

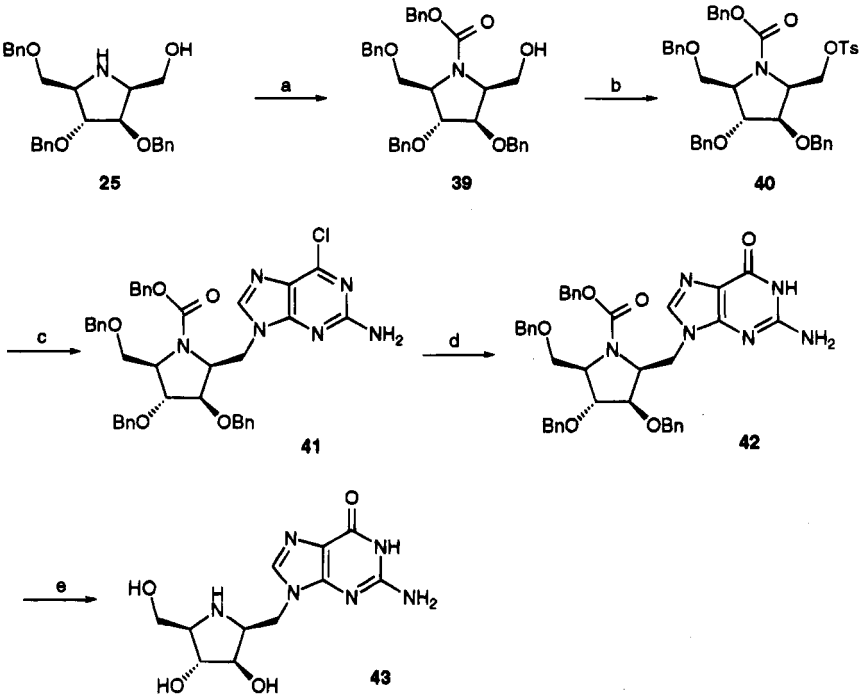
4-Amino-4,5-dideoxy-2,3-*O*-isopropylidine-L-lyxose Dimethyl Acetal (9). Aziridine **8** (1.70 g, 4.58 mmol) was dissolved in dry THF, and the reaction mixture was cooled to −78 °C. Red-Al (3.4 M in toluene) (2.4 mL, 8.0 mmol) was added; the reaction mixture allowed to attain room temperature, and stirring continued for 20 h. The reaction mixture was then cooled to 0 °C and quenched with a saturated solution of sodium potassium tartrate (15 mL) and the mixture stirred until the white solids dissolved. The reaction mixture was then extracted with ether (5 × 25 mL), the combined extracts were dried over magnesium sulfate and filtered, and the solvent was evaporated. Purification of the residue by silica gel chromatography using 1:1 hexanes/EtOAc afforded 4,5-dideoxy-2,3-O-isopropenyl-4-(*N*-tosylamino)-L-lyxose dimethyl acetal (1.71 g, 100%) as a colorless oil: $[\alpha]^{24}_D$ −38.4 (*c* 1.1, $CHCl_3$); IR 3301, 2986, 2939, 2832, 1599, 1494, 1455, 1408, 1376, 1336, 1214, 1162, 1093, 969, 869, 815, 674 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.28 Hz, 2H), 7.31 (d, J = 8.04 Hz, 2H), 4.76 (d, J = 7.96 Hz, 1H), 4.63 (d, J = 7.92 Hz, 1H), 4.14 (dd, J_1 = 7.80 Hz, J_2 = 6.96 Hz, 1H), 3.96 (dd, J_1 = 6.88 Hz, J_2 = 3.48 Hz, 1H), 3.71 (dqd, J_1 = 7.92 Hz, J_2 = 6.64 Hz, J_3 = 3.44 Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.42 (s, 3H), 1.46 (s, 3H), 1.33 (s, 3H), 1.03 (d, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.29, 138.52, 129.59, 127.02, 108.60, 101.10, 79.38, 76.19, 54.25, 53.89, 48.23, 26.74, 24.29, 21.45, 19.57; HRMS calcd for $C_{17}H_{27}NO_6S$ (M + Na^+) 396.1457, found 396.1461. The sulfonamide (418 mg, 1.12 mmol) was dissolved in dry THF (3 mL), and ammonia (15 mL) was condensed into the reaction vessel. Sodium (ca. 100 mg) was added until the reaction mixture maintained a blue color. After 30 min the reaction was quenched with saturated ammonium chloride (1 drop) and the ammonia was allowed to evaporate. THF (25 mL) and triethylamine (1.5 mL) were added to the reaction mixture and the mixture filtered through Celite. Evaporation followed by purification of the residue by silica gel chromatography (3:1 EtOAc/Et_3N) afforded amine **9** (217 mg, 88%) as a colorless oil: $[\alpha]^{24}_D$ +21.0 (*c* 1.9 $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.56 (d, J = 7.56 Hz, 1H), 4.09 (dd, J_1 = 7.60 Hz, J_2 = 5.96 Hz, 1H), 3.86 (dd, $J_1 = J_2$ = 6.24 Hz, 1H), 3.43 (s, 3H), 3.40 (s, 3H), 3.06 (dq, $J_1 = J_2$ = 6.36 Hz, 1H), 1.55 (br s, 2H), 1.49 (s, 3H), 1.37 (s, 3H), 1.14 (d, J = 6.36 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.97, 101.60, 82.29, 75.63, 54.45, 52.76, 45.43, 27.33, 25.16, 21.12; HRMS calcd for $C_{10}H_{21}NO_4$ (M + H^+) 220.1549, found 220.1556.

Imine 1. Amine **9** (102 mg, 0.47 mmol) was stirred in methanol and 1 N HCl (1:1, 5 mL) for 65 h. The volatiles were removed *in vacuo* (aspirator to dryness and then high vacuum for 2 d) to afford **1** (73 mg, quant) as a white solid, mp 96–100 °C dec. Data for the mixture of imine, 1-hydroxy, and dimer forms: IR 3085, 2989, 2940, 1718, 1637, 1618, 1560, 1542, 1508, 1458, 1388, 1203, 1153, 1122, 1107 cm^{-1}. At high pH the imine form is predominate: ^1H NMR (400 MHz, D_2O/NaOD) δ 7.33 (d, J = 3.0 Hz, 1H, H-1 imine), 1.06 (d, J = 7.2 Hz, 3H, H-5 imine); ^{13}C NMR (62.5 MHz, D_2O/NaOD) δ 174.1, 81.3, 72.9, 68.4, 14.5 (imine); HRMS calcd for $C_{10}H_{18}N_2O_4$ (dimer) (M + H^+) 231.1345, found 231.1345.

