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TETRAHEDRON

Bicyclic Diazasugars 2. Synthesis and Structures of L-Arabinose and D-Ribose Analogues

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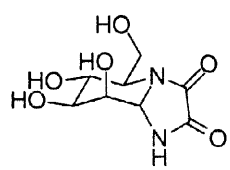
Abstract: Bicyclic diazasugar analogues of L-arabinose and D-ribose have been prepared and characterized by x-ray crystallography and NMR spectroscopy. The crystalline arabinose analogue is the β-anomer in the ring-flipped $^1C_4$ conformation (**7**), but in D_2O solution this is a minor component with the major being the α-anomer in the $^4C_1$ conformation (**6**). The crystalline ribose analogue is the β-anomer in the $^4C_1$ conformation (**10**) which is also the major component in D_2O solution and is accompanied by a minor form which is probably the α-anomer in the ring-flipped $^1C_4$ conformation (**11**).

Azasugars, natural and synthetic products which have a nitrogen atom in place of the ring oxygen of sugars, have been of wide-spread interest because of their glycosidase-inhibitory properties.[1,2] Such inhibitors have been used to probe the functions of the glyco moieties of glycoproteins[3,4] and have potential as contraceptives[5] and as chemotherapeutic agents against tuberculosis,[6] cancer,[7,8] diabetes, and viruses including AIDS.[9] Of the structurally diverse bicyclic azasugars that have been discovered in nature, kifunensine **1**[10] and nagstatin **2**[11] are particularly interesting because they are diazasugars, that is, sugar analogues in which both the ring and anomeric oxygen atoms have been replaced by nitrogen atoms. We recently reported the synthesis of a novel diazaxylose analogue **3** which, like kifunensine and other azasugars with a glycosidic heteroatom, may be a pseudosubstrate of glycosidases and undergo glycosidic bond cleavage with a transition state resembling that of the natural glycoside substrates.[12] This synthetic work has now been extended to L-arabinose and D-ribose compounds; an L-arabinose analogue is of interest as a potential inhibitor of D-galactosidases and L-arabinopyranosidases.[13,14]



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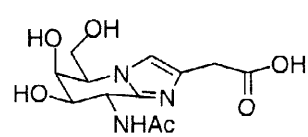

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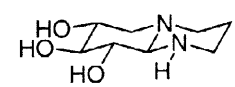

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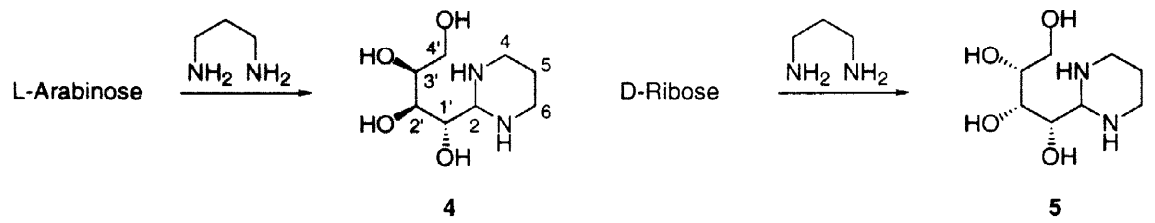
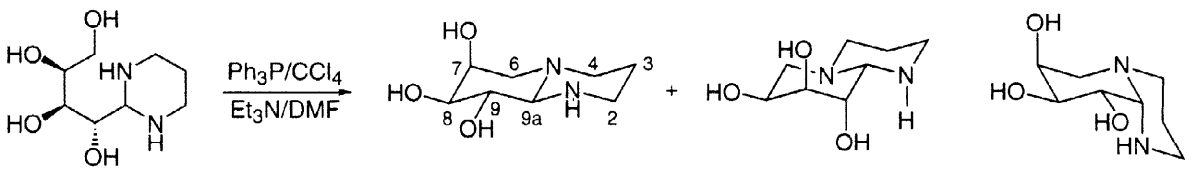
Analogous to the first step in the synthesis of **3**, aminals **4** and **5** were prepared in near quantitative yield from L-arabinose and D-ribose, respectively, by dissolution in excess 1,3-propanediamine followed by evaporation of excess diamine and crystallization from chloroform.



