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Inhibition of Nonmammalian Glycosidases by Azetidine Iminosugars Derived from Stable 3,5-Di-*O*-triflates of Pentoses

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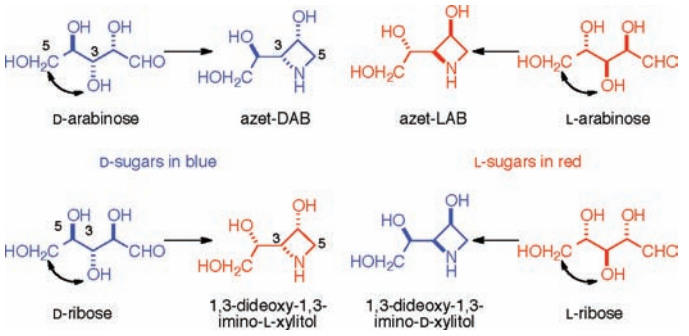
ABSTRACT



Efficient ring closure of stable crystalline 3,5-di-*O*-triflates of pentofuranosides with amines to form azetidines allowed preliminary evaluation of four-ring iminosugars as glycosidase inhibitors; significant and specific inhibition of nonmammalian α-glucosidases is shown by L-*xylo*- and L-*arabino*-iminosugar azetidines.

There are over 200 naturally occurring iminosugars[1] in which the oxygen of the sugar ring is replaced by nitrogen. For example, the pyrrolidine DAB **1D** [Scheme 1] is a 1,4-dideoxy-1,4-imino-pentitol formally derived from a reductive amination from a nitrogen at C4 with the C1 aldehyde of D-arabinose. DAB **1D**, first isolated from *Angylocaly boutiqueanus* and *Arachnoides standishii*,[2] has been found in a wide range of plants and is a potent competitive inhibitor of α-D-glucosidases and of glycogen phosphorylase;[3] its enantiomer LAB **1L** is a more potent and

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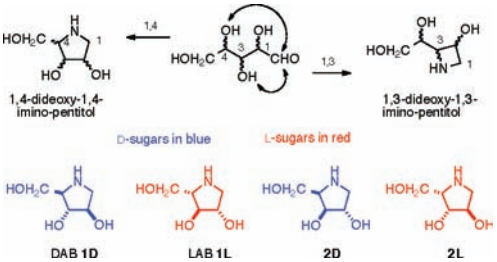
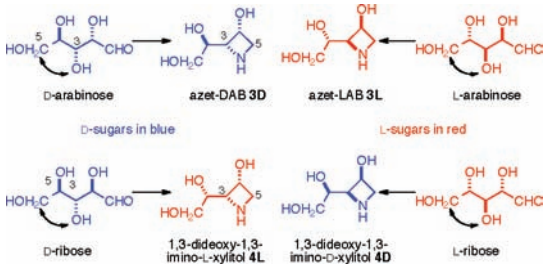
specific noncompetitive inhibitor of α-D-glucosidases[4] and an equally potent competitive inhibitor of an α-L-arabinofuranosidase.[5] The D-iminoxylitol **2D**, isolated from *Angylocalyx pynaertii*, shows no significant glycosidase inhibition;[6] there are many syntheses of both xylitol enantiomers **2D** and **2L**.[7] Because of the biological properties of iminosugars and their promise as chemotherapeutic agents,[8] many pyrrolidine, piperidine, and azepane carbohydrate mimics have been studied. In contrast, there are few examples of carbohydrate azetidines;[9] there is only one report of any glycosidase inhibition studies on azetidines in which 1,3-dideoxy-1,3-imino-L-xylitol **4L** [Scheme 2] was shown to be a specific inhibitor of amyloglucosidases.[10]

Scheme 1. Azetidine and Pyrrolidine Iminosugars



This paper reports the syntheses of both enantiomers of the azetidine analogues **3** and **4** of the arabinose **1** and xylose **2** pyrrolidines. Formation of the azetidine ring by nucleophilic displacement by nitrogen of triflate leaving groups at C5 and C3 (with inversion) of a protected D-arabinose gave azet-DAB **3D**, whereas a corresponding derivative of L-arabinose gave azet-LAB **3L** [Scheme 2]. A similar sequence on protected derivatives of D- and L-ribose gave the L-iminoxylitol azetidine **4L** and its enantiomer **4D**, respectively.