3(*R*),4(*S*)-Dihydroxy-2(*S*)-methylpyrrolidine (2). To a solution of imine hydrochloride **1** (157 mg, 0.93 mmol) dissolved in methanol (10 mL), pH 6.0, was added $NaCNBH_3$ (62 mg, 0.96 mmol) and the reaction mixture stirred for 72 h while maintaining the pH at 6.0 (0.1 N HCl). 12 N HCl was added and the reaction mixture filtered through Celite. The residue was dissolved in methanol and stirred with Dowex 1X2-400 until a pH of 11 was maintained. The mixture was filtered and evaporated and the residue purified by preparative TLC (7:3:1 CH_2Cl_2/MeOH/NH_4OH) to give **2** (13 mg, 12%) as an oil: $[\alpha]^{25}_D$ +20.5 (*c* 0.65, D_2O); ^1H NMR (400 MHz, D_2O) δ 4.31 (ddd, $J_1 = J_2$ = 7.72 Hz, J_3 = 4.28 Hz, 1H), 3.95 (dd, $J_1 = J_2$ = 3.92 Hz, 1H), 3.32 (dd, J_1 = 6.84 Hz, J_2 = 3.60 Hz, 1H), 3.24 (dd, J_1 = 12.04 Hz, J_2 = 7.92 Hz, 1H), 2.88 (dd, J_1 = 12.00 Hz, J_2 = 7.40 Hz, 1H), 1.15 (d, J = 6.84 Hz, 3H); ^{13}C NMR (62.5 MHz, D_2O) δ 72.3, 71.4, 57.6, 48.2, 12.3; HRMS calcd for $C_5H_{11}NO_2$ (M + H^+) 118.0868, found 118.0868.

Nitrile 10. Amine **9** (145 mg, 0.66 mmol) was dissolved in 1 N HCl and the reaction mixture was stirred at room temperature for 7 h. The volatiles were removed *in vacuo*, the resulting white solid was dissolved in dioxane (2 mL) and water (0.4 mL), potassium cyanide (43 mg, 0.66 mmol) was added, and the reaction mixture was stirred at room temperature for 3 d. The solvent was evaporated and the residue

Scheme 7



[a] (a) Benzyl chloroformate, Et_3N (88%); (b) *p*-TsCl, pyridine (88%); (c) 2-amino-6-chloropurine, K_2CO_3 in DMF (50%); (d) NaOMe, mercaptoethanol in MeOH (49%); (e) BCl_3 (37%).

chromatographed on silica gel (10:2:1 CH_3CN/H_2O/AcOH) to afford β-nitrile **10** (58 mg, 62%) as an oil: $[\alpha]^{24}_D$ -45.0 (*c* = 0.3 H_2O); ^1H NMR (400 MHz, D_2O) δ 4.48 (dd, J_1 = 7.84 Hz, J_2 = 4.04 Hz, 1H), 3.92 (d, J = 7.88 Hz, 1H), 3.88 (dd, $J_1 = J_2$ = 3.48 Hz, 1H), 3.19 (qd, J_1= 6.64 Hz, J_2 = 2.92 Hz, 1H), 1.01 (d, J = 6.72 Hz, 3H); ^{13}C NMR (100 MHz, D_2O) δ 123.75, 79.89, 75.40, 58.11, 53.82, 15.32; HRMS calcd for $C_6H_{10}O_2N_2$ (M + H^+) 143.0821, found 143.0826. Data for α-nitrile: ^1H NMR (400 MHz, D_2O) δ 4.36 (dd, J_1 = 8.04 Hz, J_2 = 4.24, 1H), 4.26 (d, J = 8.0 Hz, 1H), 3.94 (dd, $J_1 = J_2$ = 4.04 Hz, 1H), 3.20 (qd, J_1 = 6.56 Hz, J_2 = 3.84 Hz, 1H), 1.05 (d, J = 6.68 Hz, 3H); ^{13}C (100 MHz, D_2O), δ 122.05, 75.16, 74.83, 57.58, 52.64, 16.68; HRMS calcd for $C_6H_{10}O_2N_2$ (M + H^+) 143.0821, found 143.0227.

Homoaminoazasugar 3. Nitrile **10** (40 mg, 0.22 mmol) was dissolved in absolute ethanol (11 mL) and concentrated hydrochloric acid (0.2 mL) followed by addition of platinum-(IV) oxide (15 mg). The reaction vessel was purged five times with hydrogen after which the hydrogen pressure was maintained at 50 psi for 3 h. The reaction mixture was filtered through Celite and the solvent evaporated under reduced pressure to afford the HCl salt of homoaminoazasugar **3** (62 mg, quant) as a white solid: mp 125–130 °C dec; $[\alpha]^{24}_D$ −26.4 (*c* = 1.05 H_2O); IR 3465, 2072, 1651, 1504, 1154, 1128, 1042, 999 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 4.21 (dd, J_1 = 9.16 Hz, J_2 = 3.68 Hz, 1H), 4.07 (dd, $J_1 = J_2$ = 3.16 Hz, 1H), 3.78 (qd, J_1 = 6.52 Hz, J_2 = 2.68 Hz, 1H), 3.67 (ddd, $J_1 = J_2 = J_3$ = 7.76 Hz, 1H), 3.45 (dd, J_1 = 14.0 Hz, J_2 = 7.82 Hz, 1H), 3.39 (dd, J_1 = 14.0 Hz, J_2 = 5.98 Hz, 1H), 1.28 (d, J = 6.8 Hz, 3H); ^{13}C (100 MHz, D_2O) δ 74.73, 71.45, 58.49, 57.64, 39.61, 11.42. HRMS calcd for $C_6H_{14}O_2N_2$ (M + H^+) 147.1134, found 147.1130.

Nitrile 13. To a suspension of $Ba(OH)_2{\cdot}8H_2O$ (641 mg) in water (15 mL) were added mannojirimycin bisulfite (**11**) (483 mg, 2.0 mmol), KCN (195 mg, 3.0 mmol), and 6 N hydrogen chloride (0.5 mL). After stirring for 4 h, the reaction mixture was filtered through Celite to give a clear solution which was treated with a saturated solution of $FeSO_4$, and the precipitates were removed by filtration through Celite. Lyophylization afforded nitrile **13** (293 mg, 78%) as a thick oil: $[\alpha]^{28}_D$ +2.4 (*c* 0.54, H_2O); IR 3364, 2238, 1654, 1094, 930, 808 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.23 (d, J = 3.0 Hz, 1H), 4.16 (t, J = 3.0 Hz, 1H), 3.84 (dd, J_1 = 11.5 Hz, J_2 = 3.0 Hz, 1H), 3.71 (dd, J_1 = 9.5 Hz, J_2 = 3.5 Hz, 1H), 3.60 (dd, J_1 =11.5 Hz, J_2 = 7.0 Hz, 1H), 3.48 (dd, $J_1 = J_2$ = 9.8 Hz, 1H), 2.79 (ddd, J_1 = 9.5 Hz, J_2 = 6.5 Hz, J_3 = 3.0 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 118.07, 72.38, 69.33, 68.23, 61.27, 58.10, 50.26; HRMS calcd for $C_7H_{12}N_2O_4$ (M + H^+) 189.0875, found 189.0879.

