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SYNTHESIS OF OXETANOCIN

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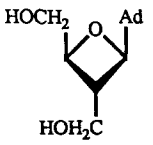
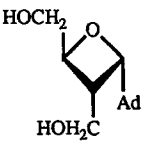
A low yield synthesis of oxetanocin and its α-epimer by reaction of adenine with a protected 3-hydroxymethyl-2-chlorooxetane is described; attempts to synthesise other C-2' alkyl analogues of oxetanocin by analogous reactions indicate a limitation of this strategy for the synthesis of oxetane nucleosides. An intermediate for the synthesis of C-nucleoside analogues of oxetanocin is reported.

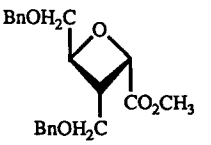
The anti-viral activity of oxetanocin (1) has prompted considerable interest in the basic chemistry of highly functionalised oxetanes.[1] Three basic strategies have been used for the syntheses of oxetane based nucleosides; (i) modification of the natural product oxetanocin (1) by enzymic or other methods,[2] (ii) the construction of the four membered oxetane ring after the nucleoside carbon nitrogen bond has been made,[3] and (iii) coupling of a nucleoside base to a suitably activated oxetanose.[4] Significant problems have been encountered in this latter strategy since displacement of oxygen leaving groups at the anomeric position may lead to undesired ring expansion of the oxetane;[5] in contrast, α-chlorooxetanes bearing protected oxygen substituents at C-3 have been shown to couple with adenine in relatively good [up to 50%] yields,[6] sometimes with remarkable stereoselectivity.[7] This paper describes the synthesis of oxetanocin (1) and its α-epimer (2) via the key oxetane carboxylic ester intermediate (3); attempts at the syntheses of the 3'-homologue (4) and the deoxy analogue (5) by the same strategy are reported.



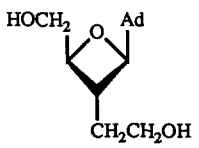
(1)



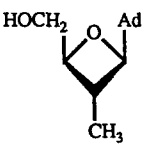
(2)



(3)



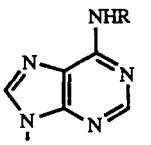
(4)



(5)

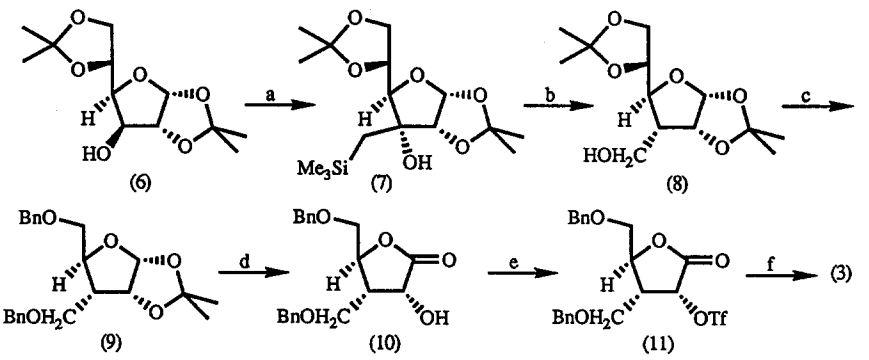
Ad = adenine, R = H

AdBz, R = COPh



For the synthesis of the oxetane ester (3), a one carbon extension was introduced at C-3 of diacetone glucose (6). Initial pyridinium chlorochromate oxidation to the ketone, followed by treatment with the Grignard reagent from chloromethyltrimethylsilane afforded the β-trimethylsilyl alcohol (7), m.p. 128-130°C; $[\alpha]_D^{20}$ +16.9° (*c*, 0.68)[8] in 90% yield. Subsequent Peterson fragmentation[9] of (7) and hydroboration gave the C-3 branched allose (8)[10] $[\alpha]_D^{20}$ +28.6° (c, 1.24) in 72% yield. Selective hydrolysis of the exocyclic acetonide of (8), followed by periodate oxidation, borohydride reduction and dibenzylation of the resulting diol according to known

