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Bicyclic Azasugars Containing a Glycosidic Heteroatom: D-Xylose Analogues

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Abstract: Bicyclic azasugar analogues of D-xylose containing a glycosidic heteroatom have been prepared and characterized by X-ray crystallography and NMR spectroscopy. Compounds in which the glycosidic heteroatom is N (substituted with H or CH_3), O, and S have been prepared, and the ring fused to the azasugar ring has been 5- or 6-membered; 7-membered analogues are either unstable or do not form. α-Anomers are present when the glycosidic heteroatom is O or S but not N, and even then they are less favored than the corresponding β–anomers.

Keywords: Carbohydrate mimetics; Aza compounds; Enzyme inhibitors; X-Ray crystal structures.

Naturally-occurring compounds which resemble sugars but have a nitrogen atom in place of the ring oxygen of sugars have been termed azasugars. Because many of these compounds inhibit glycosidases, they have been the subject of substantial interest.[1,2] These azasugars frequently have been the objects of synthetic efforts, and, in addition, a great many analogues of the natural products have also been prepared with the aim of finding compounds with improved inhibitory properties. In the development of glycosidase inhibitors, it is very desirable to discover ways to produce selectivity for a single class of enzymes or even among members within a class. The majority of azasugars reported so far consist of either one ring or two rings which share a nitrogen atom. Most have lacked a heteroatom comparable to the glycosidic oxygen atom present in sugars. It is well known that glycosidases are exquisitely selective regarding the anomeric configuration of their substrates and are consequently named based on that selectivity, for example, as α-glucosidases. This selectivity is apparently a consequence of the placement within the active sites of these enzymes of catalytic carboxylic acid residues which serve to protonate the glycosidic oxygen atom. A few azasugars have been reported which contain a singly-bonded glycosidic heteroatom; these include the natural products nojirimycin **1**[3] and related compounds mannojirimycin[4] and galactostatin[5] (all three exist as mixtures of anomers), the unusual natural product kifunensine **2**,[6] synthetic 1-β-amino-1-deoxynojirimycin **3**,[7] and thia-analogues such as **4**[8] and **5**.[9] More recently we have reported the preparation of bicyclic diazasugars such as **6**.[10,11] It appears that those azasugars with a singly-bonded glycosidic heteroatom and a strong preference for a single anomeric configuration (**2**, **3**, and **6**) are very selective inhibitors of the glycosidases that cleave glycosides of the same anomeric configuration; those azasugars that are mixtures of anomers (**1** and related compounds) or have no anomeric heteroatom (1-deoxy analogues) are not selective and inhibit both α- and β-glycosidases. Azasugars which possess an anomeric heteroatom may act as pseudosubstrates of glycosidases, and this may account for their inhibitory selectivity.

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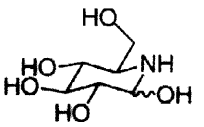

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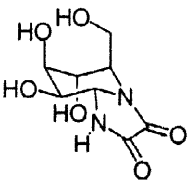

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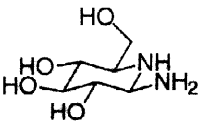

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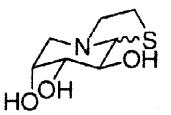

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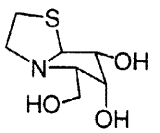

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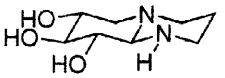

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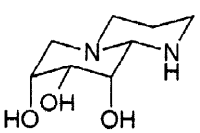
In light of these observations, we have set as research objectives the preparation of bicyclic azasugars with nearly exclusively α-configurations and others which are essentially only β-anomers. Our previous experience with octahydropyrido[1,2-*a*]pyrimidines such as **6** has shown that the "glycosidic" nitrogen atom has an extremely strong preference for an equatorial orientation relative to the piperidine ring. For example, **7** and **8** are the preferred conformations for the α-D-ribose and β-L-arabinose analogues, respectively; two axial hydroxyl groups are preferred over one and an axial NHR group which is consistent with reported A-values for these groups[12] and the possible involvement of an exo-anomeric effect.[13] Based on the presumed desirability of mimicking a sugar glycoside in the $^1C_4$ conformation, we have also set conformational control as another of our objectives. Herein we report the syntheses, configurations and conformational preferences of D-xylose azasugar analogues **9** in which X and n have been varied.



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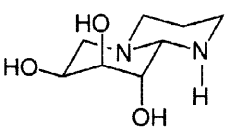

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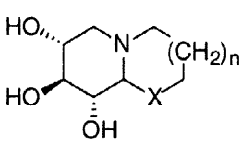

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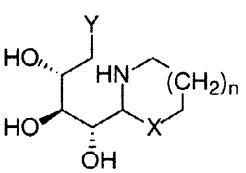
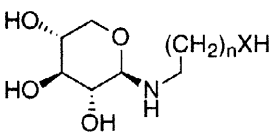
Our previous syntheses of bicyclic diazasugars have involved initial preparation of sugar aminals followed by internal displacement of a hydroxyl group which was activated *in situ*. Application of this method to prepare bicyclic azasugars that were not octahydropyrido[1,2-*a*]pyrimidines failed when attempts to prepare the requisite heterocycles **10** led to the xylosylamines **11** instead. A simple approach to overcoming this problem involved blocking and concomitantly activating the primary hydroxyl group of xylose (e.g. **12**) to allow both formation of the requisite heterocycles **13** and promote the final cyclization reactions to give the desired products **9**.[14]



10 (Y = OH)
13 (Y = leaving group)



