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Bicyclic diazasugars. Part 3: β-D-Mannose and 6-deoxy-β-L-gulose analogues

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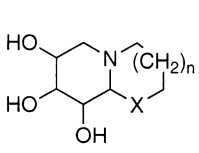
Abstract—A bicyclic analogue of β-D-mannopyranose with nitrogen atoms replacing the ring and glycosidic oxygen atoms has been prepared in a single step from 5-*O*-mesyl-D-mannofuranose by a process that likely involves double displacement and an epoxide intermediate. A similar but protected bicyclic analogue of 6-deoxy-β-L-gulopyranose has been prepared by an electrophilic cyclization reaction.

1. Introduction

'Azasugar' is a name that has been given to a class of sugar analogues that contain a nitrogen atom in place of the ring oxygen atom of sugars (both pyranose and furanose forms). These compounds have been of considerable interest because many of them inhibit glycosidases, enzymes that catalyze the hydrolysis of glycosidic bonds in polysaccharides and glycoproteins. Some azasugars have been shown to have therapeutic utility in the treatment of diabetes and cancer, and other medical applications of azasugars have been and are being investigated.[1–3] The azasugar research reported by this laboratory[4–7] has focused on the incorporation of a singly bonded glycosidic heteroatom into analogues (**1**; X=O, N, or S; n=0 or 1), a feature found in only a few naturally occurring azasugars. Examples include polyhydroxylated piperidines **2** such as nojirimycin,[8] mannonojirimycin,[9] and galactostatin,[10] which have a glycosidic hydroxyl group and exist as mixtures of anomers. Kifunensine (**3**) is a bicyclic azasugar with a glycosidic nitrogen atom in the form of an amide.[11] Azasugars with a glycosidic heteroatom have the potential of acting as pseudosubstrates for glycosidases and be converted by these enzymes into transition states and intermediates resembling those of the normal reaction pathway with sugar substrates. Consequently, these analogues may be potent and selective glycosidase inhibitors.



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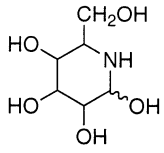

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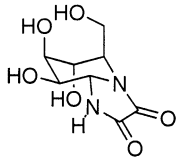

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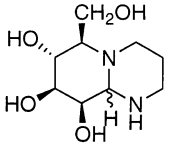

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The previous synthetic azasugar analogues **1** reported by this laboratory have all lacked the hydroxymethyl group common to the hexopyranoses. Because a hydroxymethyl group has been shown to be an important azasugar substituent for the inhibition of some glycosidases,[12] incorporation of this group into azasugars with a glycosidic heteroatom has been the object of the research reported herein. These initial efforts have focused on D-mannose analogues which might inhibit mannosidases and have utility in cancer chemotherapy as does the α-mannosidase inhibitor swainsonine. Attention has been directed toward diazasugar analogue **4** since previous analogues with oxygen or sulfur as the glycosidic heteroatom had poorer inhibitory activity than their nitrogen atom counterparts.[7] Based on observations with analogues reported earlier, it was recognized that a diazasugar analogue may exist predominantly as the β-anomer which probably will make it unsuitable as an α-mannosidase pseudosubstrate. Consequently, a parallel effort at controlling the anomeric preferences of azasugars is ongoing in this laboratory.

Keywords: carbohydrate mimetics; aza compounds; enzyme inhibitors; X-ray crystal structure.
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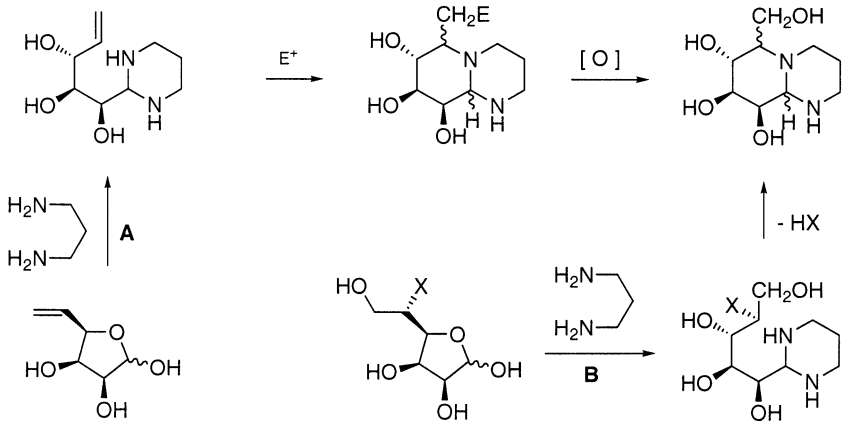


Scheme 1.

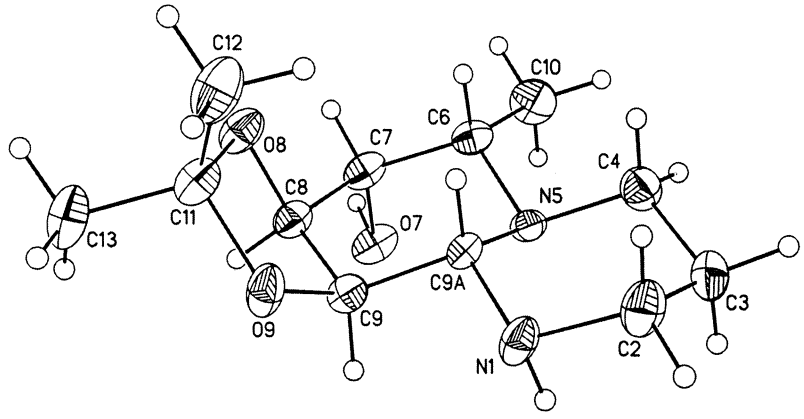


Figure 1. X-Ray structure of (6*R*,7*R*,8*S*,9*R*,9a*S*)-octahydro-7-hydroxy-6-methyl-8,9-[(1-methylethylidine)bis(oxy)]-2*H*-pyrido[1,2-*a*]pyrimidine (**10**).

Table 1. Crystal data and summary of X-ray experimental conditions

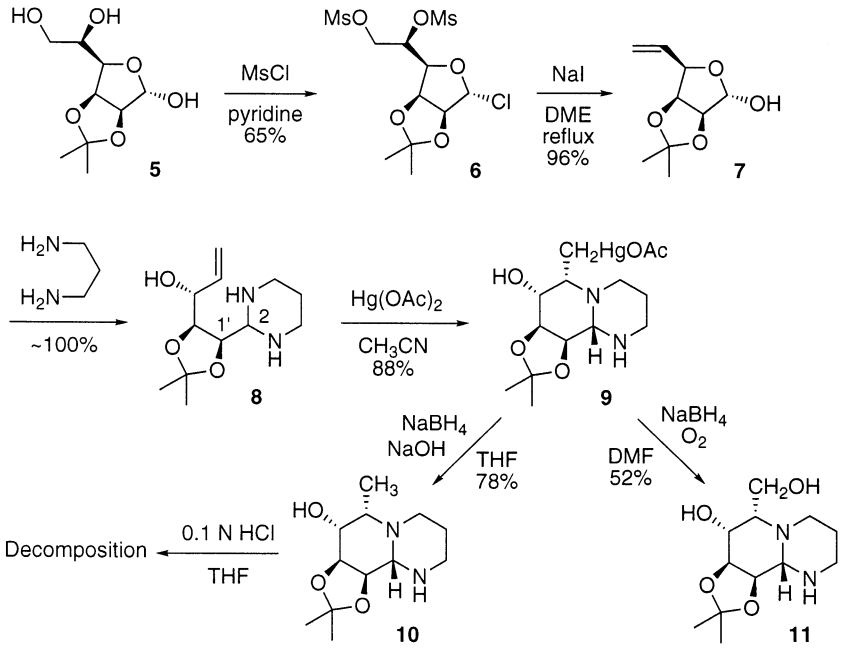
Compound	**10**
Formula	$C_{12}H_{22}N_2O_3$
Formula weight	242.32
F (000)	264
Crystal size (mm^3)	0.35×0.25×0.08
μ (mm^{-1})	0.090
Crystal system	Monoclinic
Space group	$P2_1$
a (Å)	7.179 (3)
b (Å)	7.043 (2)
c (Å)	13.104 (5)
β (°)	103.45 (3)
V (Å^3)	644.4
Z	2
D (g/cm^3)	1.249
2θ range (°)	2.92–25.06
Independent data	1236 (R_{int}=0.0415)
Data/restraints/parameters	1236/0/154
Final R indices [$I>2\sigma(I)$]	R_1=0.0580, wR^2=0.1138
Goodness of fit on F^2	1.052
Largest peak	0.219
Hole in difference map (eÅ^{-3})	−0.192

Tables containing the structure determination summary, atomic positional and thermal parameters, bond lengths, and bond angles for these compounds have been deposited in the Cambridge Crystallographic Data Center. These data can be obtained from the Director, Cambridge Crystallographic Center, University Chemical Laboratory, Lensfield Road, Cambridge, CB2 IEW, UK.

