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SYNTHESIS OF THE OXETANE NUCLEOSIDES α- AND β-NOROXETANOCIN

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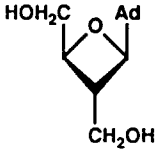
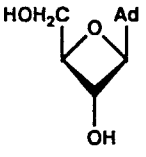
The oxetane nucleosides β-noroxetanocin [9-(β–D-erythro-oxetanosyl)adenine] and the α-epimer are synthesised from 3,5-di-O-benzyl-D-ribonolactone.

Oxetanocin A (1)[1] was the first example of a new family of nucleosides[2] containing an oxetane, rather than a furan, ring as the sugar moiety. This paper describes the synthesis of noroxetanocin (2), together with its α-isomer (3), from 3,5-di-O-benzyl-ribonolactone via 3 key steps: contraction of the trifluoromethanesulphonate ester of an α-hydroxy-γ-lactone to an oxetane-2-carboxylate,[3] introduction of an α-chloride into the oxetane by the Barton modification of the Hunsdiecker reaction,[4] and displacement of the chloride with adenine.



(1)



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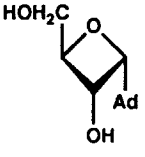

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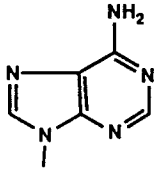
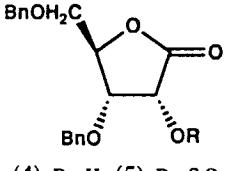
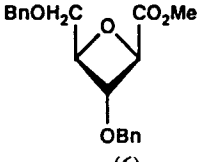


Diacetone glucose was converted into the dibenzyl lactone (4) in 8 steps[3] in an overall yield of 52%. Esterification of the sole free hydroxyl function in the ribonolactone (4) with trifluoromethanesulphonic anhydride in dichloromethane in the presence of pyridine gave the triflate (5)[5] in 95% yield. Treatment of (5) with potassium carbonate in dry methanol afforded the oxetane (6), in which the substituents at C-2 and C-3 of the oxetane are *trans* to each other, as the major product; a small amount of the epimer (7) was also formed [combined yield 82% in a ratio of approximately 8:1]. Partial separation of the epimeric mixture was achieved allowing full characterisation of (6), but it was not possible to obtain a pure sample of (7). The arabinono-triflate (8), epimeric at C-2 with (5), also underwent high yield ring contraction to (6); however, (8) is much less kinetically stable, so that the ring contraction of the ribono-triflate (5) is a much better method for the preparation of larger amounts of the oxetane (6).



(4) R=H (5) R=SO2CF3



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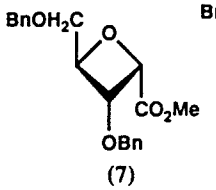

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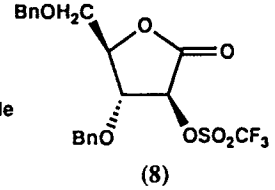
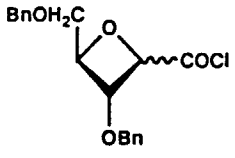


(8)

Hydrolysis of the mixture of the epimeric oxetanes (6) and (7) with aqueous sodium hydroxide in methanol, followed by acidification and treatment of the crude acids with oxalyl chloride and a catalytic amount of dimethylformamide, gave the acid chlorides (9). Addition of (9) directly to a refluxing suspension of the sodium salt of N-hydroxypyridine-2-thione in tetrachloromethane in the presence of AIBN and 4-dimethylaminopyridine afforded, after purification by flash column chromatography, the epimeric β- (10)[6] and

α-chlorides (11)[7] in a β/α ratio of 6/5 and an overall yield of the two chloro compounds of 53% from the esters (6) and (7). The relative stereochemistry of the chorooxetanes was established by equilibrium nOe measurements: thus a significant 1,3-cis relationship is indicated by a 4.6% enhancement between H-2 and H-4 of the β-chlorooxetane (10), with no enhancement between H-2 and H-3. In contrast, the α-chloro isomer (11) exhibited a 7.5% enhancement between H-2 and H-3 with no enhancement between H-2 and H-4.



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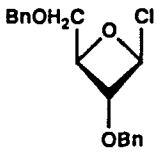

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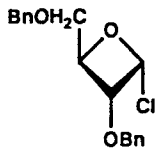

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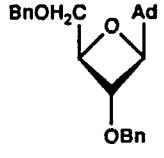

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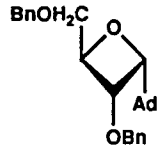

(13)

The α–chlorooxetane (11) was treated with adenine, potassium carbonate, and 18-crown-6, in a 1 : 1 mixture of dimethylformamide and acetonitrile for 4 h at 80°C, to give the protected β-oxetane nucleoside (12),[8] (20% yield) separable by flash chromatography from the α-nucleoside (13),[9] (10% yield). The β-chlorooxetane (10) gave, under similar conditions in 1 h at 80°C, the α– and β–oxetane nucleosides in a ratio of 7 to 1 and a combined yield of 46%; thus there is a large degree of S_N2 character in the displacment of the β-chloride by adenine. The increased lack of selectivity in the displacement of the α-chloride reflects the longer reaction time; there is significant interconversion of the α and β chlorides under the reaction conditions, and it may be that the slower and less stereoselective displacement of the α-halide also proceeds predominantly by S_N2 displacement. Debenzylation of both (12) and (13) was achieved by transfer hydrogenation by palladium hydroxide and cyclohexene in ethanol in 85% yield to give, respectively, noroxetanocin (2)[10] m.p. 237°C, $[\alpha]_D^{20}$ -11.25 (c, 0.24 in H_2O) and the epimeric α–nucleoside (3).[11] The biological assay of α- and β-noroxetanocins against HIV-1 *in vitro* is described in the following paper.[12]

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4 D. H. R. Barton, D. Crich, and W. B. Motherwell, *Tetrahedron*, 1985, 41, 3901.