4 **5**

Cyclization of **4** was effected using triphenylphosphine, carbon tetrachloride, and triethylamine in anhydrous DMF as described previously for the preparation of **3**; several related cyclizations involving nucleophilic attack by a nitrogen-containing heterocycle have been reported.[15-17] After chromatographic purification, the product was crystallized from ethanol containing a small amount of water. ^{13}C and ^{1}H NMR spectra of a solution of the product in D_2O indicated the presence of two isomeric compounds in a 7:3 ratio after rapid equilibration. The major component had ^{1}H -^{1}H coupling constants (see Table 1) consistent with the α-anomeric product **6**; the minor component, based on its ^{1}H -^{1}H coupling constants, appeared to be the β-anomer in the ring-flipped $^{1}C_4$ conformation **7** rather than conformation **8**. X-ray crystallography established that the crystalline product was in fact the minor isomer with the configuration and conformation of structure **7** (see Figure 1 and Table 2); the NH bond is axial.



4 **6** **7** **8**

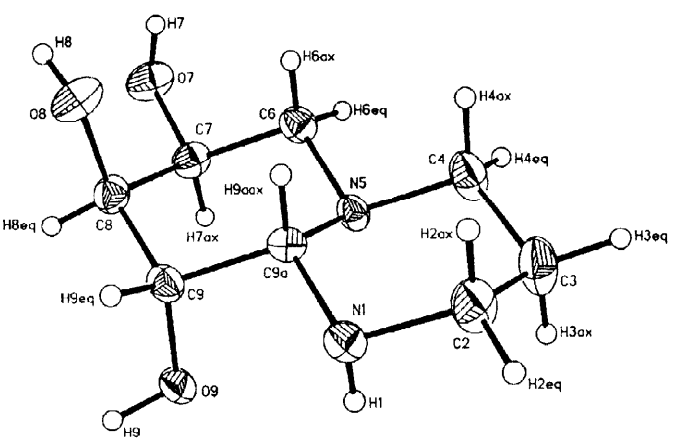


Figure 1. X-ray Structure of (7*S*,8*S*,9*S*,9a*S*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine (**7**)

Table 1. ^{1}H NMR Spectral Data for Bicyclic Diazasugars in D_2O[a]

Data Type	Compounds as Free Bases				
	3	**6**	**7**[b]	**10**	**11**
δ H-6ax, mult.	1.92 dd	2.15 dd	2.20 t	2.24 t	obsc.[c]
$J_{6ax.6eq}$ (Hz)	11.7	13.2	11.1	11.2	obsc.
δ H-6eq, mult.	2.61 dd	2.62 dd	~2.7 obsc.	2.40 dd	obsc.
$J_{6eq.7}$ (Hz)	4.9	3.0	4.6	4.9	small[d]
δ H-7, mult.	3.35 ddd	3.79 ddd	3.87 ddd	3.63 ddd	3.57 m
$J_{6ax.7}$ (Hz)	11.0	1.8	11.1	11.2	small
δ H-8, mult.	3.08 dd	3.34 dd	3.78 dd	3.90 t	3.48 m
$J_{7.8}$ (Hz)	9.5	3.7	3.0	2.9	small
δ H-9, mult.	2.92 dd	3.28 dd	3.54 dd	3.18 dd	3.80 br s
$J_{8.9}$ (Hz)	9.3	9.8	(4.4)	2.9	small
δ H-9a, mult.	2.57 d	2.52 d	2.94 br s	2.84 d	2.67 br s
$J_{9.9a}$ (Hz)	8.9	8.5	(2.0)	9.3	small

[a] Internal standard acetone (δ 2.04) except for **3** for which dioxane (δ 3.53) was used.

[b] Coupling constants in parentheses were obtained from the spectrum of a partial hydrochloride of **7** which had less overlapping signals and better resolution.

[c] 'obsc.' means the signal was partially or totally obscured by another peak.

[d] 'small' means peaks were broadened with some showing shoulders but were not defined well enough to accurately determine coupling constants.

In the same manner, cyclization of **5** was effected, but, depending on the method of workup, the product could be isolated as crystals of the hydrochloride salt (**9**) or the free base (**10**). X-ray crystallographic analysis (see Table 2) established that both the hydrochloride (see Figure 2) and the free base (see Figure 3) are β-anomers in the expected $^4C_1$ conformation; the NH bond is axial in **10**, and the proton from the hydrogen chloride is on the secondary amine in **9**. When either crystalline product was dissolved in D_2O, two isomeric compounds in a 7:3 ratio were observed by ^{1}H NMR. The major component of the free base was assigned structure **10** based on its ^{1}H-^{1}H coupling constants, but the minor component had a ^{1}H NMR spectrum suggestive of the α-anomer in the ring-flipped $^1C_4$ conformation **11** (see Table 1 for data on the free base components). A definitive assignment of structure **11** for the minor isomer was not possible because the proton signals of this compound both overlapped with other signals and were poorly resolved. The coupling constants of the protons at positions 7, 8, 9, and 9a of the minor component are quite small, and therefore none of these protons have a *trans* diaxial relationship with another proton which is consistent with structure **11** rather than alternative conformer **12** which should have a large coupling between the proton at position 7 and the axial proton at position 6. The observation of **7** as a the minor component for the L-arabinose analogue is also supportive of this assignment.

