δ-Lactams: Synthesis from D-Glucose, and Preliminary Evaluation as a Fucosidase Inhibitor, of L-Fuconic-δ-lactam

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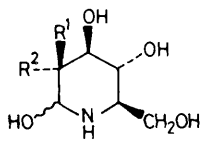
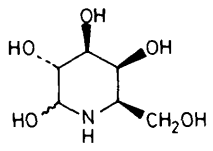
Polyhydroxylated δ-lactams are a potential class of glycosidase inhibitors; the synthesis of L-fuconic-δ-lactam (**7**), which preliminary studies have shown to be a weak but specific α-L-fucosidase inhibitor, is described.

Three 5-amino-5-deoxyhexoses, analogues of pyranoses in which the ring oxygen has been replaced by nitrogen, have been isolated from *Streptomyces* species. Nojirimycin (**1**)[1] has been shown to be an inhibitor of several glucosidases,[2,3] whereas nojirimycin B (**2**)[4] inhibits several mannosidases;[5] a number of galactosidases are inhibited[6] by galactostatin (**3**).[7] 1,5-Dideoxy-1,5-iminohexitols, related to 5-amino-5-deoxyhexoses by the removal of the anomeric hydroxy group, are also glycosidase inhibitors;[8] *e.g.*, 1,5-dideoxy-1,5-L-iminofucitol (**4**)[9] is a powerful and specific inhibitor of several α-L-fucosidases.[10] The δ-lactams (**5**)[1,11] and (**6**),[4] formed by microbial oxidations of nojirimycin (**1**) and nojirimycin B (**2**),



(1) R^1 = H, R^2 = OH
(2) R^1 = OH, R^2 = H



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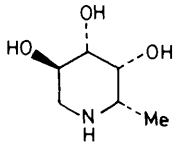

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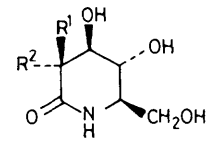
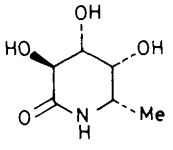


(5) R^1 = H, R^2 = OH
(6) R^1 = OH, R^2 = H



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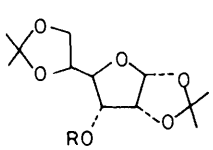
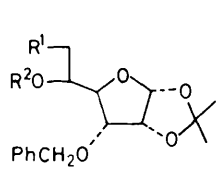
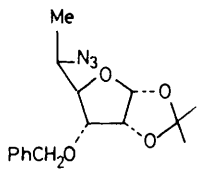


(8) R = H
(9) R = CH_2Ph





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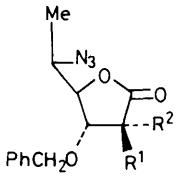
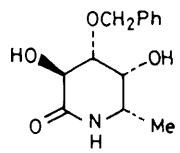


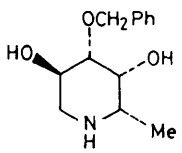
(15) R^1 = H, R^2 = OH
(16) R^1 = OH, R^2 = H

(10) R^1 = OH, R^2 = H
(11) R^1 = OTs, R^2 = H
(12) R^1 = R^2 = H
(13) R^1 = H, R^2 = $MeSO_2$

(Ts = tosyl)



(17)



(18)

respectively, are also glycosidase inhibitors and it may be that polyhydroxylated δ-lactams constitute another class of glycosidase inhibitor with specificities different from those of the 1,5-dideoxy-1,5-iminohexitols. This paper describes the synthesis and preliminary evaluation as a glycosidase inhibitor of L-fuconic-δ-lactam (7).