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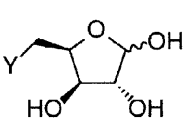
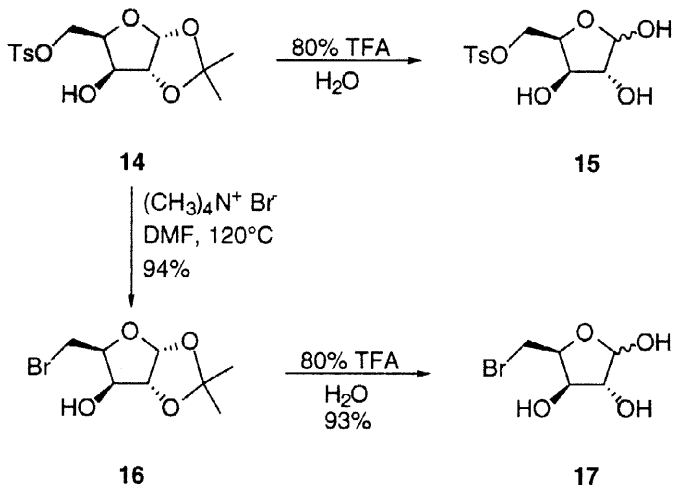


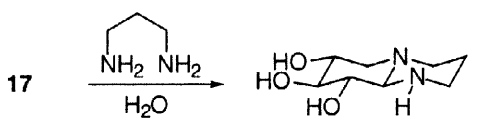
12

The synthesis of a terminally blocked and activated D-xylose derivative began with readily available 1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose **14**. Although **14** itself could be deblocked to **15**, a functional precursor to the final products, the instability of **15** prompted the conversion of **14** to bromide **16** followed by deblocking with trifluoroacetic acid to the more stable bromide **17**.[15]



14 **15** **16** **17**

To confirm the utility of this synthetic approach, an aqueous solution of **17** was treated with 1,3-propanediamine to give known bicyclic diazasugar **6** which could be isolated by simply treating the reaction mixture with an anion-exchange resin to remove HBr, evaporation to dryness, and crystallization. Using this method with 3-amino-1-propanol produced **18**, the oxygen analogue of **6**, as a mixture of anomers. The β-anomer (**18**β) crystallized from a concentrated solution of the mixture in ethanol. Upon dissolution of the crystals in D_2O, an equilibrium mixture containing 12% of the α-anomer (**18**α) was established within less than three days. Analysis of ^1H-^1H three-bond coupling constants for the protons of the azasugar ring (see Table 1) established the conformations of the anomers as shown in **18**α and **18**β; due to signal overlap, in some instances a coupling constant for **18**α was obtained from only one signal. In contrast to compounds **7** and **8** which prefer conformations with the anomeric nitrogen atom equatorial to the piperidine ring, compound **18**α prefers to have the anomeric oxygen atom axial. This must be a consequence of the presence of a strong endo-anomeric effect when the anomeric atom is oxygen and the requirement of having three hydroxyl groups be axial in order for the anomeric oxygen atom to be equatorial. In contrast to compound **6** which is only the β-anomer, the occurrence of some of the α-anomer of **18** must be due to the endo-anomeric effect compensating for the repulsive steric interactions introduced by the axial anomeric oxygen atom. Both anomers of **18** mimic the preferred conformations of the anomers of D-xylose.



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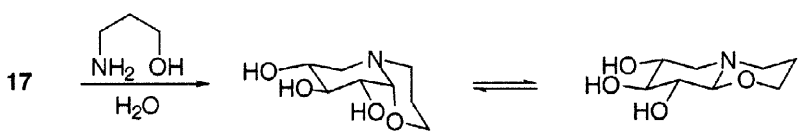
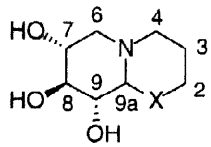
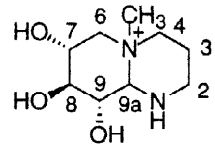


18α **18**β

Table 1. Selected ^{1}H-^{1}H NMR Coupling Constants of Bicyclo[4.4.0]azasugars in D_2O



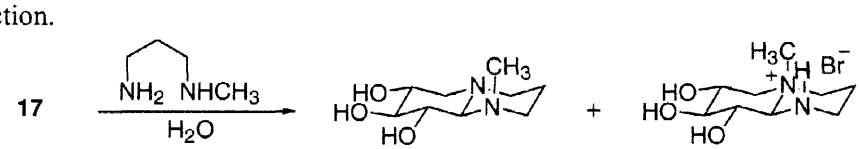
6, 18α, 18β, 19



20

Compounds		J (Hz)					
No.	X	$J_{6ax,6eq}$	$J_{6eq,7}$	$J_{6ax,7}$	$J_{7,8}$	$J_{8,9}$	$J_{9,9a}$
6	NH	11.7	4.9	11.0	9.5	9.3	8.9
18α	O	11.0	4.9	11.0	9.8	9.8	3.1
18β	O	11.7	4.9	10.7	9.3	9.4	7.6
19	NCH_3	11.7	4.9	10.7	9.3	9.3	8.8
20		11.7	5.0	9.3	9.3	9.3	9.3

Since none of the α-anomer of compound **6** was observed, preparation of an N-substituted analogue was undertaken to determine the effect of this substitution on anomeric preference. Compound **17** was treated with N-methyl-1,3-propanediamine, and a mixture of two products in about a 5:1 ratio was obtained from which the major was obtained pure by repeated crystallizations. ^{1}H NMR spectral data (Table 1) showed this compound to be **19** which was present in solution as only the β-anomer. X-ray structure analysis (see Figure 1 and Table 2) confirmed this structure and showed the methyl group to be axial in the crystalline state. The conformation of **19** in solution was also confirmed by observation of Nuclear Overhauser Effects (NOE's) between H-6ax, H-8, and H-9a, and the orientation of the methyl group in solution was also determined to be primarily axial by the observation of NOE's between it and the H-3ax and H-9 protons. Such a preference for an axial N-methyl group has been previously observed in related heterocyclic systems[16] and may be ascribed to the presence of an exo-anomeric effect; from the X-ray data, the length of the N_1-C_{9a} bond was determined to be slightly shorter (0.013 Å) than that of the N_5-C_{9a} bond which is consistent with an exo-anomeric effect.[17] The minor component formed in this reaction could be favored over **19** in a ratio of 2:1 by the addition of three equivalents of triethylamine to the reaction. It was then possible to purify it by crystallization. ^{1}H NMR spectral data (Table 1) suggested that the minor component was also a β-anomer, and its structure was determined by X-ray crystallography to be **20** (see Figure 2 and Table 2); a very strong exo-anomeric effect is suggested to be present in this compound by the much shorter (0.177 Å) length of the N_1-C_{9a} bond than that of the N_5-C_{9a} bond.[18] The influence of triethylamine on the product ratio may be a consequence of it scavenging HBr and freeing the more basic and more nucleophilic methylamino group for participation in the displacement reaction.



