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SYNTHESIS OF THE POTENT ANTIVIRAL OXETANE NUCLEOSIDE EPINOROXETANOCIN FROM D-LYXONOLACTONE

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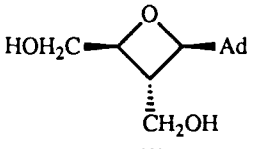
A short synthesis of epinoroxetanocin [9-(β–D-threo-oxetanosyl)adenine], free from its α-anomer, from D-lyxonolactone is described. The X-ray crystal structure of a benzylidene-protected derivative of epinoroxetanocin is reported. A comparison of the *in vitro* activity against HIV-1 of oxetanocin, noroxetanocin and epinoroxetanocin as anti-viral agents is given.

The anti-viral activity of oxetanocin (1)[1,2] and of its guanine analogue[3] have stimulated considerable interest in the synthesis of oxetane-containing nucleosides,[4] as well as in cyclobutane analogues.[5,6,7] Recently, studies on the synthesis[8] of noroxetanocin (3) indicated that competing ring expansion is a serious disadvantage in S_N1-like displacement of leaving groups from C-2 of oxetanes; that paper also reported that epinoroxetanocin (2) exhibited more potent antiviral activities than did oxetanocin itself, though no synthesis of epinoroxetanocin was described. This paper reports a short synthesis of epinoroxetanocin (2) from D-lyxonolactone (5),[9,10] which - although readily available from oxygenation of galactose[11] - has rarely been used as a starting material from the chiral pool.[12] A comparison of oxetanocin, epinoroxetanocin and β- (3) and α-noroxetanocin (4) indicates that, while substitution of the 2'-hydroxymethyl group in oxetanocin by a 2'-hydroxyl group to give noroxetanocin (3) causes all activity of the oxetane nucleoside against HIV-1 to be lost, such a substitution accompanied by inversion of configuration at C-2' gives a compound (2) with significant anti-viral activity.



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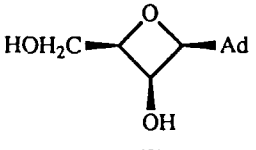

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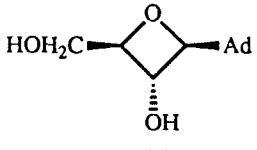

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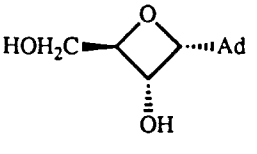

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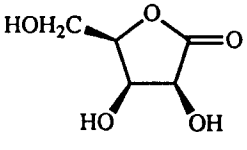

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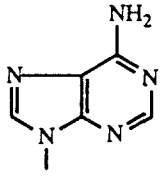

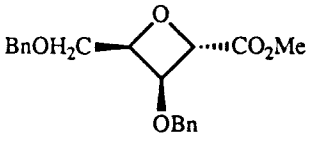

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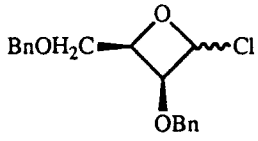

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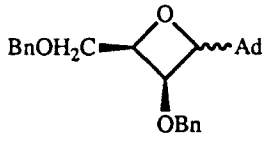
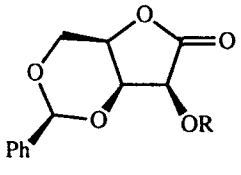
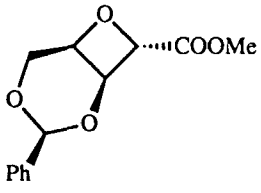


(8)

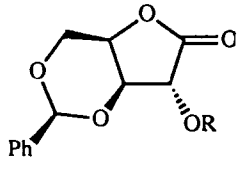
An initial attempt to make epinoroxetanocin (2) used an analogous route to that of the synthesis of noroxetanocin (3).[13] The oxetane carboxylic ester (6), prepared in eight steps from diacetone glucose,[14] was converted by the Barton modification of the Hunsdiecker reaction[15] to the epimeric chlorides (7) which underwent displacement by adenine to give an anomeric mixture of the protected nucleosides (8). However, unlike the anomers of noroxetanocin which could readily be separated by chromatography, no success was achieved in separation of either the dibenzyl protected nucleosides (8) or the deprotected epinoroxetanocins. Thus the synthesis reported from lyxonolactone has two major advantages over such an approach: (i) the lactone triflate required for the ring contraction to the oxetane is formed in only two steps and, more importantly, (ii) a single chloro compound undergoes clean displacement by adenine to give only a β-oxetane nucleoside.



