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Synthesis of 2-Acetamido-1,2,4-Trideoxy-1,4-Imino-D-Galactitol, A New Hexosaminidase Inhibitor

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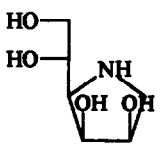
Abstract: 2-Acetamido-1,2,4-trideoxy-1,4-imino-D-galactitol was synthesised from 2-acetamido-2-deoxy-D-glucose in 12 steps and was shown to be a modest hexosaminidase inhibitor.

Much effort in recent years has been directed towards the synthesis of imino-alditols in the continued search for glycosidase inhibitors with optimum activity and greater selectivity. Polyhydroxylated piperidines and pyrrolidines, resembling sugars in the pyranose and furanose configurations, are often inhibitors of the corresponding glycosidase (for example: 1,4-dideoxy-1,4-imino-D-mannitol **1** is a potent inhibitor of several mannosidases[1]). 1,5-Imino-hexitols with a 2-acetamido group (**2-6**), and also the 2-acetamido-2-deoxy analogue **7**[2] of nojirimicin **8**, have been prepared[2-8] as inhibitors of hexosaminidases. Several β-*N*-acetylglucosaminidases were inhibited by **2** and **7**, however **3** has shown no hexosaminidase inhibitory activity. Thus far no 2-acetamido-1,4-imino-hexitols have been investigated. This report outlines the first synthesis of 2-acetamido-1,2,4-trideoxy-1,4-imino-D-galactitol **9** and the results of preliminary enzyme inhibition studies.



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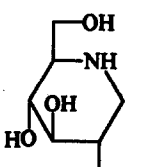

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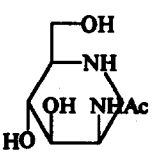

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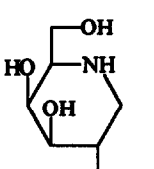

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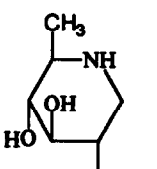

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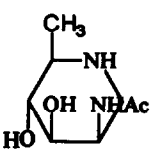

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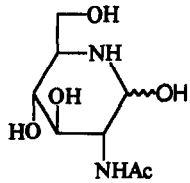

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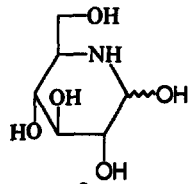

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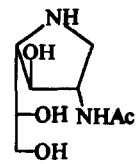
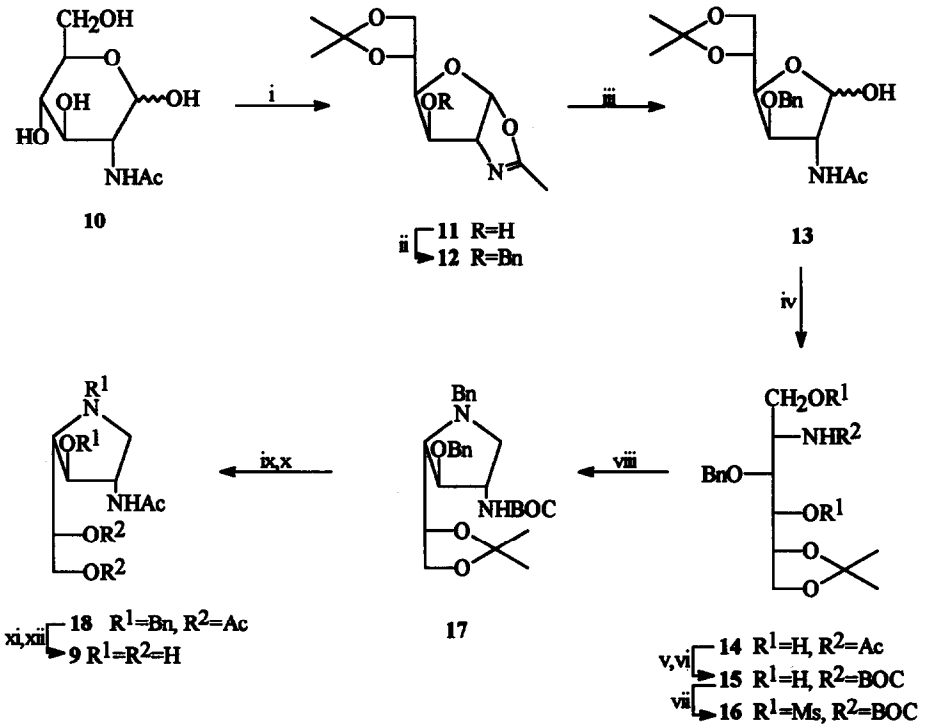


