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OXETANE NUCLEOSIDES WITH FLUORINE AND AZIDE SUBSTITUENTS: NUCLEOPHILIC DISPLACEMENTS ON AN OXETANE RING

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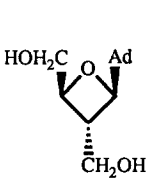
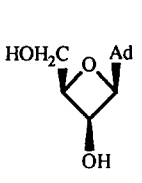
Fluorine and azide substituents are introduced into an oxetane ring by nucleophilic displacement reactions; the syntheses and anti-viral activities of 9-(2'-azido-2'-deoxy-β-D-*erythro*-oxetanosyl)-adenine and of 9-(2'-deoxy-2'-fluoro-β-D-*erythro*-oxetanosyl)-adenine are reported.

The potent anti-viral activity of the naturally occurring oxetane nucleoside oxetanocin (1)[1] has stimulated much interest in synthetic analogues[2] and in oxetane chemistry in general.[3] A ring contraction of the α-triflate of a γ-lactone, induced by potassium carbonate in methanol, to an oxetane carboxylic ester[4] was a key step in the synthesis of norepioxetanocin (2),[5] a powerful antiviral compound;[6] the same strategy has also been used in a synthesis of oxetanocin.[7] In view of the interest in the biological activity of fluoro and azido furanosyl nucleosides,[8] we have investigated several approaches to the synthesis of oxetane nucleosides containing fluoro and azido functional groups; for example, it has been shown that elimination, rather than ring contraction, predominates on treatment of α-triflates of γ-lactones containing β-azide or β-fluorine substituents with potassium carbonate in methanol.[9] An alternative strategy is to introduce the fluoro and azido functionalities by nucleophilic substitution at position 3 of an oxetane ring; however, very few examples of such reactions have previously been reported, even in relatively unsubstituted oxetanes.[10] This paper describes the synthesis of azido- (3) and fluoro- (4) oxetane nucleosides by apparent S_N2 reactions on derivatives of 3-hydroxy-oxetane-2-carboxylic esters.



(1)



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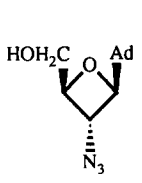

(3)

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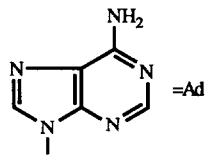
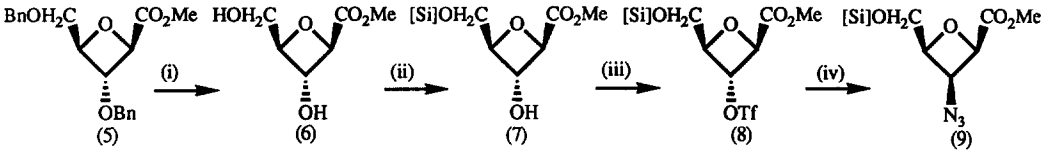


Synthesis of azido oxetanes. Hydrogenolysis of the benzyl protecting groups in the oxetane intermediate (5), obtainable from diacetone glucose in 41% yield,[4] in methanol in the presence of palladium black gave an 86% yield of the crystalline diol ester (6),[11] m.p. 46-49°C $[\alpha]_D^{20}$ + 28.5 (*c*, 0.48 in MeOH). Treatment of (6) with *tert*-butylchlorodiphenylsilane in dimethylformamide in the presence of imidazole at 5°C resulted in the selective formation of the silyl ether (7), $[\alpha]_D^{20}$ +18.8 (c, 1.49), [85% yield] which, on esterification with triflic anhydride, afforded the required triflate (8), $[\alpha]_D^{20}$ +7.53 (*c*, 0.73) in 92% yield. It is noteworthy that the four membered ring β-hydroxy ester (6) does not undergo a reverse aldol reaction during the introduction

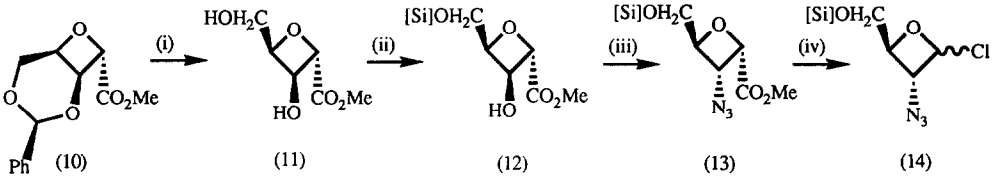
of the protecting silyl group under base catalysed conditions. Treatment of the highly hindered triflate (8) with sodium azide in dimethylformamide at room temperature gave the azide (9),[12] m.p. 85-87°C, $[\alpha]_D^{20}$ -11.2 (*c*, 1.06), in 90% yield. The all *cis* stereochemistry of the product (9) was indicated by n.O.e. studies[13] and confirmed by single crystal X-ray analysis.[14] The stereochemical result of this nucleophilic displacement - in high yield and with complete inversion of configuration - indicates an easy S_N2 reaction; no competing elimination reaction was observed, even though the triflate in (8) is β to the ester function.