2. Results and discussion

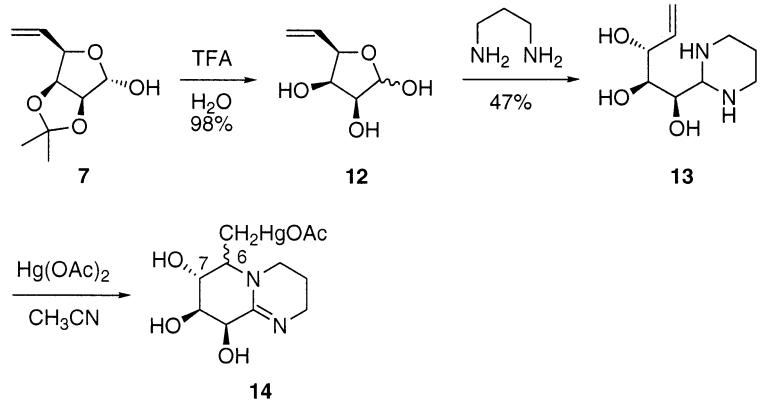
The approaches that were considered for the synthesis of diazamannose analogues are (A) electrophilic addition to a vinyl sugar aminal derivative and (B) nucleophilic displacement of a leaving group from the 5-position of a sugar aminal derivative (Scheme 1). The first approach had the possible advantage of avoiding the use of protecting groups and the potential drawback of leading to the wrong epimer or a mixture of epimers at the 5-position. The second would be expected to give stereoisomeric control at the 5-position but undoubtedly would require selective activation through use of protecting groups; without hydroxyl group protection, internal displacement might also occur to form epoxides, which could be precursors to other unwanted products. The route involving electrophilic addition was chosen for initial exploration because it appeared to be more direct.

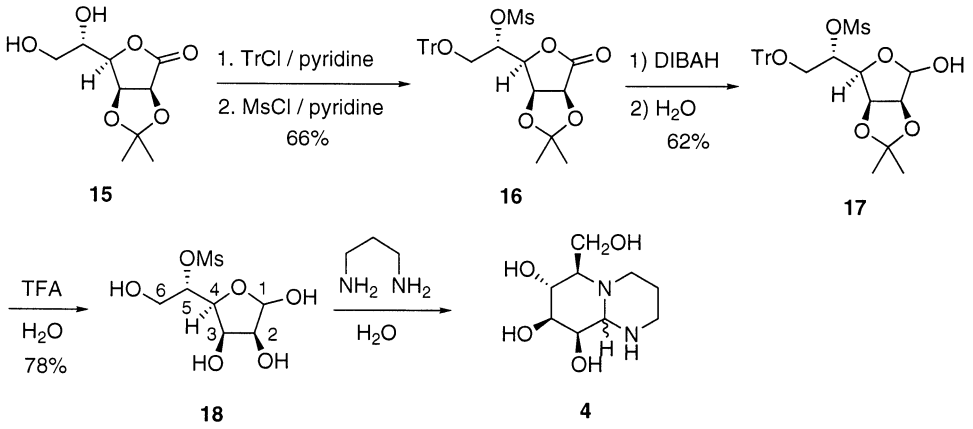
The synthesis began with conversion of 2,3-*O*-isopropylidene-α-D-mannofuranose (**5**)[13] to dimesyl α-D-mannofuranosyl chloride derivative **6** (65%). Treatment of **6** with sodium iodide in refluxing 1,2-dimethoxyethane effected elimination of both mesylate groups and aqueous workup gave known vinyl sugar derivative **7** (96%).[14] Electrophilic cyclization was first tried using this protected



compound. Treatment of **7** with 1,3-propanediamine gave aminal **8** which, without purification, was treated with mercuric acetate to bring about cyclization to a single mercury derivative (88%) that was determined to have the structural skeleton shown for **9** based on the appearance in its ^{13}C NMR spectrum of a methylene signal at 28.8 ppm (CH_2Hg) and a methine signal at 59.3 ppm (CHN) in place of the vinyl carbons of **8**. The stereochemistry of **9** could not be determined at this point. However, reduction of the organomercurial with sodium borohydride gave the corresponding methyl derivative **10** (78%) which was obtained in crystalline form and subjected to X-ray crystallography which showed the stereochemistry to be L-*gulo* as depicted in structure **10** (Fig. 1 and Table 1). Since the reduction is a free radical process,[15] it is expected that **9** has the same stereochemistry as **10**. An attempt to remove the acetonide protecting group from **10** using dilute hydrochloric acid in tetrahydrofuran gave a material with no ^{13}C NMR signals characteristic of an azasugar; one or more pyridinium compounds probably resulted by analogy with a similar dehydration process that occurred when nojirimycin was treated with acid.[8] Compound **9** was converted into the corresponding hydroxymethyl compound **11** (60%) by free radical trapping of dioxygen and reduction of the resulting hydroperoxide.[16] However, compound **11** was of limited interest since the stereochemistry was anticipated to also be L-*gulo* and deprotection of it was expected to be problematic.

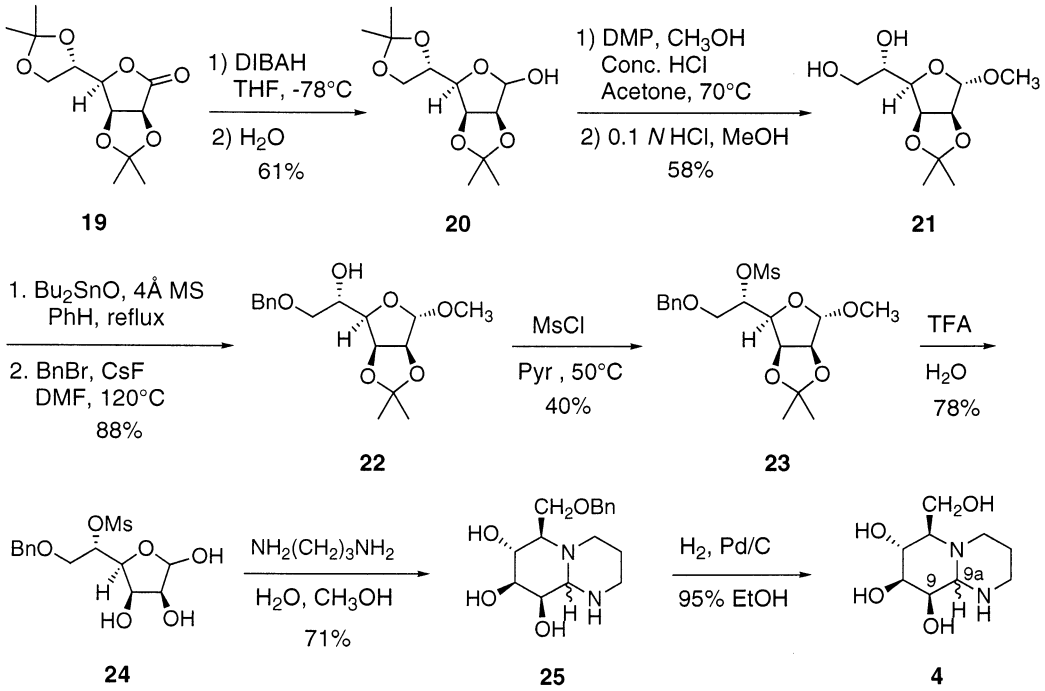
In order to avoid having to remove an acetonide protecting group and to hopefully obtain the desired D-*manno* stereochemistry, the electrophilic cyclization method was applied to unprotected vinyl sugar **12** that was obtained (98%) from **7** by treatment with a mixture of trifluoroacetic acid (TFA) and water. Compound **12** was converted to crystalline aminal **13** (47%) by treatment with 1,3-propanediamine. Treatment of **13** with mercuric acetate unexpectedly gave **14**, a mercury-containing amidino sugar instead of a diazasugar. The stereochemistry of the CH_2HgOAc group was not definitively determined although **14** is thought to also possess the L-*gulo* configuration; the coupling between protons at positions 6 and 7 is only 5.0 Hz and not near 9 Hz as expected for a compound with the D-*manno* configuration whose favored conformation places these two coupled protons in pseudoaxial orientations. Apparently, the mercuric acetate effected a dehydrogenation of the aminal functional group. Followup to this observation has led to the preparation of a number of amidino sugars from diazasugars, and these results will be reported separately.