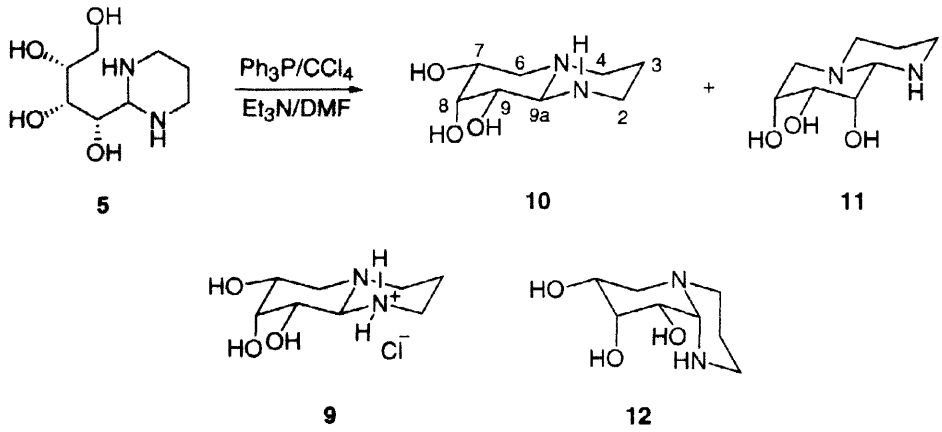


Table 2. Crystal Data and Summary of X-ray Experimental Conditions[a]

Compound	7[b]	9[b]	10[b,c]
Formula	$C_8H_{16}N_2O_3$	$C_8H_{16}N_2O_3 \cdot HCl$	$C_8H_{16}N_2O_3$
Formula Weight	188.2	224.7	188.2
F (000)	408	240	408
Crystal size, mm	0.12 x 0.35 x 0.30	0.12 x 0.18 x 0.20	0.21 x 0.33 x 0.55
μ, mm^{-1}	0.103	0.354	0.103
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	$P2_12_12_1$	$P2_1$	$P2_1$
a, Å	7.894 (2)	6.871 (3)	7.5250 (10)
b, Å	10.067 (3)	11.010 (4)	10.260 (2)
c, Å	11.622 (3)	7.512 (3)	12.418 (2)
β, deg	90	114.31 (2)	105.750 (10)
V, $Å^3$	923.6	517.8	922.8
Z	4	2	4
Dx, g/cc	1.354	1.441	1.355
2θ range, deg	4.5 to 50.0	4.0 to 45.0	4.0 to 55.0
Independent data	1130	718 (Rint = 2.96)	2252 (Rint = 6.85)
Observed data	934 (F>4.0σ(F))	569 (F>2.5σ(F))	1741 (F>4.0σ(F))
Data/parameter ratio	5.6:1	4.5:1	7.4:1
R	0.030	0.0524	0.0478
Rw	0.035	0.0573	0.0618
Weighting scheme	$w^{-1}= \sigma^2(F)+0.0004F^2$	unit weights	$w^{-1}=\sigma^2(F)+0.0021F^2$
Goodness of fit	1.11	0.97	1.05
Largest peak and	0.17	0.33	0.37
hole in difference map, eA^{-3}	-0.15	-0.30	-0.32

[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 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.

[b] All of the hydrogen atoms bonded to nitrogen and oxygen atoms of the molecules are involved in intermolecular hydrogen bonds; there are no intramolecular hydrogen bonds in the molecules.

[c] There are two crystallographically independent but chemically identical molecules of **10** in the asymmetric unit. The conformations of the two molecules are similar so only one is shown in Figure 3.