9

The readily available 2-acetamido-2-deoxy-D-glucose **10** was converted to the glucofurano[2,1-*d*]oxazoline **11** in 71% yield by the method of Brossmer.[9] Protection of the C-3 hydroxy group gave the benzyl ether derivative **12** and aqueous acetic acid hydrolysis of the oxazoline ring afforded the free sugar **13**, 53% yield from **11**, as a 4:1 anomeric mixture. Subsequent sodium borohydride reduction of the mixture provided the diol **14** (91%). By analogy to Fleet's method for the formation of 1,4-imino-alditols,[10] the corresponding dimesylate of diol **14** was required for subsequent cyclisation upon treatment with benzylamine. However, attempts to produce a dimesylate from **14** failed due to intramolecular participation of the acetamido function and reformation of an oxazoline ring. The amide was therefore transformed to a carbamate having a less nucleophilic carbonyl group. Base catalysed hydrolysis of the acetamide and treatment of the free amine with di-*t*-butyl dicarbonate gave the *N*-*t*-butyloxycarbonyl derivative **15** (82%). Mesylation now proceeded without difficulty to give **16** (89%) which was then heated with benzylamine at 70° overnight to yield the fully protected 1,4-imino-D-galactitol derivative **17**[11] (66%). Regeneration of the 2-acetamido moiety was accomplished quantitatively by acid catalysed hydrolysis followed by peracetylation. De-*O*-acetylation of **18** followed by hydrogenolytic cleavage of the benzyl groups over 10% palladium on charcoal in acetic acid/ethanol gave the desired 2-acetamido-1,2,4-trideoxy-1,4-imino-D-galactitol **9**[12,13] (53%) isolated as its crystalline hydrochloride salt after treatment with dilute hydrochloric acid.

Preliminary screens for inhibition of human liver glycosidases showed that only *N*-acetyl-β-D-glucosaminidase (82%) and *N*-acetyl-β-D-galactosaminidase (59%) activities were inhibited by **9** at a concentration of 1 mM. The assay procedure using a final substrate concentration of 0.5 mM was as described by Cenci di Bello et al.[14]

The pyrrolidine **9** was found to be a reversible competitive inhibitor of hexosaminidase activity towards the 4-methylumbelliferyl-*N*-acetylglucosaminide and -*N*-acetylgalactosaminide substrates with values of I_{50}, using 0.5 mM substrate, of 2.5 and 6.0 x 10^{-4} M respectively and values of K_i of 1 and 2 x 10^{-4} M respectively at pH 4.0.



Reagents: (i) $FeCl_3$, Me_2CO; (ii) NaH, BnBr, DMF; (iii) aq. HOAc, MeOH; (iv) $NaBH_4$, MeOH; (v) 1M NaOH; (vi) $(BOC)_2O$, $KHCO_3$, dioxane, H_2O; (vii) MsCl, DMAP, py; (viii) $BnNH_2$; (ix) 1M HCl; (x) Ac_2O, py; (xi) NaOMe, MeOH; (xii) H_2, 10% Pd-C.

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11. **17**: mp 99-101°. $[\alpha]_D$ -36.7° (c1.0, $CHCl_3$). δ_H ($CDCl_3$, 300MHz) 1.34, 1.39 (2 x 3H, s, Me), 1.46 (9H, s, Bu^t), 2.61-2.72 (3H, m, H-1, 4), 3.35 (1H, d, J 13.2 Hz, NBn), 3.45 (1H, br s, H-3), 3.63 (1H, t, J 8.0 Hz, H-6), 3.95 (1H, q, J 3.7 Hz, H-2), 4.13 (1H, q, J 7.1 Hz, H-5), 4.36 (1H, d, J 13.2 Hz, NBn), 4.55, 4.75 (2H, AB, J 11.8 Hz OBn), 5.03 (1H, d, J 7.8 Hz, NH), 7.21-7.38 (10H, m, Ar). δ_C ($CDCl_3$, 75MHz) 25.8 q, 26.7 q, 28.5 q, 53.7 d, 57.5 t, 59.5 t, 66.7 t, 71.3 t, 72.0 d, 79.0 d, 79.6 s, 86.6 d, 109.5 s, 127.1 d, 127.9 d, 128.4 d, 128.7 d, 129.0 d, 137.8 s, 139.1 s, 155.2 s. *m/z* calcd. for $C_{28}H_{39}N_2O_5$ 483.2859, obsd. 483.2856.
12. **9** hydrochloride salt: mp 168° (Found: C, 39.83; H, 6.85; N, 11.43. $C_8H_{17}N_2O_4Cl$ requires C, 39.92; H, 7.12; N, 11.64%). $[\alpha]_D$ -6.4° (c1.2, H_2O). δ_H (D_2O, 500MHz) 3.23 (1H, dd, J 12.2, 7.5 Hz, H-1), 3.58 (1H, dd, J 7.8, 4.4 Hz, H-4), 3.68 (1H, dd, J 12.0, 4.9 Hz, H-6), 3.74 (1H, dd, J 12.5, 7.8 Hz, H-1), 3.77 (1H, dd, J 12.0, 3.8 Hz, H-6), 4.05 (1H, q, J 4.4 Hz, H-5), 4.26-4.32 (2H, m, H-2,3). δ_C (D_2O, 75 MHz) 24.8 q, 49.1 t, 57.1 d, 66.1 t, 67.0 d, 70.4 d, 76.8 d, 177.7 s. *m/z* calcd. for $C_8H_{17}N_2O_4$ 205.1188, obsd. 205.1186.
13. The synthesis of the C-4 epimer of **9** (2-acetamido-1,2,4-trideoxy-1,4-imino-D-glucitol) is currently in progress in our laboratories.
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