1-Amino-1-deoxy-2,6-dideoxy-2,6-imino-D-*glycero*-D-*talo*-heptopyranose (4). To a solution of nitrile **13** (50 mg, 0.27 mmol) in methanol (20 mL) were added anhydrous hydrogen chloride (1.0 N in ether, 1.0 mL, 1.0 mmol) and 10% Pd/C (50 mg). The mixture was purged with hydrogen (4 × 50 psi) and agitated at 50 psi for 1 day. The mixture was filtered through Celite, the solvent evaporated, and the residue purified using Bio Gel P2 with water as eluent to afford **4** (40 mg, 78%) as a thick oil: $[\alpha]^{28}_D$ +1.4 (*c* 2.57, H_2O); IR 3405, 1618, 1162, 1078, 889, 758 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 4.21 (dd, J_1 = 5.5 Hz, J_2 = 3.0 Hz, 1H), 3.99 (dd, J_1 = 12.5 Hz, J_2 = 7.5 Hz, 1H), 3.95 (dd, $J_1 = J_2$ = 7.5 Hz, 1H), 3.90 (dd, J_1 = 12.5 Hz, J_2 = 3.5 Hz, 1H), 3.85–3.88 (m, 1H), 3.81 (dd, J_1 = 7.5 Hz, J_2 = 3.0 Hz, 1H), 3.48 (dd, J_1 = 6.0 Hz, J_2 = 3.0 Hz, 2H), 3.40 (ddd, J_1 = 7.5 Hz, J_2 = 7.5 Hz, J_3 = 3.5 Hz, 1H); ^{13}C NMR (500 MHz, D_2O) δ 69.58, 67.77, 66.22, 57.45, 37.61; HRMS calcd for $C_7H_{16}N_2O_4$ (M + H^+) 193.1188, found 193.1178.

1-Amino-1-deoxy-2,6-dideoxy-2,6-imino-D-*glycero*-D-*ido*-heptopyranose (5). To a solution of nitrile **14**[5] (38 mg, 0.2 mmol) in ethanol (25 mL) were added anhydrous hydrogen chloride (1.0 N in ether, 0.55 mL, 0.55 mmol) and 10% Pd/C (44 mg). The mixture was purged with hydrogen (4 × 50 psi) and agitated at 50 psi for 2.5 d. The mixture was filtered through Celite to afford **5** (39 mg, 100%) as a thick oil: $[\alpha]^{28}_D$ +2.5 (*c* 1.0, H_2O); IR 3384, 1618, 1100, 1033, 900, 838 cm^{-1}; ^1H NMR (500 MHz, D_2O) δ 3.99 (dt, J_1 = 7.5 Hz, J_2 = 5.3 Hz, 1H), 3.94 (dd, J_1 = 9.0 Hz, J_2 = 5.4 Hz, 1H), 3.91 (dd, J_1 = 13.0 Hz, J_2 = 4.8 Hz, 1H), 3.86 (dd, J_1 = 13.0 Hz, J_2 = 3.3 Hz, 1H), 3.68 (t, J = 9.0 Hz, 1H), 3.67 (dd, J_1 = 14.0 Hz, J_2 = 7.5 Hz, 1H), 3.58 (dd, J_1 = 10.0 Hz, J_2 = 9.0 Hz, 1H), 3.37 (dd, J_1 = 14.0 Hz, J_2 = 5.4 Hz, 1H), 3.26 (ddd, J_1 = 10.0 Hz, J_2 = 4.8 Hz, J_3 = 3.3 Hz, 1H); ^{13}C NMR (125 MHz, D_2O) δ 72.81, 69.33, 68.21, 57.95, 57.08, 52.94, 36.72; HRMS calcd for $C_7H_{16}N_2O_4$ (M + H^+) 193.1188, found 193.1186.

8(*R*)-(Hydroxymethyl)-6(*R*),7(*R*)-dihydroxy-5(*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one (23). The azasugar **22** (3.45 g, 21.4 mmol) was dissolved in 10% aqueous $NaHCO_3$ (72 mL), and triphosgene (6.5 g, 21.4 mmol) in toluene (30 mL) was added to this solution. After 1 h, the aqueous layer was extracted with toluene (30 mL) and concentrated to dryness

under vacuum. The residual solid was triturated with MeOH (2 × 100 mL), and the organic layer was filtered through Celite and evaporated under vacuum. Flash chromatography (6:1 EtOAc/MeOH) gave 3.70 g (92%) of **23** as an oil: ^{1}H NMR (500 MHz, CD_3OD) δ 3.48 (dt, J = 4.5, 4.8 Hz, 1H, C*H*N), 3.71 (m, 1H, CO_2CH_2CHN), 3.96 (dd, J = 4.8, 11.5 Hz, 1H, CH_2OH), 4.09 (dd, J = 4.5, 11.5 Hz, 1H, CH_2OH), 4.17 (t, J = 1.0 Hz, 1H, C_1HOH), 4.44 (m, 2H, CH_2OCO), 4.45 (m, 1H, C_3HOH); ^{13}C NMR (125.7 MHz, CD_3OD) δ 59.71 (C-1), 64.25 (C-6), 64.91 (C-2), 68.23 (C-5), 74.44 (C-3), 83.84 (C-4), 160.51 (C=0) (numbering is from right to left) $^{2,3}J_{C-H}$ of C-6, 1.25 Hz; $^{2,3}J_{C-H}$ of C-1, 1.38 and 3.59 Hz; HRMS calcd for 190.0715 (M + H$^+$), found 190.0720.