5 All new compounds reported in this paper have spectroscopic data consistent with the structures proposed. Satisfactory microanalytical data has been obtained for compounds (4), (5), (6), (10), (11), (12) and (13).

6 Data for β-chlorooxetane (10):$[\alpha]_D^{20}$ -3.2 (*c*, 1.4 in $CHCl_3$) δ_C ($CDCl_3$): 137.98, 136.82 (2 s, Ar), 128.77, 128.56, 128.48, 128.26, 127.83 (5 d, Ar), 95.08 (d, 1-C), 84.46 (d, 2-C), 82.40 (d, 3-C), 73.60, 72.19 (2 t, 2 Ph*C*H_2), 69.70 (t, 4-C).

7 Data for α-chlorooxetane (11): $[\alpha]_D^{20}$ +130.2 (*c*, 0.9 in $CHCl_3$) δ_C ($CDCl_3$): 137.91, 137.01 (2s, Ar), 128.67, 128.37, 128.03 and 127.87 (4 d, Ar), 99.12 (d, 1-C), 89.04 (d, 3-C), 73.60, 72.20 (2 t, 2 Ph*C*H_2), 72.11 (d, 3-C), 68.46 (t, 4-C).

8 Data for β-nucleoside (12): oil, $[\alpha]_D^{20}$ +18.5 (*c*, 0.47 in $CHCl_3$) δ_C ($CDCl_3$): 155.36 (s, 6-C), 153.17 (d, 2-C), 149.80 (s, 4-C), 139.59 (d, 8-C), 137.52, 136.79 (2 s, Ar), 128.61, 128.52, 128.22, 128.14, 128.05 and 127.87 (6 d, Ar), 119.55 (s, 5-C), 85.67 (d, 1'-C), 81.38 (d, 3'-C), 79.00 (d, 2'-C), 73.74, 72.68 (2 t, Ph*C*H_2), 69.34 (t, 4'-C).

9 Data for α-nucleoside (13): m.p. 133°C, $[\alpha]_D^{20}$ +7.33 (*c* 0.51 in $CHCl_3$) δ_H 8.34 (2 H, 2 s, H-2, H-8), 7.38-6.97 (10 H, m, Ar), 6.78 (1 H, d, $J_{1',2'}$, 1'-H), 5.70 (2 H, brs, NH_2), 4.98 (1 H, m, 2'-H), 4.87 (1 H, m, 2'-H), 4.75 (2 H, 2 d, J_{gem} 12.5 Hz, Ph*C*H_2), 4.22 (2 H, 2 d, J_{gem} 12.5 Hz, Ph*C*H_2), 3.70 (2 H, m, 4'-H, 4"-H); δ_C 155.60 (s, 6-C), 153.02 (d, 2-C), 149.67 (s, 4-C), 140.78 (d, 8-C), 137.79, 136.16 (2 s, Ar), 128.67, 128.59, 128.295, 128.06 and 127.9 (5 d, Ar), 119.13 (s, 5-C), 87.11 (d, 1'-C), 84.16 (d, 3'-C), 74.96 (d, 2'-C), 73.70, 72.98 (2 t, Ph*C*H_2), 69.30 (t, 4'-C); *m/z* (NH_3 DCI) 418 (MH^+, 100%).The structure of (13) was firmly established by X-ray crystallographic analysis at Glaxo Group Research.

10 Data for β-noroxetanocin (2): m.p. 237°C, $[\alpha]_D^{20}$ -11.25 (*c*, 0.24 in H_2O); δ_C (d_5 pyridine) 157.35 (s, 6-C), 153.59 (d, 2-C), 150.10 (s, 4-C), 139.95 (d, 8-C), 120.36 (s, 5-C), 88.25 (d, 1'-C), 85.70 (d, 3'-C), 72.46 (d, 2'-C), 62.06 (t, 4'-C).

11 Data for α-noroxetanocin (3): m.p. 140°C, $[\alpha]_D^{20}$ -11.6 (*c*, 0.29 in H_2O); δ_C (d_5 pyridine) 157.24 (s, 6-C), 153.50 (d, 2-C), 150.41 (s, 4-C), 141.39 (d, 8-C), 120.01 (s, 5-C), 91.69 (d, 1'-C), 86.11 (d, 3'-C), 68.56 (d, 2'-C), 62.44 (t, 4'-C).

12 This project has been supported by Glaxo Group Research, the AIDS Committee of the Medical Research Council and the Science & Engineering Research Council.