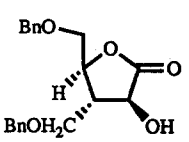
procedures[6], afforded the fully protected branched ribose (9) {$[\alpha]_D^{20}$ +39.9° (c, 1.35), Lit.[10] no rotation data supplied} in 70% yield over the 4 steps. Treatment of (9) with aqueous trifluoroacetic acid, followed by bromine water oxidation, gave the *ribono*lactone (10) $[\alpha]_D^{20}$ +9.12° (c, 1.54) which, on esterification with triflic anhydride, produced the lactone triflate (11), m.p. 75-76°C, $[\alpha]_D^{20}$ -4.18° (c, 0.11) [72% yield from (9)]. Addition of (11) to a stirred suspension of potassium carbonate in methanol caused ring contraction with predominant inversion of configuration at C-2 to give the oxetane (3) $[\alpha]_D^{20}$ -7.74° (c, 2.3) in 56% yield [20% from (6)]. Reaction of the triflate (11) with sodium trifluoroacetate, followed by methanol, gave the *arabinono*lactone (12), $[\alpha]_D^{20}$ +1.3° (c, 0.96) [94% yield]. Esterification of (12) with triflic anhydride in dichloromethane in the presence of pyridine at -40°C gave the corresponding triflate which on treatment with potassium carbonate in methanol underwent ring contraction, again with predominant inversion of configuration at C-2, to the oxetane ester (13), $[\alpha]_D^{20}$ +14.3° (c, 0.5), providing a suitable intermediate for the synthesis of C-nucleoside analogues of oxetanocin.[11]



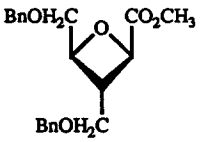
a) PCC, 4Å sieves / CH_2Cl_2 then Me_3SiCH_2MgCl; b) NaH / THF then BH_3-DMS then aq. NaOH; c) aq. AcOH then $NaIO_4$ / aq. EtOH then $NaBH_4$ / EtOH then NaH, BnBr / DMF; d) aq. TFA then Br_2, barium benzoate / aq. dioxane; e) Tf_2O, pyridine / CH_2Cl_2 at -30°C; f) K_2CO_3 / dry methanol.

The oxetane ester (3) was converted to the required chlorooxetanes (16) by the Barton modification of the Hunsdiecker reaction.[12] Hydrolysis of the methyl ester (3) and treatment with oxalyl chloride gave the acid chloride (14) which was converted to the corresponding thiohydroxamic ester (15) by treatment with the sodium salt of N-hydroxypyridine-2-thione. The radical decarboxylative chlorination of the thiohydroxamic ester (15) to give the epimeric chlorides (16) was problematic, due to the instability of the chlorides (16) to a variety of work-up conditions; attempts to react the crude chlorides (16) with adenine, or N-benzoyl or silylated adenine did not give coupled products. However, the chlorides (16) were trapped by addition of thiophenol with potassium carbonate and 18-crown-6 to give the relatively stable thioglycosides (17)[13] in 54% yield overall from the ester (3). Regeneration of the chlorides (16) from the thioglycosides (17) with chlorine in chloroform, followed by addition of benzoyl-adenine and potassium carbonate, gave an epimeric mixture of the protected oxetanocins (18)[14] and (19)[15] [9% and 14% yields respectively from (17)] which could be separated chromatographically. Subsequent deprotection of (18) and (19) with sodium hydroxide in methanol, followed by transfer hydrogenation with palladium hydroxide and cyclohexene in an atmosphere of hydrogen, gave oxetanocin (1)[16] and α-oxetanocin (2)[17] in 71 and 60% yields respectively. The oxetanocin prepared was identical spectroscopically to an authentic sample; the ^1H and ^{13}C NMR spectra of both the synthetic material and

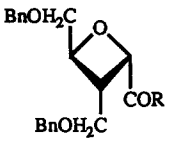
authentic oxetanocin were run in d_4-MeOH and were superimposable.[18] Additionally, the properties of both oxetanocin (1) and the α-epimer (2) as anti-viral agents against HIV *in vitro* were compared;[19] oxetanocin [I_{50} 0.5-1.5 μg/ml] showed significant activity whereas α–oxetanocin (2) showed no such anti-viral effects at concentrations up to 100 μg/ml. The lack of antiviral activity of the α-nucleoside (2) demonstrates that the chromatographic separation of the protected nucleosides (18) and (19) was efficient.