19 **20**

To test the effect of ring size on anomeric preference, the preparation of analogues in which n = 0 (see **9**) was undertaken. Treatment of **17** with 2-aminoethanethiol gave sulfur analogue **21** as a mixture of anomers

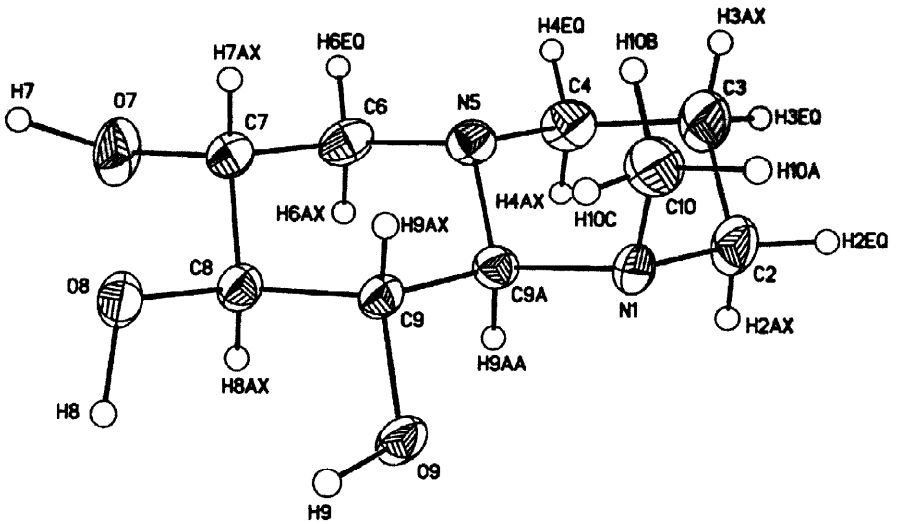


Figure 1. X-ray Structure of [7*R*-(7α,8β,9α,9aα)]-Octahydro-1-methyl-2*H*-pyrido [1,2-*a*]pyrimidine-7,8,9-triol (**19**)

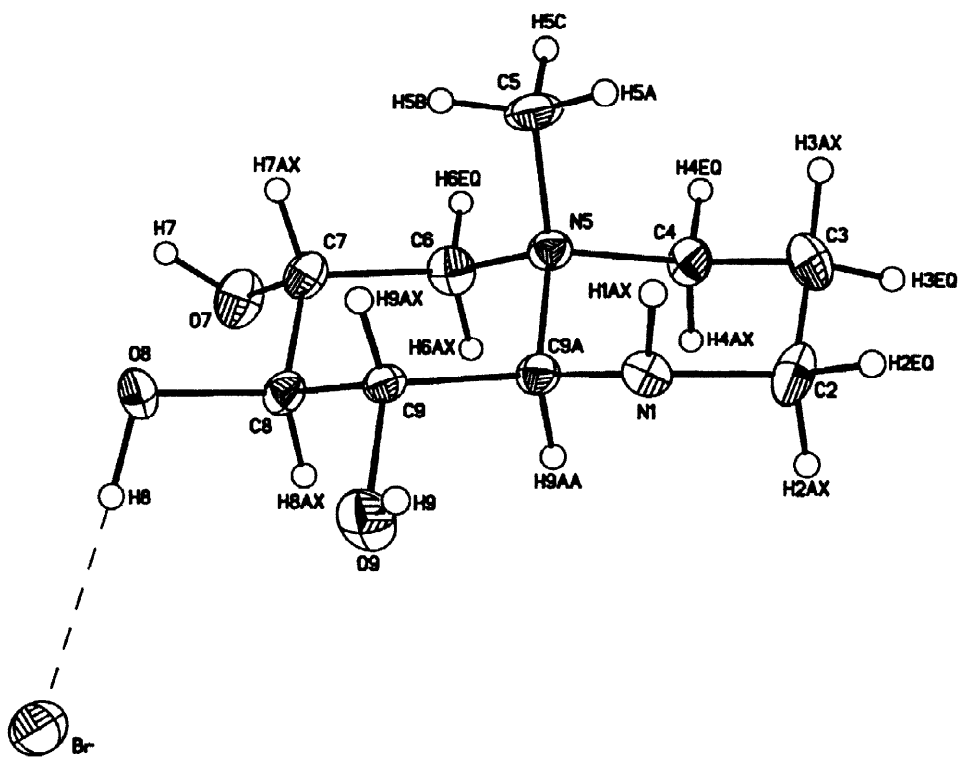
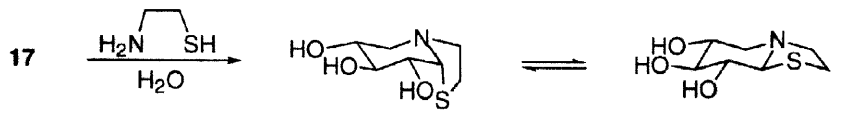


Figure 2. X-ray Structure of [5*S*-(5α,7β,8α,9β,9aβ)]-Octahydro-7,8,9-trihydroxy-5-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-5-ium bromide (**20**)

with the α-anomer (**21α**) constituting 30% of the mixture at equilibrium. As with the oxygen analogue, the β-anomer crystallized. Three-bond ^{1}H-^{1}H coupling constants (Table 3) for the anomers were consistent with the conformations shown in **21α** and **21β**; difference NOE's were used to confirm the conformational assignments and distinguish between H-3a and H3b. Like **18α**, the α-anomer prefers to have the glycosidic atom axial.