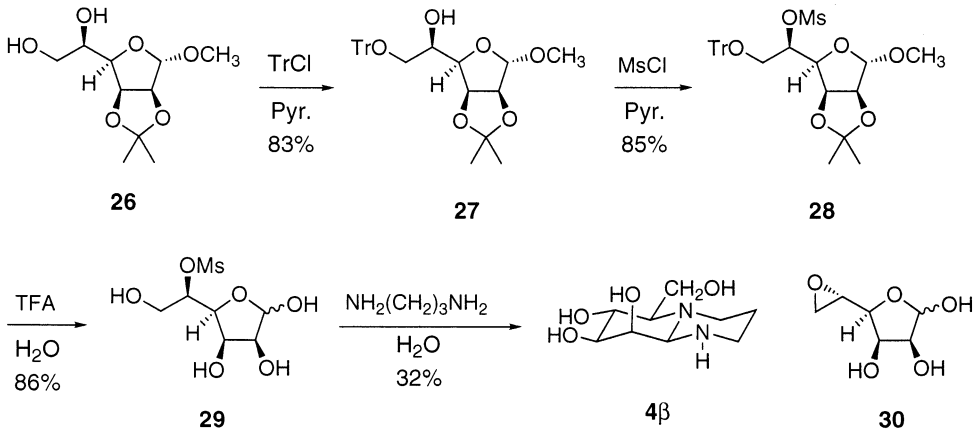




In view of the unsuccessful attempts to obtain the D-mannose diazasugar analogue using electrophilic addition, the approach utilizing nucleophilic displacement was investigated. A direct route to **4** beginning with readily available 2,3-*O*-isopropylidene-L-gulono-1,4-lactone (**15**)[17] was chosen. Tritylation of the primary hydroxyl group followed by mesylation of the secondary alcohol gave lactone **16** (66%) which was then reduced with diisobutylaluminum hydride to produce gulofuranose derivative **17** (62%). Complete deprotection of **17** was effected by cautious treatment with a TFA/water mixture to give 5-*O*-mesyl-L-gulose **18** (78%). Treatment of **18** in aqueous solution with 1 equiv. of 1,3-propanediamine added all at once gave a mixture of two products which were difficult to separate. Quantitative ^{13}C NMR was used to distinguish the peaks belonging to each product. Comparison of these ^{13}C chemical shift data with those for the analogue of **4** lacking the hydroxymethyl group[7] led to the conclusion that the mixture contained target compound **4** along with an unknown azasugar. It was considered likely that the other azasugar arose via an epoxide intermediate formed by base-catalyzed internal displacement of the mesylate by a vicinal hydroxyl group.

Since the 6-hydroxy group seemed more likely to have been involved in epoxide formation, it was protected prior to the cyclization reaction. L-Gulono-1,4-lactone derivative **19**[17] was reduced to the protected gulofuranose **20**[18] (61%) which was then converted to the methyl glycoside and partially deprotected to give **21** (58%).[19,20] Selective 6-*O*-benzylation was effected (88%) by first formation of the dibutylstannylene derivative and then reaction of this intermediate with benzyl bromide promoted by cesium fluoride. The product **22**[21] was converted to mesylate **23** (40%) which was then deprotected to 6-*O*-benzyl-5-*O*-mesyl-L-gulose **24** (77%) with a TFA/water mixture. Treatment of **24** with 1 equiv. of 1,3-propanediamine added all at once gave a mixture of products. However, when only half an equivalent of 1,3-propanediamine was added at first followed by a second half equivalent 30 min later, primarily the desired benzyl derivative **25** (71%) was obtained. Vicinal $^{1}H-^{1}H$ coupling constants (Table 2) corresponded





with those of D-mannose in the $^4C_1$ conformation. The anomeric stereochemistry was not definitively deduced at this point since $J_{9,9a}$ was 1.5 Hz which conceivably could have fit either anomer. Hydrogenolytic removal of the benzyl group gave **4** contaminated with by-products that were difficult to remove.

The difficulty of purifying **4** obtained from the first two displacement processes prompted the investigation of a third route. Inasmuch as it was felt that formation of epoxide intermediates was leading to mixtures of cyclization products, it was decided to try to exploit epoxide formation and use it in a double-displacement process to get the D-*manno* configuration from a D-*manno* precursor. If a mannose derivative could be converted to an epoxide with inversion at the 5-position, then attack at this position of the epoxide would give back the D-*manno* configuration. To this end, methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**26**)[22] was selectively tritylated at the 6-position to give **27**[21] (83%) which was then converted to mesylate **28** (85%). Cautious deprotection of **28** gave 5-*O*-mesyl-D-mannofuranose (**29**, 86%). One equivalent of 1,3-propanediamine added all at once to an aqueous solution of **29** produced **4** as the major product (32% purified yield). ^{1}H NMR spectral data (difference nOe data in Fig. 2 and ^{1}H–^{1}H vicinal couplings in Table 2) established that in aqueous solution the product was, within the limits of detection, only the β-anomer **4**β in the conformation depicted; it follows, therefore, that **25** was also the β-anomer. It is likely that the intermediate epoxide involved in the formation of **4**β is compound **30** which should form more readily than the more sterically encumbered 4,5-epoxide. When formation of only the 4,5-epoxide was possible (reaction of **24** with the diamine), a more complex mixture of products was formed suggesting that cyclization to a pyrrolidine type of product was competitive with formation of **4**β. With epoxide **30**, cyclization to a seven-membered ring product would not be expected to be very competitive with formation of **4**β.

Table 2. Selected ^{1}H–^{1}H NMR coupling constants of compounds **4**β and **25** in D_2O

Compound	*J* (Hz)						
	$J_{6,10a}$	$J_{6,10b}$	$J_{10a,10b}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,9a}$
4β	2.4	2.9	12.7	9.8	9.8	3.4	1.5
25	2.0	3.4	11.2	9.8	9.8	3.4	1.5

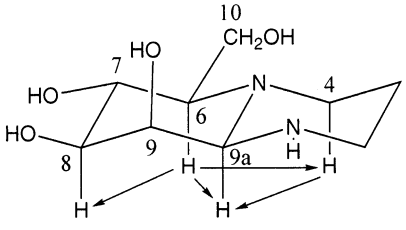


Figure 2. Difference nOe data used in determining the configuration and conformation of compound **4**β: H_{4ax} to H_{9a} (3.8%); H_6 to H_{4ax} (3.6%), H_6 to H_8 (6.2%); H_6 to H_{9a} (6.2%).

In conclusion, a bicyclic diazasugar analogue of D-mannose has been prepared, structurally characterized, and found to be the β-anomer, **4**β. It was formed both by direct displacement using an L-gulose derivative and by way of an epoxide intermediate from a D-mannose derivative. Diazasugar analogues of L-gulose were formed by an electrophilic addition process. A side reaction in a variation of the latter process formed an amidinosugar, and this observation has led to additional work on this class of compounds, which is being reported separately. Inasmuch as the mannose analogue prepared exists almost exclusively as the β-anomer rather than the desired α-anomer, means to remotely control anomeric preference are also being explored with hopes of finding a way to get predominantly an α-anomer.

3. Experimental

3.1. General

General methods and procedures are described in previous publications from this laboratory.[4–7] Unless indicated otherwise, the following were used as NMR reference signals in the solvents indicated: $CDCl_3$, for ^{1}H NMR either TMS or residual $CHCl_3$ (δ 7.26) and for ^{13}C NMR the center peak of $CDCl_3$ (δ 77.23); CD_3OD, for ^{1}H NMR the center peak of CHD_2OD (δ 3.31) and for ^{13}C NMR the center peak of CD_3OD (δ 49.15); CD_3SOCD_3, for ^{1}H NMR the center peak of CD_3SOCHD_2 (δ 2.51). In instances where noted, a small amount of NH_4OH was added to an NMR sample to effect a change in chemical shift allowing the multiplicity and coupling of signals to be ascertained.

