JOURNAL OF THE CHEMICAL SOCIETY

Chemical Communications

Number 13
1985

Synthesis from D-Glucose of 1,5-Dideoxy-1,5-imino-L-fucitol, a Potent α-L-Fucosidase Inhibitor

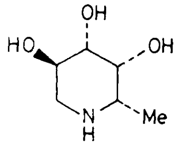
George W. J. Fleet,[a]* Antony N. Shaw,[a] Stephen V. Evans,[b] and Linda E. Fellows[b]*

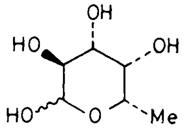
[a] *Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, U.K.*
[b] *Jodrell Laboratory, Royal Botanic Gardens, Kew, Richmond, Surrey TW9 3DS, U.K.*

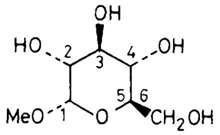
1,5-Dideoxy-1,5-imino-L-fucitol (**1**), synthesised from methyl α-D-glucopyranoside, is a potent competitive inhibitor of the hydrolysis of *p*-nitrophenyl α-L-fucopyranoside catalysed by α-L-fucosidase (*ex.* bovine epididymis) causing 50% inhibition of enzymic activity at 2.5×10^{-8} M.

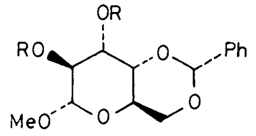
Several polyhydroxylated piperidines and pyrrolidines have been shown to be competitive inhibitors of glycosidases from many sources and are proving useful biochemical tools; several derivatives of 5-amino-5-deoxyglucose (nojirimycin) and of 5-amino-5-deoxymannose have been used as glucosidase and mannosidase inhibitors.[1,2] To date, no compound of this class having fucosidase inhibitory activity has been described; yet glycans containing both D-fucose and L-fucose (**2**) are widespread in nature. In particular, α-L-fucose is the immunodominant sugar of many complex carbohydrate antigens, and the L-fucose content of some animal glycans is known to change under certain pathological conditions, such as transformation to tumorogenesis.[3] Specific inhibitors of α-L-fucosidase are likely to find wide application, not only in the investigation of the structure/function relationships of fucose containing glycans, but also in understanding the pathology of inherited disorders characterised by a deficiency of α-L-fucosidase.[4] This paper reports the synthesis of 1,5-dideoxy-1,5-imino-L-fucitol (**1**) from methyl α-D-glucopyranoside (**3**); (**1**) is shown to be a very potent competitive inhibitor of bovine epididymis α-L-fucosidase, but to have no inhibitory action on a range of other glycosidases.

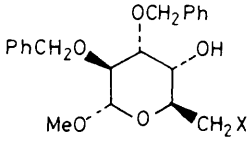
The synthesis of (**1**) from (**3**) requires inversion of configuration at C-2 and C-3, deoxygenation of C-6, and the formation of the piperidine ring between C-1 and C-5 with inversion of configuration at C-5. The protected altrose (**4**), prepared from (**3**) by standard procedures,[5] was benzylated [(benzyl bromide, sodium hydride, tetrabutylammonium iodide in tetrahydrofuran (THF)] to give (**5**), m.p. 91—92 °C (lit.[6] 90—91 °C), in 84% yield. Hydrolysis of the benzylidene acetal by acetic acid:water (4:1) gave diol (**6**) which underwent selective esterification of the primary hydroxy group with toluene-*p*-sulphonyl chloride in pyridine at −20 °C to form (**7**),† $[\alpha]_D^{20}$ +52° (*c* 0.70, $CHCl_3$), in 75% yield.

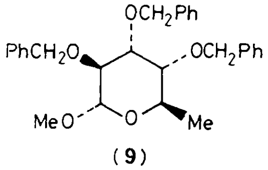

(**1**)

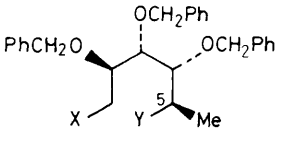

(**2**)

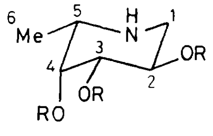

(**3**)


(**4**) R = H
(**5**) R = CH_2Ph


(**6**) X = OH
(**7**) X = $OSO_2C_6H_4Me$
(**8**) X = H


(**9**)


(**10**) X = Y = OH
(**11**) X = Y = OSO_2Me
(**12**) X = N_3, Y = OSO_2Me


(**13**) R = CH_2Ph
(**1**) R = H

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† Satisfactory spectral and/or analytical data were obtained for all new compounds.