(i) MeOH, H_2, Pd black; (ii) $^tBuPh_2SiCl$, imidazole, DMF; (iv) Tf_2O, py, CH_2Cl_2; (v) NaN_3, DMF.

The isomeric azide (13) was synthesised from the benzylidene oxetane (10), available in 3 steps from D-lyxonolactone.[5] Hydrogenolysis of the benzylidene protecting group in (10) gave the diol (11), $[\alpha]_D^{20}$ -22.3 (*c*, 1.18 in acetone), which on reaction with *tert*-butylchlorodiphenylsilane afforded the mono-silyl ether (12) $[\alpha]_D^{20}$ +2.4 (*c*, 1.25) [66% yield from (10)]. Esterification of the free hydroxy group in (12) with triflic anhydride, followed by treatment of the resulting triflate with sodium azide in dimethylformamide, gave the corresponding azido-oxetane (13)[15] $[\alpha]_D^{20}$ + 35.4 (*c*, 1.25) in 86% yield. The azide (13) was identical in all respects to the material obtained from the ring contraction of the *arabino*-azide (15);[9] thus the displacement of the triflate by azide ion again proceeds in high yield with inversion of configuration, indicating a clean S_N2 reaction.

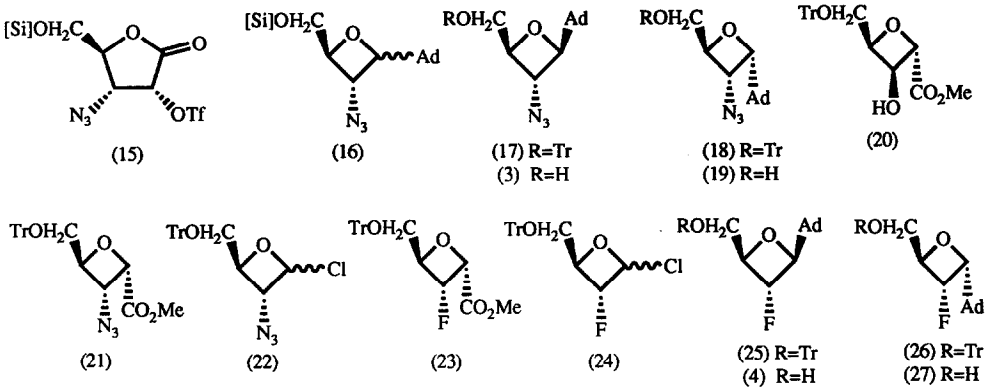
The azido-oxetane (13) was converted by the Barton modification of the Hunsdiecker reaction[16] to a 1:1 epimeric mixture of chlorides (14) [71% yield], which on treatment with adenine in dimethylformamide in the presence of sodium carbonate gave an anomeric mixture (α:β, 1.3:1) of the protected nucleosides (16) in 48% yield. Although no success was achieved in the separation of the anomers (16) at this stage, removal of the silyl protecting group by tetrabutylammonium fluoride in tetrahydrofuran gave the epimeric nucleosides (3),[17] $[\alpha]_D^{20}$ +12.1 (*c*, 0.42 in methanol), and (19),[18] $[\alpha]_D^{20}$ +28.2 (*c*, 0.14 in methanol), which were readily separated by flash chromatography and their relative stereochemistries established by n.O.c. analysis.[19]



(i) MeOH, AcOH, H_2, Pd black; (ii) $^tBuPh_2SiCl$, imidazole, DMF; (iii) Tf_2O, py, CH_2Cl_2 then NaN_3, DMF; (iv) NaOH, MeOH then $(COCl)_2$, benzene then *N*-hydroxypyridine-2-thione, Na salt, CCl_4

