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Efficient synthesis from D-lyxonolactone of 2-acetamido-1,4-imino-1,2,4-trideoxy-L-arabinitol LABNAc, a potent pyrrolidine inhibitor of hexosaminidases

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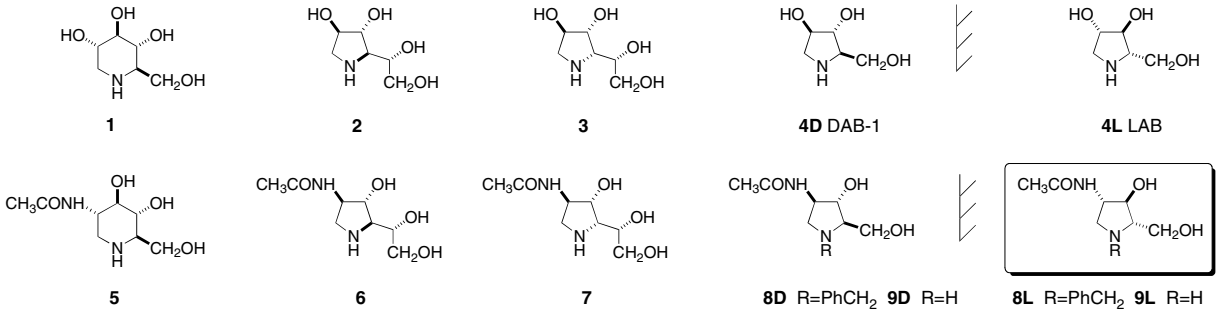
Abstract—The synthesis from D-lyxonolactone of 2-acetamido-1,4-imino-1,2,4-trideoxy-L-arabinitol LABNAc proceeded in an overall yield of 25%; the enantiomer, 2-acetamido-1,4-imino-1,2,4-trideoxy-D-arabinitol DABNAc, was prepared from L-lyxonolactone. LABNAc and *N*-benzyl LABNAc are potent non-competitive inhibitors of D-hexosaminidase, whereas *N*-benzyl DABNAc exhibits weak competitive inhibition of the enzyme; this provides further evidence in support of Asano's hypothesis that while D-imino sugar mimics inhibit D-glycohydrolases competitively, their L-enantiomers show non-competitive inhibition and in the case of iminofuranoses L-enantiomers are usually more potent inhibitors.

Specific inhibition of individual D-hexosaminidases may lead to new strategies for the treatment of many diseases, including cancer,[1] arteriosclerosis[2] and some lysosomal storage diseases;[3] such compounds also have potential as antifungal agents[4] and catalysts for biomass degradation.[5] Replacement of the oxygen by nitrogen in a sugar gives a broadly based class of both synthetic and naturally occurring glycosidase inhibitors.[6] Thus, replacement of the ring oxygen in glucose gives the natural product deoxynojirimycin **1**, which is a powerful glucosidase inhibitor;[7] derivatives of **1** have been used in the treatment of diabetes[8] and Gaucher's disease,[9] and are antiviral compounds.[10] Pyrrolidine imino sugar **2**, which is the furanose analogue of glucose,[11] is a much weaker inhibitor of glucosidases than **1**; similarly, galactofuranose analogue **3** is a much weaker galactosidase



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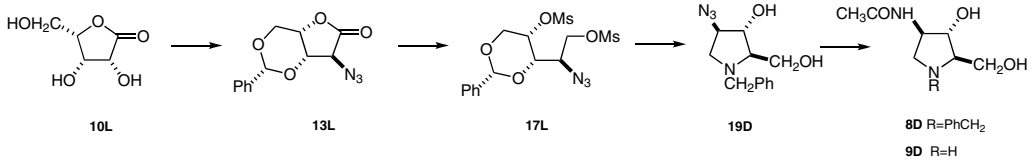
inhibitor than the pyranose analogue deoxygalactonojirimycin.[12] In contrast, the naturally occurring[13] pyrrolidine DAB-1 **4D** with the shorter side chain is a powerful competitive inhibitor of D-glucosidases, and also has potential for the treatment of late onset diabetes since it also inhibits glycogen phosphorylase.[14] The synthetic enantiomer LAB **4L** is a potent and highly specific non-competitive inhibitor of glucosidases.[15]

Piperidine analogue **5** of *N*-acetylglucosamine (NAG) is a good inhibitor of many hexosaminidases.[16] There are several good D-hexosaminidase inhibitors which are pyranose analogues of NAG containing a piperidine ring.[17] Both the iminofuranose analogue of glucose **6**[18] and of galactose **7**[19] are, however, relatively weak inhibitors of hexosaminidases. This Letter, reports the synthesis and D-hexosaminidase inhibition of both the enantiomers of 2-acetamido-1,4-imino-1,2,4-trideoxy-L-arabinitol, DABNAc **9D** and LABNAc **9L**, and their respective *N*-benzyl derivatives **8D** and **8L**.

