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SYNTHESIS OF DEOXYNOJIRIMYCIN AND OF NOJIRIMYCIN δ-LACTAM

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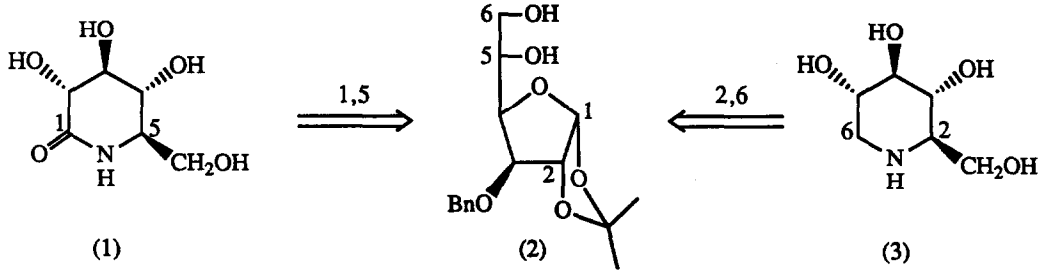
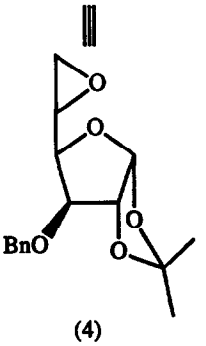
The syntheses of nojirimycin δ-lactam and of deoxynojirimycin from a divergent ido-furanose intermediate are reported.

The two basic strategies for the synthesis of nojirimycin derivatives from the L-idofuranose (2) involve formation of the piperidine ring by connection of nitrogen either (a) between C-1 and C-5 with inversion of configuration at C-5 [the equivalent of double inversion at C-5 of glucose], or (b) between C-2 and C-6 with inversion of configuration at C-2. This paper describes the use of the epoxide (4)[1] as a divergent intermediate for the synthesis of nojirimycin δ-lactam (1) by the former strategy and of deoxynojirimycin (3) by the latter strategy.



(1) (2) (3)

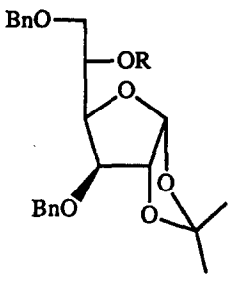
Bn = CH_2Ph



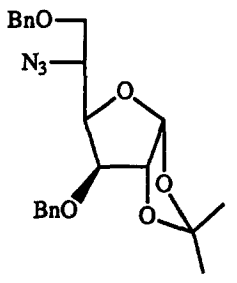
(4)

a) Synthesis of nojirimycin δ-lactam (1). The properties of deoxynojirimycin[2] as a glucosidase inhibitor and the recognition of the potential applications of such compounds[3] have led to considerable studies on the synthesis of nojirimycin derivatives.[4,5] Although the most common strategy for the synthesis of nojirimycin derivatives has been by the introduction of nitrogen with retention of configuration at C-5 of glucose,[6,7] the only reported stereospecific synthesis of nojirimycin δ-lactam was by hypoiodite oxidation of nojirimycin.[8] Treatment of epoxide (4) with sodium hydride and benzyl

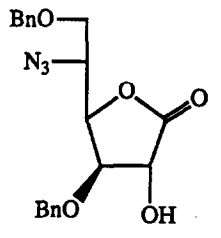
alcohol in dimethylformamide gave the dibenzyl ido-furanose (5) m.p. 70°-71°C [lit.[6] 74°C] in an overall yield of 49% from diacetone glucose. Esterification of the free hydroxyl group in (5) with trifluoromethanesulphonic anhydride in dichloromethane in the presence of pyridine, followed by treatment of the resulting triflate (6) with sodium azide in dimethylformamide afforded the gluco-azide (7), m.p. 66°-67°C [lit.[9] 74°C] in 75% yield. The isopropylidene protecting group was removed from (7) by hydrolysis with aqueous trifluoroacetic acid and the resulting lactol was oxidised by bromine in aqueous dioxane in the presence of barium benzoate to give the azidolactone (8), ν_{max} 2100 (N_3), 1790 (C=O) cm^{-1}, in 74% yield.[10]



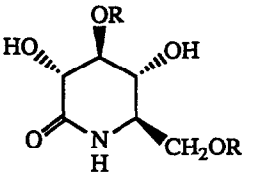
(5) R = H
(6) R = SO_2CF_3



(7)



(8)