Reduction of (**7**) with lithium aluminium hydride in THF to (**8**), followed by benzylation of the remaining free hydroxy group, gave methyl 6-deoxy-2,3,4-tri-*O*-benzyl-α-D-altropyranoside (**9**), $[\alpha]_D^{20}$ +81° (*c* 0.84, $CHCl_3$), in 64% yield. Hydrolysis of (**9**) by trifluoroacetic acid : water (4 : 1), followed by reducton with sodium borohydride in ethanol, gave the protected 6-deoxy-D-altritol (**10**), m.p. 74.5—75.5 °C, $[\alpha]_D^{20}$ +7.9° (*c* 0.88, $CHCl_3$), in 85% yield [38% yield from (**4**)]. Conversion into the bis(methanesulphonate) (**11**) [3 equiv. methanesulphonyl chloride in pyridine, 0 °C], followed by treatment with tetrabutylammonium azide in dimethylformamide (DMF) gave azidomethanesulphonate (**12**) in 60% yield, $\nu_{max.}$ 2095 cm^{-1} (azide) and ^1H n.m.r. ($CDCl_3$) showing H-5 as a quartet of doublets at δ 5.1. Hydrogenation of (**12**) in the presence of palladium catalysts gave a mixture of products in which some hydrogenolysis of the benzyl ethers accompanied reduction of the azide; however, treatment with sodium hydrogen telluride[7] smoothly transformed (**12**) directly to the required piperidine (**13**), $[\alpha]_D^{20}$ −42° (*c* 0.80, $CHCl_3$), in 75% yield. Removal of the benzyl protecting groups from (**13**) by hydrogenolysis in the presence of palladium black in ethanol gave (**1**);‡ the ^1H n.m.r. spectra of (**13**) in $CDCl_3$ and of (**1**) in D_2O show that both compounds are in a chair conformation.

The inhibitory action of (**1**) on the hydrolysis of the corresponding nitrophenyl glycopyranosides catalysed by α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans), β-galactosidase (*Aspergillus niger*), α-mannosidase (Jack Bean), β-xylosidase (*Aspergillus niger*), and α-L-fucosidase was determined.§ A concentration of (**1**) of only 2.5 × 10^{-8} M was sufficient to cause 50% inhibition of α-L-fucosidase-catalysed hydrolysis of *p*-nitrophenyl α-L-fucopyranoside; a Lineweaver–Burk plot shows that (**1**) is a competitive inhibitor (K_I 4.8 × 10^{-9} M). In contrast, none of the other enzymes was appreciably inhibited at a concentration of (**1**) of 5 × 10^{-4} M. Should this specificity be maintained over a wide range of mammalian enzymes, 1,5-dideoxy-1,5-imino-L-fucitol (**1**) is likely to prove a research tool of exceptional usefulness.

Received, 9th April 1985; Com. 479

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‡ *Spectroscopic data* for (**1**): an oil, $[\alpha]_D^{20}$ −48.8 ° (*c* 0.64, H_2O); *M* + H^+ 148 (NH_3-chemical ionisation); ^1H n.m.r. (300 MHz) in D_2O δ 0.94 (d, CH_3), 2.22 (dd, H_{1a}), 2.92 (dd, H_{1e}), 3.55 (m, H_2), 3.32 (dd, H_3), 3.64 (m, H_4), 2.67 (qd, H_5); *J*(1e, 1a) 13.0, *J*(1a, 2) 11.0, *J*(1e, 2) 5.4, *J*(2, 3) 9.7, *J*(3, 4) 3.1, *J*(4, 5) 1.2, *J*(5, Me) 6.8 Hz; ^{13}C n.m.r. (125 MHz) in D_2O δ 75.61 (d, CHOH), 73.06 (d, CHOH), 68.20 (d, CHOH), 53.94 (d, CHN), 49.25 (t, CH_2N), 16.70 (q, CH_3).

§ The enzymes and nitrophenyl glycopyranoside substrates were obtained from Sigma. Details of the enzyme assay procedures are given in ref. 2.