3.1.1. [6*R*-(6α,7β,8α,9α,9aβ)]Octahydro-6-hydroxymethylpyrido[1,2-*a*]pyrimidine-7,8,9-triol (4β). *From* **18**. A solution of **18** (74 mg, 0.29 mmol) and 1,3-propanediamine (27.2 μL, 0.33 mmol) in H_2O was stirred for 0.5 h and then treated with Amberlite CG-400 anion exchange resin (hydroxide form). The solvent was evaporated to give a gum (83 mg) whose ^{13}C NMR spectrum showed two compounds. **4**: ^{13}C NMR (D_2O, reference CH_3CH_2OH δ 17.31) δ 75.6, 74.3, 71.4, 67.8, 66.9, 57.8, 50.3, 43.6, 25.9. Unknown: ^{13}C NMR (D_2O, reference CH_3CH_2OH δ 17.31) δ 80.7, 73.4, 72.7, 70.9, 69.5, 64.1, 52.8, 44.4, 25.3; HRMS (CI): calcd for $C_9H_{18}N_2O_4$: 219.1345 (M+1), found 219.1341.

From **25**. A solution of **25** (120 mg, 0.390 mmol) in 95% EtOH containing Pd/C (380 mg, 10 wt% Pd) was stirred for 12 h under an H_2 atmosphere (60 psi). The catalyst was removed by filtration, and the solvent was evaporated to give a gum (80 mg) whose ^{13}C NMR spectrum showed a mixture including a component matching **4** from the previous method of preparation; HRMS (CI): calcd for $C_9H_{18}N_2O_4$: 219.1345 (M+1), found 219.1351.

From **29**. A solution of **28** (1.3 g, 2.3 mmol) in TFA (9 mL) and H_2O (3.9 mL) was stirred for 12 h. Water (20 mL) was added, and a white precipitate formed at once. The solid was removed by filtration, and solution was evaporated under vacuum. Then another 20 mL of H_2O was added to the residue and evaporated. The same procedure was repeated two more times. The residue was dissolved in H_2O and treated with Amberlite CG-400 anion exchange resin (hydroxide form) until the solution reached neutral pH. Removal of the H_2O under vacuum gave 5-*O*-methanesulfonyl-D-mannofuranose (**29**) as a gum which was a mixture of anomers (520 mg, 86.0%): major anomer ^{13}C NMR (D_2O, reference MeOH δ 49.15) δ 101.2, 80.4, 77.5, 76.8, 71.0, 60.7, 38.3; HRMS (CI): calcd for $C_7H_{14}O_8S$: 163.0607 (M−CH_3SO_3), found 163.0610. A solution of **29** (330 mg, 1.28 mmol) and 1,3-propanediamine (107 μL) in H_2O (2 mL) was stirred for 0.5 h and then treated with Amberlite CG-400 anion exchange resin (hydroxide form) to remove methanesulfonic acid. After evaporation under vacuum, Et_2O was added to an EtOH solution of the residue, and a white solid precipitated that was separated from the solvent by centrifugation. The solid was dissolved in EtOH, and Et_2O was added to produce a solid again. The same procedure was repeated one more time, and then the resulting solid was dissolved in H_2O and lyophilized to give **4**β (90 mg, 32%); ^1H NMR (D_2O, NH_4OH, reference CH_3CN δ 1.94, COSY) δ 3.84 (dd, *J*=2.4, 12.7 Hz, 1H, H-10a), 3.69 (dd, *J*=2.9, 12.7 Hz, 1H, H-10b), 3.65 (dd, *J*=1.5, 3.4 Hz, 1H, H-9), 3.52 (t, *J*=9.8 Hz, 1H, H-7), 3.47 (dd, *J*=3.4, 9.8 Hz, 1H, H-8), 3.24 (bd, *J*=11.7 Hz, 1H, H-4eq), 2.93 (d, *J*=1.5 Hz, 1H, H-9a), 2.91 (bd, *J*=13.7 Hz, 1H, H-2eq), 2.46 (ddd, *J*=6.3, 9.3, 13.7 Hz, 1H, H-2ax), 2.03 (ddd, *J*=6.4, 9.0, 11.7 Hz, 1H, H-4ax), 1.82 (ddd, *J*=2.4, 2.9 9.8 Hz, 1H, H-6), 1.51 (m, 2H, H-3); difference nOe: $H_6 \rightarrow H_{10a}$ (2.2%), $H_6 \rightarrow H_{10b}$ (2.1%), $H_6 \rightarrow H_8$ (6.2%), $H_6 \rightarrow H_{9a}$ (6.2%), $H_6 \rightarrow H_{4a}$ (3.6%), $H_{4a} \rightarrow H_{4e}$ (19.5%), $H_{4a} \rightarrow H_{9a}$ (3.8%), $H_{4a} \rightarrow H_{2a}$ (2.9%), $H_{4a} \rightarrow H_6$ (4.9%), $H_{4a} \rightarrow H_{3a}$ (2.1%), $H_{2a} \rightarrow H_{2e+9a}$ (30.3%), $H_{2a} \rightarrow H_{4a}$ (1.5%), $H_{2a} \rightarrow H_{3a}$ (1.7%), $H_{4e} \rightarrow H_{10a+10b}$ (5.8%), $H_{4e} \rightarrow H_{4a}$ (20.6%), $H_{4e} \rightarrow H_{3e}$ (4.7%); ^{13}C NMR (D_2O, NH_4OH, reference CH_3CN δ 1.39, HETCOR) δ 75.6 (C-9a), 74.4 (C-8), 71.4 (C-9), 67.9 (C-7), 66.8 (C-6), 57.9 (C-10), 50.3 (C-4), 43.6 (C-2), 26.0 (C-3); HRMS (CI): calcd for $C_9H_{18}N_2O_4$: 219.1345 (M+1), found 219.1343.

3.1.2. 2,3-*O*-Isopropylidene-5,6-*O*-dimethanesulfonyl-α-D-mannofuranosyl chloride (6). To a solution of 2,3-*O*-isopropylidene-α-D-mannofuranose (**5**)[13] (2.7 g, 12 mmol) in 100 mL of anhydrous pyridine in an ice bath was added slowly methanesulfonyl chloride (4.8 mL, 61 mmol). The solution was stirred for 4 h and then was concentrated. Water was added followed by extraction with $CHCl_3$ and evaporation of the extract to give a gum (3.0 g, 65%). Crystallization from EtOAc/hexane gave needles: mp 123.5–124.5°C; ^1H NMR ($CDCl_3$, COSY) δ 6.07 (s, 1H, H-1), 5.13 (ddd, $J_{4,5}$=7.6 Hz, $J_{5,6a}$=2.2 Hz, $J_{5,6b}$=4.6 Hz, 1H, H-5), 4.99 (dd, $J_{2,3}$=5.9 Hz, 1H, H-2), 4.91 (dd, $J_{3,4}$= 3.7 Hz, 1H, H-3), 4.70 (dd, $J_{6a,6b}$=12.0 Hz, 1H, H-6a), 4.52 (dd, 1H, H-4), 4.42 (dd, 1H, H-6b), 3.15, 3.09 (2s, each 3H, both OSO_2CH_3), 1.50, 1.34 (2s, each 3H, acetonide CH_3); ^{13}C NMR ($CDCl_3$, DEPT, HETCOR) δ 113.7 (acetonide C), 96.5 (C-1), 88.9 (C-2), 78.8 (C-4), 77.8 (C-3), 75.0 (C-5), 68.4 (C-6), 38.7, 37.5 (both OSO_2CH_3), 25.8, 24.7 (both CH_3); HRMS (CI) calcd for $C_{11}H_{19}O_9ClS_2$ (M+1) 395.0237, 397.0208, found 395.0248, 397.0202.

