Pergamon

Tetrahedron 55 (1999) 14251–14260

TETRAHEDRON

# Bicyclic Azasugars Containing a Glycosidic Heteroatom 2: D-Lyxose Analogues

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Received 12 August 1999; accepted 5 October 1999

***Abstract***: Bicyclic azasugar analogues of D-lyxose containing a glycosidic heteroatom that is O, N, or S have been prepared from 5-*O*-tosyl-D-lyxose and characterized by NMR spectroscopy. The nitrogen analogue has an overwhelming preference to be the β-anomer, but the oxygen and sulfur compounds exist as mixtures of anomers with the α-anomer predominating in the latter case. The α-anomers undergo conformational equilibration with the sulfur analogue being fast at room temperature but the oxygen compound requiring 60°C to achieve fast exchange and a sharply resolved $^1$H NMR spectrum at 500 MHz.

*Keywords:* Carbohydrate mimetics; Aza compounds; Enzyme inhibitors; Conformation.

Azasugars are compounds which resemble sugars but have a nitrogen atom in place of the ring oxygen of sugars. These compounds have been of considerable interest because many of them inhibit glycosidases, enzymes which catalyze the hydrolysis of glycosidic linkages in polysaccharides and glycoproteins. Some have been shown to have therapeutic utility in the treatment of diabetes and cancer, and there is potential application in other medical areas such as viral infections and immunomodulation.[1-3] In the development of synthetic 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. Inasmuch as glycosidases are exquisitely selective for the configuration of the glycosidic linkage they cleave, it seems quite reasonable to design new inhibitors which have such a glycosidic heteroatom. To date, there have only been a few of these types of structures found in nature or prepared in the laboratory.[4] Some of these compounds have been shown to be extremely potent glycosidase inhibitors. Since these compounds have a glycosidic heteroatom, they may, in fact, act as pseudosubstrates for the enzymes and be converted to intermediates and transition states resembling those of the normal reaction pathway with sugars. Through this process of mimicry, pseudosubstrates may show inhibitory action at multiple stages of the catalytic mechanism.

Examples of inhibition at different steps of the reaction pathway of glycosidases have been reported or postulated. The first step of the enzymatic mechanism involves protonation of the glycosidic oxygen atom. Evaluation of a series of D-*gluco*, D-*manno*, and D-*galacto* analogues of general structure **1** has shown that inhibitory potency correlates with the basicity of the glycosidic atom suggesting that protonation of this atom

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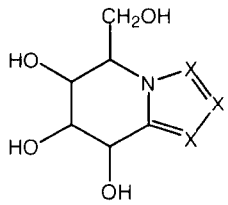
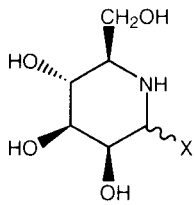
0040-4020/99/$ - see front matter 
*PII:* S0040-4020(99)00901-1

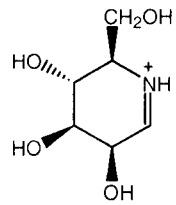
is important for inhibition.[5] The second step of the mechanism involves loss of the protonated glycosidic group and leads to an oxocarbenium ion-like intermediate or transition state. Mannojirimycin (**2a**) possesses a glycosidic hydroxyl group and is about sixty-fold more potent an inhibitor of the α-mannosidase from jack beans than its 1-deoxy analogue (**2b**).[6] The greater activity of **2a** than **2b** may be a consequence of the loss of water to give iminium ion **3** which mimics the oxocarbenium ion. In the case of retaining glycosidases, the oxocarbenium ion reacts with a carboxylate residue in the active site to form a covalent adduct with the enzyme. The time-dependent inhibition of an α-fucosidase by an imine has been postulated to involve formation of a covalent adduct (**4**) like that occurring with natural substrates.[7]



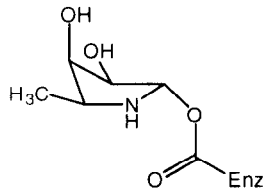
**1** (X = N or CH)