21α **21β**

Table 2. Crystal Data and Summary of X-ray Experimental Conditions[a]

Compound	**19**	**20**
Formula	$C_9H_{18}N_2O_3$	$C_9H_{19}BrN_2O_3$
Formula Weight	202.25	283.17
F (000)	1320	584
Crystal size, mm	0.7 x 0.3 x 0.08	0.5 x 0.22 x 0.16
μ, mm^{-1}	0.096	3.577
Crystal system	Orthorhombic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$
a, Å	8.804 (2)	6.4679 (6)
b, Å	11.956 (4)	12.832 (2)
c, Å	29.854 (11)	13.812 (2)
V, $Å^3$	3143	1146.3
Z	12	4
Dx, g/cc	1.283	1.641
2θ range, deg	4.0 to 45.0	4.0 to 50.0
Independent data	2536 (Rint = 0.0219)	1231 (Rint = 0.041)
Data/restraints/parameters	2507/0/380	1231/0/139
Final R indices [I>2σ (I)]	R_1 = 0.0528, wR^2 = 0.1176	R_1 = 0.0339, wR^2 = 0.0812
Goodness of fit on F^2	1.096	1.051
Largest peak and	0.258	0.565
hole in difference map, $eÅ^{-3}$	-0.244	-0.510

[a] 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, U.K.

When **17** was treated with 1,2-ethanediamine, two products formed which could not be separated. However, it was possible to assign conformational structure **22** (a β-anomer) to the major component based on analysis of its ^{1}H-^{1}H NMR coupling constants (Table 3). It was not possible to definitively assign the structure of the minor compound, but based on its ^{13}C NMR signals, it appears to be ring-contracted analogue **23** which might arise through the intermediacy of an epoxide.[19] When **17** was treated with 2-aminoethanol, a mixture of products formed that appeared to be primarily the anomers of compound **24**. The latter had very limited stability and could not either be purified or, consequently, characterized by ^{1}H NMR. However, quantitative ^{13}C NMR and ^{13}C chemical shift comparison with **18α** and **18β** led to the conclusion that **24** was a 1:2 mixture of α- and β-anomers. This was based on two characteristics of the ^{13}C NMR spectra of **18α** and **18β** and also xylosides and glucosides: the anomeric carbon and the 3-position carbon of the β-anomers appear considerably farther downfield than the corresponding carbons in the α-anomers or any other carbons in these

types of compounds. The major anomer had peaks at 94.3 and 77.2 ppm while the minor had a peak at 92.4 ppm with the next highest at 73.9 ppm.

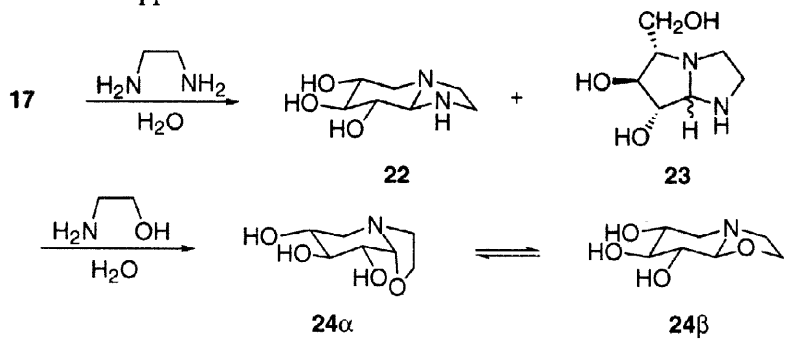
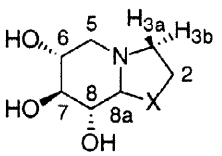
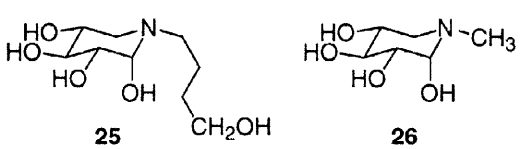


Table 3. Selected ^{1}H-^{1}H NMR Coupling Constants of Bicyclo[4.3.0]azasugars in D_2O



Compounds		J (Hz)					
No.	X	$J_{5ax.5eq}$	$J_{5eq.6}$	$J_{5ax.6}$	$J_{6.7}$	$J_{7.8}$	$J_{8.8a}$
21α	S	10.7	4.9	9.3	10.3	9.3	4.9
21β	S	11.2	5.4	10.8	9.3	9.3	9.3
22	NH	11.2	5.4	10.7	8.5	8.9	8.7

Attempts to prepare bicyclic azasugar analogues in which n = 2 (see compound **9**) were not successful. Treatment of **17** with 1,4-butanediamine gave a mixture of four unstable products which were not analyzed further. On the other hand, 4-amino-1-butanol gave principally the monocyclic azasugar **25** whose structure was deduced by comparison of its ^{13}C NMR spectrum with that of the product **26** derived from reaction of N-methylamine with **17**. Compound **25** had limited stability and was not characterized further.



In conclusion, bicyclic azasugar analogues of D-xylose containing a glycosidic heteroatom (N, O, and S) have been prepared and structurally characterized. Those compounds with a six-membered ring fused to the azasugar ring have long-term stability in aqueous solution, but those with fused five-membered rings, with the exception of the thiazolidine analogue, have limited stability. Those with fused seven-membered rings either do not form or are very unstable. When the glycosidic heteroatom is O or S, α-anomers are present in solution but the β-anomers predominate; when the heteroatom is N, only a β-anomer is present. α-Anomers favor having the glycosidic heteroatom axial to the azasugar ring while β-anomers have a very strong preference for the heteroatom to be equatorial. Results of the evaluation of the inhibitory potency and selectivity of these compounds will be reported separately.