3.1.3. 5,6-Dideoxy-2,3-*O*-isopropylidene-α-D-*lyxo*-hex-5-enofuranose (7). A solution of **6** (2.0 g, 5.3 mmol) and NaI (6.0 g, 40 mmol) in 200 mL anhydrous 1,2-dimethoxyethane was heated at reflux for 24 h. The solvent was evaporated, and the residue was partitioned between $CHCl_3$ and a 10% aqueous $Na_2S_2O_3$ solution. The $CHCl_3$ extract was washed with water, dried, and evaporated to give the product as a gum (0.95 g, 96%). Crystals were obtained from ether/hexane: mp 60°C (lit. 61°C);[14] ^1H NMR ($CDCl_3$) δ 5.99 (ddd, $J_{4,5}$=7.3 Hz, $J_{5,6a}$=17.7 Hz, $J_{5,6b}$= 10.3 Hz, 1H, H-5), 5.41 (ddd, $J_{4,6a}$=1.5 Hz, $J_{6a,6b}$=1.5 Hz, 1H, H-6a), 5.41 (s, 1H, H-1), 5.34 (m, $J_{4,6b}$=1.0 Hz, 1H, H-6b), 4.73 (dd, $J_{2,3}$=5.9 Hz, $J_{3,4}$=3.4 Hz, 1H, H-3), 4.63 (d, 1H, H-2), 4.61 (m, 1H, H-4), 1.47, 1.32 (2s, each 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 132.4, 119.5, 112.9, 101.2, 85.9, 81.7, 81.6, 26.1, 24.9 (^1H NMR assignments were in accord with those in the literature).

3.1.4. (6*R*,7*R*,8*S*,9*R*,9a*S*)-6-(Acetoxymercuriomethyl)-octahydro-7-hydroxy-8,9-[(1-methylethylidene)bis(oxy)]-2*H*-pyrido[1,2-*a*]pyrimidine (9). A solution of **7** (0.64 g, 3.5 mmol) in 5 mL of 1,3-propanediamine was stirred under nitrogen overnight. Excess diamine was removed under high vacuum to give hexahydro-2-[[D-*lyxo*-3-hydroxy-1,2-[(1-methylethylidene)bis(oxy)]-4-pentenyl]]pyrimidine (**8**) as a gum (0.84 g, 100%) which was used without purification; ^1H NMR ($CDCl_3$) δ 6.06 (ddd, $J_{3',4'}$=4.9 Hz, $J_{4',5a'}$=17.1 Hz, $J_{4',5b'}$=10.3 Hz, 1H, H-4′), 5.40 (ddd, $J_{3',5a'}$=2.0 Hz, $J_{5a',5b'}$=2.0 Hz, 1H, H-5a′), 5.20 (ddd, $J_{3',5b'}$=2.0 Hz, 1H, H-5b′), 4.36 (m, 1H, H-4), 4.27 (dd, $J_{1',2'}$=7.8 Hz, $J_{2',3'}$=1.5 Hz, 1H, H-2′), 4.12 (dd, 1H, H-1′), 3.82 (d, $J_{1',2}$=2.9 Hz, 1H, H-2), 3.22 (m, 2H, H-4a), 2.78 (m, 2H, H-4b), 1.6–1.8 (m, 2H, H-5a and H-5b); ^{13}C NMR ($CDCl_3$) δ 139.1, 115.1, 108.6, 80.1, 80.0, 70.0, 69.5, 45.6, 44.6, 27.0, 26.4, 24.1; HRMS (CI) calcd for $C_{12}H_{22}N_2O_3$ (M+1) 243.1709, found 243.1711. A

suspension of **8** (0.48 g, 1.9 mmol) and $Hg(OAc)_2$ (0.72 g, 2.3 mmol) in 50 mL of anhydrous CH_3CN was stirred under N_2 overnight. A gray precipitate formed. The solution was filtered, and the filtrate was evaporated to give a yellow solid (0.87 g, 88%); ^{1}H NMR (CD_3OD, COSY) δ 4.41 (dd, $J_{8,9}$=5.4 Hz, $J_{9,9a}$=6.8 Hz, 1H, H-9), 4.34 (dd, $J_{7,8}$= 2.4 Hz, 1H, H-8), 4.10 (d, 1H, H-9a), 3.83 (dd, $J_{6,7}$= 1.5 Hz, 1H, H-7), 3.56 (m, 1H, H-4a), 3.54 (m, 1H, H-2a), 3.24 (m, 1H, H-2b), 2.97 (dd, $J_{6,10a}$=5.4 Hz, $J_{6,10b}$<1 Hz, 1H, H-6), 2.23 (m, 1H, H-4b), 2.15 (dd, $J_{10a,10b}$=12.5 Hz, 1H, H-10a), 2.15 (m, 1H, H-3a), 2.03 (m, 1H, H-3b), 1.93 (s, 3H, acetate CH_3), 1.71 (br d, 1H, H-10b), 1.54, 1.39 (2s, each 3H, CH_3); ^{13}C NMR (CD_3OD, DEPT, HETCOR) δ 178.3 (C=O), 112.0 (acetonide C), 82.9 (C-9a), 77.3 (C-8), 75.8 (C-9), 69.5 (C-7), 59.3 (C-6), 50.9 (C-4), 49.0 (C-2), 28.8 (C-10), 28.2 (C-3), 27.3, 26.6 (both acetonide CH_3), 23.1 (acetate CH_3); HRMS (FAB) calcd for dialkylmercury form $C_{24}H_{42}{}^{200}HgN_4O_6$ (M−1) 681.2709, found 681.2717.

3.1.5. (6*R*,7*R*,8*S*,9*R*,9a*S*)-Octahydro-7-hydroxy-6-methyl-8,9-[(1-methyl-ethylidine)bis(oxy)]-2*H*-pyrido[1,2-*a*]-pyrimidine (10). To **9** (78 mg, 0.16 mmol) in 10 mL of THF was added 1 mL of a 0.5 M $NaBH_4$ solution in 3.0 M NaOH. The mixture was stirred for 15 min and centrifuged to separate the two layers. After saturation with NaCl, the aqueous layer was extracted with THF. The THF extract was dried and evaporated to give a gum (30 mg, 78%). Crystallization from ether gave needles: mp 140–141°C; ^{1}H NMR ($CDCl_3$, COSY) δ 4.27 (dd, $J_{7,8}$=2.9 Hz, 1H, H-8), 3.75 (dd, $J_{8,9}$=5.4 Hz, 1H, H-9), 3.71 (dd, $J_{6,7}$= 1.5 Hz, 1H, H-7), 3.12 (m, $J_{3ax,4eq}$=3.0 Hz, $J_{3eq,4eq}$=3.0 Hz, $J_{4ax,4eq}$=11.2 Hz, 1H, H-4eq), 3.06 (m, $J_{2ax,2eq}$=12.7 Hz, $J_{2eq,3ax}$=2.0 Hz, $J_{2eq,3eq}$=2.0 Hz, 1H, H-2eq), 2.93 (d, $J_{9,9a}$=7.8 Hz, 1H, H-9a), 2.61 (m, $J_{6,10}$=6.8 Hz, 1H, H-6), 2.60 (m, $J_{2ax,3ax}$=12.7 Hz, $J_{2ax,3eq}$=3.9 Hz, 1H, H-2ax), 2.03 (m, $J_{3ax,4ax}$=11.2 Hz, $J_{3eq,4ax}$=4.4 Hz, 1H, H-4ax), 1.63 (m, 2H, H-3a and H-3b), 1.53, 1.36, (2s, each 3H, CH_3), 1.17 (d, 3H, H-10); ^{13}C NMR ($CDCl_3$) δ 109.7, 79.8, 77.3, 76.4, 70.0, 55.3, 49.8, 44.6, 27.9, 27.1, 26.2, 15.4; HRMS (FAB) calcd for $C_{12}H_{22}N_2O_3$ (M+1) 243.1708, found 243.1701. X-ray crystallography confirmed the structure.

3.1.6. (6*R*,7*R*,8*S*,9*R*,9a*S*)-Octahydro-7-hydroxy-6-hydroxymethyl-8,9-[(1-methylethylidene)bis(oxy)]-2*H*-pyrido-[1,2-*a*]pyrimidine (11). Through a solution of $NaBH_4$ (76 mg, 0.20 mmol) in 4 mL of DMF in a 25 mL 2-neck round-bottom flask capped with a rubber stopper containing a small syringe needle as a vent and a 25 mL additional funnel was bubbled oxygen gas for 20 min. A solution of **9** (61 mg, 0.13 mmol) in 4 mL of DMF was also saturated with oxygen and then was added dropwise via the addition funnel over a 2 h period to the $NaBH_4$ solution. After complete addition, a vigorous flow of oxygen was maintained for 2 h. A gray precipitate formed. The solution was filtered, and the filtrate was concentrated to a gum which was chromatographed on silica gel using a step gradient of 10–50% CH_3OH in CH_2Cl_2 containing 1% NH_4OH to give the product as a gum (20 mg, 60%) that still contained minor impurities; ^{13}C NMR (CD_3OD) δ 111.1, 86.3, 78.0, 75.6, 70.3, 70.2, 63.9, 59.0, 43.7, 28.3, 26.5, 21.8; HRMS (FAB) calcd for $C_{12}H_{22}N_2O_4$ (M+1) 259.1658, found 259.1662.