8(*R*)-[(Benzyloxy)methyl]-6(*R*),7(*R*)-bis(benzyloxy)-(5*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one (24). To a solution of azasugar **23** (1 g, 5.3 mmol) in DMF (10 mL) were added KI (125 mg, 0.76 mmol), NaH (0.85 g, 21.2 mmol), and BnBr (3.62 g, 21.2 mmol) at room temperature. After stirring for 12 h, aqueous NH_4Cl (10%, 20 mL) was added to this reaction mixture, and after stirring for another 10 min the mixture was diluted with water (30 mL) and extracted with EtOAc (2 × 50 mL). The organic layer was washed with H_2O (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2:1 hexane/EtOAc) gave 2.2 g (88%) of **24** as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (t, *J* = 10.0 Hz, 1H), 3.50 (t, *J* = 10.0 Hz, 1H), 3.66 (d, *J* = 3.0 Hz, 1H), 3.79 (dd, *J* = 4.5, 10.0 Hz, 1H), 4.22 (d, *J* = 12.0 Hz, 1H), 4.29 (s, 1H), 4.34 (d, *J* = 7.0 Hz, 1H), 4.37 (dd, *J* = 3.0, 5.5 Hz, 1H), 4.40 (m, 1H), 4.42 (d, *J* = 12.5 Hz, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.48 (d, *J* = 12.5 Hz, 1H), 4.53 (dd, *J* = 4.5, 9.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.63 (d, *J* = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.59, 62.38, 62.59, 66.10, 70.79, 71.12, 73.27, 78.86, 84.48, 127.65, 127.68, 127.84, 127.93, 128.02, 128.35, 128.48, 128.55; HMRS calcd for 460.2124 (M + H$^+$), found 460.2125.

5(*R*)-[(Benzyloxy)methyl]-3(*R*),4(*R*)-bis(benzyloxy)-2(*S*)-(hydroxymethyl)pyrrolidine (25). To a solution of azasugar **24** (880 mg, 1.91 mmol) in ethylene glycol (20 mL) was added an aqueous solution (10 mL) of KOH (1.07 g, 19.1 mmol). The reaction mixture was heated at 100 °C for 24 h. The solvent was concentrated under vacuum and the residue was chromatographed (20:1 $CHCl_3$/MeOH) to give **25** (750 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (m, 2H), 3.56 (dd, *J* = 5.1, 9.4 Hz, 1H), 3.60 (dd, *J* = 5.1, 9.4 Hz, 1H), 3.77 (dd, *J* = 4.6, 11.6 Hz, 1H), 3.83 (dd, *J* = 4.4, 11.6 Hz, 1H), 3.92 (dd, *J* = 2.3, 4.9 Hz, 1H), 4.05 (dd, *J* = 2.3, 5.4 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.51 (s, 2H), 4.52 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.8 Hz, 1H), 7.24−7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 61.02, 61.55, 63.14, 70.79, 71.51, 71.87, 73.123, 84.67, 86.13, 127.57, 127.61, 127.71, 127.87, 128.31, 128.38, 128.49, 137.56, 137.99, 138.05; HRMS calcd for 434.2331 (M + H$^+$), found 434.2350.

5(*R*)-[(Benzyloxy)methyl]-3(*R*),4(*R*)-bis(benzyloxy)-2(*S*)-(hydroxymethyl)-*N*-methylpyrrolidine (26). Amino alcohol **4** (600 mg, 1.39 mmol, 1.0 equiv) was dissolved in MeOH (20 mL). Paraformaldehyde (150 mg, 4.84 mmol, 3.5 equiv) was added, and the suspension was heated with reflux for 20 min. The clear solution was cooled to 0 °C, and $NaCNBH_3$ (870 mg, 13.8 mmol, 10.0 equiv) was added. After 3 h, the reaction was quenched with 10% Na_2CO_3 (10 mL) and extracted into $CHCl_3$; the $CHCl_3$ extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The oily residue was coevaporated with 2 × 50 mL 1:1 THF/MeOH to ensure a complete removal of borate esters. Flash chromatography (20: CH_2CL_2/MeOH) gave 594 mg (81%) of **5** as a light tan oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (s, 3H), 2.75 (m, 2H), 3.52 (dd, *J* = 9.5, 6.5 Hz, 1H), 3.60 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.75 (2H), 3.91 (dd, *J* = 4.5, 3.0 Hz, 1H), 4.02 (dd, *J* = 6.0, 3.0 Hz, 1H), 4.50 (ABq, *J* = 12.0 Hz, 2H), 4.53 (ABq, *J* = 7.0 Hz, 2H), 4.57 (ABq, *J* = 4.0 Hz, 2H), 7.33−7.26 (m, 15H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 40.5, 59.5, 67.5, 70.2, 70.4, 71.6, 71.7, 73.1, 83.0, 83.9, 127.5, 127.62, 127.66, 127.76, 127.76, 127.82, 128.26, 128.30, 128.44, 137.70, 138.10, 138.20; HRMS calcd for 580.1464 (M + Cs$^+$), found 580.1460.

5(*R*)-[(Benzyloxy)methyl]-3(*R*),4(*R*)-bis(benzyloxy)-2(*S*)-formyl-*N*-methylpyrrolidine (27). To a solution of oxalyl chloride (0.165 mL, 0.326 mmol) in CH_2Cl_2 (2.0 mL) was added DMSO (50 μL, 0.652 mmol) at −78 °C. After 15 min, the solution of azasugar **26** (71 mg, 0.163 mmol) in CH_2Cl_2 was added and stirred for 30 min. To this reaction mixture, triethylamine (0.11 mL, 0.78 mmol) was added and the mixture was warmed to 0 °C over 10 min. Saturated aqueous solution of NH_4Cl was added, and the resulting mixture was extracted with CH_2Cl_2 (20 mL × 3). The organic layer was dried ($MgSO_4$), filtered, and concentrated. This crude aldehyde **27** was used directly in the next coupling reaction without further purification.

(Methoxycarbonyl)octyl 2-Acetamido-3,4,6-tri-*O*-acetyl-β-D-glucopyranoside (29). To solid *N*-acetylglucosamine (**28**) (5.1 g, 23.2 mmol) was added acetyl chloride (8.2 mL, 1.6 mmol). After 12 h, water (250 mL) was added and the resulting mixture was extracted with CH_2Cl_2 (400 mL). The organic layer was washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. This residue was dissolved in benzene (50 mL), and hydroxynonanoic acid methyl ester (7.5 g, 39.6 mmol), mercuric cyanide (10.2 g, 40.6 mmol), and anhyd. $CaSO_4$ (15 g) were added. After 3 d, the mixture was diluted with CH_2Cl_2 (400 mL) and filtered through Celite. The filtrate was washed with brine (100 mL × 2), saturated $NaHCO_3$ (50 mL × 2), dried over $MgSO_4$, filtered, and concentrated to give **29** (11 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (m, 8H), 1.56 (m, 4H), 1.93 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.07 (s, 3H), 2.29 (t, *J* = 8.5 Hz, 2H), 3.45 (m, 1H), 3.66 (s, 3H), 3.82 (m, 2H), 4.11 (dd, *J* = 12.1, 1.8 Hz, 1H), 4.25 (dd, *J* = 12.1, 4.5 Hz, 1H), 4.68 (d, *J* = 8.9 Hz, 1H), 5.05 (t, *J* = 9.8 Hz, 1H), 5.31 (t, *J* = 9.8 Hz, 1H), 5.49 (d, *J* = 8.9 Hz, 1H).

