

Short Efficient Synthesis of the α -L-Fucosidase Inhibitor, Deoxyfuconoijirimycin [1,5-Dideoxy-1,5-imino-L-fucitol] from D-Lyxonolactone

George W. J. Fleet,^a Sigthor Petursson,^{a,b} Arthur L. Campbell,^c Richard A. Mueller,^c James R. Behling,^c Kevin A. Babiak,^c John S. Ng,^c and Mike G. Scaros^c

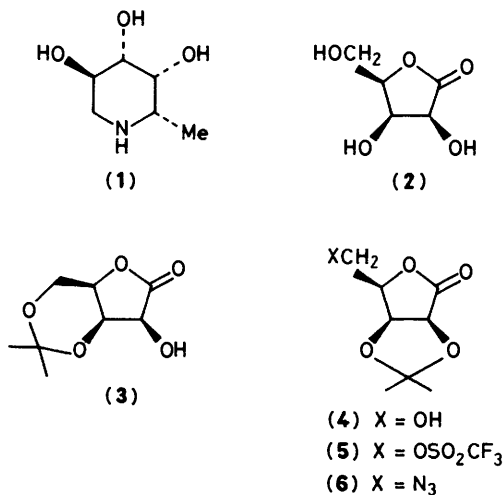
^a Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QY

^b Glycobiology Unit, Biochemistry Department, South Parks Road, Oxford, OX1 3QU

^c G. D. Searle, 4901, Searle Parkway, Skokie, Illinois 60077, U.S.A.

The only protection required in a five-step synthesis of the α -L-fucosidase inhibitor, deoxyfuconoijirimycin [1,5-dideoxy-1,5-imino-L-fucitol] from D-lyxonolactone, a readily available chiral pool material, is a single isopropylidene group.

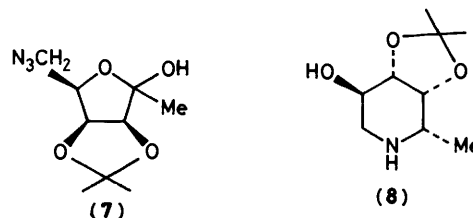
Deoxyfuconoijirimycin [1,5-dideoxy-1,5-imino-L-fucitol] (**1**) is a powerful and specific inhibitor of several α -L-fucosidases;^{1,2} for example, (**1**) has a K_i of 4×10^{-11} M for the inhibition of a canine α -L-fucosidase.³ Derivatives of deoxyfuconoijirimycin (**1**) have been demonstrated to inhibit HIV cytopathicity at concentrations which were non-cytotoxic.^{4,5} The two published^{1,3} syntheses of (**1**) from D-glucose involve many steps and are not suitable for the preparation of any substantial amount of material. This paper describes a short synthesis of deoxyfuconoijirimycin from D-lyxonolactone (**2**) which uses only a single isopropylidene protecting group and may be conducted on a large scale.



Although D-lyxonolactone (**2**) has not previously been used as a starting material from the chiral pool, D-lyxonolactone is an easily crystallised lactone,⁶ m.p. 112.5 °C, $[\alpha]_D^{20} + 72.9^\circ$ (*c*, 4.0 in H₂O) [lit.,⁷ m.p. 114 °C, $[\alpha]_D^{20} + 82.5^\circ$ (*c*, 4.0 in H₂O)] which may be readily prepared by the Humphlett procedure for the oxygenation of an alkaline solution of D-galactose, followed by treatment of the resulting lyxonate salt with hydrogen chloride in isopropyl alcohol.⁸ Treatment of D-lyxonolactone with acetone in the presence of anhydrous copper sulphate gave a mixture of the two acetonides (**3**) and (**4**)^{9,10} in a combined yield of 81% [together with 13% of recovered (**2**)]. The mixture is readily separated by chromatography to give 3,5-*O*-isopropylidene-D-lyxonolactone (**3**), m.p. 140–141 °C [lit.,¹¹ m.p. 137–138 °C] in 20% yield and 2,3-*O*-isopropylidene-D-lyxonolactone (**4**), m.p. 96–97 °C [lit.,¹¹ m.p. 88–93 °C] in 60% yield.

Esterification of the free hydroxy group in (**4**) with trifluoromethanesulphonic anhydride in dichloromethane afforded the

corresponding triflate (**5**) which with sodium azide in dimethylformamide at 0 °C gave the azidolactone (**6**),¹¹ m.p. 59.7 °C, in 89% yield. Reaction of the lactone (**6**) with methyl lithium in tetrahydrofuran at –78 °C gave the adduct (**7**), m.p. 86.2 °C, as a single stereoisomer in a yield of 97%;¹² the stereochemistry at the new chiral centre in (**7**) has not yet been determined, although in a similar case it has been established that the product is derived from attack by the alkyl-lithium from the most hindered side.¹³ Hydrogenation of the azido lactol (**7**) in the presence of palladium black in ethanol results in reduction of the azide to the amine, followed by intramolecular reductive amination to give the isopropylidene protected iminofucitol (**8**), m.p. 184 °C (83% yield), in which the



stereochemistry of the reduction of the intermediate imine is completely controlled by the adjacent isopropylidene group. The sequence from (**2**) may be readily carried out on a multigram scale giving an overall yield of (**8**) of 41%. Treatment of (**8**) with aqueous trifluoroacetic acid results in the removal of the isopropylidene group in quantitative yield to give, after purification by ion exchange chromatography, deoxyfuconoijirimycin (**1**), identical with an authentic sample.¹

Azapyranose analogues of sugars are a general class of specific glycosidase inhibitors; the value of sugar lactones, previously illustrated by the synthesis of mannonolactam and deoxymannonojirimycin from L-gulonolactone^{14,15} in short and efficient syntheses of such inhibitors is further demonstrated by this conversion of D-lyxonolactone to deoxyfuconoijirimycin. This synthesis provides easy access to deoxyfuconoijirimycin as a powerful and specific fucosidase inhibitor, and should now allow the development of this class of fucosidase inhibitor as a biochemical tool.^{16,17}

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