3.1.7. 5,6-Dideoxy-D-*lyxo*-hex-5-enofuranose (12). After a solution of **7** (0.13 g, 0.70 mmol) in 5 mL of 6:4 CF_3CO_2H/H_2O was stirred for 1.5 h, it was diluted with water and evaporated partially. This process of dilution and partial evaporation was repeated several times to eventually give a gum consisting of two anomers (0.10 g, 98%); ^{13}C NMR (D_2O) δ major: 133.2, 120.3, 101.2, 82.0, 78.1, 73.4; minor: 134.1, 119.9, 96.0, 82.2, 72.3, 72.0; HRMS (CI) calcd for $C_6H_{10}O_4$ (M+1) 147.0658, found 147.0666.

3.1.8. Hexahydro-2-(D-*lyxo*-1,2,3-trihydroxy-4-pentenyl)-pyrimidine (13). A solution of **12** (0.10 g, 0.71 mmol) in 3 mL of 1,3-propanediamine was stirred under N_2 overnight. Excess diamine was removed under high vacuum to give the product as a gum. Crystallization from Et_2O/CH_2Cl_2 gave needles (0.066 g, 47%): mp 108–109°C; ^{1}H NMR (DMSO-d_6) δ 5.91 (ddd, $J_{3',4'}$=5.4 Hz, $J_{4',5a'}$= 16.1 Hz, $J_{4',5b'}$=10.7 Hz, 1H, H-4′), 5.17 (ddd, $J_{3',5a'}$= 2.0 Hz, $J_{5a',5b'}$=2.0 Hz, 1H, H-5a′), 5.21 (ddd, $J_{3',5b'}$= 2.0 Hz, 1H, H-5b′), 4.10 (m, 1H, H-3′), 3.50 (d, $J_{1',2}$= 3.9 Hz, 1H, H-2), 3.38 (dd, $J_{1',2'}$=7.8 Hz, $J_{2',3'}$=2.0 Hz, 1H, H-2′), 3.36 (dd, 1H, H-1′), 3.02 (m, $J_{4ax,4eq}$=12.7 Hz, $J_{4eq,5ax}$=2.0 Hz, $J_{4eq,5eq}$=2.0 Hz, 2H, H-4eq and H-6eq), 2.65 (m, $J_{4ax,5ax}$=12.7 Hz, $J_{4ax,5eq}$=3.4 Hz, 2H, H-4ax and H-6ax), 1.38 (m, $J_{5ax,5eq}$=12.2 Hz, 1H, H-5ax), 1.29 (m, 1H, H-5eq); ^{13}C NMR (DMF-d_7, reference center peak at δ 163.15) δ 141.5, 114.4, 76.1, 74.3, 72.9, 72.6, 45.9, 45.8, 27.7; HRMS (CI) calcd for $C_9H_{18}N_2O_3$ (M+1) 203.1396, found 203.1403.

3.1.9. (6*R*,7*R*,8*S*,9*R*)-6-(Acetoxymercuriomethyl)-3,4,6,7,8,9-hexahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-*a*]-pyrimidine (14). A suspension of **13** (42 mg, 0.21 mmol) and $Hg(OAc)_2$ (66 mg, 0.21 mmol) in 20 mL of anhydrous DMF was stirred under N_2 overnight. The solution was filtered and evaporated to give a gum; ^{1}H NMR (D_2O, COSY) δ 4.87 (d, $J_{8,9}$=3.2 Hz, 1H, H-9), 4.30 (dd, $J_{7,8}$=5.0 Hz, 1H, H-8), 4.24 (dd, $J_{6,7}$=4.1 Hz, 1H, H-7), 4.19 (ddd, $J_{6,10a}$=8.7 Hz, $J_{6,10b}$=3.7 Hz, 1H, H-6), 3.78 (m, $J_{3ax,4ax}$=9.2 Hz, $J_{3eq,4ax}$=4.1 Hz, $J_{4ax,4eq}$=13.3 Hz, 1H, H-4ax), 3.60 (m, $J_{2ax,2eq}$=13.3 Hz, $J_{2eq,3ax}$=5.0 Hz, $J_{2eq,3eq}$= 5.0 Hz, 1H, H-2eq), 3.51 (m, $J_{3eq,4ax}$=4.6 Hz, $J_{3eq,4eq}$= 4.6 Hz, 1H, H-4eq), 2.15 (m, $J_{2ax,3ax}$=8.7 Hz, $J_{2ax,3eq}$= 4.6 Hz, 1H, H-2ax), 2.28 (dd, $J_{10a,10b}$=12.4 Hz, 1H, H-10a), 2.22 (m, 1H, H-3e), 2.19 (m, 1H, H-10b), 2.09 (m, 1H, H-3a), 2.09 (s, 3H, acetate CH_3); ^{13}C NMR (D_2O, reference DMF δ 163.17, DEPT, HETCOR) δ 178.0, 159.3, 67.8, 66.5, 62.5, 57.8, 42.6, 36.4, 20.7, 19.1, 16.5.

3.1.10. 2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-6-*O*-triphenylmethyl-L-gulono-1,4-lactone (16). A solution of 2,3-*O*-isopropylidene-L-gulono-1,4-lactone (**15**)[17] (3.80 g, 17.4 mmol) and triphenylmethyl chloride (7.3 g, 26 mmol) in pyridine (40 mL) was stirred for 12 h. A ^{13}C NMR spectrum confirmed the presence of 2,3-*O*-isopropylidene-6-*O*-triphenylmethyl-L-gulono-1,4-lactone, and no starting material was left. The product was used directly without purification. ^{13}C NMR ($CDCl_3$) δ 173.9, 143.7, 128.7, 128.1, 127.4, 114.2, 86.9, 80.1, 76.4, 76.2, 70.2, 63.7, 26.7, 25.7. To the solution of 2,3-*O*-isopropylidene-6-*O*-triphenylmethyl-L-gulono-1,4-lactone in pyridine was added methanesulfonyl chloride (5.40 mL, 115 mmol). The reaction was followed by TLC (CH_2Cl_2). After stirring

4 h at 60°C, the pyridine was removed under vacuum, and the residue was purified by chromatography on silica gel. Elution with CH_2Cl_2 gave **16** which was crystallized from CH_2Cl_2 and MeOH (6.2 g, 66%, yield based on two steps): mp 125–126°C; ^{1}H NMR ($CDCl_3$, COSY) δ 7.47 (d, J=7.3 Hz, 6H, H-2′ and 6′, phenyl ring), 7.33 (t, J=7.3 Hz, 6H, H-3′ and 5′), 7.26 (t, J=7.3 Hz, 3H, H-4′), 4.98 (dd, J=3.2, 8.8 Hz, 1H, H-4), 4.88 (dt, J=2.4, 8.8 Hz, 1H, H-5), 4.77 (d, J=4.9 Hz, 1H, H-2), 4.35 (dd, J=3.2, 4.9 Hz, 1H, H-3), 3.84 (dd, J=2.4, 11.2 Hz, 1H, H-6a), 3.29 (dd, J=2.4, 11.2 Hz, 1H, H-6b), 3.15 (s, 3H, CH_3SO_2), 1.35 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, HETCOR) δ 172.9 (C-1), 143.1 (C-1′), 128.6 (C-3′ or C-2′), 128.3 (C-2′ or C-3′), 127.6 (C-4′), 114.6 [$C(CH_3)_2$], 87.1 (CPh_3), 81.1 (C-5), 77.7 (C-4), 76.2 (C-2), 75.3 (C-3) 63.4 (C-6), 39.0 (CH_3SO_2), 26.9 (CH_3), 25.8 (CH_3). Anal. calcd for $C_{29}H_{30}O_8S$: C, 64.67; H 5.61. Found: C, 64.56; H, 5.70.