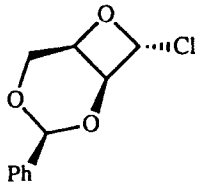
(9) R=H (10) $R=SO_2CF_3$



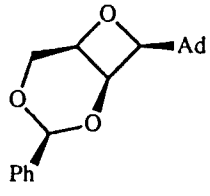
(11)



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



(14)



(15)

Treatment of lyxonolactone (5) with benzaldehyde and concentrated hydrochloric acid gives the protected benzylidene derivative (9)[16] [95% yield] in which only the α-hydroxyl group of the lactone remains unprotected. Esterification of the free hydroxyl group in (9) with trifluoromethanesulphonic anhydride and pyridine in tetrahydrofuran at -10°C gave the corresponding triflate[17] (10) in 76% yield.[18] Reaction of the lyxono-triflate (10) with anhydrous potassium carbonate in methanol gave the oxetane ester (11)[19] in 38% yield [28% overall yield from D-lyxonolactone]. Reaction of the triflate with sodium trifluoroacetate in dimethylformamide afforded the protected xylono-lactone (12)[20] [96% yield] which was converted to the triflate (13)[21] in 78% yield. The ring contraction of the xylono-triflate (13) with potassium carbonate in

methanol to the oxetane (11) was much more efficient [80% yield] than the contraction of the lyxono-triflate (10); however the additional two steps necessary for the inversion of the C-2 stereochemistry make the shorter, but lower yielding, route the method of choice for the preparation of (11).

Attempts to convert the oxetane ester (11) to the chlorooxetane (14) by the Barton-Hunsdiecker reaction were unsuccessful; however, hydrolysis of (11) by methanolic sodium hydroxide, followed by treatment of the resulting sodium carboxylate with N-chlorosuccinimide and lead tetraacetate in a mixture of acetic acid and dimethylformamide[22] gave a single chlorooxetane (14)[23] in 58% yield. Reaction of the chlorooxetane (14) with adenine, potassium carbonate and 18-crown-6 in dimethylformamide at 150°C allowed the isolation of a single oxetane nucleoside (15)[24] in 35% yield; the structure of (15), which arises out of a clean S_N2 displacment of the choride in (14), was firmly established by single crystal X-ray analysis (FIGURE).[25] The benzylidene protecting group in (15) was removed by trifluoroacetic acid in methanol to give epinoroxetanocin (2)[26] in 80% yield.