EXPERIMENTAL

General

Reactions were run at room temperature unless indicated otherwise. Thin-layer chromatography (TLC) was run on Whatman Al Sil G/UV plates. Compounds were located on TLC plates by using molybdate spray reagent [$Ce(SO_4)_2$, 10 g; $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 25 g; H_2O, 900 mL; 98% H_2SO_4, 100 mL]. Flash column chromatography was performed on silica gel G (Fisher Scientific, S704-25, 60-200 mesh). Melting points were determined on a *Thomas* Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were determined by M-H-W Laboratories in Phoenix, AZ. Fourier Transform Nuclear Magnetic Resonance (FT-NMR) spectra were recorded on a Varian 200, 300, or 500 MHz spectrometer; unless indicated otherwise, ^1H spectra were obtained at 500 MHz and ^{13}C spectra at 125 MHz. HETCOR, COSY, and NOE experiments were used to make assignments of the ^1H and ^{13}C NMR spectra. The NMR program 'gNMR' (Cherwell Scientific Publishing, Ltd., Oxford, U.K., 1996) was used to simulate the ^1H NMR peaks for the protons of the hydroxylated ring of compounds **18**β and **22** and H-2 through H-4 of **19**, and the reported coupling constants and chemical shifts were obtained from these simulations. Mass spectra (MS) were determined using a Jeol JMS-SX102A double-focusing, high-resolution spectrometer; CH_5^+ was used for positive ion chemical ionization (CI), and xenon was used as the FAB gas with thioglycerol as the matrix. High-resolution mass spectra (HRMS) were measured at 10,000 or better resolution and calibrated with high-boiling perfluorokerosene (CI) or poly(ethylene glycol) (FAB). X-ray crystal and intensity data were collected using MoKa radiation (λ = 0.71073Å) and a Siemens R3m/V automated diffractometer for compound **19** and a Bruker P4 diffractometer for compound **20**.

[7*R*-(7α,8β,9α,9aα)]-Octahydro-2*H*-pyrido[1,2-*a*]pyrimidine-7,8,9-triol (6). A solution of **17** (150 mg, 0.70 mmol) and 1,3-propanediamine (59 μL, 0.70 mmol) in water (2 mL) was stirred for 10 min and then treated with Amberlite CG-400 ion exchange resin (hydroxide form) to remove HBr. Removal of the water under vacuum gave a slightly yellow syrup which gave colorless crystals of **6** (55 mg, 27%, mp 176.5-178°C) from ethanol. NMR spectral data for the product (**6**) were identical with those reported previously.[10]

5-Bromo-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (16).[15] A solution of **1,2-*O*-isopropylidene-5-*O*-tosyl-α-D-xylofuranose (14)** (10.0 g, 29.1 mmol) and tetramethylammonium bromide (18.0 g, 117 mmol) in anhydrous DMF (180 mL) under a nitrogen atmosphere was heated at 120°C for 6 h. The reaction was followed by a TLC system of 40% EtOAc in hexane. A precipitate formed, and it was removed by filtration. The DMF was evaporated under vacuum, and the residue was purified by silica gel chromatography. Elution with 20% ethyl acetate in hexane gave **16** as a white powder (6.9 g, 94%, mp 99-100°C). ^1H NMR (200 MHz, $CDCl_3$, reference TMS) δ 5.96 (d, J = 3.4 Hz, 1H), 4.56 (d, J = 3.4 Hz, 1H), 4.43 (m, 2H), 3.51 (m, 2H), 1.93 (d, J = 5.2 Hz, OH, D_2O exchange), 1.52 (s, 3H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$, reference $CDCl_3$ δ 77.0) δ 112.1, 105.3, 85.0, 80.2, 74.4, 26.8, 26.8, 26.2. HRMS (CI): calcd for $C_8H_{13}BrO_4$: 253.0075 (M+1, ^{79}Br), found 253.0086; 255.0055 (M+1, ^{81}Br), found 255.0056.

5-Bromo-5-deoxy-α-D-xylofuranose (17α) and 5-bromo-5-deoxy-β-D-xylofuranose (17β). A solution **16** (2.0 g, 7.9 mmol) in TFA (8 mL) and H_2O (2 mL) was stirred for 15 min. Water (15 mL) was added, and the solvent was removed under vacuum. Then another 15 mL water was added and evaporated. The same procedure was repeated two more times. The residue was dissolved in water and treated with Amberlite CG-400 ion exchange resin (hydroxide form) until the solution was neutralized. Removal of the water under vacuum gave **17** as a gum, which was a mixture of α- and β-anomers (1.6 g, 93%). The product crystallized from ethanol and chloroform (mp 79-81°C). At equilibrium in D_2O the product was an approximately 1:1 mixture of α- and β-anomers. **17α** ^1H NMR (D_2O, reference acetone δ 2.04) δ 5.29 (d, J =

4.4 Hz, 1H, H-1), 4.32 (m, 1H, H-4, overlaps with H-4 of β anomer), 4.14 (dd, J = 3.6, 5.2 Hz, 1H, H-3), 3.98 (dd, J = 3.6, 4.4 Hz, 1H, H-2), 3.41 (d, J = 10.7 Hz, 1H, H-5), 3.29 (dd, J = 7.3, 10.7 Hz, 1H, H-5); ^{13}C NMR (75 MHz, D_2O, reference acetone δ 29.80) δ 95.7 (C-1), 78.1 (C-4), 75.4 (C-2), 74.8 (C-3), 29.8 (C-5). **17β** ^{1}H NMR (D_2O, reference acetone δ 2.04) δ 5.06 (br s, 1H, H-1), 4.30 (m, 1H, H-4, overlaps with H-4 of α anomer), 4.06 (dd, J = 2.1, 4.5 Hz, 1H, H-3), 3.96 (br s, 1H, H-2), 3.50 (dd, J = 5.8, 10.3 Hz, 1H, H-5), 3.40 (dd, J = 2.1, 10.3 Hz, 1H, H-5); ^{13}C NMR (75 MHz, D_2O, reference acetone δ 29.80) δ 101.6 (C-1), 81.5 (C-4), 80.0 (C-2), 74.4 (C-3), 29.9 (C-5). Anal. Calcd for $C_5H_9BrO_4$: C, 28.19; H, 4.26. Found: C, 28.12; H, 4.43.