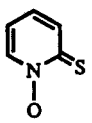
(12)

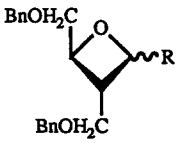


(13)

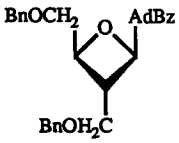


(14) R = Cl

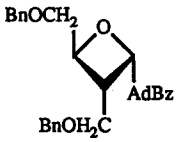
(15) R= 



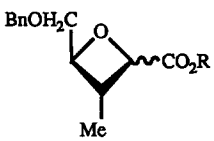
(16) R = Cl
(17) R = SPh



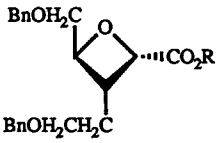
(18)



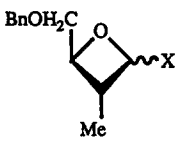
(19)



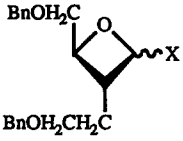
(20) R = Me
(21) R = H



(22) R = Me
(23) R = H



(24) X = Cl
(25) X = OCOMe



(26) X = Cl
(27) X = OCOMe

All attempts to convert the methyl carboxylates (20) [epimeric mixture, α:β ratio 8:1] and (22) [α-isomer][20] to the analogous chlorooxetanes (24) and (26) by similar methodology failed; their thiopyridinehydroxamic esters gave no indication of oxetanosyl chloride formation under decarboxylation conditions. Unlike (16), these chlorides could not be trapped with thiophenol. Hydrolysis of esters (20) and (22) gave the oxetane carboxylic acids (21) and (23) {$[\alpha]_D^{20}$ -25.7° (c, 0.44)}, respectively. In both cases, the reactions of the acids (21) and (23) with lead tetraacetate and N-chlorosuccinimide in a mixture of dimethyl formamide and acetic acid gave the oxetanosyl acetates (25)[21] and (27)[22] [in 75% and 69% yield respectively] rather than the expected chlorides.[23,24] Oxetanosyl acetates have also been formed by the Baeyer Villiger reaction of 1-acetyloxetanes;[25] great care in choice of protecting groups is necessary to acheive Lewis acid mediated coupling of such species to oxetanocins even in modest yield.[4,5] However, all attempts to couple the acetates (25) and (26) with adenine, silylated adenine or benzoyl adenine under either basic or acidic conditions gave very complex reaction mixtures. No materials were isolated which contained adenine connected to an oxetane ring; small amounts of materials with either a furanose or an open chain structure were obtained. It is clear from their behaviour that α-chlorooxetanes having only carbon substituents at C-3 of the oxetane are much less stable than are those having inductively withdrawing oxygen, azide or fluoro[26] substituents at C-3. While chlorooxetanes with β-electron withdrawing

substituents undergo nucleoside coupling reactions with adenine in moderate to good yields,[6,7] chlorooxetanes lacking such substituents are much less attractive synthetic intermediates.[27]

