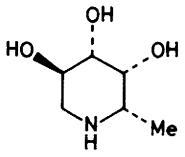
Short Efficient Synthesis of the α-L-Fucosidase Inhibitor, Deoxyfuconojirimycin [1,5-Dideoxy-1,5-imino-L-fucitol] from D-Lyxonolactone

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]

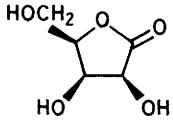
[a] *Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QY*
[b] *Glycobiology Unit, Biochemistry Department, South Parks Road, Oxford, OX1 3QU*
[c] *G. D. Searle, 4901, Searle Parkway, Skokie, Illinois 60077, U.S.A.*

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

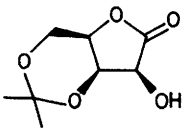
Deoxyfuconojirimycin [1,5-dideoxy-1,5-imino-L-fucitol] (**1**) is a powerful and specific inhibitor of several α-L-fucosidases;[1,2] for example, (**1**) has a K_i of 4×10^{-11} M for the inhibition of a canine α-L-fucosidase.[3] Derivatives of deoxyfuconojirimycin (**1**) have been demonstrated to inhibit 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 deoxyfuconojirimycin from D-lyxonolactone (**2**) which uses only a single isopropylidene protecting group and may be conducted on a large scale.



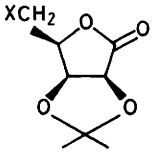
(**1**)



(**2**)



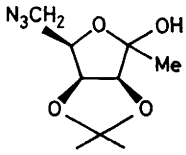
(**3**)



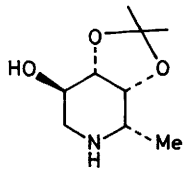
(**4**) X = OH
(**5**) X = OSO_2CF_3
(**6**) X = N_3

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° (*c*, 4.0 in H_2O) [lit.,[7] m.p. 114 °C, $[\alpha]_D^{20}$ +82.5° (*c*, 4.0 in H_2O)] 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



(**7**)



(**8**)

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 trifluoracetic acid results in the removal of the isopropylidene group in quantitative yield to give, after purification by ion exchange chromatography, deoxyfuconojirimycin (**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 deoxymannojirimycin from L-gulonolactone[14,15] in short and efficient syntheses of such inhibitors is further demonstrated by this conversion of D-lyxonolactone to deoxyfuconojirimycin. This synthesis provides easy access to deoxyfuconojirimycin 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]

References

1 G. W. J. Fleet, A. N. Shaw, S. V. Evans, and L. E. Fellows, *J. Chem. Soc., Chem. Commun.*, 1985, 841.
2 R. Nuck, D. Sauvageot, H. Paulsen, R. Tauber, and W. Reutter, 'Proceedings of the 9th International Symposium on Glycoconjugates,' E37, Lille, France, 6—11 July, 1987; this communication proposes the name deoxyfuconojirimycin for (**1**).

3 G. W. J. Fleet, N. G. Ramsden, R. A. Dwek, T. W. Rademacher, L. E. Fellows, R. J. Nash, D. C. Green, and B. Winchester, *J. Chem. Soc., Chem. Commun.*, 1988, 483.
4 A. Karpas, G. W. J. Fleet, R. A. Dwek, S. Petursson, S. K. Namgoong, N. G. Ramsden, G. S. Jacob, and T. W. Rademacher, *Proc. Natl. Acad. Sci. USA*, 1988, **85**, 9229.
5 G. W. J. Fleet, A. Karpas, R. A. Dwek, L. E. Fellows, A. S. Tyms, S. Petursson, S. K. Namgoong, N. G. Ramsden, P. W. Smith, J. C. Son, F. X. Wilson, D. R. Witty, G. S. Jacob, and T. W. Rademacher, *FEBS Lett.*, 1988, **237**, 128.
6 H. S. Isbell, *J. Res. Natl. Bur. Stand.*, 1942, **29**, 227.
7 A. Thompson and M. L. Wolfrom, *J. Am. Chem. Soc.*, 1946, **68**, 1509.
8 W. J. Humphlett, *Carbohydr. Res.*, 1967, **4**, 157.
9 R. J. Schaffer, *J. Res. Natl. Bur. Stand., Sect. A*, 1961, **65**, 507.
10 S. Morgenlie, *Acta Chem. Scand. B*, 1975, **29**, 367.
11 Satisfactory spectral and microanalytical data were obtained for all new compounds reported in this paper.
12 Addition of alkyl-lithiums to sugar lactones to produce monoadducts is a well established procedure; see H. Ogura and H. Takahashi, *J. Org. Chem.*, 1974, **39**, 1374, and references therein.
13 H. Ogura, K. Furuhata, H. Takahashi, and Y. Iitaka, *Chem. Pharm. Bull.*, 1978, **26**, 2782.
14 G. W. J. Fleet, N. G. Ramsden, and D. R. Witty, *Tetrahedron Lett.*, 1988, **29**, 2871; G. W. J. Fleet, N. G. Ramsden, and D. R. Witty, *Tetrahedron*, 1989, **45**, 319.
15 T. K. M. Shing, *J. Chem. Soc., Chem. Commun.*, 1988, 1221.
16 Assistance from K. T. McLaughlin, Owen Goodmonson, Michael L. Prunier, and Pat Finnegan of G.D. Searle Research and Development is gratefully acknowledged.
17 An alternative synthesis of compound (**1**) from 2-azidogalactose has been reported: H. Paulsen and M. Maatske, *Liebigs Ann. Chem.*, 1988, in press.

Received 1*st November*, 1988; *Paper* 8/04342F