(7*R*,8*S*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido[1,2-*a*]pyrimidine: A Bicyclic Diazasugar

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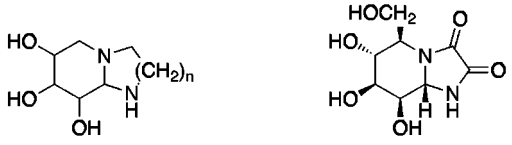
Naturally occurring "azasugars" and isomeric and homologous compounds have been the object of numerous synthetic efforts because of the glycosidase-inhibitory properties of many members of this class of compounds.[1] These inhibitors have potential chemotherapeutic utility against diabetes, AIDS, and cancer.[2] They are also useful as probes of the functions of the glyco moieties of glycoproteins.[3] Rational design has produced interesting and unique structural analogues such as amidino sugars[4] and "isoazasugars" (isomers of "azasugars" in which the nitrogen atom and the 1-position carbon atom have exchanged locations).[5] As part of a program directed toward the preparation of enzyme-activated, irreversible glycosidase inhibitors, we herein report the synthesis of an octahydrotrihydroxypyrido[1,2-*a*]pyrimidine, the first example of a new class of bicyclic "diazasugars" of general formula **1** that are structurally related to the natural products and potent glycosidase inhibitors kifunensine **2**[6] and nagstatin **3**.[7] The initial synthetic objective of this research was xylose analogue **4**.



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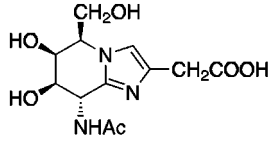

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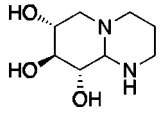
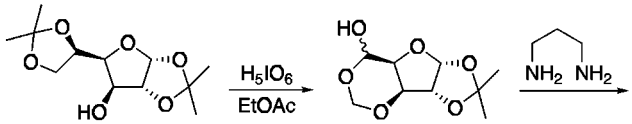
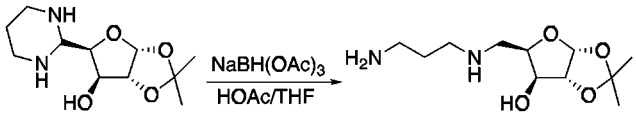


4

Periodic acid cleavage/oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**5**) gave hemiacetal **6** rather than the expected aldehyde.[8] Reaction of **6** with 1,3-propanediamine produced the crystalline aminal **7** which upon reduction by sodium triacetoxyborohydride in the presence of acetic acid gave diamine **8**. It was anticipated that cleavage of the isopropylidene group of **8** would lead to spontaneous cyclization to **4**. The desired reaction apparently happened, but under the reaction conditions,[9] concomitant dehydration to pyridine-type product(s) also occurred as has been reported for related compounds.[10]



5 **6**



7 **8**

Based on the ease of preparation and stability of aminal **7**, an alternative route to **4** was selected which required D-xylose aminal **9** that was prepared in high yield by reaction of the sugar with excess diamine. Cyclization of **9** to **4** was effected in fair yield by treatment with triphenylphosphine and carbon tetrachloride.[11] This preparative method is notable for its simplicity, amenability to scale-up, and low cost. X-ray crystallography of **4** showed it to be the β-anomer in the conformation shown in **10**. In D_2O solution a single isomer was observed by ^1H and ^{13}C NMR which was assigned the same structure and conformation; all substituents in the hydroxylated ring were determined to be equatorial based on the large axial-axial ^1H-^1H coupling constants (9−11 Hz) for the ring protons.

Application of this same method to prepare homologues **11** and **12** failed when attempts to form the corresponding aminals instead produced the glycosylamines (**13a** and **13b**). The biological rationale for this study and bioassay results will be published separately.

In summary, a very simple and inexpensive method to prepare novel "diazasugar" **10** has been developed. Efforts are ongoing to produce analogous "diazasugars" from other pentoses and to develop alternative routes to **11** and **12**.

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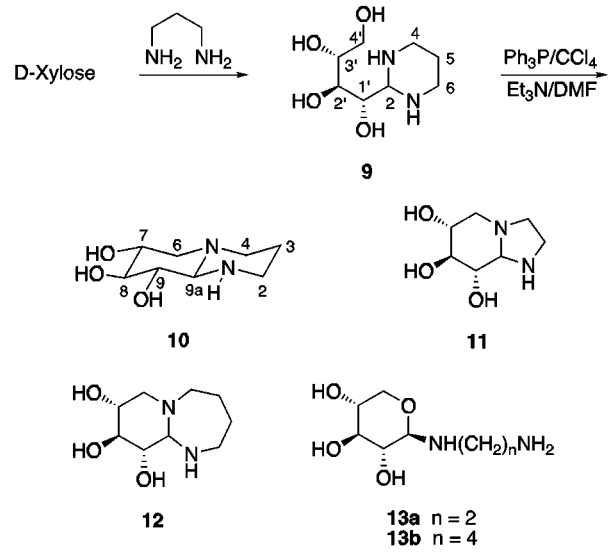