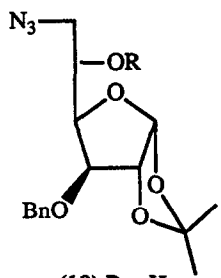


(1) R = H
(9) R = Bn

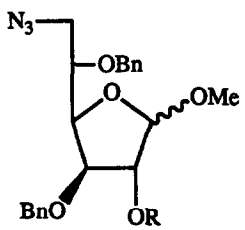
Reduction of the azidolactone (8) by tin(II) chloride in methanol,[11] followed by treatment with potassium carbonate, gave the dibenzyl lactam (9), m.p. 110°-112°C, $[\alpha]_D^{20}$ +10.8° (*c*, 0.83 in $CHCl_3$), in 56% yield.[12] The benzyl groups were removed from (9) by hydrogenation in ethanol in the presence of palladium black to give nojirimycin δ-lactam (1), m.p. 204°-205°C, $[\alpha]_D^{20}$ +57° (*c*, 0.63 in H_2O) [lit.[8] m.p. 203°-205°C, $[\alpha]_D^{22}$ +63° (H_2O)].[13]

b)Synthesis of deoxynojirimycin (3). The formation of a piperidine ring between C-2 and C-6 of a sugar involves nucleophilic substitution by nitrogen at C-2; although intermolecular displacement of triflate at C-2 of a furanose by azide occurs smoothly if the anomeric substituent is *cis*- to the leaving group, the displacement if the leaving group is *trans*- to the anomeric substituent is very much less efficient.[14] In contrast, intramolecular substitution of a triflate at C-2 by an amino function at C-6 occurs readily with both furanose anomers. Thus introduction of nitrogen at C-6 initially, rather than at C-2, is the preferred

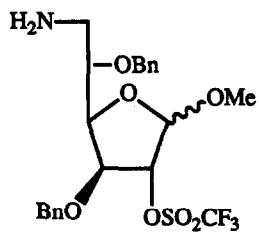
strategy.[15] Reaction of the epoxide (4) with sodium azide in dimethylformamide gave the ido-azide (10) (87% yield) which with sodium hydride, benzyl bromide and tetrabutylammonium iodide in tetrahydrofuran afforded the dibenzyl ether (11), m.p. 40°-41°C, in 91% yield. Treatment of (11) with methanolic hydrogen chloride gave the methyl furanosides (12)[16] (67% yield) which were esterified with trifluoromethanesulphonic anhydride to give the corresponding triflates (13) [88% yield for α anomer; 54% yield for β anomer].



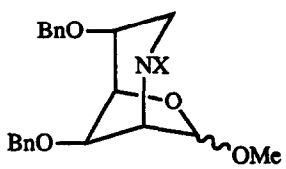
(10) R = H
(11) R = Bn



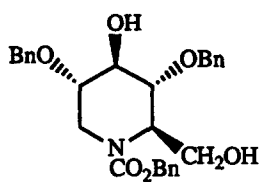
(12) R = H
(13) R = SO_2CF_3



(14)



(15) X = H
(16) X = CO_2CH_2Ph



(17)

Reduction of a mixture of the azidotriflates (13) with tin(II) chloride in methanol gave the aminotriflates (14) which on stirring with sodium acetate in ethanol gave the bicyclic amines (15); reaction with benzyl chloroformate gave the protected carbamates (16) [67% overall yield from (13)]. Thus the intramolecular cyclisation of both anomers occurs smoothly, even though the two O-benzyl substituents would be in a 1,3-diaxial relationship in the bicyclic amine. Subsequent hydrolysis of the furanosides (16) by trifluoroacetic acid in aqueous dioxane to the lactol, followed by reduction by sodium borohydride in ethanol, afforded the protected deoxynojirimycin (17), m.p. 85°-87°C, $[\alpha]_D^{20}$ 0.0° (c. 0.29 in MeOH) in 49% yield. Subsequent hydrogenation of (17) in acetic acid in the presence of palladium black gave, after purification by ion exchange chromatography, deoxynojirimycin (3),[17] identical with authentic material and readily crystallised as the hydrochloride, m.p. 204°-205°C (lit.[14] 203°C).[18]

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10 ^{13}C NMR of azidolactone (8) ($CDCl_3$), non-aromatic carbons: δ 175.07 (s, C=O), 79.47 (d), 78.38 (d), 71.62 (d), 59.79 (d), 73.58 (t), 72.59 (t), 69.73 (t).

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12 ^{13}C NMR of dibenzyl lactam (9) ($CDCl_3$), non-aromatic carbons: δ 172.15 (s, C=O), 81.15 (d), 72.13 (d), 68.15 (d), 55.00 (d), 74.22 (t), 73.46 (t), 70.95 (t).

13 ^{13}C NMR of nojirimycin lactam (1) (D_2O): δ 174.38 (s, C=O), 74.06 (d), 71.39 (d), 68.25 (d), 57.66 (d), 61.04(t).

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16 The anomer ratio of (12) was α:β 2:1. The subsequent reactions were carried out on both anomers separately and on the mixture; there is no advantage in separating the anomers.

17 ^{13}C NMR of deoxynojirimycin (3) as free base (D_2O): δ 79.0 (d), 72.1 (d), 71.1 (d), 61.9 (t), 61.0 (d), 49.2 (t, C-1).

18 ^{13}C NMR of deoxynojirimycin (3) as hydrochloride (D_2O): δ 77.1 (d), 68.6 (d), 67.8 (d), 60.8 (d), 58.5 (d),46.7 (t, C-1).

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