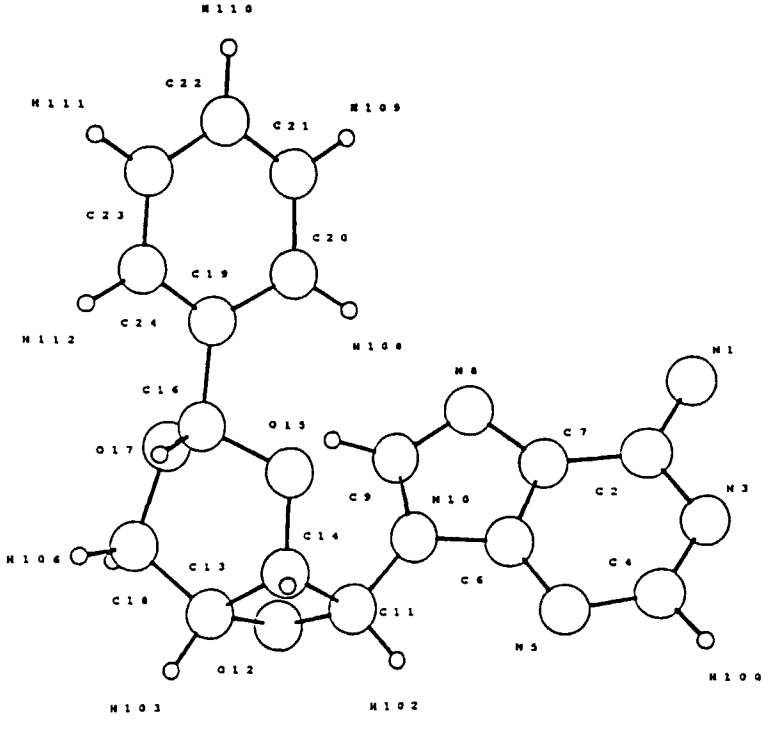


FIGURE X-Ray molecular structure of 9-(2,4-O(*R*)-benzylidene-β–D-threo-oxetanosyl)adenine (15), with crystallographic numbering scheme.

The properties of oxetanocin,[27] β- and α-noroxetanocins and of epinoroxetanocin as antiviral agents against HIV-1 *in vitro* were compared;[28] both oxetanocin [I_{50} 0.5-1.5 μg/ml] and epinoroxetanocin [I_{50} 0.5-1.5 μg/ml] showed significant activity whereas both β- and α-noroxetanocins showed no such activity at concentrations up to 100 μg/ml. This and the preceding paper clearly demonstrate the viability of the γ-lactone ring contraction strategy for the synthesis of oxetane nucleosides.[29,30]

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17 All new compounds reported in this paper have satisfactory microanalytical and spectroscopic data consistent with the structures proposed.
18 Data for lyxonotriflate (10): m.p. 163°-165°C, $[\alpha]_D^{20}$ +60.5 (*c*, 1.0 in acetone)
19 Data for oxetane ester (11): m.p. 122°-124°C, $[\alpha]_D^{20}$ -28.2 (*c*, 1.0 in chloroform); δ_C: 52.37 (q), 69.32 (t), 72.47 (d), 75.24 (d), 84.22 (d), 98.21 (PhCH), 126.27, 128.38, 128.52, 129,39 (Ar), 170.55 (C=O).
20 Data for xylonolactone (12): m.p. 124°-126°C, $[\alpha]_D^{20}$ +63.3 (*c*, 1.0 in acetone).
21 Data for xylonotriflate (13): m.p. 94°-96°C, $[\alpha]_D^{20}$ +63.6 (*c*, 1.0 in acetone)
22 K. B. Becker, M. Giesel, C. A. Grob and F. Kuhnen, *Synthesis*, **1973**, 493; J. K. Kochi, *J. Am. Chem. Soc.*, 1965, **87**, 2500.
23 Data for chlorooxetane (14): m.p. 108°-110°C, $[\alpha]_D^{20}$ +40.8 (*c*, 0.73 in chloroform); δ_C 68.51 (t), 74.52 (d), 77.64 (d), 98.03 (d), 98.38 (d), 126.22, 128.59, 129.56, 129.92 (ArC).
24 Data for protected nucleoside (15): m.p. 220°-225°C, $[\alpha]_D^{20}$ +96.2 (*c*, 0.26 in methanol); δ_C (d4-methanol): 69.79 (t), 71.35 (d), 74.51 (d), 81.94 (d), 98.27 (PhCH), 127.25, 129.20, 129.94 (ArC), 142.00 (d), 154.20 (d) .
25 The atomic coordinates are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this paper.
26 Data for epinoroxetanocin (2): m.p. 236°C, $[\alpha]_D^{20}$ -12.8 (*c*, 0.12 in DMF); δ_C (d6-DMSO): 61.30 (t) , 69.66 (d), 85.10 (d), 85.43 (d), 142.40 (d), 152.25 (d).
27 Oxetanocin was synthesised from diacetone glucose (unpublished results) and shown to be identical to an authentic sample kindly provided by Professor Yamamura.
28 We thank Dr. J. A. V. Coates, Miss H. Inggall and Dr. N. Cammock of the Virology Department, Glaxo Group Research, Greenford for biological evaluation of these compounds.
29 This project has been supported by Glaxo Group Research, the AIDS Committee of the Medical Research Council and the Science & Engineering Research Council.
30 The material in this and the preceding paper was presented at the 199th ACS meeting, Boston, April 23rd 1990 at a symposium in recognition of the Claude S. Hudson award to Professor Bert Fraser-Reid.