Synthesis of (7) from glucose requires inversion of configuration of the C-2 and C-3 hydroxy groups, the introduction of nitrogen with inversion of configuration at C-5, and subsequent cyclisation of the nitrogen onto C-1 at the carboxylic acid level of oxidation. The configuration at C-3 of glucose was inverted by treatment of diacetone glucose with pyridinium chlorochromate in the presence of molecular sieve, followed by reduction of the resulting ketone with sodium borohydride to afford diacetone allose (**8**) which, with benzyl bromide and sodium hydride in the presence of tetrabutylammonium iodide, gave the fully protected sugar (**9**) {m.p. 65—66 °C, $[\alpha]_D^{20}$ +106° (*c* 0.25, $CHCl_3$); lit.[12] m.p. 64—65 °C, $[\alpha]_D^{20}$ +110° (*c* 1, MeOH)}. Selective hydrolysis of the side chain acetonide with aqueous acetic acid gave the diol (**10**) {m.p. 63—65 °C, $[\alpha]_D^{20}$ +119.4° (*c* 0.25, $CHCl_3$); lit.[12] oil, $[\alpha]_D^{20}$ +103° (*c* 0.6, MeOH)} in 79% yield from diacetone glucose on a 20 g scale. Esterification of the primary hydroxy group in (**10**) with toluene-*p*-sulphonyl chloride in pyridine gave the tosylate (**11**) (85% yield), which, with lithium triethylborohydride in tetrahydrofuran, gave 3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose (**12**)† {94% yield; $[\alpha]_D^{20}$ +110.4° (*c* 1.02, $CHCl_3$)}. Reaction of (**12**) with methanesulphonyl chloride in pyridine in the presence of 4-(dimethylamino)pyridine gave the crude mesylate (**13**), which, with sodium azide in dimethylformamide (DMF), formed 5-azido-3-*O*-benzyl-5,6-dideoxy-1,2-*O*-isopropylidene-β-L-talofuranose (**14**) {84% yield; $[\alpha]_D^{20}$ +160.0° (*c* 1.21, $CHCl_3$)}. Hydrolysis of the talofuranose (**14**) with aqueous trifluoroacetic acid, followed by oxidation of the resulting lactol with bromine in aqueous dioxane in the presence of barium carbonate, gave the talonolactone (**15**) {m.p. 85—86 °C, $[\alpha]_D^{20}$ +95.5° (*c* 0.99, $CHCl_3$)} in 78% yield. Inversion of the configuration of the C-2 hydroxy group in (**15**) was achieved in an overall yield of 81% by initial esterification of (**15**) with trifluoromethanesulphonic anhydride in the presence of pyridine, followed by reaction of the resulting triflate with sodium trifluoroacetate in DMF and treatment of the crude product with methanol–water to give 5-azido-3-*O*-benzyl-5-deoxy-L-fucono-1,4-lactone (**16**) {$[\alpha]_D^{20}$ +171.6° (*c* 1.49, $CHCl_3$)}.

Hydrogenation of the azide (**16**) in the presence of 5% palladium on carbon in ethyl acetate permitted the isolation of the benzyl protected lactam (**17**) {m.p. 191—192 °C, $[\alpha]_D^{20}$ −70.3° (*c* 0.90, EtOH)}, in 81% yield. Further hydrogenation of (**17**) in the presence of palladium black in ethanol in the presence of a trace of hydrogen chloride gave L-fuconic-δ-lactam (**7**)‡ in 91% yield (overall yield from diacetone glucose 24%).

The structure of the lactam (**7**) was confirmed by conversion into the iminofucitol (**4**); reduction of the benzyl lactam (**17**) with borane–dimethyl sulphide, followed by decomposition of the resulting amine–borane complex with trifluoroacetic acid gave (**18**) (85% yield), which, on hydrogenation in the presence of palladium black in acetic acid, gave (**4**), identical to an authentic sample.[9]

L-Fuconic-δ-lactam (**7**) is a weak competitive inhibitor of bovine kidney α-L-fucosidase, K_i 3.0 × 10^{-4} M, and of human liver α-L-fucosidase, K_i 4.0 × 10^{-4} M at pH 5.5 (optimum pH of the enzymes). When human liver α-L-fucosidase and the lactam (**7**) were preincubated for different periods of time before addition of substrate, the inhibition was found to increase, reaching a limiting value after about 1 h preincubation, indicating that (**7**) may be a slow binding inhibitor; inhibition also increased with pH over the pH range 5.0—7.0. None of ten other human liver glycosidases (nor yeast α-glucosidase, almond β-glucosidase, Jack bean α-mannosidase, *Aspergillus niger* β-xylosidase, and green coffee bean α-galactosidase[13]) were inhibited by more than 5% by 1 mM-(**7**). Thus, L-fuconic-δ-lactam (**7**) is seen to be a more effective inhibitor of α-L-fucosidases than L-fuconolactone (K_i 8.1 × 10^{-3} M),[14] although (**7**) is a very much weaker inhibitor than is the iminofucitol (**4**) (K_i 4 × 10^{-11} M for canine α-L-fucosidase).

In summary, this paper reports the synthesis of L-fuconic-δ-lactam (**7**), a specific, though weak, inhibitor of α-L-fucosidases.

† Satisfactory spectral data were obtained for all new compounds; satisfactory microanalytical data (C, H, and N) were obtained for (**4**), (**7**), (**12**), and (**14**)—(**17**).

‡ *Selected data* for (**7**): m.p. 226—227 °C, $[\alpha]_D^{20}$ −137.2° (*c* 0.83, H_2O); ^{13}C n.m.r. (D_2O): δ 173.86 (s), 73.23 (d), 71.61 (d), 69.77 (d), 50.18 (d), and 16.61 (q).

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