**2a** (X = OH)
**2b** (X = H)

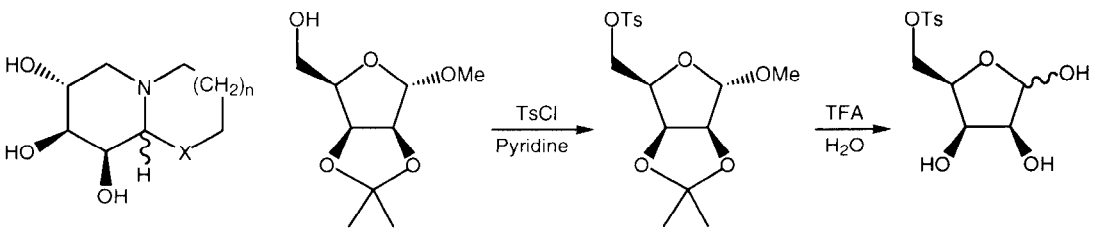


**3**



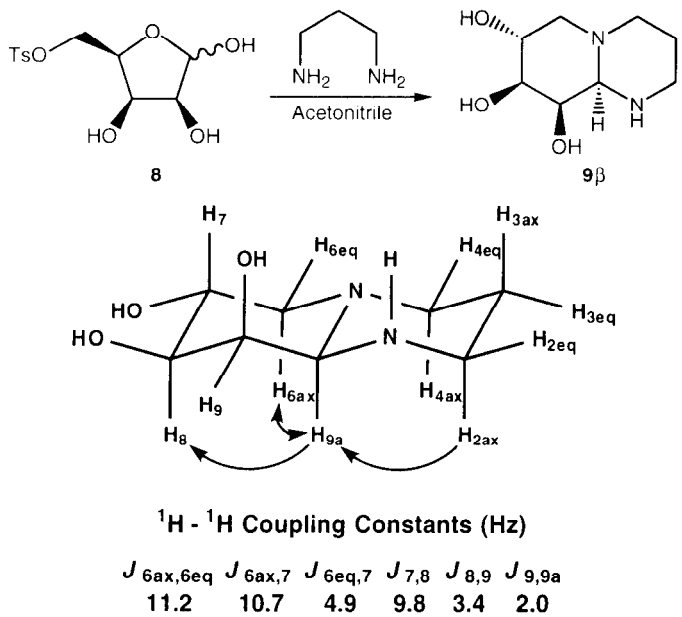
**4**

We have previously reported the preparation of a number of azasugar analogues of D-xylose which contain a glycosidic heteroatom,[4] and herein we describe similar analogues of D-lyxose which have general structure **5**. It was envisioned that these analogues might interfere with multiple steps of the catalytic process by acting as protonated substrate analogues like **1**, by being converted to oxocarbenium ion analogues like **2a** going to **3**, and then by reacting with an active site carboxylate residue to give a covalent adduct like **4**. The versatility of a synthetic approach to bicyclic azasugars involving a 5-position-activated pentose was exemplified with the D-xylose analogues, and therefore tosylate **8** was determined to be a key intermediate for the current work. Protected D-lyxose derivative **6** was prepared from D-mannose by a reported method.[8] Tosylation and then treatment of the product **7** with a 70% solution of trifluoroacetic acid (TFA) in water produced the desired tosylate **8**. The lipophilicity of the tosylate group greatly decreased the water solubility of **8** relative to D-lyxose, and **8** precipitated from aqueous solution after evaporating most of the TFA. The advantage of the tosylate group over a mesylate, which had been explored first, was realized when **8** could be easily isolated and purified by filtration and washing with water to give a sample of analytical purity and in almost quantitative yield. Although **8** was readily prepared, care needed to be exercised in the process of removing the acid, and the compound was best stored in a freezer since on several occasions it decomposed to a black tar when left for days at room temperature.




**5** **6** **7** **8**

Reaction of tosylate **8** with various substituted amines to give products of general structure **5** was explored. Since the tosylate was insoluble in water, other solvents were tried for these reactions. Acetonitrile was found to be very advantageous for the reaction of **8** with 1,3-propanediamine. The product precipitated from acetonitrile, whereas the by-product, a tosylate salt of 1,3-propanediamine, was soluble thereby making separation simple. Crystallization of the precipitate from acetonitrile/methanol gave needles of **9** in good yield. Nuclear magnetic resonance (NMR) spectral studies of **9** showed it to be a single anomer. $^{1}H$ and $^{13}C$ NMR spectra were completely assigned using COSY and HETCOR techniques. The large values of $J_{7,8}$ (9.8 Hz) and $J_{6ax,7}$ (10.7 Hz) indicated that $H_7$ and $H_8$ occupy axial positions in a chair conformation. Nuclear Overhauser effects (NOE's) between $H_8$ and $H_{9a}$, $H_{6ax}$ and $H_{9a}$, $H_{2ax}$ and $H_{9a}$ showed that **9** is in a chair-chair conformation and is the β-anomer, **9β**, as shown in Figure 1.