[7*R*-(7α,8β,9α,9aβ)]-Hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine-7,8,9-triol (18α) and [7*R*-(7α,8β,9α,9aα)]-hexahydro-2*H*,6*H*-pyrido[2,1-*b*][1,3]oxazine-7,8,9-triol (18β). A solution of **17** (100 mg, 0.47 mmol) and 3-amino-1-propanol (36 μL, 0.47 mmol) in water (1 mL) was stirred for 10 min and then treated with Amberlite CG-400 ion exchange resin (hydroxide form) to remove HBr. Evaporation under vacuum gave a slightly yellow syrup which upon crystallization from ethanol gave colorless crystals that were only the β-anomer (31 mg, 35%, mp 141-141.5°C). At equilibrium in D_2O the ratio of α- (**18α**) to β-anomers (**18β**) was 12:88. **18α** ^{1}H NMR (D_2O, reference CH_3OH δ 3.30) δ 4.48 (d, J = 3.1, Hz, 1H, H-9a), 4.11 (dd, J = 4.8, 11.6 Hz, 1H, H-2eq), 3.75 (dt, J = 2.7, 11.6 Hz, 1H, H-2ax), 3.53[20] (obscured, 1H, H-7), 3.45 (t, J = 9.8 Hz, 1H, H-8), 3.43[20] (obscured, 1H, H-9), 3.13 (dt, J =3.1, 13.7 Hz partly obscured, 1H, H-4ax), 3.09 (t, J = 11.0 Hz partly obscured, 1H, H-6ax), 2.92 (dm, J = 13.7 Hz, 1H, H-4eq), 2.64 (dd, J = 4.9, 11.0 Hz, 1H, H-6eq), 2.21 (m, 1H, H-3ax), 1.19 (br d, J ~ 14.8 Hz, 1H, H-3eq); ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 89.0 (C-9a), 73.6 (C-8), 71.5 (C-9), 70.1 (C-7), 68.8 (C-2), 50.2 (C-4), 48.6 (C-6), 19.0 (C-3). **18β** ^{1}H NMR (D_2O, reference CH_3OH δ 3.30) δ 4.03 (dd, J = 4.8, 11.6 Hz, 1H, H-2eq), 3.55 (ddd, J = 4.9, 9.3, 10.7 Hz, 1H, H-7), 3.51 (m, obscured, 1H, H-2ax), 3.41 (d, J = 7.6, 9.4 Hz, 1H, H-9a), 3.28 (dd, J = 9.3, 9.4 Hz, 1H, H-8), 3.25 (dd, J = 7.6, 9.4 Hz, 1H, H-9), 2.95 (br d, J ~ 11.7 Hz, 1H, H-4eq), 2.82 (dd, J = 4.9, 11.7 Hz, 1H, H-6eq), 2.36 (ddd, J = 3.1, 12.0, 12.3 Hz, 1H, H-4ax), 2.13 (dd, J = 10.7, 11.7 Hz, 1H, H-6ax), 1.85 (m, 1H, H-3ax), 1.57 (br d, J ~ 13.7 Hz, 1H, H-3eq); ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 93.8 (C-9a), 76.6 (C-8), 73.5 (C-9), 68.6 (C-7), 67.3 (C-2), 55.0 (C-6), 52.2 (C-4), 24.7 (C-3). Anal. Calcd for $C_8H_{15}NO_4$: C, 50.78; H, 7.99; N, 7.40. Found: C, 51.00: H, 7.78; N, 7.51.

[7*R*-(7α,8β,9α,9aα)]-Octahydro-1-methyl-2*H*-pyrido[1,2-*a*]pyrimidine-7,8,9-triol (19). A solution of **17** (107 mg, 0.50 mmol) and N-methyl-1,3-propanediamine (53 μL, 0.50 mmol) in water (2 mL) was stirred 10 min and then treated with Amberlite CG-400 ion exchange resin (hydroxide form) to remove HBr. ^{1}H NMR showed the presence of **19** and **20** in a ratio of 5:1. Evaporation of the water under vacuum gave a slightly yellow syrup part of which crystallized from 95% ethanol as a 1:7 mixture of **19** and **20** (6 mg). The filtrate was evaporated under vacuum and then crystallized from ethanol to give pure **19** (45 mg, 44%, mp 148.5-150.5°C). ^{1}H NMR (D_2O, reference CH_3OH δ 3.30) δ 3.46 (ddd, J = 4.9, 9.3, 10.7 Hz, 1H, H-7), 3.32 (dd, J = 8.8, 9.3 Hz, 1H, H-9), 3.26 (t, J = 9.3 Hz, 1H, H-8), 2.97 (d, J = 8.8 Hz, 1H, H-9a), 2.91 (ddt, J = 2.0, 3.9, 12.2 Hz, 1H, H-2eq), 2.88 (ddt, J = 2.0, 3.9, 13.2 Hz, 1H, H-4eq), 2.75 (dd, J = 4.9, 11.7 Hz, 1H, H-6eq), 2.75 (dt, J = 3.0, 13.2 Hz, 1H, H-4ax), 2.34 (s, 3H, CH_3), 2.24 (dt, J = 3.1, 12.2 Hz, 1H, H-2ax), 2.03 (dd, J = 10.7, 11.7 Hz, 1H, H-6ax), 1.94 (dddd, J = 3.9, 12.2, 13.2, 14.2 Hz, 1H, H-3ax), 1.31 (dddt, J = 2.0, 3.0, 3.1, 14.2 Hz, 1H, H-3eq); ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 81.0 (C-9a), 77.6 (C-8), 70.4 (C-9), 68.4 (C-7), 57.5 (C-6), 54.9 (C-2), 52.5 (C-4), 33.0 (CH_3), 18.4 (C-3). Anal. Calcd for $C_9H_{18}N_2O_3$: C, 53.45; H, 8.97; N, 13.85. Found: C, 53.25; H, 8.85; N, 13.67.