The diol (11) could also be mono-protected as its trityl ether (20) $[\alpha]_D^{20}$ + 39.6 (*c*, 2.4) [75% yield] which, on treatment with trifluoromethanesulphonic anhydride followed by sodium azide in dimethylformamide, afforded the corresponding azido-oxetane (21)[20] $[\alpha]_D^{20}$ + 55.1 (*c* 1.76) in 90% yield. Hydrolysis of (21),

followed by treatment of the resulting sodium salt with *N*-chlorosuccinimide and lead tetraacetate in a mixture of acetic acid and dimethylformamide,[21] afforded the epimeric chlorides (22) (α:β, 2:1) in 55% yield. Treatment of (22) with adenine, potassium carbonate and 18-crown-6 in dimethylformamide at 100 °C, caused an apparently clean S_N2 displacement to afford a separable anomeric mixture (α:β, 1:2) of nucleosides (17)[12] m.p. 63-65°C, $[\alpha]_D^{20}$ -12.6 (*c*, 0.22) and (18)[13] m.p. 75-76°C, $[\alpha]_D^{20}$ - 1.25 (*c*, 0.4) in a combined yield of 55%. Removal of the trityl protecting group from (17) and (18) by trifluoroacetic acid in methanol at room temperature gave (3) and (19) in 95% yields, identical to the samples produced above.



Bn = $PhCH_2$; [Si] = $^tBuPh_2Si$; Tr = Ph_3C; Tf = CF_3SO_2

Synthesis of fluoro oxetanes. Treatment of the trityl protected alcohol (20) with diethylaminosulphur trifluoride gave a single fluoro compound[22] (23), $[\alpha]_D^{20}$ -9.09 (*c*, 0.44), in 60% yield. Hydrolysis of the ester function in (23) and treatment of the resulting sodium salt with *N*-chlorosuccinimide and lead tetraacetate in a mixture of acetic acid and dimethylformamide gave an anomeric mixture of chloro products (24; α: β ratio 3:1) in 60% yield over the two steps. Reaction of (24) with adenine gave an anomeric mixture of protected fluoro oxetane nucleosides (25) and (26), from which the β-isomer (25), m.p. 100-102°C, $[\alpha]_D^{20}$ -13.3 (*c*, 0.3) could be separated in 40% yield; the structure of (25) was firmly established by single crystal X-ray analysis,[14] showing that the fluorine substituent had been introduced into the oxetane ring with inversion of configuration. Deprotection of compound (25) was achieved in 80% yield by treatment with trifluoroacetic acid in methanol for 10 minutes, and afforded 9-(2'-deoxy-2'-fluoro-β-D-*erythro*-oxetanosyl)-adenine (4), m.p. 203-205°C, $[\alpha]_D^{20}$ -13.2 (*c*, 0.31 in dimethylformamide).[23] The protected α-fluorooxetane (26), m.p. 85-87°C, $[\alpha]_D^{20}$ -15.3 (*c*, 0.46), was similarly converted into the α-nucleoside (27), $[\alpha]_D^{20}$ -8.0 (*c*, 0.38 in MeOH).

Antiviral Activity. The properties of the azido (3) and fluoro (4) analogues were compared with oxetanocin (1) [I_{50} 0.5-1.5 μg/ml] as anti-viral agents against HIV (RF Strain) *in vitro*;[24] the azido oxetane (3) [I_{50} 6 μg/ml] showed significant anti-viral activity, whereas the fluoro analogue (4) was inactive at concentrations up to 100 μg/ml.

In summary, this paper reports some surprisingly easy nucleophilic displacements in oxetane rings and further demonstrates the value of α-chlorooxetanes with β-electron withdrawing substituents in the synthesis of oxetane nucleosides.[25]

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11. All new compounds reported in this paper have satisfactory spectroscopic data consistent with the structures proposed. Specific rotations were determined in chloroform except where otherwise stated. All NMR data in this paper were obtained in deuteriochloroform unless otherwise stated. Satisfactory microanalyses have been obtained for compounds (4), (6), (7), (8), (9), (11), (17), (20), (21), (22), (23), (24), (25).