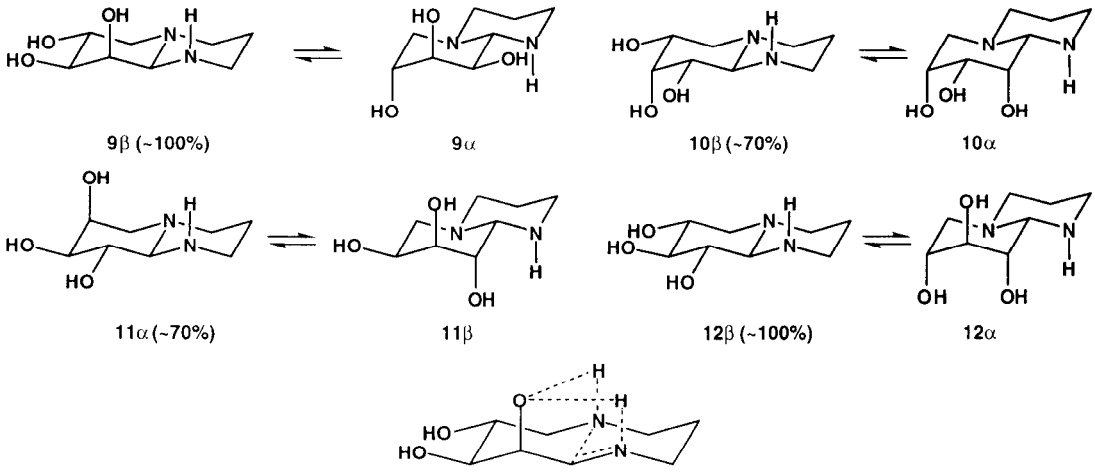

**$^{1}H$ - $^{1}H$ Coupling Constants (Hz)**

| $J_{6ax,6eq}$ | $J_{6ax,7}$ | $J_{6eq,7}$ | $J_{7,8}$ | $J_{8,9}$ | $J_{9,9a}$ |
|---|---|---|---|---|---|
| 11.2 | 10.7 | 4.9 | 9.8 | 3.4 | 2.0 |

**Figure 1. Conformation and $^{1}H$ NMR Data for Compound 9β.**
(Arrows show NOE's used to confirm the configuration at C-1)

That **9** was a single anomer was unexpected since the corresponding D-*ribo* and L-*arabino* analogues (**10** and **11**, respectively) consisted of 7:3 mixtures of anomers[9] with the structure corresponding to **9β** favored in each case (**10β** and **11α**). The D-*xylo* analogue, however, was only the β-anomer, **12β**.[10] Based only on the presence of axial hydroxy groups, the anomeric equilibrium for **9** should resemble those for **10** and **11** more closely than that for **12**. Since this was not observed, some additional effect clearly must be operative. Both anomers of compounds **9** through **12** are shown below in their preferred conformations; **9α** and **12α** have not been observed but are assumed to prefer conformations comparable to **10α** and **11β** which have been observed. All N-H bonds are shown as axial in accordance with an *exo* anomeric effect. The preferred anomer in every case has the lesser number of axial hydroxy groups. Anomers **9β**, **10α**, **11β**, and **12α** have an extra possible mode of stabilization. Structure **13**, derived from **9β**, illustrates this effect which involves intramolecular

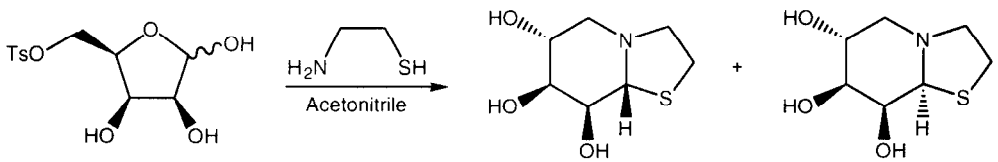
hydrogen bonding that is accentuated by an *exo* anomeric effect (indicated by partial C-N bonds). This effect could account for the strong preference for **9β** and the occurrence of **10α** and **11β**.[11] In the case of **12α**, three axial hydroxy groups may result in so much steric hindrance that the special stabilization effect is totally overcome and only **12β** is observed.






13

Reaction of **8** with 2-aminoethanethiol in acetonitrile followed by anion exchange resin treatment and purification on a cation-exchange resin (ammonium ion form) afforded **14** as a mixture of two anomers (67% α-anomer). $^1$H NMR data for **14β** matched well those expected for the conformation shown in Figure 2. However, the three-bond $^1$H-$^1$H coupling constants for **14α** did not correspond well with those expected for either chair conformation shown in Figure 2. NOE experiments indicated spatial relationships that could not be explained by either individual conformer. These data suggested that there was a fast conformational equilibrium between the two **14α** conformers as shown in Figure 2. The formation of primarily the α-anomer in this case can be ascribed to an *endo* anomeric effect which stabilizes only that anomer and is more significant than *exo* anomeric effects that stabilize both anomers. The extra stabilization accorded **9β** by hydrogen bonding is less significant for **14β** because of the weaker *exo* anomeric effect and the possibility of only one hydrogen bond with the latter.