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8. Unless otherwise stated, all specific rotations were determined in chloroform and NMR spectra were run in deuteriochloroform; all new compounds in this paper had consistent spectral data and satisfactory CHN microanalyses were obtained for: (3) (7) (9) (10) (11) (12) (13) (17) (18) (19) (20).
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13. For the epimeric thioglycosides (17): α:β 1.7:1; ^{1}H NMR δ 7.21-7.51 (m, 15H, Ar), 6.16 (d, 0.37H, H-1β, $J_{1,2}$ 7.8Hz), 5.8 (d, 0.63H, H-1α, $J_{1,2}$ 6.7 Hz), 4.79-4.86 (ddd, 0.37H, H-3β, J 3.7 Hz, 6.4 Hz), 4.50-4.72 (m, 4.63 H, H-3α, 2 x PhCH_2), 3.76-3.89 (m, 0.74 H, H-2'β), 3.57-3.71 (m, 2.37 H, H-2'α, H-4β, H-2β), 3.45-3.48 (m, 1.26 H, H-4α), 2.92-3.04 (m, 0.63 H, H-2α). *m/z* (CI NH_3) 424 (MNH_4^+, 1%), 149 (100%).
14. Data for (18): ^{13}C NMR δ 164.80 (s), 152.96 (d), 149.56 (s), 142.76 (d), 137.76 (s), 137.51 (s), 137.44 (s), 133.84 (s), 132.89 (d), 129.68 (d), 128.99 (d), 128.77 (d)128.63 (d), 128.44 (d), 128.19 (d), 127.98 (d), 127.76 (d), 127.63 (d) 85.35 (d), 77.47 (d), 73.60 (t), 73.34 (t), 70.36(t), 67.02 (t), 44.63 (d); $[\alpha]_D^{20}$ -21.8° (c, 0.39).
15. Data for (19): ^{13}C NMR δ 164.76 (s), 152.87 (d), 149.55 (s), 141.93 (d), 137.89 (s), 137.07 (s), 133.84 (s), 132.93 (d), 129.03 (d), 128,76 (d), 128.67 (d)138.45 (d), 128.20 (d), 127.98 (d), 127.75 (d), 127.07 (s), 85.35 (d), 81.38 (d), 73.70 (t), 73.27 (t), 71.05 (t), 65.88 (t), 41.26 (d); $[\alpha]_D^{20}$ -36.8° (c, 0.44).
16. Data for (1): ^{1}H NMR (d_4 MeOH) δ 3.70-3.95 (5H), 4.85 (1H), 6.49 (1H, J 5.3 Hz), 8.20 (1H) and 8.65 (1H) [lit (N. Shimada, S. Harada, T. Tomisawa, A. Fujii and T. Takita, *J. Antibiot.*, 1986, 39, 1623) (in d_6-DMSO): 3.66-3.78 (5H), 4.55 (1H), 5,40 (1H, OH), 5.04 (1H, OH), 6.42 (1H, J 5.5 Hz), 7.37 (2H, NH_2), 8.18 (1H), and 8.65 (1H)]; ^{13}C NMR (d_4 MeOH) δ 157.50 (s), 153.86 (d), 150.29 (s), 141.77 (d), 137.26 (s), 83.25 (d), 80.13 (d), 64.02 (t), 50.36 (t), 46.89 (d); $[\alpha]^{20}$ (c 0.35 in MeOH): (λ °) 589 -20.0; 578 -21.2; 546 -24.1; 436 -44.3; 365 -83.8.
17. Data for (2): ^{1}H NMR (d_4 MeOH) δ 3.54-3.59 (3H), 3.79-3.89 (2H),4.98 (1H), 6.70 (1H), 8.19 (1H) and 8.45 (1H) [lit (ref 4) (in d_6-DMSO): 2.72 (1H), 3.55 (2H), 3.92 (1H), 4.00 (1H), 4.23 (1H), 6.05 (1H, J 3.9 Hz), 8.15 (1H), and 8.36 (1H)]; ^{13}C NMR (d_4 MeOH) δ 157.38 (s), 153.90 (d), 150.23 (s), 141.14 (d), 139.26 (s), 86.38 (d), 84.83 (d), 64.56 (t), 59.43 (t), 43.87 (d); $[\alpha]^{20}$ (c 0.35 in MeOH): (λ °) 589 -13.7; 578 -14.4; 546 -16.2; 436 -23.6; 365 -12.4.
18. We are grateful for an authentic sample of oxetanocin and for spectra kindly provided by Professor Yamamura of Keio University.
19. We thank Dr. J. A. V. Coates, Miss H. Inggall and Dr. N. Cammack of the Virology Department, Glaxo Group Research, Greenford for biological evaluation of these compounds.
20. F.X.Wilson, G.W.J.Fleet, S. Choi, K.Vogt, Y. Wang, D.R.Witty, R.Storer, P.L.Myers, C.J.Wallis, accompanying paper.
21. Data for epimeric acetates (25): α:β 1:1; ^{13}C NMR δ 11.26 and 14.45 (2q, MeCH), 20.90 (COMe), 35.57 and 38.77 (2d, C-2). 71.34, 72.17, 73.42 and 73.52 (4t, C-4 and PhCH_2), 82.45 and 86.01 (2d C-3), 98.87 and 101.22 (2d C-1), 127.76 (d), 128.49 (d), 138.28 (s), 170.01 and 170.19 (2s, COMe); ν_{max} (film) 1746 (C=O) cm^{-1}.
22. Data for epimeric acetates (27): α:β 1:1.2; ^{13}C NMR δ 20.6 (q, Me-α), 20.95 (q. Me-β), 26.30 (t, C-2'α), 29.21 (t, C-2'β), 38.88 (d, C-2α), 41.98 (d, C-2β, 62.56 (t, C-2"β), 62.62 (t, C-2"α), 99.38 (d, C-1β), 128.37, 128.46, 129.52, 129.73, 129.81, 130.58 (6d, C-ArHαβ), 133.16, 133.22 (2s, C-Arαβ), 166.19 (s, C=Oβ), 169.60 (s, C=Oα); ν_{max} (film) 1719 (C=O) cm^{-1}.
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