[5*S*-(5α,7β,8α,9β,9aβ)]-Octahydro-7,8,9-trihydroxy-5-methyl-2*H*-pyrido[1,2-*a*]pyrimidin-5-ium bromide (20). A solution of **17** (126 mg, 0.59 mmol), triethylamine (0.25 mL, 1.8 mmol), and N-methyl-1,3-propanediamine (68 μL, 0.65 mmol) in water (2 mL) was stirred 10 min and then treated with Amberlite CG-400 ion exchange resin (hydroxide form) to remove HBr. ^{1}H NMR showed the presence of **19** and **20** in a ratio of 1:2. Evaporation of the water under vacuum gave a syrup which produced colorless crystals of **20** (70 mg, 41%, mp 209-210°C) from ethanol. ^{1}H NMR (D_2O, reference CH_3CN δ 1.94) δ 4.14 (d, J = 9.3 Hz, 1H, H-9a), 3.97 (ddd, J = 5.0, 9.3, 11.7 Hz, 1H, H-7), 3.52 (m, 1H, H-4eq), 3.49 (dd, J = 9.3, 9.3 Hz, 1H, H-9), 3.48 (dd, J = 5.0, 12.7 Hz, 1H, H-6eq), 3.45 (dd, J = 9.3, 9.3 Hz, 1H, H-8), 3.39 (dt, J = 3.4, 13.2, 13.2 Hz, 1H, H-4ax), 3.14 (dd, J = 5.1, 13.9 Hz, 1H, H-2ax), 3.05 (dd, J = 11.7, 12.7 Hz, 1H, H-6ax), 2.93 (s, 3H, CH_3), 2.77 (ddd, J = 3.9, 13.2, 13.7 Hz, 1H, H-2eq), 2.05 (m, 1H, H-3ax), 1.60 (br d, J = 15.6 Hz, 1H, H-3eq); ^{13}C NMR (75 MHz, D_2O, reference CH_3CN δ 1.40) δ 85.6 (C-9a), 77.1 (C-8), 68.6 (C-9), 65.7 (C-4), 65.2 (C-7), 62.2 (C-6), 42.5 (C-2), 39.3 (CH_3), 19.9 (C-3). Anal. Calcd for $C_9H_{19}N_2O_3Br$: C, 38.18; H, 6.76; N, 9.89. Found: C, 38.14; H, 6.61; N, 9.66.

[6*R*-(6α,7β,8α,8aβ)]-Hexahydro-5*H*-thiazolo[3,2-*a*]pyridine-6,7,8-triol (21α) and [6*R*-(6α,7β,8α,8aα)]-hexahydro-5*H*-thiazolo[3,2-*a*]pyridine-6,7,8-triol (21β). A solution of **17** (398 mg, 1.88 mmol), 2-aminoethanethiol hydrochloride (218 mg, 1.92 mmol), and sodium carbonate (204 mg, 1.92 mmol) in water (4 mL) was stirred overnight and then evaporated under vacuum. The residue was chromatographed on silica gel eluting with 5% CH_3OH in CH_2Cl_2 first followed by 8% CH_3OH in CH_2Cl_2. The product was crystallized from ethanol as only the β-anomer (81 mg, 23%, mp 168-170°C). At equilibrium in D_2O solution, the product consisted of a 3:7 mixture of α- (**21**α) and β-anomers (**21**β). **21**α ^{1}H NMR (D_2O, reference CH_3CN δ 1.95) δ 4.81 (d, J = 4.9 Hz, 1H, H-8a), 3.93 (dd, J = 4.9 9.3 Hz, 1H, H-8), 3.57 (dd, J = 9.3, 10.3 Hz, 1H, H-7), 3.48 (ddd, J ~ 4.9, 9.3, 10.7 Hz, 1H, H-6), 3.33 (m, 1H, H-3b), 2.98 (m, 1H, H-2), 2.90 (m, 1H, H-3a), 2.82 (m, 1H, H-2), 2.61 (dd, J ~ 4.9, 11.2 Hz, 1H, H-5eq), 2.45 (dd, J ~ 10.7, 11.2 Hz, 1H, H-5ax); ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 76.1 (C-8a), 73.5 (C-7), 71.0 (C-8), 69.5 (C-6), 58.2 (C-3), 50.2 (C-5), 27.5 (C-2). **21**β ^{1}H NMR (D_2O, reference CH_3CN δ 1.95) δ 3.58 (ddd, J = 5.4, 9.3, 10.8 Hz, 1H, H-6), 3.46 (d, J = 9.3 Hz, 1H, H-8a), 3.29 (dd, J = 9.3, 9.3 Hz, 1H, H-8), 3.28 (m, 1H, H-3a), 3.21 (dd, J = 9.3, 9.3, 1H, H-7), 3.20 (dd, J = 5.4, 11.2 Hz, 1H, H-5eq), 2.91 (m, 2H, H-2), 2.52 (ddd, J ~ 7.6, 9.8, 9.8, 1H, H-3b), 2.17 (dd, J ~ 10.8, 11.2 Hz, 1H, H-5ax); ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 78.3 (C-7), 75.4 (C-8), 71.6 (C-8a), 70.1 (C-6), 56.1 (C-3), 54.2 (C-5), 28.4 (C-2). Anal. Calcd for $C_7H_{13}NO_3S$: C, 43.96; H, 6.85; N, 7.32. Found: C, 43.83; H, 6.67; N, 7.06.