8 14α 14β

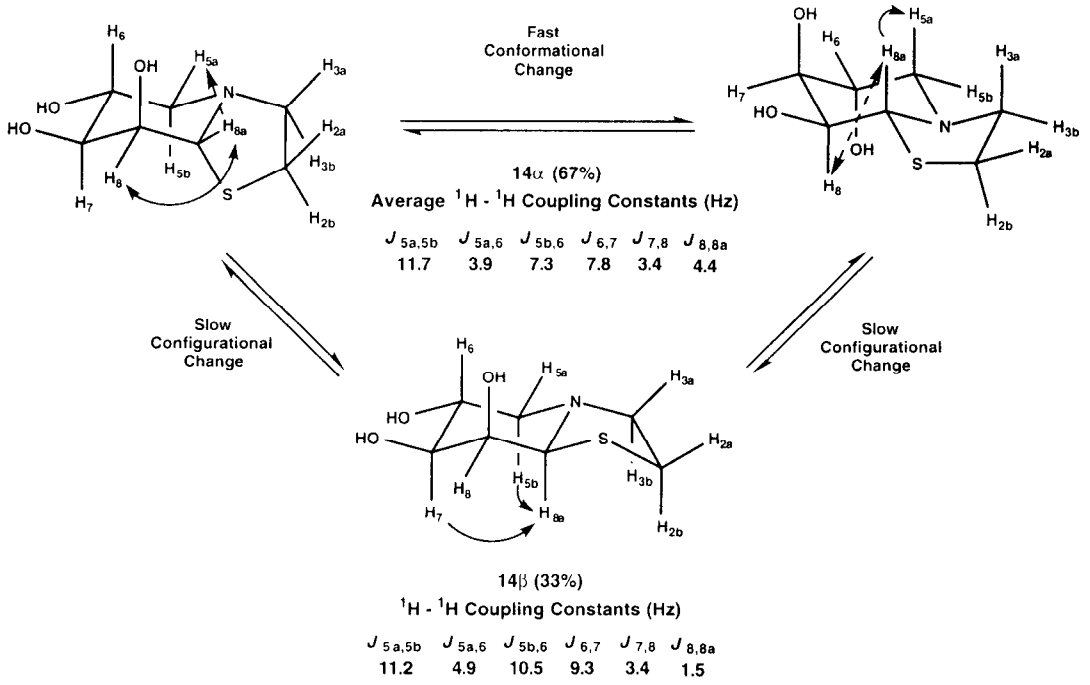
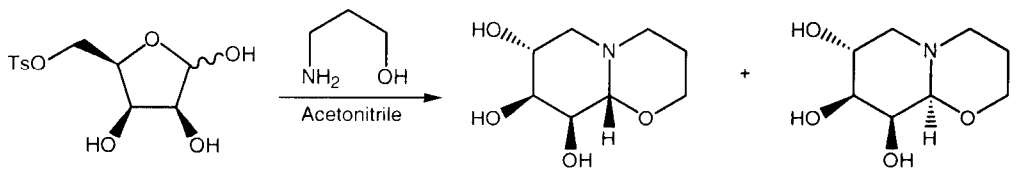



**Figure 2.** **Configurational and Conformational Equilibria and $^1$H NMR Data for Compounds 14α and 14β.** (Arrows show NOE's observed; expected are solid and unexpected are dashed.)

Treatment of **8** with 3-amino-1-propanol gave **15** as an equilibrium mixture of two anomers (55% β-anomer). Similar to the preceding pair of anomers, the conformation of **15β** was determined to be as shown in Figure 3. The $^1$H NMR signals of **15α** were poorly resolved suggesting a conformational equilibrium which was slower than that of **14α**. However, a spectrum obtained at 60°C had sharp multiplets from which coupling constants for the averaged conformations could be obtained. The presence of less of the α-anomer in this case than with **14** may be a reflection of a less powerful *endo* anomeric effect with oxygen than with sulfur because the latter can more readily accommodate a buildup of negative charge on its glycosidic heteroatom.