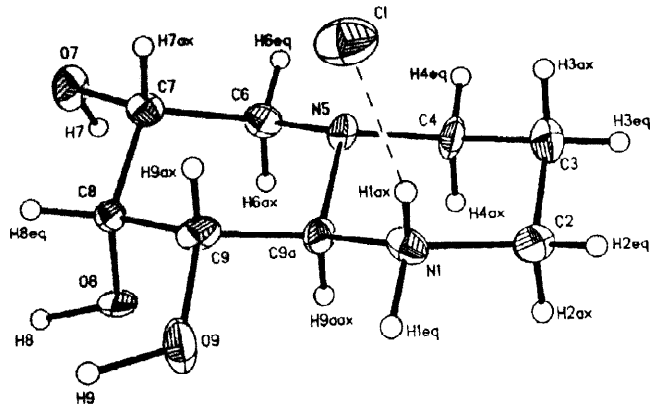


Figure 2. X-ray Structure of (7*R*,8*R*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine Hydrochloride (**9**)

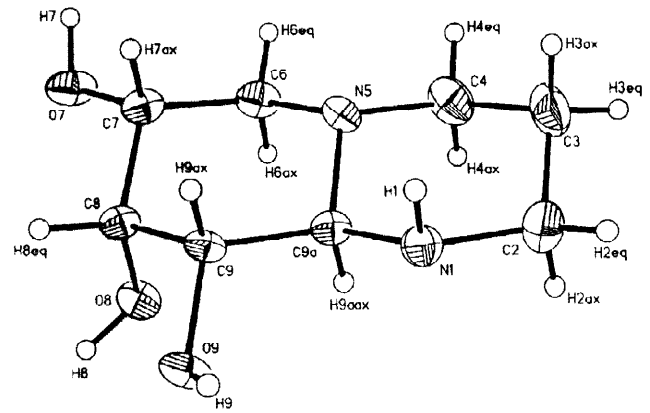


Figure 3. X-ray Structure of (7*R*,8*R*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine (**10**)

Both in the solid state and in solution, the diazasugars **3**, **6**, **7**, **10**, and **11** adopt conformations in which N1 is equatorial to the hydroxylated ring even when hydroxyl groups consequently become axially oriented in those favored conformations. Compounds **3** and **10** are mimics of the corresponding D-sugar β-glycosides while compound **6** resembles an L-arabinose α-glycoside; neither **7** nor **11** resemble natural glycosides. It is of interest to be able to prepare bicyclic azasugar analogues in which the glycosidic atom is axial to the hydroxylated ring because they will be mimics of the α-anomers of D-sugar glycosides and the β-anomers of L-sugar glycosides. The synthesis of bicyclic analogues with axially disposed glycosidic heteroatoms is a current objective of this research.

In summary, new diazasugar analogues of L-arabinose and D-ribose have been prepared by a very simple route amenable to large scale synthesis. The anomeric and conformational preferences of these products have been determined in D_2O solution as well as in the crystalline state. The glycosidase inhibition profiles of these compounds are being determined and will be published separately along with data on related compounds.

EXPERIMENTAL

General

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; $(NH_4)_6Mo_7O_{24}4H_2O$, 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 Gemini-500 spectrometer (^1H spectra were obtained at 500 MHz and ^{13}C spectra at 125 MHz). HETCOR and COSY experiments were used to make assignments of the ^1H and ^{13}C NMR spectra. NMR spectra of the aminals **4** and **5** were obtained rapidly in D_2O solution before significant hydrolysis had occurred; methanol was used as an internal reference (^1H δ 3.30, ^{13}C δ 49.15). 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 bicyclic diazasugar products and protons on C-2 and C-1' through C-4' for the aminals, and the reported coupling constants and chemical shifts were obtained from these simulations. Mass spectra (MS) were determined using a Hewlett Packard 5890-II spectrometer; CH_5^+ was used for positive ion chemical ionization (CI). High resolution mass spectra (HRMS) were measured at 10,000 or better resolution and calibrated with high-boiling perfluorokerosene. X-ray crystal and intensity data were collected using a Siemens R3m/V automated diffractometer using MoKa radiation (λ = 0.71073Å).