Experimental Section

Melting points are uncorrected. HETCOR, COSY, and DEPT experiments were used to make assignments of some of the ^{1}H and ^{13}C NMR spectra; when these methods were used, the corresponding acronym is included with the assignments. Optical rotation was measured on a Perkin-Elmer 241 Polarimeter. Elemental analyses were determined by M-H-W Laboratories in Phoenix, AZ. High-resolution mass spectra (HRMS) were obtained on a JEOL SX 102 A double focusing mass spectrometer; methane was used for positive ion chemical ionization (CI) spectra, and thioglycerol was used as the matrix for FAB spectra. X-ray crystallography was done on a Siemens P3m/V diffractometer. Thin-layer chromatography (TLC) was run on Whatman Al Sil G/UV plates. Spots were visualized with a spray consisting of $Ce(SO_4)_2$ (10 g), $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (25 g), H_2O (900 mL), and concentrated H_2SO_4 (100 mL). Flash chromatography was performed with Fisher S704-25 grade 60−200 mesh silica gel. Amberlite XAD-7, a nonionic polymeric adsorbent, was obtained from Aldrich Chemical Co.

1,2-*O*-Isopropylidene-3,5-*O*-methylidene-5-hydroxy-α-D-xylofuranose (6). A mixture of **5** (4.00 g, 15.4 mmol) and H_5IO_6 (5.47 g, 24.0 mmol) in anhydrous EtOAc was stirred for 2 h. The suspension was then filtered, and the solvent was evaporated. Chromatography (0−2% CH_3OH in CH_2Cl_2) gave 2.92 g (87%) of **6** as a gum; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.02 (d, J = 3.6 Hz, 1H), 5.37 (br s, 1H), 5.21 (d, J = 6.4 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 4.54 (d, J = 3.6 Hz, 1H), 4.35 (d, J = 2.0 Hz, 1H), 3.96 (br d, J = 2.0 Hz, 1H), 3.13 (br s, 1H), 1.50 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ 111.9 (quaternary), 104.9 (CH), 89.1 (CH), 83.1 (CH_2), 83.1 (CH), 75.6 (CH), 74.2 (CH), 26.4 (CH_3), 26.0 (CH_3). Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.61; H, 6.22.

4-(Hexahydropyrimidin-2-yl)-1,2-*O*-isopropylidene-β-L-threofuranose (7). A solution of **6** (1.00 g, 4.58 mmol) and 1,3-propanediamine (2.3 mL, 27 mmol) in anhydrous CH_3OH (95 mL) was stirred for 3.5 d. After evaporation of the CH_3OH, silica gel chromatography (10% CH_3OH in CH_2Cl_2) gave 0.84 g (75%) of **7** as an oil which crystallized on standing and was recrystallized from ether/petroleum ether (bp 35−60 °C): mp 117−119 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (d, J = 3.4 Hz, 1H), 4.49 (dd, J = 0.7, 3.4 Hz, 1H), 4.29 (dd, J = 0.7, 2.9 Hz, 1H), 4.17 (dd, J = 2.0, 2.9 Hz, 1H), 4.00 (d, J = 2.0 Hz, 1H), 3.21 (m, 2H), 2.89 (m, 2H), 1.49 (m, 2H), 1.47 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$, DEPT) δ 111.7 (quaternary), 105.0 (CH), 85.3 (CH), 79.9 (CH), 75.8 (CH), 70.2 (CH), 45.2 (CH_2), 44.6 (CH_2), 27.3 (CH_2), 26.7 (CH_3), 26.1 (CH_3). Anal. Calcd for $C_{11}H_{20}N_2O_4$: C, 54.08; H, 8.25; N, 11.47. Found: C, 54.11; H, 8.02; N, 11.36.

5-N-(3-Aminopropyl)amino-5-deoxy-1,2-*O*-isopropylidene-α-D-xylofuranose (8). To a suspension of $NaBH_4$ (0.76 g, 2.0 mmol) in 2 mL of dry THF was added dropwise HOAc (0.39 mL, 6.8 mmol). After 1 h, **7** (0.17 g, 0.70 mmol) in 3 mL of dry THF was added, and stirring was continued for 47 h. To the reaction was added concentrated aqueous NH_4OH (0.5 mL), and then the solvent was evaporated. The resulting solid was dissolved in water and added to a column of Amberlite XAD-7 resin. The column was eluted first with water and then a gradient of 0−99% CH_3OH in water. The product was found in the initial water fractions suggesting it was still a borate derivative. These fractions were combined and dissolved in aqueous 1 N NaOH. Extraction with CH_2Cl_2 and evaporation of the extract gave the product as an oil (103 mg, 60%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.95 (d, J = 3.4 Hz, 1H), 4.49 (d, J = 3.4 Hz, 1H), 4.27 (d, J = 2.4 Hz, 1H), 4.20 (br s, 1H), 3.45 (very br s, 4H), 3.37 (dd, J = 3.4, 12.9 Hz, 1H), 2.97 (br d, J = 12.9 Hz, 1H), 2.7−2.8 (m, 3H), 2.65 (m, 1H), 1.65 (quintet, J = 6.8 Hz, 2H) 1.48 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, DEPT) δ 111.3 (quaternary), 104.9 (CH), 85.9 (CH), 77.9 (CH), 76.9 (CH), 48.4 (CH_2), 47.2 (CH_2), 39.8 (CH_2), 32.7 (CH_2), 26.7 (CH_3), 26.1 (CH_3). HRMS (FAB+) calcd for $C_{11}H_{23}N_2O_4$ (M + 1) 247.1658, found 247.1651.