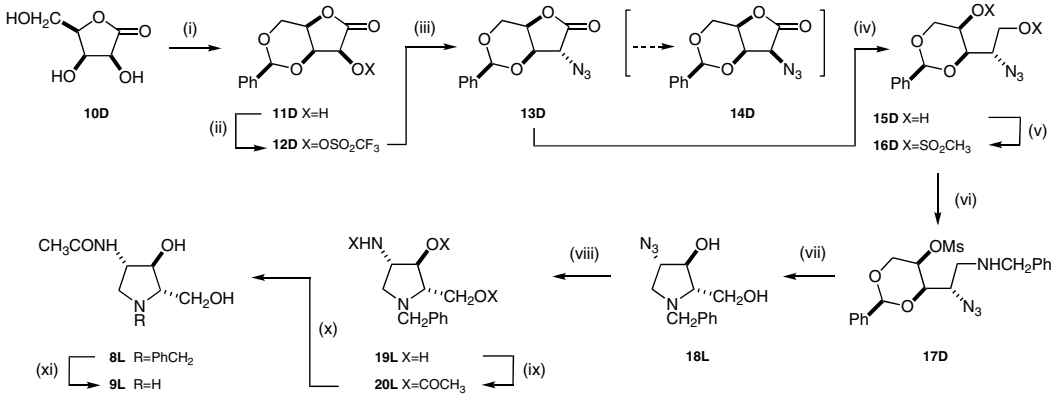
The synthesis of DABNAc **9D** from L-lyxonolactone **10L**, readily available from D-ribose,[20] is outlined in Scheme 1. Protection of the 3- and 5-hydroxyls in **10L** by formation of a benzylidene acetal allowed the introduction of an azide function with inversion of configuration at C-2 to give **13L**. Reduction of lactone **13L** to the corresponding diol and activation of the 1- and 4-hydroxyl groups gave L-*lyxono*-dimesylate **17L** from which the pyrrolidine ring could be formed by a double nucleophilic displacement using benzylamine with inversion at C-4 to afford the D-*arabino*-pyrrolidine **19D**. The presence of azide in **19D** as the precursor to the acetamido group in the target compound **9D** made the compound non-polar and easy to purify and manipulate. Hydrogenation and acetylation of **19D** afforded the required *N*-benzyl-**8D** and DABNAc **9D**.

The preparation of LABNAc **9L** from D-lyxonolactone **10D**, obtained by oxygenation of an alkaline solution of D-galactose,[21] is detailed in Scheme 2. Treatment of lactone **10D** with benzaldehyde and aqueous hydrochloric acid gave the highly crystalline benzylidene acetal **11D**[22] in 90% yield. Esterification of the free hydroxyl group in **11D** with trifluoromethanesulfonic (triflic) anhydride afforded *lyxono*-triflate **12D** (89% yield)[23] which on reaction with sodium azide in DMF for 1 h gave inverted *xylono*-azide **13D**[24] in 92% yield. If the reaction mixture was left longer, *xylono*-azide **13D** equilibrated to the more stable *lyxono*-azide **14D**.[25] Epimeric azides **13D** and **14D** were easily distinguished by their ^{13}C and ^{1}H NMR spectra; it was necessary to monitor the reaction carefully since the epimerisation of 2-azidolactones to the more stable azide is a well established phenomenon.[26]

Reduction of azidolactone **13D** with lithium borohydride in THF afforded diol **15D** (98% yield) which was converted into dimesylate **16D** by treatment with excess methanesulfonyl chloride in dichloromethane in the presence of triethylamine (81% yield). Reaction of dimesylate **16D** with benzylamine in 1,4-dioxane at 95 °C gave only displacement of the primary mesylate to give D-*xylono*-amino mesylate **17D** in 75% yield. There was no detectable amount of a product arising either from further attack by benzylamine on the secondary mesylate or by intramolecular nucleophilic ring closure to a pyrrolidine. Although aminomesylates rapidly close to pyrrolidines in general, in this case the cyclisation would lead to a *trans*-benzylidene acetal fused to the new pyr-

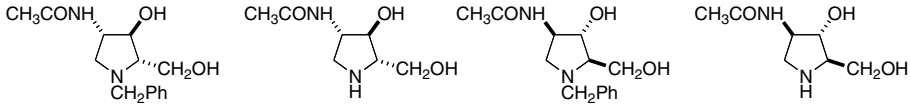


Scheme 1.