(Methoxycarbonyl)octyl 2-Acetamido-4,6-isopropylidene-β-D-glucopyranoside (30). To a solution of compound **29** (6.5 g, 12.6 mmol) in dry methanol (70 mL) was added 25% NaOMe/MeOH solution (5.2 mmol, 1.1 mL) under Ar. After 15 h, Dowex 50 × 8 was added to this mixture until pH 7.0, which was then filtered and concentrated. This residue was dissolved in DMF (120 mL), and 2,2-dimethoxypropane (7.7 mL, 63.0 mmol) and TosOH (160 mg, 0.84 mmol) were added. After 1.5 h, triethylamine (4 mL) was added, the solvent was concentrated, and the residue was chromatographed (5:2:1 $CHCl_3$/EtOAc/MeOH) to give **30** (5.11g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (m, 8H), 1.44 (s, 3H), 1.52 (s, 3H), 1.59 (m, 4H), 2.05 (s, 3H), 2.30 (t, *J* = 8.1 Hz, 3H), 3.29 (dt, *J* = 6.2, 9.0 Hz, 1H), 3.44 (m, 2H), 3.67 (s, 3H), 3.81 (m, 1H), 3.92 (m, 2H), 4.32 (d, *J* = 4.0 Hz, 1H), 4.60 (d, *J* = 9.0 Hz, 1H).

(Methoxycarbonyl)octyl 2-Acetamido-4,6-isopropylidene-β-D-allopyranoside (31). To a solution of alcohol **30** (3.0 g, 6.96 mmol) in dry pyridine (20 mL) was added mesyl chloride (0.6 mL, 7.7 mmol) at 0 °C. After 5 h, more mesyl chloride (0.24 mL, 3.08 mmol) was added and the mixture was stirred overnight. The solution was concentrated, and the residue was dissolved in $CHCl_3$ (200 mL), washed with saturated NH_4Cl (50 mL × 1), 10% Na_2CO_3 (50 mL × 1), and brine (50 mL × 1), dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in 2-methoxyethanol (50 mL)−H_2O (2.5 mL), and NaOAc (3.5 g, 42.6 mmol) was added. After 18 h at 100 °C, the mixture was concentrated, the residue was dissolved in $CHCl_3$/EtOAc (3:1, 400 mL), and 25% NaOMe/MeOH (0.5 mL, 2.3 mmol) was added. After 1 d, saturated NH_4Cl (10 mL) was added and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated to give **31** (2.55 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (m, 8H), 1.39 (s, 3H), 1.49 (s, 3H), 1.56 (m, 4H), 2.01 (s, 3H), 2.29 (t, *J* = 7.7 Hz, 2H), 3.40 (m, 1H), 3.63 (s, 3H), 3.78 (m, 3H), 3.91 (t, *J* = 6.0 Hz, 1H), 4.09 (m, 3H), 4.58 (d, *J* = 8.7 Hz, 1H).

(Methoxycarbonyl)octyl 2-Acetamido-3-*O*-mesyl-4,6-isopropylidene-β-D-allopyranoside (32). To a solution of alcohol **10** (2.2 g, 5.1 mmol) in pyridine (25 mL) was added mesyl chloride (1.0 mL, 12.8 mmol) at 0 °C. After 2 d, the reaction mixture was concentrated and the residue was dissolved in $CHCl_3$ (150 mL). The organic layer was washed with 1 N HCl (40 mL), saturated Na_2CO_3 (40 mL), and brine (70 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (1:1 $CHCl_3$/EtOAc) to give **11**

(2.63 g, 98%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.27 (m, 8H), 1.55 (m, 4H), 1.37 (s, 3H), 1.46 (s, 3H), 2.00 (s, 3H), 2.27 (t, J = 7.4 Hz, 2H), 3.09 (s, 3H), 3.40 (m, 1H), 3.64 (s, 3H), 3.78 (m, 4H), 3.92 (m, 1H), 4.17 (dt, J = 2.7, 8.6 Hz, 1H), 4.57 (d, J = 8.6 Hz, 1H), 5.07 (m, 1H).

(Methoxycarbonyl)octyl 2-Acetamido-3-deoxy-3-azido-4,6-isopropylidene-β-D-glucopyranoside (33). To a solution of mesylate **32** (1.5 g, 2.95 mmol) in DMF (40 mL) was added NaN_3 (790 mg, 12.1 mmol) and the mixture was heated at 90 °C. After 4 d, the mixture was concentrated and the residue was dissolved in $CHCl_3$ (200 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (1:1:1, $CHCl_3$/EtOAc/hexanes) to give **33** (1.15 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (m, 8H), 1.40 (s, 3H), 1.48 (s, 3H), 1.56 (m, 4H), 1.98 (s, 3H), 2.28 (t, J = 8.1 Hz, 2H), 3.06 (m, 1H), 3.39 (m, 2H), 3.49 (t, J = 8.6 Hz, 1H), 3.63 (s, 3H), 3.76 (m, 2H), 3.90 (dd, J = 6.4, 9.4 Hz, 1H), 4.21 (t, J = 9.4 Hz, 1H), 4.91 (d, J = 8.6 Hz, 1H).

(Methoxycarbonyl)octyl 2-Acetamido-3-deoxy-3-azido-β-D-glucopyranoside (34). Acetonide sugar **33** (400 mg, 0.866 mmol) was suspended in 80% AcOH (20 mL) and heated to 95 °C for 2 h, and the solution was concentrated and coevaporated with toluene to yield a solid which was purified by silica gel chromatography (5:2:1, $CHCl_3$/EtOAc/MeOH) to afford 330 mg (90%) of the diol azide **34** as a white solid: ^{1}H NMR (500 MHz, CD_3OD) δ 1.19 (br, s, 9H), 1.44 (m, 4H), 1.85 (s, 3H), 2.19 (t, J = 7.5 Hz, 2H), 3.22 (q, J = 9.5 Hz, 2H), 3.33 (m, 2H), 3.45 (dd, J = 11, 8.5 Hz, 1H), 3.52 (s, 3H), 3.55 (dd, J = 12.0, 5.0 Hz, 1H), 3.74 (m, 2H), 4.33 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125.7 MHz, CD_3OD) δ 22.9, 26.0, 27.0, 30.1, 30.3, 30.4, 30.5, 34.7, 52.0, 55.5, 62.4, 68.6, 70.6, 70.7, 78.6, 102.4, 173.3, 178.2; HRMS calcd for 549.1325 (M + Cs^+), found 549.1325.