3.1.11. 2,3-*O*-Isopropylidene-5-*O*-methanesulfonyl-6-*O*-triphenylmethyl-L-gulofuranose (17). To a solution of **16** (760 mg, 1.41 mmol) in CH_2Cl_2 (10 mL) at −78°C was added diisobutylaluminum hydride (1.0 M in THF, 1.92 mL). The reaction was followed by TLC (CH_2Cl_2). After stirring at −78°C for 1 h, the reaction was allowed to warm to room temperature, and H_2O was added. After stirring overnight, the solvent was removed under vacuum. The residue was extracted with CH_2Cl_2 (3×30 mL). Evaporation of the solvent gave **17** which crystallized from CH_2Cl_2 and MeOH (470 mg, 62%): mp 152.5–153.5°C; ^{1}H NMR ($CDCl_3$, COSY) δ 7.47 (d, J=7.8 Hz, 6H, H-2′ and 6′, phenyl ring), 7.31 (t, J=7.8 Hz, 6H, H-3′ and 5′), 7.24 (t, J=7.8 Hz, 3H, H-4′), 5.39 (d, J=2.4 Hz, 1H, H-1), 4.93 (ddd, J=2.4, 3.4, 8.8 Hz, 1H, H-5), 4.58 (dd, J=3.4, 8.8 Hz, 1H, H-4), 4.54 (d, J=5.9 Hz, 1H, H-2), 4.40 (dd, J=3.4, 5.9 Hz, 1H, H-3), 3.71 (dd, J=2.4, 10.7 Hz, 1H, H-6a), 3.30 (dd, J=3.4, 10.7 Hz, 1H, H-6b), 3.07 (s, 3H, CH_3SO_2), 2.72 (d, J=2.4 Hz, 1H, OH), 1.35 (s, 3H, CH_3), 1.12 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, HETCOR) δ 143.5 (C-1′), 128.8 (C-3′ or C-2′), 128.2 (C-2′ or C-3′), 127.4 (C-4′), 112.8 [$C(CH_3)_2$], 101.4 (C-1), 87.1 (CPh_3), 85.9 (C-2), 82.0 (C-5), 79.5 (C-4), 79.1 (C-3) 63.5 (C-6), 38.8 (CH_3SO_2), 26.2 (CH_3), 24.6 (CH_3). Anal. calcd for $C_{29}H_{32}O_8S$: C, 64.43; H, 5.97. Found: C, 64.50; H, 5.98.

3.1.12. 5-*O*-Methanesulfonyl-L-gulofuranose (18). A solution of **17** (1.2 g, 2.2 mmol) in TFA (9 mL) and H_2O (3.9 mL) was stirred for 3 h. Water (20 mL) was added, and a white precipitate formed at once. The solid was removed by filtration, and solution was evaporated under vacuum. Water (20 mL) was added and evaporated. The same procedure was repeated two more times. The residue was dissolved in H_2O and treated with Amberlite CG-400 anion exchange resin (hydroxide form) until the solution reached neutral pH. Removal of the H_2O under vacuum gave **18** as a gum (450 mg, 78%) which consisted primarily of one anomer and was used without purification in a reaction with 1,3-propanediamine; ^{13}C NMR (D_2O, reference CH_3COOH δ 21.03) δ 101.1, 84.6, 78.3, 78.0, 71.6, 61.0, 38.7; HRMS (CI): calcd for $C_7H_{14}O_8S$: 163.0603 ($M-CH_3SO_3$), found 163.0611.

3.1.13. 2,3:5,6-Di-*O*-isopropylidene-L-gulofuranose (20). To a solution of 2,3:5,6-di-*O*-isopropylidene-L-gulonolactone (**19**)[17] (5.00 g, 19.4 mmol) in CH_2Cl_2 (10 mL) at −78°C was added dropwise DIBAH (1.0 M in THF, 50 mL). The reaction was followed by TLC (CH_2Cl_2). After stirring at −78°C for 4 h, the reaction was allowed to warm to room temperature, and H_2O was added. After stirring overnight, the solvent was evaporated under vacuum, and a white precipitate formed. The solid was extracted with CH_2Cl_2 (3×50 mL), and the solvent was evaporated to give **20** as a single anomer (3.08 g, 61.0%); ^{13}C NMR ($CDCl_3$) δ 113.0, 109.9, 101.5, 85.8, 82.3, 80.0, 75.7, 66.1, 26.8, 26.1, 25.6, 24.8 (matched literature values).[18]

3.1.14. Methyl 2,3-*O*-isopropylidene-β-L-gulofuranoside (21). A mixture of acetone (58 mL), MeOH (58 mL), 2,2-dimethoxypropane (63 mL), concentrated HCl (0.86 mL), and **20** (3.08 g, 11.8 mmol) was heated at 70°C for 3 h. Water (120 mL) was added, the solution was concentrated to 100 mL, and then MeOH (85 mL) and concentrated HCl (2 mL) were added. After stirring for another 6 h, the reaction was stopped by adding saturated $NaHCO_3$ solution until the pH was 7–8. The solution was concentrated to 10 mL and extracted with CH_2Cl_2 (3×30 mL). After drying ($MgSO_4$), the CH_2Cl_2 solution was evaporated to give **21**[19,20] as a slightly yellow oil (1.6 g, 58%); ^{13}C NMR ($CDCl_3$) δ 112.6, 106.8, 85.2, 79.8, 79.7, 71.1, 63.2, 54.5, 25.8, 24.4; HRMS (CI): calcd for $C_{10}H_{18}O_6$: 234.1103 (M), found 234.1094.

3.1.15. Methyl 6-*O*-benzyl-2,3-*O*-isopropylidene-β-L-gulofuranoside (22). A solution of **21** (1.60 g, 6.84 mmol) and dibutyltin oxide (1.70 g, 6.82 mmol) in anhydrous benzene (250 mL) was heated at reflux for 15 h in a soxhlet apparatus containing 4 Å molecular sieves. The solvent was evaporated under vacuum leaving a white solid (3.1 g). A solution of the solid (2.60 g, 5.59 mmol), benzyl bromide (1.30 mL, 10.9 mmol), and CsF (3.0 g, 20 mmol) in DMF (60 mL) was stirred at 120°C for 12 h. The reaction was followed by TLC (3% MeOH in CH_2Cl_2). The DMF was evaporated under vacuum, and the residue was purified by chromatography on silica gel. Elution with a gradient of 1:1 hexanes and CH_2Cl_2 to only CH_2Cl_2 followed by 3% MeOH in CH_2Cl_2 gave **22** as a yellow oil (1.6 g, 88% for 2 steps); ^{13}C NMR ($CDCl_3$) δ 138.3, 128.6, 128.0, 128.0, 112.9, 107.0, 85.6, 80.6, 79.2, 73.7, 71.0, 69.9, 54.8, 26.2, 24.7 (matched literature values);[21] HRMS (CI): calcd for $C_{17}H_{24}O_6$: 324.1573 (M), found 324.1581.

3.1.16. Methyl 6-*O*-benzyl-2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-β-L-gulofuranoside (23). A solution of **22** (1.60 g, 4.94 mmol) and methanesulfonyl chloride (1.50 mL, 19.3 mmol) in pyridine was stirred at 50°C for 4 h. The reaction was followed by TLC (CH_2Cl_2). The pyridine was evaporated under vacuum, and the residue was purified by chromatography on silica gel. Elution with 20% EtOAc in hexanes first and then CH_2Cl_2 gave **23** as an oil (803 mg, 40.0%); ^{1}H NMR ($CDCl_3$, COSY) δ 7.34 (m, 5H, Ph), 4.96 (ddd, J=2.2, 3.7, 9.0 Hz, 1H, H-5), 4.91 (s, 1H, H-1), 4.73 (d, J=11.8 Hz, 1H, OCH_2Ph), 4.61 (dd, J=3.4, 5.7 Hz, 1H, H-3), 4.55 (d, J=5.7 Hz, 1H, H-2), 4.52 (d, J=11.8 Hz, 1H, OCH_2Ph), 4.27 (dd, J=3.4, 9.0 Hz, 1H, H-4), 3.93 (dd, J=3.7, 11.8 Hz, 1H, H-6a), 3.85 (dd, J=2.2,

11.8 Hz, 1H, H-6b), 3.30 (s, 3H, OCH_3), 3.11 (s, 3H, CH_3SO_2), 1.43 (s, 3H, CH_3), 1.24 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, HETCOR) δ 137.7 (Ph), 128.6 (Ph), 128.1 (Ph), 113.0 [$C(CH_3)_2$], 107.2 (C-1), 85.4 (C-2), 82.0 (C-5), 79.4 (C-3), 78.5 (C-4), 73.8 (OCH_2Ph), 69.7 (C-6), 54.8 (CH_3), 38.6 (CH_3SO_2), 26.3 (CH_3), 24.9 (CH_3); HRMS (CI): calcd for $C_{18}H_{26}O_8S$: 402.1349 (M), found 402.1339.