**8** **15α** **15β**

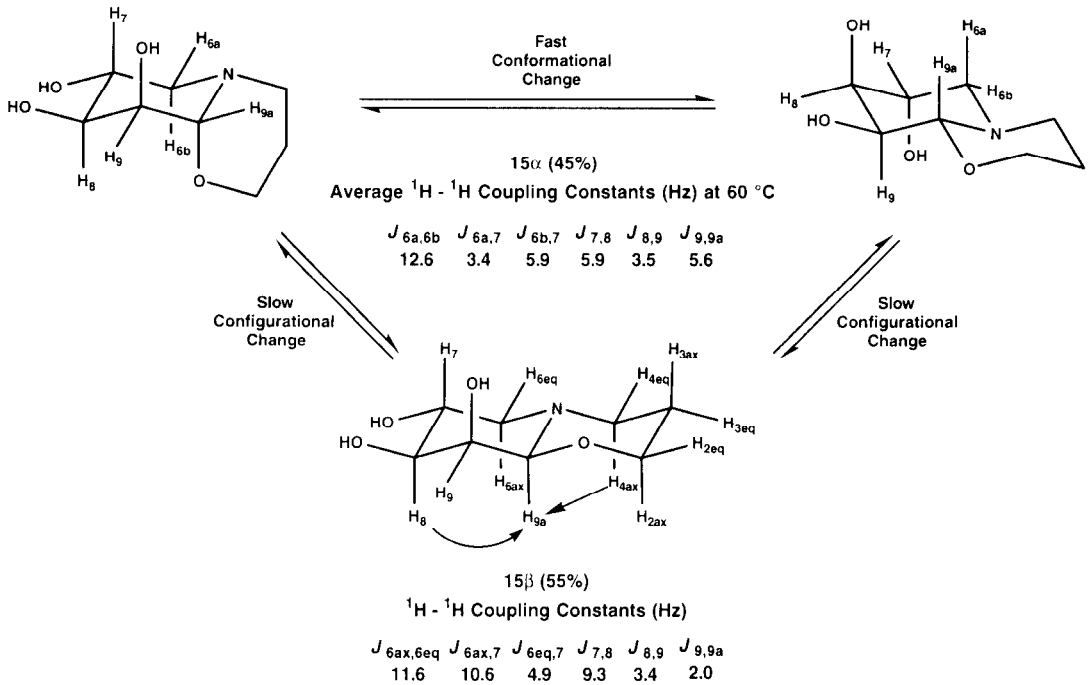



**Figure 3. Configurational and Conformational Equilibria and $^1$H NMR Data for Compounds 15α and 15β.** (Arrows show NOE's used to confirm the configuration of **15β**.)

Preliminary evaluation of these new D-*lyxo* bicyclic azasugars and related compounds in the D-*xylo*, D-*ribo*, and L-*arabino* series has shown that those compounds with a nitrogen as the glycosidic heteroatom have reasonably good inhibitory activity against only β-glycosidases which cleave substrates with the configuration corresponding to the azasugar. The compounds in which the heteroatom is oxygen or sulfur, however, have shown little activity. All of these compounds have lacked the hydroxymethyl group common to all the substrates. The extent of the effect of the absence of this group on inhibitory activity will be assessed when compounds possessing it are evaluated; the preparation of some of these compounds is underway. The poor activity of compounds with a glycosidic heteroatom that is oxygen or sulfur suggests that these compounds may, at best, be bound as substrate analogues and not be protonated inside the active site or enter the site already protonated. It is expected that these compounds are less basic than those with a nitrogen as the glycosidic heteroatom whose inhibitory activity may be a consequence of tighter binding due to electrostatic attraction of the protonated form to anionic residues in the active site. Protonation in the active site may require distortion of the substrate which also may be more difficult with bicyclic structures.

In conclusion, bicyclic azasugar analogues of D-lyxose containing a glycosidic heteroatom (N, O, and S) have been prepared and structurally characterized. When the glycosidic heteroatom is O or S, both α- and β-anomers are present in solution; when the heteroatom is N, only the β-anomer is present. The varying populations of anomers when the anomeric heteroatom is changed probably is a consequence of differences in anomeric effects and intramolecular hydrogen bonding in these structures.

## EXPERIMENTAL

### *General*

All reactions were performed at room temperature unless otherwise indicated. Acetonitrile was dried by distillation from $CaH_2$. Thin-layer chromatography (TLC) was run on Whatman® Al Sil G/UV plates. Compounds were located on TLC plates by using 254 nm UV light, $I_2$, or 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 measured on a Thomas Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories in Phoenix, AZ. Fourier Transform Nuclear Magnetic Resonance (FTNMR) spectra were taken on Varian 200, 300 and 500 MHz NMR spectrometers; HETCOR, COSY, DEPT, INADEQUATE, and NOE experiments were used to make assignments of some of the $^1H$ and $^{13}C$ NMR spectra. When these methods were used, the corresponding acronym is included with the assignments in the text. 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).

**Methyl 2,3-*O*-Isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-lyxofuranoside (7).** A solution of **6**[8] (393 mg, 1.93 mmol) and *p*-toluenesulfonyl chloride (2.11 g, 11.1 mmol) in 16.0 mL of anhydrous pyridine was stirred for 8 h, and TLC (5% acetone in methylene chloride) showed that no starting material was left and one product had formed. The pyridine was removed *in vacuo* at a temperature lower than 40°C. The residue was dissolved in chloroform, and the solution was washed with 1N HCl solution and then distilled water and dried over $Na_2SO_4$. The organic phase was evaporated to give a slightly yellow solid. Recrystallization from chloroform gave 670 mg (96%, mp 77-8°C) of product: $^1H$ NMR (200 MHz, $CDCl_3$, ref. TMS, COSY) δ 1.25 (s, 3H, $CH_3$), 1.34 (s, 3H, $CH_3$), 2.46 (s, 3H, $CH_3$), 3.29 (s, 3H, $CH_3$), 4.15 (br dd, $J$ = 3.7, 4.0 Hz, 1H, H-4), 4.19 (dd, $J$ = 7.0, 10.5 Hz, 1H, H-5b), 4.31 (dd, $J$ = 4.4, 10.5 Hz, 1H, H-5a), 4.52 (d, $J$ = 5.7 Hz, 1H, H-2), 4.68 (dd, $J$ = 3.7, 5.7 Hz, 1H, H-3), 4.86 (s, 1H, H-1), 8.34 (m, 4H); $^{13}C$ NMR (50 MHz, $CDCl_3$, ref. 77.0) δ 144.8, 132.8, 129.7, 128.0, 112.8, 107.2, 84.7, 79.3, 77.2, 67.9, 54.7, 25.8, 24.6, 21.6. HRMS (CI) calcd for $C_{16}H_{23}O_7S$ (M+1) 359.1164, found 359.1166. Anal. Calcd for $C_{16}H_{22}O_7S$: C, 53.62; H, 6.19. Found: C, 53.44; H, 5.98.