(Methoxycarbonyl)octyl 2-Acetamido-3-deoxy-3-amino-β-D-glucopyranoside (35). The diol azide **34** (325 mg, 0.781 mmol) was dissolved in MeOH (40 mL), and Lindlar catalyst (150 mg) was added. The suspension was sealed with a three-way system and subjected to three degas/H_2 refill cycles. After 18 h, the suspension was filtered through Celite, rinsed with MeOH (20 mL), and concentrated to leave pure **35** as a fluffy white solid (301 mg, 99%): ^{1}H NMR (500 MHz, CD_3OD) δ 4.28 (d, J = 8.5, 1H), 3.77 (m, 2H), 3.57 (dd, J = 12.0, 5.5 Hz, 1H), 3.54 (s, 3H), 3.49 (dd, J = 11.0, 8.5 Hz, 1H), 3.35 (dt, J = 9.5, 6.5 Hz, 1H), 3.20 (m, 1H), 3.10 (appt, J = 9.5 Hz, 1H), 2.59 (dd, J = 11.0, 9.0 Hz, 1H), 2.20 (t, J = 7.5 Hz, 2H), 1.88 (s, 3H), 1.47 (m, 4H), 1.22 (br, s, 9H); ^{13}C NMR (125.7 MHz, CD_3OD) δ 23.7, 26.6, 27.7, 30.8, 30.9, 31.0, 3.1, 31.2, 35.4, 52.7, 57.0, 59.3, 63.4, 71.1, 72.7, 79.6, 103.6; HRMS calcd for 523.1420 (M + Cs^+), found 523.1401.

Pseudodisaccharide 36. To a solution of amine **35** (223 mg, 0.57 mmol, 1.0 equiv) and the aldehyde **27** (265 mg, 0.6 mmol, 1.04 equiv) in 15.0 mL of MeOH was added $MgSO_4$ (anhydrous, 900 mg). The reaction mixture was sealed and stirred at ambient temperature for 16 h. Filtration through Celite and solvent elution (10 mL MeOH) left a clear yellow solution which was treated with $NaBH_4$ (43 mg, 1.14 mmol, 2.0 equiv) at 0 °C. After 3 h, the solution was quenched with 3 mL of acetone and 3 mL of water and extracted with 75 mL of EtOAc. The organic layer was dried over $MgSO_4$, filtered, and concentrated. The residual oil was purified by silica gel chromatography (10:1 CH_2Cl_2/MeOH) to provide the protected pseudodisaccharide **36** (250 mg, 60%) as an oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.34 (m, 15H), 4.50 (m, 7H), 4.01 (m, 2H), 3.78 (m, 3H), 3.65 (s, 3H), 3.53 (m, 4H), 3.36 (m, 4H), 2.87 (m, 4H), 2.70 (br, q, J = 4.5 Hz, 1H), 2.38 (s, 3H), 2.29 (t, J = 7.5 Hz, 2H), 1.88 (s, 3H), 1.60 (m, 4H), 1.26 (br, s, 8H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 23.2, 24.8, 25.7, 28.90, 28.96, 29.0, 29.3, 33.9, 40.8, 51.4, 62.5, 69.5, 69.6, 71.7, 72.4, 73.1, 76.5, 77.2, 82.6, 83.8, 101.5, 127.65, 127.6, 127.7, 127.8, 128.0, 128.1, 128.31, 128.38, 128.5, 137.3, 138.0, 138.1, 170.6, 174.2; HRMS calcd for 952.3724 (M + Cs^+), found 952.3701.

Synthesis of 38. To a solution of **37** (9.9 g, 30 mmol) in 180 mL of anhydrous dichloromethane/tetrahydrofuran (1:1) were added 2-methoxypropene (2.4 mL, 25 mmol) and p-toluenesulfonic acid (3 g) under N_2. The solution was stirred at room temperature. After 20 h, additional 2-methoxypropene (1.2 mL) was added, and the solution was allowed to stir for 26 h. Saturated sodium bicarbonate solution (10 mL) was added to terminate the reaction. The organic solvent was removed under reduced pressure. Water (50 mL) was then added, and the mixture was extracted with ethyl acetate (50 mL × 3). The organic layer was dried over Na_2SO_4 and then evaporated, and the residue purified by silica gel column chromatography (ethyl acetate:n-hexane = 1:1–1:0) to yield 4.8 g of monoacetate **38** and 3.2 g of recovered substrate. **38**: R_f = 0.18 (ethyl acetate:n-hexane = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$/TMS) δ 1.29 (s, 3H), 1.30 (s, 3H), 3.08 (dd, J = 5.0 Hz and 10.3 Hz, 1H), 3.25 (ddd, J = 5.2 Hz, 5.9 Hz and 6.4 Hz, 1H), 3.32 (dd, J = 5.9 Hz and 11.7 Hz, 1H), R_f = 0.19 (chloroform:methanol = 9:1); ^{1}H NMR (500 MHz, $CDCl_3$–TMS) δ 1.29 (s, 3H), 1.30 (s, 3H), 3.08 (dd, J = 5.0 and 10.3 Hz, 1H, C_5-*H*), 3.25 (ddd, J = 5.2, 5.9 and 6.4 Hz, 1H, C_2-*H*), 3.32 (dd, J = 5.9 and 11.7 Hz, 1H, C_1-H), 3.38 (dd, J = 6.4 and 11.7 Hz, 1H, C_1-H), 3.51 (dd, J = 5.0 and 10.5 Hz, 1H, C_6-H), 3.66 (dd, J = 10.3 and 10.5 Hz, 1H, C_6-H), 4.18 (s, 1H, C_4-H), 4.20 (d, J = 5.0 Hz, 1H, C_3-H), 5.11 (s, 1H), 7.15–7.55 (m, 10H); ^{13}C-NMR (125 MHz, $CDCl_3$–TMS) δ 21.86 (CH_3), 26.51 (CH_3), 63.01 (C-2), 64.04 (C-1), 64.31 (C-6), 72.26 (N*C*HPh$_2$), 74.02 (C-5), 78.40 (C-4), 79.40 (C-3), 99.79 (*C*Me$_2$) (numbering is from right to left) $^{2,3}J_{C-H}$ of C-1, 1.01 Hz; $^{2,3}J_{C-H}$ of C-6, 2.20 and 4.55 Hz. The X-ray crystal structure was determined to confirm the structure (Figure 5).