Scheme 2. Strategy for the Formation of Azetidines from Protected Pentoses



For the synthesis of azet-DAB **3D**, D-arabinose was converted to the diol **5D**[11] in three steps in an overall yield of 33% as previously described [Scheme 3].[12] Esterification of **5D** with triflic anhydride in dichloromethane in the presence of pyridine gave the stable crystalline ditriflate **6D** [mp 67−68 °C; $[\alpha]_D^{25}$ +7.2 (*c* 1.1, $CHCl_3$)] in 95% yield. Reaction of **6D** with benzylamine in acetonitrile in the presence of diisopropylethylamine (DIPEA) afforded the azetidine **7Da** [mp 60−63 °C; $[\alpha]_D^{25}$ −74.6 (*c* 1.0, $CHCl_3$)] in 86% yield. On selective triflation at the primary alcohol, an oxetane cannot be formed as it would be *trans*-fused to the THF ring. Successful cyclizations of ditriflates by double displacements by amines have been reported for the formation of azetidine,[13] pyrrolidine,[14] and piperidine[15] rings. Removal of the acetonide protecting group in **7Da** with aqueous trifluoroacetic acid gave the lactol which on reduction by sodium borohydride gave the azetidine triol **8Da** [mp 96−97 °C; $[\alpha]_D^{25}$ −66.2 (*c* 0.39 in H_2O)]. Hydrogenolysis of the benzyl group in **8Da** with 10% Pd/C and ammonium formate in anhydrous methanol[16] gave the parent azet-DAB **3D**[17] [for the HCl salt $[\alpha]_D^{25}$ −32.4 (*c* 0.37 in H_2O)] in 99% yield. A similar sequence of reactions on the enantiomeric diol **5L** derived

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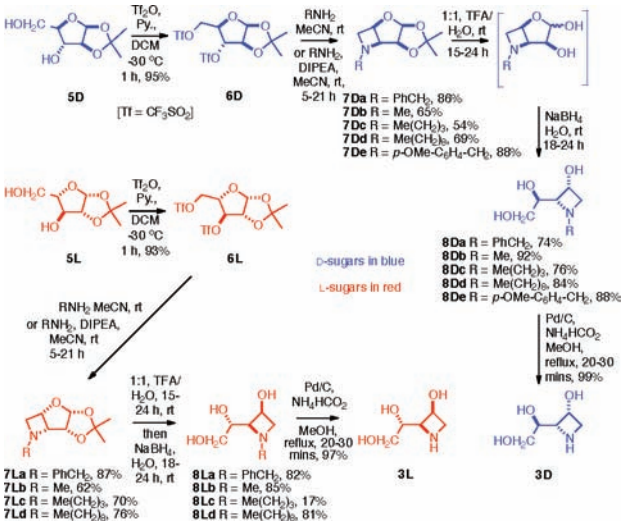
(17) Selected data for azet-DAB **3D** [as the HCl salt]: δ_H (D_2O, 500 MHz): 3.70−3.73 (1H, dd, H5, $J_{5,4}$ 5.0 Hz, J_{gem} 12.0 Hz), 3.73−3.76 (1H, dd, H5′, $J_{5',4}$ 5.4 Hz, J_{gem} 12.0 Hz), 3.87−3.90 (1H, dd, H1, $J_{1,2}$ 4.4 Hz, J_{gem} 11.6 Hz), 4.28−4.31 (1H, a-dt, H4, $J_{4,5}/J_{4,5'}$ 5.2 Hz, $J_{4,3}$ 7.2 Hz), 4.34−4.37 (1H, dd, H1′, $J_{1',2}$ 6.8 Hz, J_{gem} 11.6 Hz), 4.58−4.61 (1H, a-t, $J_{3,4}/J_{3,2}$ 6.9 Hz), 4.81−4.85 (1H, m, H2); δ_C (D_2O, 125 MHz): 53.9 (C1), 62.5 (C5), 65.1 (C2), 65.4 (C3), 68.3 (C4).

from L-arabinose gave azet-LAB **3L** [for the hydrochloride salt $[\alpha]_D^{25}$ +31.7 (*c* 0.31 in H_2O)].

Scheme 3. Synthesis of azet-DAB **3D** and azet-LAB **3L**



N-Alkylation of iminosugars significantly modifies the glycosidase inhibition profile of the parent iminosugar,[18] so a series of *N*-alkyl azetidines was prepared. Reaction of the ditriflate **6D** with methylamine, butylamine, nonylamine, and *p*-methoxybenzylamine gave the corresponding azetidines **7Db** [65%], **7Dc** [54%], **7Dd** [69%], and **7De** [88%] which on subsequent hydrolysis and reduction afforded the *N*-methyl- **8Db** [92%], *N*-butyl- **8Dc** [76%], *N*-nonyl- **8Dd** [84%], and *N*-*p*-methoxybenzyl- **8De** [88%] azetidines, respectively, for biological assays. The corresponding enantiomers were prepared from the L-arabinose ditriflate **6L**.