3.1.17. [6*R*-(6α,7β,8α,9α,9aβ)]-6-(Benzyloxymethyl)-octahydropyrido[1,2-*a*]pyrimidine-7,8,9-triol (25). A solution of **23** (100 mg, 0.249 mmol) in TFA (2 mL) and H_2O (0.5 mL) was stirred for 5 h. Water (2 mL) was added, and the solvent was removed under vacuum. Then another 2 mL of H_2O was added and evaporated. The same procedure was repeated two more times. Removal of the H_2O under vacuum gave 6-*O*-benzyl-5-*O*-methanesulfonyl-L-gulofuranose (**24**) as a gum (67 mg, 77%) which was a mixture of anomers: major anomer ^{13}C NMR (D_2O, reference CH_3CN δ 1.39) δ 136.4, 128.3, 128.2, 128.0, 100.1, 81.7, 77.1, 77.0, 72.7, 70.5, 67.6, 37.7. A solution of **24** (67 mg, 0.19 mmol) and 1,3-propanediamine (8.0 μL, 0.096 mmol) in H_2O (2 mL) was stirred for 0.5 h, and then additional 1,3-propanediamine (8.0 μL, 0.096 mmol) in MeOH (10 mL) was added. After stirring overnight, the solution was treated with Amberlite CG-400 anion exchange resin (hydroxide form) to remove methanesulfonic acid. The solvent was evaporated to give a gum, which was dissolved in EtOH. Ether was added to the EtOH solution, and a slightly yellow syrup precipitated. The syrup was separated from the solvent by centrifugation. The syrup was dissolved in EtOH, and ether was added to form the syrup again. The same procedure was repeated one more time to give **25** (42 mg, 71%); ^1H NMR (D_2O, NH_4OH, reference CH_3CN δ 1.94, COSY) δ 7.31 (m, 5H, Ph), 4.45 (d, *J*=11.7 Hz, 1H, C*H*$_2$Ph), 4.38 (d, *J*=11.7 Hz, 1H, C*H*$_2$Ph), 3.75 (dd, *J*=2.0, 11.2 Hz, 1H, H-10a), 3.64 (dd, *J*=1.5, 3.4 Hz, 1H, H-9), 3.58 (dd, *J*=3.4 11.2 Hz, 1H, H-10b), 3.47 (t, *J*=9.8 Hz, 1H, H-7), 3.35 (dd, *J*=3.4, 9.8 Hz, 1H, H-8), 3.10 (bd, *J*=11.7 Hz, 1H, H-4eq), 2.89 (bd, *J*=13.7 Hz, 1H, H-2eq), 2.88 (d, *J*=1.5 Hz, 1H, H-9a), 2.44 (ddd, *J*=6.8, 9.3, 13.7 Hz, 1H, H-2ax), 1.98 (ddd, *J*=6.4, 9.2, 11.7 Hz, 1H, H-4ax), 1.92 (ddd, *J*=2.0, 3.4, 9.8 Hz, 1H, H-6), 1.46 (m, 2H, H-3); ^{13}C NMR (D_2O, NH_4OH, reference CH_3CN δ 1.39, HETCOR) δ 137.9 (Ph), 129.2 (Ph), 128.8 (Ph), 75.5 (C-9a), 74.4 (C-8), 73.3 (OCH_2Ph), 71.4 (C-9), 68.2 (C-7), 67.2 (C-10), 65.7 (C-6), 50.5 (C-4), 43.5 (C-2), 26.0 (C-3); HRMS (CI): calcd for $C_{16}H_{24}N_2O_4$: 309.1814 (M+1), found 309.1819.

3.1.18. Methyl 2,3-*O*-isopropylidene-6-*O*-triphenylmethyl-α-D-mannofuranoside (27). A solution of methyl 2,3-*O*-isopropylidene-α-D-mannofuranoside (**26**)[22] (4.7 g, 20 mmol) and triphenylmethyl chloride (8.4 g, 30 mmol) in pyridine (60 mL) was stirred for 36 h. The pyridine was evaporated under vacuum, and the residue was purified by chromatography on silica gel. Elution with 10% EtOAc in hexane gave **27** (7.9 g, 83%). Crystals were obtained from EtOAc and hexane: mp 121–122°C (lit. 120–122°C);[22] ^1H NMR ($CDCl_3$, COSY) δ 7.47 (d, *J*=7.8 Hz, 2H, Ph), 7.30 (t, *J*=7.3, 7.8 Hz, 2H, Ph), 7.23 (t, *J*=7.3 Hz, 1H, Ph), 4.87 (s, 1H, H-1), 4.82 (dd, *J*=3.4, 5.9 Hz, 1H, H-3), 4.54 (d, *J*=5.9 Hz, 1H, H-2), 4.11 (m, *J*=3.4, 4.8, 7.3 Hz, 1H, H-5), 4.01 (dd, *J*=3.4, 7.3 Hz, 1H, H-4), 3.46 (dd, *J*=3.4, 9.8 Hz, 1H, H-6a), 3.32 (dd, *J*=4.8, 9.8 Hz, 1H, H-6b), 3.26 (s, OCH_3), 2.97 (d, *J*=6.8 Hz, 1H, OH), 1.46 (s, CH_3), 1.32 (CH_3); ^{13}C NMR ($CDCl_3$, HETCOR) δ 144.1 (Ph), 128.9 (Ph), 128.0 (Ph), 127.3 (Ph), 112.7 ($C(CH_3)_2$), 107.3 (C-1), 86.8 (CPh_3), 85.1 (C-2), 80.6 (C-3), 79.1 (C-4), 69.5 (C-5), 65.3 (C-6), 54.7 (CH_3), 26.1 (CH_3), 24.8 (CH_3); HRMS (CI): calcd for $C_{29}H_{32}O_6$: 476.2198 (M), found 476.2206.

3.1.19. Methyl 2,3-*O*-isopropylidene-5-*O*-methanesulfonyl-6-*O*-triphenylmethyl-α-D-mannofuranoside (28). A solution of **27** (7.8 g, 16 mmol) and methanesulfonyl chloride (3.6 mL, 47 mmol) in pyridine (60 mL) was stirred at 60°C for 1.5 h and at rt overnight. The reaction was followed by TLC (CH_2Cl_2). The pyridine was evaporated under vacuum, and the residue was taken up in CH_2Cl_2 (150 mL) and H_2O (60 mL). The H_2O layer was extracted three times with CH_2Cl_2, and the combined organic phase was washed with H_2O and dried ($MgSO_4$). After filtration, a dark solution was obtained. It was decolorized by treatment with activated carbon to a light yellow solution, which was evaporated to give a light yellow syrup. Crystallization of the syrup from 30% EtOAc in hexane gave colorless crystals of **28** (7.7 g, 85%): mp 115–116°C; ^1H NMR ($CDCl_3$, COSY) δ 7.48 (d, *J*=8.3 Hz, 2H, Ph), 7.30 (t, *J*=7.8, 8.3 Hz, 2H, Ph), 7.23 (t, *J*=7.8 Hz, 1H, Ph), 4.97 (brd, *J*=8.3 Hz, 1H, H-5), 4.80 (s, 1H, H-1), 4.79 (dd, *J*=3.4, 5.9 Hz, 1H, H-3), 4.58 (d, *J*=5.9 Hz, 1H, H-2), 4.48 (dd, *J*=3.4, 8.3 Hz, 1H, H-4), 3.73 (d, *J*=11.0 Hz, 1H, H-6a), 3.33 (dd, *J*=3.4, 11.0 Hz, 1H, H-6b), 3.21 (s, OCH_3), 3.05 (s, CH_3SO_3), 1.34 (s, CH_3), 1.29 (CH_3); ^{13}C NMR ($CDCl_3$, HETCOR) δ 143.8 (Ph), 128.9 (Ph), 128.1 (Ph), 127.3 (Ph), 113.0 ($C(CH_3)_2$), 107.2 (C-1), 86.7 (CPh_3), 85.1 (C-2), 79.3 (C-5), 79.3 (C-3), 76.9 (C-4), 63.4 (C-6), 54.9 (CH_3O), 38.8 (CH_3SO_3), 26.2 (CH_3), 25.1 (CH_3). Anal. calcd for $C_{30}H_{34}O_8S$: C, 64.96; H, 6.18. Found: C, 65.12; H, 6.30.

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