**5-*O*-(*p*-Toluenesulfonyl)-D-lyxofuranose (8).** Compound **7** (3.24 g, 9.08 mmol) was dissolved in a solution of trifluoroacetic acid (20 mL) and water (8 mL). After 16 h sitting in the dark, water was added to dilute the reaction mixture. Half the solvent mixture was removed *in vacuo* at 25°C, more water was added, and the process was repeated several times before most of trifluoroacetic acid was removed to afford a white precipitate in the aqueous solution. Filtration gave the product as a white powder (2.71 g, 98.0%) which was shown by $^{13}C$ NMR to consist of a 1:1 mixture of two anomers: $^{13}C$ NMR (75 MHz, $CD_3CN$, ref. $\delta$ 1.39,

DEPT) $\delta$ 146.6, 133.7, 131.1, 128.9, 102.7, 97.4, 78.2, 77.8, 77.7, 72.8, 71.8, 71.7, 71.4, 71.3, 21.7; HRMS (FAB) calcd for $C_{12}H_{16}O_7S$ (M+Na) 327.0514, found 327.0516. Anal. Calcd for $C_{12}H_{16}O_7S \cdot H_2O$: C, 47.36; H, 5.30. Found: C, 47.03; H, 5.23.

**[7*R*-(7α,8β,9β,9aα)]-Octahydropyrido[1,2-*a*]pyrimidine-7,8,9-triol (9β).** To a suspension of **8** (1.33 g, 4.37 mmol) in anhydrous acetonitrile (20 mL) was added 1,3-propanediamine (0.73 mL, 8.74 mmol). A clear solution formed immediately which quickly became cloudy. After 30 min, a light-yellow gummy precipitate was isolated by decanting the clear supernatant. The gum crystallized on standing in a mixture of acetonitrile and methanol (10:1) to afford the product as white needles (0.59 g, 71%): mp 176-8°C; $^1$H NMR (500 MHz, $D_2O$, methanol ref. $\delta$ 3.30, COSY) $\delta$ 3.79 (ddd, $J$ = 4.9, 9.8, 10.7 Hz, 1H, H-7), 3.75 (dd, $J$ = 2.0, 3.4 Hz, 1H, H-9), 3.39 (dd, $J$ = 3.4, 9.8 Hz, 1H, H-8), 3.00 (ddd, $J$ = 2.0, 3.9, 13.7 Hz, 1H, H-2eq), 2.89 (d, $J$ = 2.0 Hz, 1H, H-9a), 2.89 (obscured, H-4eq), 2.75 (dd, $J$ = 4.9, 11.2 Hz, 1H, H-6eq), 2.53 (ddd, $J$ = 3.9, 12.2, 13.7 Hz, 1H, H-2ax), 2.25 (ddd, $J$ = 3.6, 11.8, 11.8 Hz, 1H, H-4ax), 1.97 (dd, $J$ = 10.7, 11.2 Hz, 1H, H-6ax), 1.58 (m, 1H, H-3a), 1.54 (m, 1H, H-3b); Difference NOE's: $H_{9a} \rightarrow H_8$ (+2.8%) and $H_{6ax}$ (+2.5%); $H_{6ax} \rightarrow H_{9a}$ (+4.7%); $H_{2ax} \rightarrow H_{9a}$ (+7.2%); $^{13}$C NMR (125 MHz, $D_2O$, methanol ref. $\delta$ 49.15, HETCOR) $\delta$ 75.7 (C-9a), 74.6 (C-8), 71.1 (C-9), 67.0 (C-7), 57.2 (C-6), 53.7 (C-4), 43.3 (C-2), 25.6 (C-3); HRMS (CI) calcd for $C_8H_{17}N_2O_3$ (M+1) 189.1240, found 189.1235. Anal. Calcd for $C_8H_{16}N_2O_3 \cdot H_2O$: C, 46.59; H, 8.80; N, 13.58. Found: C, 46.71; H, 8.60; N, 13.28.