Hexahydro-2-(D-*xylo*-1,2,3,4-tetrahydroxybutyl)pyrimidine (9). D-Xylose (15.5 g, 0.103 mol) and 1,3-propanediamine (20 mL, 0.24 mol) were stirred under nitrogen for 2 days. Excess 1,3-propanediamine was removed under reduced pressure, the resulting gum was dissolved in $CHCl_3$ (50 mL) plus CH_3OH (5 mL), and then the solvents were evaporated under reduced pressure. This process was repeated until colorless crystals of product formed (20.0 g, 94%): mp 81 °C; ^{1}H NMR (500 MHz, D_2O, acetone ref δ 2.04, COSY) δ 3.62 (ddd, J = 3.7, 4.3, 7.3 Hz, 1H, H-3′), 3.54 (dd, J = 3.7, 4.9 Hz, 1H, H-2′), 3.51 (dd, J = 4.3, 11.8 Hz, 1 H, H-4′), 3.45 (d, J = 4.5 Hz, 1H, H-2), 3.45 (dd, J = 7.3, 11.8 Hz, 1H, H-4′), 3.42 (dd, J = 4.5, 4.9 Hz, 1H, H-1′), 2.93 (m, 2H, H-4 & H-6), 2.59 (m, 2H, H-4 & H-6), 1.33 (m, 2H, H-5); ^{13}C NMR (125 MHz, D_2O, acetone ref δ 29.8, HETCOR) δ 72.9 (C-1′), 70.7 (C-3′), 70.1 (C-2′), 69.6 (C-2), 62.3 (C-4′), 43.8 (C-4), 43.6 (C-6), 25.2 (C-5). $[\alpha]^{25}_D$ −33.6° (*c* 0.99, CH_3OH; taken immediately after dissolution). Anal. Calcd for $C_8H_{18}N_2O_4$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.55; H, 8.60; N, 13.35. HRMS (CI+) calcd for $C_8H_{19}N_2O_4$ (M + 1) 207.1345, found 207.1331.

(7*R*,8*S*,9*S*,9a*R*)-Octahydro-7,8,9-trihydroxy-2*H*-pyrido-[1,2-*a*]pyrimidine (10). A solution of **9** (1.0 g, 5.0 mmol), Ph_3P (1.3 g, 5.0 mmol), CCl_4 (1.4 mL, 15 mmol), and Et_3N (0.8 mL, 6.0 mmol) in anhydrous DMF (20 mL) were stirred overnight. The solution was filtered and concentrated under vacuum until the product separated as colorless needles (0.37 g, 40%): mp 139−141 °C, dec. If the product did not crystallize directly, chromatography on silica gel pretreated with 1% concentrated aqueous NH_4OH in a 1:9 mixture of CH_3OH and CH_2Cl_2 and eluting with a gradient of 10−30% CH_3OH in CH_2Cl_2 containing 0.4% concentrated aqueous NH_4OH gave the product which could then be crystallized from ethanol containing a small amount of water. ^{1}H NMR (500 MHz, D_2O, 1,4-dioxane ref δ 3.53, COSY) δ 3.35 (ddd, J = 4.9, 9.5, 11.0 Hz, 1H, H-7), 3.08 (dd, J = 9.3, 9.5 Hz, 1H, H-8), 2.92 (dd, J = 8.9, 9.3 Hz, 1H, H-9), 2.82 (br d, J ~12.7 Hz, 1H, H-2eq), 2.72 (br d, J ~11.7 Hz, 1H, H-4eq), 2.61, (dd, J = 4.9, 11.7 Hz, 1H, H-6eq), 2.57 (d, J = 8.9 Hz, 1H, H-9a), 2.32 (m, 1H, H-2ax), 2.06 (m, 1H, H-4ax), 1.92 (dd, J = 11.0, 11.7 Hz, 1H, H-6ax), 1.41 (m, 2H, H-3); ^{13}C (125 MHz, D_2O, 1,4-dioxane ref δ 66.5, HETCOR) δ 77.7 (C-9a), 76.9 (C-8), 73.6 (C-9), 68.5 (C-7), 56.5 (C-6), 53.1 (C-4), 43.1 (C-2), 24.5 (C-3); $[\alpha]^{25}_D$ −28.9° (*c* 0.99, CH_3OH). Anal. Calcd for $C_8H_{16}N_2O_3$: C, 51.05; H, 8.57; N, 14.88. Found: C, 50.88; H, 8.40; N, 14.80.

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Supporting Information Available: ^{1}H NMR spectra of **8** and **10** and X-ray data with an ORTEP drawing for **10** (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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