[6*R*-(6α,7β,8α,8aα)]-Octahydroimidazo[1,2-*a*]pyridine-6,7,8-triol (22). A solution of **17** and 1,2-diaminoethane in water was stirred for 0.5 h and then treated with CG-400 anion exchange resin (hydroxide form). The solvent was evaporated to give a gum whose ^{1}H and ^{13}C NMR spectra showed a major and a minor compound. The major was assigned structure **22**: ^{1}H NMR (D_2O, reference CH_3OH δ 3.30) Major δ 3.63 (m, J = 5.4, 8.5, 10.7 Hz, 1H, H-6), 3.29 (dd, J = 8.5, 8.9 Hz, 1H, H-7), 3.26 (dd, J_1 = 8.7, 8.9 Hz, 1H, H-8), 3.19 (dd, J = 5.4, 11.2 Hz, 1H, H-5eq), 3.06 (m, 1H, H-3b), 3.05 (m, 2H, H-2a and H-2b), 2.89 (d, J = 8.7 Hz, 1H, H-8a), 2.43 (dt, J ~ 8.3, 11.2, 1H, H-3a), 2.18 (dd, J = 10.7, 11.2 Hz, 1H, H-5ax); ^{13}C NMR (D_2O, reference CH_3OH δ 49.15) δ 80.2, 77.9, 73.6, 70.3, 52.4, 51.0, 43.2. Minor ^{13}C NMR (D_2O, reference CH_3OH δ 49.15) δ 82.4, 79.7, 75.4, 67.9, 62.8, 52.9, 39.3. HRMS (CI): calcd for $C_7H_{14}N_2O_3$: 175.1083 (M+1), found 175.1075.

Reaction of 5-bromo-5-deoxy-D-xylofuranose with 2-aminoethanol. A solution of **17** (30 mg, 0.14 mmol) and 2-aminoethanol (13 μL, 0.21 mmol) in D_2O (0.7 mL) was monitored by ^{13}C NMR which showed the formation of a major and a minor product in an approximate ratio of 2:1. Based on their ^{13}C NMR chemical shifts, the major and minor appear to be **24β** and **24α**, respectively. ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) major: δ 94.3, 77.2, 73.1, 70.1, 66.4, 50.6, 49.9; minor: 92.4, 73.9, 73.5, 70.6, 69.4, 52.8, 51.6. HRMS (CI): calcd for $C_7H_{13}NO_4$: 176.0923 (M+1), found 176.0933.

Reaction of 5-bromo-5-deoxy-D-xylofuranose with 4-amino-1-butanol. A solution of **17** (27 mg, 0.13 mmol) and 4-amino-1-butanol (12 μL, 0.13 mmol) in D_2O (0.7 mL) was monitored by ^{13}C NMR which showed a single product that was assigned structure **25** based on comparison of its ^{13}C NMR spectrum with that of compound **26**. ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 82.7, 73.9, 72.6, 70.0, 61.8, 52.4, 49.4, 29.7, 23.0. HRMS (CI): calcd for $C_9H_{19}NO_5$: 222.1341 (M+1), found 222.1343.

[2*R*-(2α,3α,4β,5α]-1-Methyl-2,3,4,5-piperidinetetrol (26). To a solution of **17** (25mg, 0.12mmol) in water (2 mL) was added 40% aqueous methylamine (30 μL, 0.36 mmol). After stirring for 10 min, the solvent was removed under vacuum. Then another 2 mL water was added and evaporated. The same procedure was repeated two more times to remove the excess methylamine. The residue was analyzed by NMR. ^1H NMR (D_2O, reference CH_3OH δ 3.30) δ 4.44 (d, J = 3.4 Hz, 1H, H-2), 3.42 (dd, J = 3.4, 9.3 Hz, 1H, H-3), 3.48 (dd, 1H, J = 9.3, 9.3 Hz H-4), 3.53 (ddd, J = 5.3, 9.3, 10.8 Hz, 1H, H-5), 2.63 (dd, J = 5.3, 11.2 Hz 1H, H-6eq), 2.54 (dd, J = 10.8, 11.2 Hz 1H, H-6ax), 2.31 (s, 3H, CH_3); ^{13}C NMR (75 MHz, D_2O, reference CH_3OH δ 49.15) δ 84.5, 73.5, 72.4, 69.9, 50.8, 40.0. HRMS (FAB): calcd for $C_6H_{13}NO_4$: 164.0923 (M+1), found 164.0914.

X-ray Crystallographic Determinations The structures of **19** and **20** were solved using direct methods. It was apparent from the crystal data that the unit cell of **19** contained twelve molecules and in as much as the compound crystallized in the space group $P2_12_12_1$, that there are three molecules in the asymmetric unit. This was verified by the solution of **19**. In the refinement process all nonhydrogen atoms of the two structures were refined anisotropically. Positions for all hydrogen atoms bonded to carbon atoms were calculated while positions for the hydrogens bonded to oxygen and nitrogen atoms were found in difference maps. All of the hydrogen atoms were allowed to ride on their neighboring heavy atom during the refinement process. The structure of **19** was solved using the program 'SHELXTL-PLUS' (Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, 1990). The programs used in the refinement and display of **19** and the solution, refinement, and display of **20** are contained in the program package 'SHELXTL' PC, version 5.03 (Bruker Analytical X-ray, Madison, Wisconsin, 1994).

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14. Similar methodology has been reported previously.[8,9]
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17. The average bond lengths from the three molecules in the asymmetric unit are: N_1-C_{9a} = 1.467Å and N_5-C_{9a} = 1.480Å. For comparison, other average N-C bond lengths in this molecule are: N_1-C_2 = 1.477Å, N_1-C_{10} = 1.478Å, N_5-C_4 = 1.474Å, and N_5-C_6 = 1.458Å.
18. The bond lengths are: N_1-C_{9a} = 1.397Å and N_5-C_{9a} = 1.574Å. For comparison, other N-C bond lengths in this molecule are: N_1-C_2 = 1.466Å, N_5-C_4 = 1.530Å, N_5-C_5 = 1.493Å, and N_5-C_6 = 1.505Å.
19. A similar transformation has been reported.[9] The ^{13}C NMR signals at 67.9 and 62.8 ppm distinguish the minor compound from all the bicyclic azasugars we have prepared and characterized but correspond more closely with the 66.4 and 62.9 ppm reported for 1,4-dideoxy-1,4-imino-L-arabinitol, a monocyclic analogue of compound **23** reported in Nash, R. J.; Williams, J. M., Bell, E. A. *Phytochemistry* **1985**, *24*, 1620-1622.
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