The protected ribofuranoses **12L** and **12D** were the key intermediates for the respective syntheses of the azetidine xylitols **4D** and **4L** [Scheme 4]. For the synthesis of **4D**, **12L** was prepared from diacetone L-glucose **9L**, readily available from D-glucoheptonolactone.[19] Oxidation of **9L** with Dess-Martin periodinane gave the corresponding ketone which, on reduction with sodium borohydride, formed diacetone L-allose **10L** [91% yield]. Selective hydrolysis of the terminal isopropylidene group with methanol and aqueous sulfuric acid gave the monoacetonide **11L** which was subjected to oxidation by sodium periodate, followed by borohydride reduction, to afford the 1,2-acetonide **12L** [mp 88−89 °C; $[\alpha]_D^{25}$ −60.2 (*c* 0.5, MeOH), 82% over three steps; 75% from **9L**]. The protected enantiomer **12D** was prepared by a similar sequence of reactions from diacetone glucose **9D**.[20] Reaction of benzylamine in the presence of DIPEA with the stable crystalline ditriflate **13L** [mp 41−42 °C; $[\alpha]_D^{25}$ −93.2 (*c* 0.55, $CHCl_3$)], from esterification of the diol **12L** by triflic anhydride in 93% yield, afforded the protected azetidine **14La** [oil, $[\alpha]_D^{25}$ −52.7 (*c* 0.51, $CHCl_3$), 95%]. Hydrolysis of the isopropylidene protecting group with aqueous trifluoroacetic acid, followed by reduction of the resulting lactol with sodium borohydride in water, produced the *N*-benzyl-azetidine **15Da** [mp 182−183 °C; $[\alpha]_D^{25}$ +106.8 (*c* 0.23, MeOH)] in 87% yield. The structure of the enantiomeric L-iminoxylitol **15La** [mp 179−180 °C; $[\alpha]_D^{25}$ −103.0 (*c* 0.23, MeOH)] was firmly established by X-ray crystallographic analysis.[21] Removal of the benzyl group in **15Da** by transfer hydrogenation with ammonium formate and 10% Pd/C in methanol gave the D-iminolyxitol **4D**[22] [for the hydrochloride salt $[\alpha]_D^{25}$ −6.9 (*c* 0.29, H_2O)] in 82% yield; the overall yield of **4D** from the L-ribose diol **12L** was 63%. The enantiomeric D-iminolyxitol **4D** [for the hydrochloride salt $[\alpha]_D^{25}$ +3.2 (*c* 0.50, H_2O)] was similarly prepared from **12D**.

Both enantiomers of the *N*-methyl- **14b**, *N*-butyl- **14c**, and *N*-*p*-methoxybenzyl- **14d** azetidines were prepared by efficient cyclizations of the ditriflates **13** with methylamine, butylamine, and *p*-methoxybenzylamine (**14Lb** 78%, **14Db** 67%, **14Lc** 91%, **14Dc** 82%, **14Ld** 86%, **14Dd** 96%). Acid hydrolysis and subsequent borohydride reduction gave the corresponding unprotected iminopentitols **15b**, **15c**, and **15d** (**15Db** 79%, **15Lb** 85%, **15Dc** 65%, **15Lc** 98%, **15Dd** 80%, **15Ld** 89%) allowing preliminary biological evaluation.

The inhibition profiles of the parent iminopentitols **3** and **4** against a range of glycosidases were investigated [Table 1]; the effect of *N*-alkylation is shown in the tables in the Supporting Information. The specific inhibition reported by Jager[10] by L-iminoxylitol azetidine **4L** was confirmed, showing good inhibition against *Rhizopus sp.* and *A. niger* amyloglucosidase [IC_{50} 25 and 414 μM, respectively]; **4L**, which also inhibited bacterial (*A. niger*) α-glucosidase, did not inhibit mammalian or plant glycosidases and thus was highly specific for bacterial enzymes. The D-*xylo*-azetidine enantiomer **4D** did not inhibit any glycosidases. azet-LAB **3L** was a good inhibitor of *A. niger* α-glucosidase, rat intestinal lactase, and *Rhizopus sp.*

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(22) Selected data for iminolyxitol **4D** [as the HCl salt]: δ_H (D_2O, 500 MHz): 3.59−3.62 (1H, dd, H5, $J_{5,4}$ 5.2 Hz, J_{gem} 12.1 Hz), 3.40−3.74 (1H, m, H5′), 3.92−3.95 (1H, dd, H1, $J_{1,2}$ 4.5 Hz, J_{gem} 11.6 Hz), 4.30−4.31 (1H, m, H4), 4.34−4.38 (1H, dd, H1′, $J_{1',2}$ 7.3 Hz, J_{gem} 11.3 Hz), 4.58−4.61 (1H, a-t, H3, $J_{3,2}/J_{3,4}$ 6.7 Hz), 4.75 (H2, under HDO peak); δ_C (D_2O, 125 MHz): 54.1 (C1), 63.2 (C5), 64.0 (C2), 67.0 (C3), 67.2 (C4).