Confirmation of the Structure of 23. A solution of azasugar **38** (1.0 g, 2.7 mmol) in MeOH (30 mL) was hydrogenated with $Pd(OH)_2$ (150 mg) under 50 psi of hydrogen for 4 h. The catalyst was removed by filtration, and the solvent was concentrated under vacuum. The residue was dissolved in 5% aqueous $NaHCO_3$ (50 mL), and triphosgene (1.48 g, 5.0 mmol) in toluene (5.0 mL) was added to this solution. After 4 h, the mixture was extracted with toluene (5 mL), and the aqueous layer was concentrated under vacuum. The residual solid was extracted with EtOAc–MeOH (3:1, 80 mL × 2), and the organic layer was filtered through Celite and evaporated under vacuum. The residue was dissolved in MeOH (15 mL), and p-toluenesulfonic acid (150 mg, 0.79 mmol) was added. After 1.5 h, $NaHCO_3$ (130 mg, 1.6 mmol) was added and the mixture was concentrated under vacuum. The residue was purified with flash chromatography (9:1 $CHCl_3$/MeOH) to give 184 mg (36%) of **23a** as regioisomer of **23**: ^{1}H NMR (500 MHz, CD_3OD) δ 3.62 (ddd, J = 4.6, 4.8, 4.9 Hz, 1H, CHNCH$_2$OH), 3.87 (m, 1H, C*H*NCH$_2$OCO), 3.92 (t, J = 4.9 Hz, 1H, C$_4$*H*OH), 3.99 (dd, J = 4.6, 11.9 Hz, 1H, C*H*$_2$OH), 4.04 (dd, J = 4.8, 11.9 Hz, 1H, C*H*$_2$OH), 4.08 (t, J = 4.9 Hz, 1H, C$_3$*H*OH), 4.19 (dd, J = 8.7 Hz, 1H, C*H*$_2$OCO), 4.56 (dd, J = 8.7 Hz, 1H, C*H*$_2$-OCO); ^{13}C NMR (125.7 MHz, CD_3OD) δ 56.79 (C-1), 62.69 (C-2), 79.31 (C-3), 79.88 (C-4), 64.79 (C-5), 70.05 (C-6), 161.41 (C=O) (numbering is from right to left) $^{2,3}J_{C-H}$ of C-6, 1.15 and 1.69 Hz; $^{2,3}J_{C-H}$ of C-1, 4.08 and 4.86 Hz.

***N*-(Benzyloxycarbonyl)-5(*R*)-[(benzyloxy)methyl]-3(*R*),4-(*R*)-bis(benzyloxy)-2(*S*)-(hydroxymethyl)pyrrolidine (39).** To a solution of compound **25** (866 mg, 2.0 mmol) and triethylamine (242 mg, 2.4 mmol) in dichloromethane (10 mL) was added benzyl chloroformate (374 mg, 2.2 mmol) at 5 °C, and the resulting mixture was stirred for 1 h. The reaction mixture was diluted with dichloromethane (50 mL) and washed with 10% aqueous sodium bicarbonate (2 × 30 mL) and water. The organic layer was dried over anhydrous sodium sulfate and evaporated under vacuum. The residue was purified with flash column chromatography to give compound **39** (998 mg, 88.0% yield): R_f 0.40 (hexane–ethyl acetate = 2:1); NMR (DMSO-d_6, 330 °K) δ 3.61 (m, 3H), 3.67 (m, 1H), 3.90 (m, 1H), 4.08 (m, 1H), 4.15 (m, 2H), 4.24 (t, J = 5.4 Hz, 1H), 4.43 (m, 2H), 4.55 (m, 3H), 4.62 (d, J = 11.8 Hz, 1H), 5.09 (s, 2H), 7.29 (m, 20H); HRMS calcd for M + Cs^+ 700.1675, found 700.1680.

***N*-(Benzyloxycarbonyl)-5(*R*)-[(benzyloxy)methyl]-3(*R*),4-(*R*)-bis(benzyloxy)-2(*S*)-[[[(4-methylphenyl)sulfonyl]oxy]-methyl]pyrrolidine (40).** The mixture of compound **39** (470 mg, 0.83 mmol) and p-toluenesulfonyl chloride (237 mg, 1.25 mmol) in pyridine (2 mL) was stirred for 18 h at room temperature and then diluted with dichloromethane (50 mL).

The solution was washed with water, cold 1 N aqueous hydrochloric acid, 10% aqueous sodium bicarbonate, and water, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue obtained was separated by flash column chromatography to give compound **40** (525 mg, 87.8% yield): R_f 0.47 (hexane–ethyl acetate = 2:1); NMR (DMSO-d_6, 330 K) δ 2.35 (s, 3H), 3.50 (d, J = 5.8 Hz, 2H), 3.86 (m, 1H), 4.06 (m, 1H), 4.10 (dd, J = 6.9, 9.4 Hz, 1H), 4.16 (dd, J = 4.6, 6.5 Hz, 1H), 4.22 (m, 1H), 4.28 (m, 1H), 4.36 (s, 2H), 4.48 (s, 2H), 4.51 (m, 2H), 5.04 (s, 2H), 7.29 (m, 24H), 7.64 (d, J = 8.1 Hz, 2H); HRMS calcd for 722.2788 (M + H^+), found 722.2795.

***N*-(Benzyloxycarbonyl)-5(*R*)-[(benzyloxy)methyl]-3(*R*),4-(*R*)-bis(benzyloxy)-2(*S*)-[(2-amino-6-chloropurin-9-yl)-methyl]pyrrolidine (41).** A mixture of compound **40** (418 mg, 0.58 mmol), 2-amino-6-chloropurine (137 mg, 0.81 mmol), and potassium carbonate (112 mg, 0.81 mmol) in *N*,*N*-dimethylformamide (2 mL) was heated for 18 h at 80 °C. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (100 mL) and washed with water. The ethyl acetate layer was dried over anhydrous sodium sulfate and evaporated under vacuum. Flash column chromatographic separation of the residue gave pure **20** (208 mg, 50.0% yield): R_f 0.10 (hexane:ethyl acetate = 2:1); NMR (DMSO-d_6, 340 K) δ 3.60 (dd, J = 3.3, 9.8 Hz, 1H), 3.83 (m, 1H), 3.90 (m, 1H), 4.13 (m, 1H), 4.21 (m, 1H), 4.28 (m, 1H), 4.33 (m, 1H), 4.50 (m, 3H), 4.62 (m, 4H), 4.94 (d, J = 12.6 Hz, 1H), 6.25 (s, 2H), 7.05 (m, 18H), 7.69 (s, 1H); HRMS calcd for 719.2749 (M + H^+), found 719.2765.