**[6*R*-(6α,7β,8β,8aβ)]-Hexahydrothiazolo[3,2-*a*]pyridine-6,7,8-triol (14α)** and **6*R*-(6α,7β,8β,8aα)]-Hexahydrothiazolo[3,2-*a*]pyridine-6,7,8-triol (14β).** 2-Aminoethanethiol hydrochloride (0.25 g, 2.2 mmol) and anhydrous ammonium carbonate (0.23 g, 2.4 mmol) were dissolved in distilled water (30 mL), and **8** (0.18 g, 0.59 mmol) was added. Acetonitrile was added to this mixture until an almost clear solution formed. After 4 h, the resulting clear light-yellow solution was concentrated *in vacuo* to give a yellow syrup. Distilled water (5 mL) was added and a milky gum formed. The aqueous layer was decanted from the gum and treated with Amberlite IRA-400 ($^-$OH) anion-exchange resin to remove the 4-methylbenzenesulfonic acid by-product. Excess 2-aminoethanethiol was then removed by preparative HPLC on Amberlite CG-50 ($^+NH_4$) cation-exchange resin (100~200 mesh), eluting with water to afford the product as a yellow gum (71 mg, 63%) which was shown by $^1$H and $^{13}$C NMR to consist of two anomers (major 67%, minor 33%). **14α** (major): $^1$H NMR (500 MHz, $D_2O$, acetonitrile ref. $\delta$ 1.94, COSY, difference NOE) $\delta$ 4.27 (d, $J$ = 4.4 Hz, 1H, H-8a), 3.99 (dd, $J$ = 3.4, 4.4 Hz, 1H, H-8), 3.85 (ddd, $J$ = 3.9, 7.3, 7.8 Hz, 1H, H-6), 3.77 (dd, $J$ = 3.4, 7.8 Hz, 1H, H-7), 3.28 (dd, $J$ = 6.8, 11.2 Hz, 1H, H-3a), 2.96 (ddd, $J$ = 6.8, 10.5, 11.2 Hz, 1H, H-2), 2.86 (m, 1H, H-2), 2.70 (ddd, $J$ = 7.3, 10.5, 11.2 Hz, 1H, H-3b), 2.59 (dd, $J$ = 3.9, 11.7 Hz, 1H, H-5a), 2.55 (dd, $J$ = 7.3, 11.7 Hz, 1H, H-5b); Difference NOE's: $H_{8a} \rightarrow H_{3a}$ (+3.7%), $H_{5a}$ (+1.6%), $H_8$ (+1.9%); $H_8 \rightarrow H_{8a}$ (+1.1%); $^{13}$C NMR (75 MHz, $D_2O$, acetonitrile ref. $\delta$ 1.39, HETCOR, DEPT) $\delta$ 72.9 (C-8a), 71.0 (C-7), 70.0 (C-8), 67.8 (C-6), 58.0 (C-3), 51.3 (C-5), 28.9 (C-2); **14β** (minor): $^1$H NMR (500 MHz, $D_2O$, acetonitrile ref. $\delta$ 1.94, COSY, difference NOE) $\delta$ 3.91 (dd, $J$ = 1.5, 3.4 Hz, 1H, H-8), 3.78 (partially obscured, m, $J$ = 4.9, 9.3, 10.5 Hz, 1H, H-6), 3.69 (br s, 1H, H-8a), 3.41 (dd, $J$ = 3.4, 9.3 Hz, 1H, H-7), 3.23 (dd, $J$ = 4.9, 11.2 Hz, 1H, H-3a), 3.16 (dd, $J$ = 4.9,

11.2 Hz, 1H, H-5a), 2.88 (m, obscured, 1H, H-2), 2.85 (m, obscured, 1H, H-2), 2.44 (m, 1H, H-3b), 2.08 (dd, $J$ = 10.5, 11.2 Hz, 1H, H-5b); Difference NOE's: $H_{5b}\rightarrow H_{8a}$ (+4.7%); $H_7\rightarrow H_{8a}$ (+2.6%); $^{13}$C NMR (75 MHz, $D_2O$, acetonitrile ref. $\delta$ 1.39, HETCOR, DEPT) $\delta$ 75.2 (C-7), 70.9 (C-8a), 67.8 (C-6), 67.6 (C-8), 56.3 (C-3), 54.2 (C-5), 29.4 (C-2); HRMS (CI) calcd for $C_7H_{14}NO_3S$ (M+1) 192.0695, found 192.0686.