Scheme 2. Reagents and conditions: (i) PhCHO, HCl, 90%; (ii) $(CF_3SO_2)_2O$, pyridine, 89%; (iii) NaN_3, DMF, 1 h, rt, 92%; (iv) $LiBH_4$, THF, 98%; (v) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 81%; (vi) $PhCH_2NH_2$, 1,4-dioxane, 75%; (vii) Amberlyst (H^+), 1,4-dioxane, H_2O, 89%; (viii) H_2, Pd, C, THF, 99%; (ix) Ac_2O, pyridine, 75%; (x) MeONa, MeOH, 96%; (xi) H_2, Pd black, 1,4-dioxane, H_2O, 99%.

Table 1. Inhibition constant (K_i) and concentration necessary to inhibit 50% of β-*N*-acetyl-D-hexosaminidase activity (IC_{50}) for pyrrolidine inhibitors



8L *N*-benzyl LABNAc **9L** LABNAc **8D** *N*-benzyl DABNAc **9D** DABNAc

β-*N*-acetyl-D-hexosaminidase ← *potent non-competitive inhibition* → ← *weaker competitive inhibition* →

Bovine kidney				
IC_{50} (μM)	0.36	0.64	41.2	326
K_i (μM)	0.28	0.095	16.9	104
Jack bean				
IC_{50} (μM)	5.2	3.4	446	Weak
K_i (μM)	3.4	1.9	ND	ND
Human placenta				
IC_{50} (μM)	2.8	13	320	Weak
K_i (μM)	3.7	15	180	ND

rolidine five-membered ring. There are other examples of the failure to close to such a strained bicyclic system.[27]

Deprotection of benzylidene acetal **17D** using an acid ion exchange resin in aqueous dioxane gave an open chain aminomesylate which spontaneously cyclised in 89% yield to L-*arabino*-azide **18L**[28] resulting from inversion at C-4 in the intramolecular nucleophilic displacement; **18L** is a relatively apolar compound and easy to purify. Hydrogenation of azide **18L** in THF in the presence of a palladium on carbon catalyst gave the corresponding amine **19L** (99% yield), which was peracylated using acetic anhydride in pyridine to afford triacetate **20L** (75% yield). De-O-acylation of **20L,** by treatment with sodium methoxide in methanol, resulted in ester exchange to give *N*-benzyl pyrrolidine **8L**[29] (96% yield), which, on hydrogenation in aqueous dioxane in the presence of palladium black, afforded LABNAc **9L**[30] in 99% yield. The structure of *N*-benzyl LABNAc **8L** was firmly established by X-ray crystallographic analysis.[31] The overall yield of LABNAc **9L** from D-lyxonolactone **10D** was 25% in 11 steps.

The inhibition of glycosidases by LABNAc **9L** and DABNAc **9D** and their *N*-benzyl analogues **8L** and **8D** was studied. No significant inhibition of any of the following glycosidases was found: α-D-glucosidase (from yeast, rice, *Bacillus stearothermophilus*, rat intestinal maltase or isomaltase), β-D-glucosidase (from almond or human placenta), α-D-galactosidase (from green coffee beans), β-D-galactosidase (from Jack bean or bovine liver), α-L-fucosidase (bovine), β-D-xylosidase (*Aspergillus niger*), naringinase (*Penicillum decumbens*) or amyloglucosidase (*A. niger*). None of the compounds had any inhibitory effect on glycogen phosphorylase b (rabbit muscle) or on α-*N*-acetyl-D-galactosaminidase (*Charonia lampas*).

However, both *N*-benzyl LABNAc **8L** and LABNAc **9L** were potent inhibitors of bovine kidney β-*N*-acetyl-D-hexosaminidase with sub-micromolar K_i (Table 1). Interestingly, *N*-benzyl DABNAc **8D** weakly inhibited human β-*N*-acetyl-D-hexosaminidase in a competitive manner, with a K_i value of 180 μM, whereas LABNAc and *N*-benzyl LABNAc were potent non-competitive inhibitors of the enzyme, with K_i values of 15 and 3.7 μM, respectively. LABNAc **9L** and *N*-benzyl LABNAc **8L** were non-competitive inhibitors for the Jack bean enzyme, although in this case *N*-benzyl LABNAc **8L** was not a stronger inhibitor of the enzyme; otherwise, introduction of the benzyl group into the imino group in LABNAc and DABNAc tended to increase their inhibitory potential.