***N*-(Benzyloxycarbonyl)-5(*R*)-[(benzyloxy)methyl]-3(*R*),4-(*R*)-bis(benzyloxy)-2(*S*)(9-guaninylmethyl)pyrrolidine (42).** A mixture of compound **41** (207 mg, 0.289 mmol), 2-mercaptoethanol (90 mg, 1.154 mmol), and sodium methoxide (62 mg, 1.148 mmol) in methanol (10 mL) was refluxed for 9 h under argon. After cooling to room temperature, the mixture was neutralized with glacial acetic acid and evaporated to dryness under vacuum. The residue was purified by preparative TLC (hexane–ethyl acetate = 1:2) to give compound **42** (R_f 0.04, 101 mg, 49.5% yield): NMR (DMSO-d_6, 340 K) δ 3.60 (d, J = 9.8 Hz, 1H), 3.80 (m 1H), 3.90 (m, 1H), 4.06 (m, 1H), 4.18 (m, 2H), 4.26 (m, 1H), 4.48 (d, J = 11.4 Hz, 1H), 4.54 (d, J = 11.4 Hz, 1H), 4.59 (s, 6H), 4.99 (d, J = 12.6 Hz, 1H), 6.11 (s, 2H), 7.13 (m 2H), 7.31 (m, 19H), 10.21 (br s, 1H); HRMS calcd for 701.3088 (M + H^+), found 701.3070.

5(*R*)-(Hydroxymethyl)-3(*R*),4(*R*)-dihydroxy-2(*S*)-(9-guaninylmethyl)pyrrolidine (43). To a solution of compound **42** (28 mg, 0.04 mmol) in dichloromethane (1 mL) was added a solution of boron trichloride in dichloromethane (1 M, 0.20 mL) at −60 °C. The resulting mixture was stirred at 0 °C and then quenched with methanol (0.5 mL). After an additional 1 h of stirring at room temperature, the reaction mixture was neutralized with ammonium hydroxide and evaporated under vacuum. The residue was separated by preparative TLC using chloroform–methanol (1:1, R_f 0.00) and then with methanol–30% aqueous ammonium hydroxide (20:1, R_f 0.30) to give pure **43** (4.4 mg, 37.2% yield): NMR (CD_3OD) δ 3.10 (m, 1H), 3.66 (dd, J = 6.2, 11.1 Hz, 1H), 3.71 (dd, J = 4.7, 11.1 Hz, 2H), 3.87 (dd, J = 2.2, 3.9 Hz, 1H), 3.89 (d, J = 2.2, 3.4 Hz, 1H), 4.21 (dd, J = 7.5, 14.1 Hz, 1H), 4.33 (dd, J = 6.8, 14.1 Hz, 1H), 4.58 (s, 1H), 7.30 (br s, 1H), 7.74 (s, 1H), 8.04 (s, 1H), 8.54 (s, 1H); ^{13}C NMR (CD_3OD) δ 44.13, 61.84, 63.60, 68.11, 78.14, 80.01; HRMS calcd for 297.1311 (M + H^+), found 297.1302.

NMR Analysis. Proton and carbon NMR spectra in CD_3OD at 21 °C were assigned by a combination of 1D and 2D techniques using a Bruker AMX-500 NMR spectrometer equipped with an X-32 computer and an ASPECT-3000 process controller. A broad band inverse probe was used for all 2D experiments and the sample was not spun. All 2D NMR data were processed, analyzed, and plotted with the Felix program (Hare Research, Woodinville, WA) run on a Silicon Graphic 4D/35 Personal Iris workstation.

The proton double quantum filtered (DQF) COSY experiment[27] was performed in the phase sensitive mode using the time proportional phase incrementation (TPPI)[28] at a spectral width of 2500 Hz. The evolution time was incremented in steps of 200 μs to obtain 512 FIDs each acquired in 1K data points in 32 scans. The relaxation delay was 1.5 s. A square sine-bell function shifted by $\pi/2$ was applied for processing in the t_2 dimension. The same window function was applied in the t_1 dimension and zero filling was used to expand the data matrix to 1K in this dimension. The {^1H, ^{13}C} one-bond shift correlation spectrum was obtained in the ^1H detection mode by an HMQC experiment.[28] The ^1H spectral width was 2500 Hz and the ^{13}C spectral width was 17 500 Hz. No ^{13}C decoupling was applied during data acquisition. By increasing t_1 in steps of 25 μs, 400 FIDs were collected, each consisting of 4K data points. The relaxation delay was 1.5 s. A sine-bell function shifted by $\pi/2$ was applied in the t_2 dimension and a Gaussian window (line broadening 5 Hz) was applied in the t_1 dimension. Zero filling to 1K was used in the t_1 dimension before Fourier transformation. The {^1H, ^{13}C} multiple bond shift correlation spectrum was obtained in the ^1H detection mode by an HMBC experiment.[29] The ^1H spectral width was 4273 Hz and the ^{13}C spectral width was 19 000 Hz. No ^{13}C decoupling was applied during data acquisition. Using these methods, the chemical shifts of compounds **22**, **23**, **23a**, and **38** were completely assigned. For **1**: ^1H-NMR (500 MHz, CD_3OD) δ 2.93 (q, J = 4.84, 6.16 Hz, 1H, C_5H), 3.21 (td, J = 6.30, 6.59 Hz, 1H, C_2H), 3.55 and 3.67 (dd, J_{AB} = 11.40 Hz, 2H, C_1-H_2), 3.54 & 3.62 (dd, J_{AB} = 11.5 Hz, 2H, C_6-H_2), 3.75 (dd, J = 2.86 Hz, 1H, C_4-H), 3.99 (dd, J = 5.06 Hz, 1H, C_3-H); ^{13}C-NMR (125.7 MHz, CD_3OD) δ 59.61 (C-1), 60.55 (C-2), 76.86 (C-3), 78.62 (C-4), 64.57 (C-5), 61.73 (C-6) (numbering is from right to left) $^{2,3}J_{C-H}$ of C-1, 3.90 Hz; $^{2,3}J_{C-H}$ of C-6, 2.89 and 2.40 Hz.

Inhibition Analysis. α-L-Fucosidase (EC 3.2.1.111) from bovine kidney, α-glucosidase type IV from brewers yeast (EC 3.2.1.20) and α-mannosidase (EC 3.2.1.24) from jack bean were purchased from Sigma. K_i determinations were run at room temperature using the corresponding *p*-nitrophenyl-α-glycosides[30] at a concentration range from 0.5–4 K_m. Assays (in 50 mM NaOAc, pH 5.5, 25 °C) run with inhibitor were preincubated for 5 min prior to analysis with concentrations ranging from 0.2–4 K_i. The conditions were the same as previously described.[6e]

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Supplementary Material Available: ^1H NMR spectra for **2–5**, **7–10**, **13**, **23–26**, **34–36**, **39–43** (21 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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