**[7*R*-(7α,8β,9β,9aβ)]-Hexahydropyrido[2,1-*b*][1,3]oxazine-7,8,9-triol (15α)** and **[7*R*-(7α,8β,9β,9aα)]-Hexahydropyrido[2,1-*b*][1,3]oxazine-7,8,9-triol (15β)**. To a suspension of **8** (0.73 g, 2.4 mmol) in anhydrous acetonitrile (13 mL) was added 3-amino-1-propanol (0.37 mL, 4.8 mmol), and a clear solution formed immediately. After 1 h, the solution was evaporated *in vacuo* to give a yellow syrup. Distilled water (15 mL) was then added to the syrup, and a gum precipitated. The aqueous layer was decanted from the gum and treated with Amberlite IRA-400 ($^-$OH) anion-exchange resin to remove the *p*-toluenesulfonic acid by-product. The aqueous solution was subjected to preparative HPLC on Amberlite CG-50 ($^+NH_4$) cation-exchange resin (100–200 mesh) eluting with water to afford the product as a yellow gum (0.23 g, 51%) which was shown by $^1$H and $^{13}$C NMR to consist of two anomers (major 55%, minor 45%). **15α** (minor): $^1$H NMR (500 MHz, $D_2O$, at 60°C, methanol ref. $\delta$ 3.30, COSY, NOE) $\delta$ 4.04 (dd, $J$ = 5.1, 11.6 Hz, 1H, H-2ax), 3.98 (d, $J$ = 5.6 Hz, 1H, H-9a), 3.83 (ddd, $J$ = 3.4, 5.9, 5.9 Hz, 1H, H-7), 3.76 (dd, $J$ = 3.5, 5.9 Hz, 1H, H-8), 3.75 (dd, $J$ = 3.5, 5.6 Hz, 1H, H-9), 3.63 (ddd, $J$ = 2.4, 11.6, 12.6 Hz, 1H, H-2eq), 2.89 (dm, $J$ = 12.6 Hz, 1H, H-4eq), 2.79 (dd, $J$ = 3.4, 12.6 Hz, 1H, H-6a), 2.65 (ddd, $J$ = 2.7, 12.6, 12.6 Hz, 1H, H-4ax), 2.60 (dd, $J$ = 5.9, 12.6 Hz, 1H, H-6b), 2.02 (m, 1H, H-3ax), 1.38 (br d, $J$ = 14.0 Hz, 1H, H-3eq); $^{13}$C NMR (75 MHz, $D_2O$, methanol ref. $\delta$ 49.15, HETCOR, INADEQUATE, DEPT) $\delta$ 91.4 (C-9a), 71.4 (C-8), 69.3 (C-9), 68.1 (C-2), 67.8 (C-7), 51.5 (C-6), 51.5 (C-4), 22.5 (C-3); **15β** (major): $^1$H NMR (500 MHz, $D_2O$, methanol ref. $\delta$ 3.30, COSY, NOE) $\delta$ 4.01 (m, 1H, H-2eq), 3.90 (dd, $J$ = 2.0, 2.9 Hz, 1H, H-9), 3.86 (ddd, $J$ = 4.9, 9.8, 10.7 Hz, 1H, H-7), 3.61 (d, $J$ = 2.0 Hz, 1H, H-9a), 3.56 (ddd, $J$ = 2.4, 12.0, 12.0 Hz, 1H, H-2ax), 3.42 (dd, $J$ = 2.9, 9.3 Hz, 1H, H-8), 2.93 (m,1H, H-4eq), 2.83 (dd, $J$ = 4.9, 11.7 Hz, 1H, H-6eq), 2.33 (ddd, $J$ = 3.6, 11.8, 11.8 Hz, 1H, H-4ax), 2.00 (dd, $J$ = 10.7, 11.2 Hz, 1H, H-6ax), 1.84 (m, 1H, H-3ax), 1.51 (br d, $J$ = 13.7 Hz, 1H, H-3eq); Difference NOE's: $H_{4ax}\rightarrow H_{9a}$ (+4.2%); $H_8\rightarrow H_{9a}$ (+3.1%); $^{13}$C NMR (75 MHz, $D_2O$, methanol ref. $\delta$ 49.15, HETCOR, INADEQUATE, DEPT) $\delta$ 91.8 (C-9a), 73.6 (C-8), 70.4 (C-9), 67.5 (C-2), 66.8 (C-7), 55.2 (C-6), 52.4 (C-4), 24.3 (C-3); HRMS (CI) calcd for $C_8H_{16}NO_4$ (M+1) 190.1079, found 190.1076.

## ACKNOWLEDGMENTS

We wish to thank Dr. Du Li for NMR help and Mr. Bruce Jackson for mass spectral analyses. We thank the Brigham Young University Cancer Research Center for financial support.

## REFERENCES


1. Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605-611.
2. Nash, R. J.; Watson, A. A.; Asano, N. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1996; Vol. 11, Chapter 5.
3. *Iminosugars as Glycosidase Inhibitors, Nojirimycin and Beyond;* Stütz, A. E., Ed.; Wiley-VCH: Weinheim, 1999.
4. For references and examples see Berges, D. A.; Fan, J.; Devinck, S.; Liu, N.; Dalley, N. K. *Tetrahedron* **1999**, *55*, 6759-6770.
5. Granier, T.; Panday, N.; Vasella, A. *Helv. Chim. Acta* **1997**, *80*, 979-987.
6. Legler, G.; Jülich, E. *Carbohydr. Res.* **1984**, *128*, 61-72.
7. Wong, C.-H.; Provencher, L.; Porco, J. A. Jr.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492-1501.
8. Xie, M.; Berges, D. A.; Robins, M. J. *J. Org. Chem.* **1996**, *61*, 5178-5179.
9. Berges, D. A.; Hong, L.; Dalley, N. K. *Tetrahedron* **1998**, *54*, 5097-5104.
10. Berges, D. A.; Ridges, M. D.; Dalley, N. K. *J. Org. Chem.* **1998**, *63*, 391-392.
11. Intramolecular hydrogen bonding in 3-hydroxypiperidines has been shown to be prominent even in aqueous solution. Terui, Y.; Tori, K. *J. Chem. Soc., Perkin Trans. 2*, **1975**, 127-133.