Hexahydro-2-(L-*arabino*-1,2,3,4-tetrahydroxybutyl)pyrimidine (4). A solution of L-arabinose (5.21 g, 34.7 mmol) in 1,3-diaminopropane (15.0 mL,13.3 g, 180 mmol) of was stirred under a nitrogen atmosphere for 69 h. A colorless syrup was left after all excess 1,3-diaminopropane was removed under high vacuum. Colorless crystals (6.78 g, 95%, mp 134-5°C, dec.) were obtained by careful partial evaporation of a solution of the syrup in chloroform containing a small amount of absolute ethanol. ^1H NMR δ 3.63 (dd, J = 2.8, 11.9 Hz, 1H, H-4'), 3.54 (ddd, J = 2.8, 6.4, 8.3 Hz, 1H, H-3'), 3.52 (dd, J = 2.1, 8.3 Hz, 1H, H-2'), 3.47 (dd, J = 6.4, 11.9 Hz, 1H, H-4'), 3.46 (dd, J = 2.1, 6.4 Hz, 1H, H-1'), 3.43 (d, J = 6.4 Hz, 1H, H-2), 2.93 (m, 2II, H-4 & H-6), 2.58 (m, 2H, H-4 & H-6), 1.35 (m, 2H, H-5); ^{13}C NMR δ 71.7 (C-1') 71.3 (C-2), 71.0 (C-3'), 70.6 (C-2'), 63.0 (C-4'), 44.4 and 44.3 (C-4 & C-6), 25.6 (C-5). CI-MS *m/z* 207 (M + 1). Anal. Calcd for $C_8H_{18}N_2O_4$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.70; H, 9.00; N, 13.52.

Hexahydro-2-(D-*ribo*-1,2,3,4-tetrahydroxybutyl)pyrimidine (5). A solution of D-ribose (4.94 g, 32.9 mmol) in 1,3-diaminopropane (10.0 mL, 8.88 g, 120 mmol) was stirred under a nitrogen atmosphere for 34 h. Removal of excess 1,3-diaminopropane under high vacuum gave slightly yellow syrup which gave colorless crystals (6.71 g, 99%, mp 105-7°C) by the same crystallization method used for **4**. ^1H NMR δ 3.80 (ddd, J = 3.1, 5.8, 7.2 Hz, 1H, H-3'), 3.73 (dd, J = 3.1, 11.7 Hz, 1H, H-4'), 3.67 (dd, J = 5.8, 7.1 Hz, 1H, H-2'), 3.62 (d, J = 2.8 Hz, 1H, H-2), 3.61 (dd, J = 7.2, 11.7 Hz, 1H, H-4'), 3.59 (dd, J = 2.8, 7.1 Hz, 1H, H-1'), 3.07 (m, 2H, H-4 & H-6), 2.57 (m, 2H, H-4 & H-6), 1.45 (m, 2H, H-5); ^{13}C NMR δ 73.6 (C-1'), 72.2 (C-2'), 71.9 (C-3'), 70.3 (C-2), 62.4 (C-4'), 44.4 and 44.1 (C-4 & C-6), 25.8 (C-5). CI-MS *m/z* 207 (M + 1). Anal. Calcd for $C_8H_{18}N_2O_4$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.45; H, 8.68; N, 13.44.

(7*S*,8*S*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine (6) and (7*S*,8*S*,9*S*,9a*S*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine (7). To a solution of hexahydro-2-(L-*arabino*-1,2,3,4-tetrahydroxybutyl)pyrimidine (**4**) (1.86 g, 9.03 mmol) in anhydrous DMF (30 mL) under a nitrogen atmosphere were added Ph_3P (2.85 g, 10.9 mmol), Et_3N (0.93 g, 9.2 mmol), and CCl_4 (1.91 g, 12.4 mmol). The mixture was stirred for 22 h, and a precipitate formed which was collected by filtration and found to be triethylamine hydrochloride. The DMF was removed from the filtrate under vacuum, and the residue was

purified by column chromatography on silica gel prepared in CH_2Cl_2 containing 10% CH_3OH and 0.4% concentrated NH_4OH. Elution with CH_3OH/CH_2Cl_2 containing 0.4% concentrated NH_4OH (first 10% and then 20% CH_3OH) gave the product as a gum. Dissolution in a minimum of H_2O followed by slow evaporation gave crystals of **7** which were collected using absolute ethanol (0.380 g, 22.3%, mp 181.5-3.5°C, dec.). X-ray crystallography results on **7** are shown in Figure 1 and Table 2. ^1H NMR of the crystals in D_2O solution showed a mixture of two components, **6** and **7**, in a ratio of 7:3. **6** ^1H NMR peaks not in Table 1: δ 2.87 (m, 1H, H-2e), 2.71 (br d, J = 11.6 Hz, 1H, H-4e), 2.34 (ddd, J = 3.2, 12.7, ~12.7 Hz, 1H, H-2a), 2.02 (m, 1H, H-4a), ~1.46 (m, 2H, H-3); ^{13}C NMR (D_2O, reference acetone, δ 29.8) δ 78.0 (C-9a), 72.8 (C-9), 70.7 (C-8), 66.9 (C-7), 56.1 (C-6), 52.9 (C-4), 42.9 (C-2), 24.3 (C-3). **7** ^1H NMR peaks not in Table 1 were all obscured by peaks of **6**; ^{13}C NMR (D_2O, reference acetone, δ 29.8) δ 71.8 (C-9a), 70.6 (C-9), 70.4 (C-8), 64.1 (C-7), 53.5 (C-6), 52.3 (C-4), 43.3 (C-2), 24.8 (C-3). HRMS (CI): calcd for $C_8H_{17}O_3N_2$: 189.1239 (M+1), found 189.1241. Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.88. Found: C, 50.96; H, 8.32; N, 15.02.