Scheme 4. Synthesis of Azetidine-xylitols **4D** and **4L**

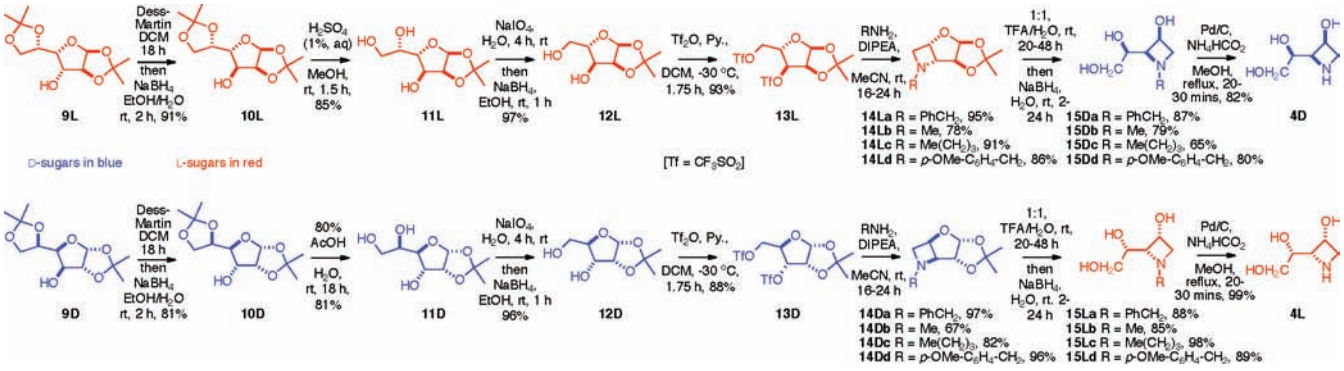

Table 1. Concentration of Iminosugars Giving 50% Inhibition of Various Glycosidases

	IC_{50} (μM)			
enzyme	4L	4D	3L	3D
α-Glucosidase				
Rice	NI[a] (0%)[b]	NI (4.8%)	NI (12.1%)	NI (11.9%)
Yeast	NI (6.7%)	NI (6.0%)	NI (16.0%)	NI (0%)
Rat intestinal maltase	NI (21.7%)	NI (17.8%)	607	NI (20.9%)
A. niger	175	NI (6.3%)	39	NI (6.4%)
β-Glucosidase				
Almond	NI (9.3%)	NI (9.6%)	347	755
Bovine liver	NI (20.5%)	NI (4.7%)	997	NI (40.7%)
α-Galactosidase				
Coffee beans	NI (14.1%)	NI (0.2%)	NI (7.6%)	NI (37.0%)
Human lysosome	NI (0%)	NI (0%)	NI (2.5%)	NI (0.6%)
β-Galactosidase				
Bovine liver	NI (0%)	NI (2.1%)	NI (25.2%)	NI (27.5%)
Rat intestinal lactase	NI (0%)	NI (0%)	70	241
α-Mannosidase				
Jack beans	NI (1.7%)	NI (0.6%)	NI (2.4%)	713
β-Mannosidase				
Snail	NI (4.9%)	NI (0%)	NI (0%)	NI (0%)
α-L-Rhamnosidase				
P. decumbens	NI (2.3%)	NI (5.7%)	634	NI (3.8%)
α-L-Fucosidase				
Bovine epididymis	NI (4.6%)	NI (0%)	NI (4.6%)	NI (8.5%)
Trehalase				
Rat intestinal trehalase	NI (0%)	NI (6.4%)	NI (11.7%)	NI (17.3%)
Amyloglucosidase				
A. niger	414	NI (5.7%)	105	NI (8.4%)
Rhizopus sp	25	NI (1.2%)	19	NI (0%)

[a] NI : No inhibition (less than 50% inhibition at 1000 μM); [b]( ) : Inhibition % at 1000 mM.

amyloglucosidase, with IC_{50} values of 39, 70, and 19 μM, respectively. The inhibition profile of **3L** was not as specific as that of **4L**. azet-DAB **3D** also showed broad, but weaker, inhibition of a number of enzymes. In particular, **3D** was a weak inhibitor of α-D-mannosidase in contrast to the weak inhibition of α-L-rhamnosidase by the enantiomer **3L**; enantiomers of inhibitors of α-D-mannosidase are usually equally potent inhibitors of α-L-rhamnosidase.[23] *N*-Alkylation of **3D** preserved the inhibition of α-D-mannosidase but significantly increased the specificity.

In summary, the reaction of amines with stable ditriflates allowed the efficient formation of 1,3-iminopentitols; the scope and limitation of the formation of iminosugar azetidines by this method has yet to be determined. While other biological properties are under investigation, it is clear that azetidine iminosugars may be easily accessible and are worthy of further investigation.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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