It has been recognised that D-imino sugar mimics inhibit D-glycosidases competitively, their L-enantiomers show non-competitive inhibition and in the case of iminofuranoses L-enantiomers are usually more potent inhibitors than D-enantiomers.[32] The present Letter suggests that this may be a more broadly based phenomenon.

In summary, efficient and convenient syntheses of the enantiomeric pyrrolidine analogues of NAG **9L** and **9D** are described. Both *N*-benzyl LABNAc **8L** and LABNAc **9L** are potent and highly specific inhibitors of β-*N*-acetyl-D-hexosaminidases. Their modes of inhibition are non-competitive, whereas *N*-benzyl DABNAc **8D** is a weak competitive inhibitor. Introduction of the benzyl group into the imino group in LABNAc and DABNAc tends to increase their inhibitory potential. This work shows that pyrrolidine analogues of NAG may be useful inhibitors of β-*N*-acetyl-D-hexosaminidases; further studies on whole cell systems and on other diastereomers of **9** will be reported in due course.

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23. Extra care must be taken in the handling of triflate **12D** since a co-worker has experienced a strong allergic response to this compound or its decomposition products.
24. Selected data for *xylono*-azide **13D**: mp 119–121 °C, $[\alpha]_D^{24}$ +143.4 (*c* 0.99, $CHCl_3$); ν_{max} (NaCl) 2117 (N_3), 1776 (C=O) cm^{-1}; δ_H (400.2 MHz, $CDCl_3$): 4.20 (1H, a-dt, $J_{5,5'}$ 13.9 Hz, *J* 1.9 Hz, H-5), 4.23 (1H, s, H-2), 4.46–4.51 (2H, m, H-3, H-4), 4.62 (1H, a-d, $J_{5',5}$ 13.9 Hz, H-5′), 5.54 (1H, d, *J* 1.1 Hz, C*H*Ph), 7.37–7.47 (5H, m, C*H*(Ar)); δ_C (100.6 MHz, $CDCl_3$): 63.2 (C-2), 66.0 (C-5), 73.1 (C-3), 75.6 (C-4), 99.5 (*C*HPh), 126.1, 128.4, 129.6 (*C*H(Ar)), 136.4 (*C*(Ar)), 171.1 (C-1).
25. Selected data for *lyxono*-azide **14D**: mp 121–122 °C (acetone); $[\alpha]_D^{24}$ +37.1 (*c* 1.0, acetone); ν_{max} (KBr): 2120 (N_3), 1795 (C=O, lactone) cm^1; δ_H (500 MHz, $(CD_3)_2CO$): 4.39 (1H, dd, H-5′, $J_{5',5}$ 13.9 Hz, $J_{5',4}$ 2.0 Hz), 4.48 (1H, d, H-5, $J_{5,5'}$13.9 Hz), 4.58 (1H, d, H-2, $J_{2,3}$ 4.1 Hz), 4.64 (1H, dd, H-4, $J_{4,3}$ 3.4 Hz, $J_{4,5'}$ 2.0 Hz), 5.12 (1H, dd, H-3, $J_{3,2}$ 4.1 Hz, $J_{3,4}$ 3.1 Hz), 5.79 (1H, s, *H*CPh), 7.37–7.50 (5H, m, C*H*(Ar)); δ_C ($(CD_3)_2CO$, 50.3 MHz): 66.8 (t, C-5), 62.8, 72.3, 75.7 (3 × d, C-2, C-3, C-4), 99.5 (*C*HPh), 126.9, 128.9, 129.8 (3 × d, *C*H(Ar)), 138.5 (s, *C*(Ar)), 172.8 (C=O).
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28. Selected data for *arabino*-azide **18L**: oil; $[\alpha]_D^{25}$ +97.3 (*c* 0.99, $CHCl_3$); ν_{max} (NaCl) 3370 (OH), 2100 (N_3) cm^{-1}; δ_H (400.2 MHz, $CDCl_3$): 2.46 (2H, s, 3-O*H*, 5-O*H*), 2.63 (1H, ddd, $J_{4,5'}$ 3.8 Hz, $J_{4,3}$ 5.7 Hz, $J_{4,5}$ 2.4 Hz, H-4), 2.82 (1H, dd, $J_{1,1'}$ 10.9 Hz, $J_{1,2}$ 6.6 Hz, H-1), 3.00 (1H, dd, $J_{1',1}$ 10.9 Hz, $J_{1',2}$ 2.5 Hz, H-1′), 3.42 (1H, d, *J* 13.2 Hz, NCH_2Ph), 3.71–3.76 (2H, m, H-5, H-2), 3.78 (1H, dd, $J_{5',5}$ 11.4 Hz, $J_{5',4}$ 3.8 Hz, H-5′), 3.99 (1H, d, *J* 13.2 Hz, NCH_2Ph), 4.28 (1H, dd, $J_{3,4}$ 5.7 Hz, $J_{3,2}$ 3.4 Hz, H-3), 7.25–7.39 (5H, m, C*H*(Ar)); δ_C (100.6 MHz, $CDCl_3$): 56.1 (C-1), 57.7 (N*C*H_2Ph), 59.4 (C-5), 65.4 (C-2), 71.6 (C-4), 78.4 (C-3), 127.5, 128.5, 128.6 (*C*H(Ar)), 137.7 (*C*(Ar)).
29. Selected data for *N*-benzyl LABNAc **8L**: mp 126–128 °C; $[\alpha]_D^{22}$ +82.1 (*c* 0.96, MeOH); ν_{max} (Ge) 3312 (OH), 1651 (C=O amide band I), 1551 (N–H amide band II) cm^{-1}; δ_H (400.2 MHz, D_2O): 1.82 (3H, s, COCH_3), 2.49 (1H, a-dt, $J_{4,3}$ 5.7 Hz, *J* 4.3 Hz, H-4), 2.55 (1H, dd, $J_{1,1'}$ 11.0 Hz, $J_{1,2}$ 2.9 Hz, H-1), 2.76 (1H, dd, $J_{1',1}$ 11.0 Hz, $J_{1',2}$ 7.2 Hz, H-1′), 3.36 (1H, d, *J* 12.7 Hz, NCH_2Ph), 3.59 (1H, dd, $J_{5,5'}$ 12.0 Hz, $J_{5,4}$ 4.0 Hz, H-5), 3.64 (1H, dd, $J_{5',5}$ 12.0 Hz, $J_{5',4}$