(7*R*,8*R*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine Hydrochloride (9), (7*R*,8*R*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine (10), and (7*R*,8*R*,9*S*,9a*S*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-a]pyrimidine (11). To the solution of hexahydro-2-(D-*ribo*-1,2,3,4-tetrahydroxybutyl)pyrimidine (**5**) (1.03 g, 4.97 mmol) in anhydrous DMF (15 mL) under a nitrogen atmosphere were added Ph_3P (1.61 g, 6.14 mmol), Et_3N (0.56 g, 5.53 mmol), and CCl_4 (1.46 g, 9.49 mmol). The mixture was stirred for 13 h, and a precipitate formed. Filtration gave 815 mg of slightly yellow solid which was washed with $CHCl_3$ to remove triethylamine hydrochloride and leave colorless crystals of the product as the free base **10** (339 mg, 36%) which when recrystallized from ethanol containing a small amount of water gave needles (mp 222-3°C, dec.). X-ray crystallography results on **10** are given in Figure 3 and Table 2. The combined DMF and $CHCl_3$ filtrates were stripped to dryness, and the residue was dissolved in a small volume of warm DMF from which crystals of the hydrochloride **9** separated (mp 197-8°C, dec.); apparently evaporation of the DMF allowed triethylamine to also evaporate leaving the hydrogen chloride as a salt with the product. X-ray crystallography results on **9** are given in Figure 2 and Table 2. **9** ^{13}C NMR (D_2O, reference CH_3OH δ 49.15) δ 73.9, 71.0, 69.7, 65.6, 52.4, 51.8, 43.5, 22.0. Anal. Calcd for $C_8H_{17}ClN_2O_3$: C, 42.77; H, 7.63; N, 12.47. Found: C, 43.00; H, 7.61; N, 12.49. **10** ^1H NMR peaks not in Table 1: δ 2.88 (m, 1H, H-2e), 2.74 (br d, J = 11.7 Hz, 1H, H-4e), 2.41 (m, 1H, H-2a), 2.14 (m, 1H, H-2a), 1.45 (m, 2H, H-7); ^{13}C NMR (D_2O, reference acetone δ 29.8) δ 73.6 (C-9a), 70.8 (C-8), 70.7 (C-9), 65.5 (C-7), 52.2 (C-6), 53.0 (C-4), 43.3 (C-2), 24.6 (C-3). **11** ^1H NMR peaks not in Table 1 were all obscured by peaks of **10**; ^{13}C NMR (D_2O, reference acetone δ 29.8) δ 75.1, 72.0, 68.9, 68.2, 56.8, 52.9, 42.5, 24.8. CI-MS *m/z* 189 (M + 1). HRMS (CI): calcd for $C_8H_{17}O_3N_2$: 189.1239 (M+1), found 189.1234.

X-ray Crystallographic Determinations The structures of **7**, **9**, and **10** were solved using direct methods. It was apparent from the crystal data that the unit cell of **10** contained four molecules and in as much as the compound crystallized in the space group $P2_1$, that there are two molecules in the asymmetric unit. This was verified by the solution of **10**. In the refinement process all nonhydrogen atoms of the three structures were refined anisotropically. Positions for all hydrogen atoms bonded to carbon atoms were calculated. Positions for the hydrogens bonded to oxygen and nitrogen atoms were found in difference maps. All of the hydrogen atoms were assigned isotropic thermal parameters which were not refined. They were allowed to ride on their neighboring heavy atom during the refinement process. All programs used in the solution, refinement, and display of these structures are contained in the program 'SHELXTL-PLUS' (Siemens Analytical X-ray Instruments, Inc., Madison, Wisconsin, 1990).

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