12. Data for (9): ν_{max} 3050, 2950 (CH), 2100 (N_3), 1730 (CO) cm^{-1}; δ_H (d_6 benzene) 7.87-7.75 (4 H, m, Ar-H), 7.26-7.15 (6 H, m, Ar-H), 4.73 (1 H, d, $J_{2,3}$ 7.4 Hz, 2-H), 4.61 (1 H, q, $J_{3,4}$ $J_{4,5}$ $J_{4,5'}$ 6.4 Hz, 4-H), 4.12 (2 H, m, 5-H, 5'-H), 3.28 (3 H, s, OCH_3), 1.16 (s, CMe_3); δ_C 169.2 (s, CO), 135.7 (d, ArCH), 133.2 (s, Ar-C), 129.8, 127.9 (2 d, Ar-CH), 83.3, 79.4 (2 d, 2-C, 4-C), 62.6 (t, 5-C), 58.2 (d, 3-C), 52.2 (q, OCH_3), 26.7 (q, $C(CH_3)_3$), 19.1 (s, $C(CH_3)_3$).

13. Irradiation of 3-H gives enhancements of 9.7% at 2-H and 9.0% at 4-H.

14. The atomic coordinates for both (9) and (25) 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.

15. Data for (13): δ_C 17.1 (s), 26.7 (q), 52.3 (q), 56.6 (d), 63.5 (t), 79.4 (d), 87.2 (d), 128.0 (d), 130.1 (d), 132.6 (s), 133.1 (s), 135.7 (d), 135.8 (d), 169.8 (s).

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17. Data for (3): δ_H (d_4 MeOH) 3.84 (1 H, dd, *J* 2.8, 13.4 Hz, 4'-H), 3.96 (1 H, dd, *J* 3.0, 13.4 Hz, 4"-H), 4.63 (1 H, ddd, *J* 6.0, 3.0, 2.8 Hz, 3'-H), 5.31 (1 H, dd, *J* 5.3, 6.1 Hz, 2'-H), 6.42 (1 H, d, *J* 5.3 Hz, 1'-H), 8.28 (1 H, s, 8-H), 8.60 (1 H, s, 2-H); δ_C (d4 MeOH) 61.9 (d), 62. 6 (t), 83.3 (d), 86.1 (d), 120.4 (s), 141.8 (d), 150.3 (s), 152.7 (d), 156.7 (s).

18. Data for (19): δ_H (d_4 MeOH) 3.86 (1 H, d, *J* 3.2 Hz, 4'-H), 3.88 (1 H, dd, *J* 3.0, 3.2 Hz, 4"-H), 5.00 (1 H, ddd, *J* 5.4, 3.1, 3.0 Hz, 3'-H), 5.56 (1 H, dd, *J* 5.6, 5.4 Hz, 2'-H), 6.8 (1 H, d, *J* 5.6 Hz, 1'-H), 8.27 (1 H, s, 8-H), 8.53 (1 H, s, 2-H); δ_C (d4 MeOH) 59.8 (d), 62. 8 (t), 86.1 (d), 88.7 (d), 120.4 (s), 141.5 (d), 150.3 (s), 153.4 (s).

19. For (3) β-isomer: Irradiate H-3' (4.63): 3.1% at 2', 5% at 1'; Irradiate H-2' (5.31): 3.1% at 1'; Irradiate H-1' (6.42): 2% at 3', 2.4% at 2'; for (19) α-isomer: Irradiate H-2' (5.56): 1.5% at 3', 11% at 1'; Irradiate H-1' (6.79): 8.5% at 2'.

20. Data for (21): δ_C 52.4 (q). 57.1 (d), 63.6 (t), 79.5 (d), 86.2 (d), 127.4 (d), 128.2 (d), 128.5 (d), 128.8 (d), 143.7 (s), 169.8 (s).

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22. Data for (23): δ_C 52.3 (MeO, q), 63.2 (CH_2O, t), 79.9 (C-4, $J_{C,F}$ 23Hz), 85.6 (C-3, $J_{C,F}$ 207Hz), 86.7 (C-2, $J_{C,F}$ 23Hz) 127.1(d), 127.4 (d), 128.2 (d), 128.7 (d), 129.3 (s), 168.2 (s); δ_F -189.8 (s)

23. Data for (4): δ_C (d_6 DMSO): 60.9 (C-4', t), 81.5 (C-3', $J_{3',F}$ 20Hz), 83.9 (C-1', $J_{1',F}$ 29Hz), 89.4 (C-2', $J_{2',F}$ 213Hz), 139.9 (C-2), 153.4 (C-8).

24. We thank Dr. J. A. V. Coates, Mrs H. J. Jenkinson and Dr. N. Cammack of the Virology Department, Glaxo Group Research, Greenford for biological evaluation of these compounds.

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