4.6 Hz, H-5′), 3.82–3.94 (3H, m, H-3, H-2, NCH_2Ph), 7.21–7.32 (5H, m, CH(Ar)); δ_C (100.6 MHz, D_2O): 22.1 (NHCOCH$_3$), 55.5 (C-2), 56.3 (C-1), 58.5 (NCH$_2$Ph), 60.3 (C-5), 71.1 (C-4), 77.9 (C-3), 128.1, 128.9, 130.2 (CH(Ar)), 137.3 (C(Ar)), 174.2 (C=O).

30. Selected data for LABNAc **9L**: colourless oil; $[\alpha]_D^{22}$ +3.9 (c 0.765, H_2O); ν_{max} (Ge) 3284 (OH), 1652 (C=O amide band I), 1558 (N–H amide band II) cm^{-1}; δ_H (400.2 MHz, D_2O): 1.87 (3H, s, COCH_3), 2.62 (1H, dd, $J_{1,1'}$ 12.0 Hz, $J_{1,2}$ 6.3 Hz, H-1), 2.89 (1H, a-dt, $J_{4,5'}$ 4.5 Hz, J 6.3 Hz, H-4), 3.10 (1H, dd, $J_{1',1}$ 12.0 Hz, $J_{1',2}$ 7.5 Hz, H-1′), 3.51 (1H, dd, $J_{5,5'}$ 11.7 Hz, $J_{5,4}$ 6.1 Hz, H-5), 3.60 (1H, dd, $J_{5',5}$ 11.7 Hz, $J_{5',4}$ 4.5 Hz, H-5′), 3.75 (1H, a-t, $J_{3,2}$ 6.3 Hz, $J_{3,4}$ 6.3 Hz, H-3), 3.97 (1H, a-dt, $J_{2,1'}$ 7.5 Hz, J 6.3 Hz, H-2); δ_C (100.6 MHz, D_2O): 22.2 (NHCOCH$_3$), 48.3 (C-1), 57.5 (C-2), 61.4 (C-5), 64.7 (C-4), 77.1 (C-3), 174.7 (C=O).

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