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ATTEMPTED RING CONTRACTION OF α-TRIFLATES OF 3-AZIDO- AND 3-FLUORO-γ-LACTONES TO OXETANES

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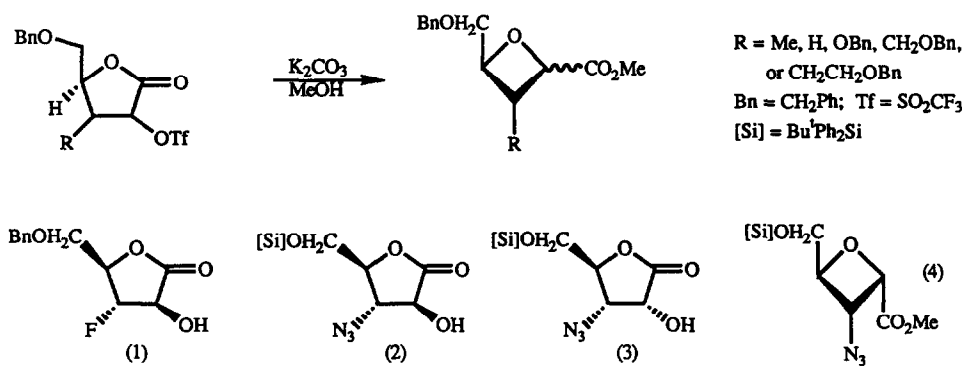
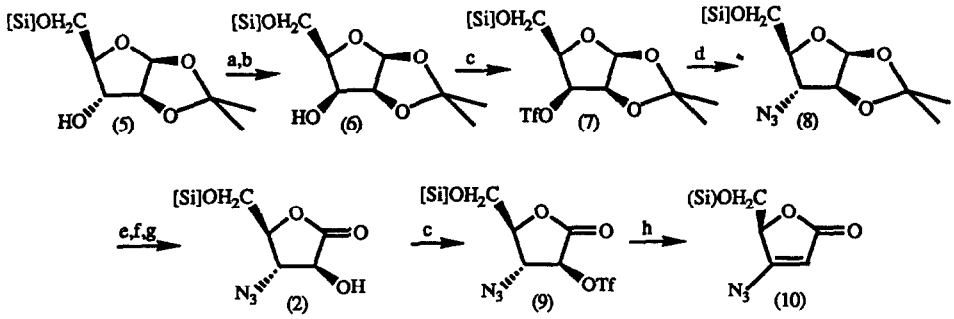
α-Triflates of 3-azido- and 3-fluoro-γ-lactones with potassium carbonate in methanol give mainly contrasting elimination products, rather than oxetanes; a methyl 3-azido-oxetane-2-carboxylate was isolated in low yield.

Oxetane nucleosides, such as the natural product oxetanocin and its analogues, constitute a novel class of anti-viral compounds with activity against HIV, human cytomegalovirus and Herpes simplex II.[1] The ring contraction of α–trifluoromethanesulphonate (triflate) esters of γ-pentonolactones to methyl oxetane carboxylic esters, initiated by potassium carbonate in methanol, proceeds in good to excellent yields for a range of substrates with hydrogen, alkyl[2] and oxygen[3,4] substituents in the β-position. Considerable interest has centered both on the use of highly functionalized oxetanes in nucleoside synthesis,[5] and in the clinical application of azido and fluoro substituted nucleoside analogues as antiviral agents.[6] In view of these considerations and in order to determine the scope of the ring contraction reaction, the β-fluoro lactone (1) and the β-azido lactones (2) and (3) were synthesised. This paper reports the attempted ring-contraction of their trifluoromethanesulphonyl esters as well as the synthesis of an azido-oxetane (4).



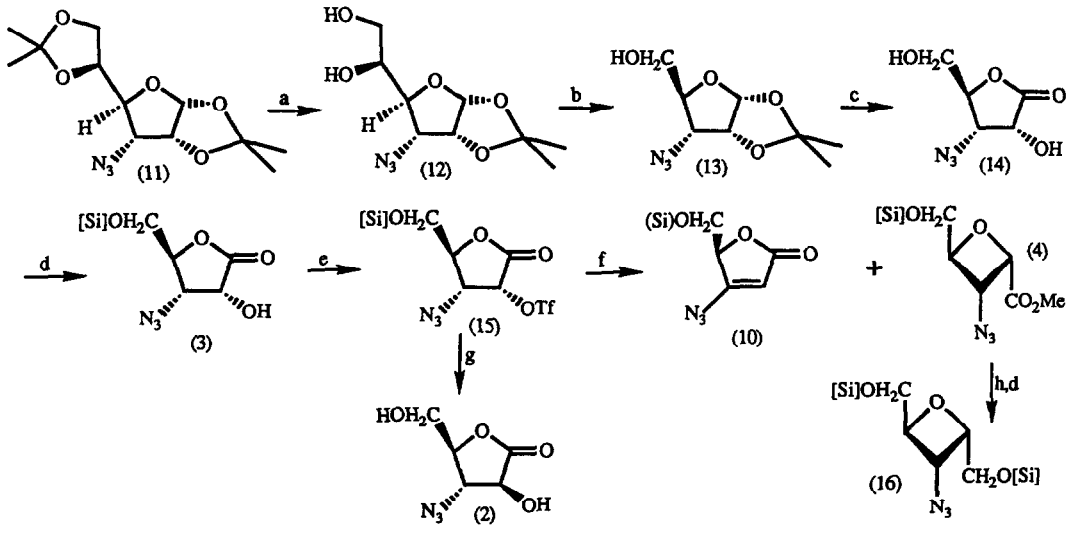
Both lactones (1) and (2) were synthesised from the readily accessible D-arabinofuranose derivative (5)[7] in which only the C-3 hydroxyl group is unprotected. Introduction of fluoro and azido substituents at C-3 with retention of configuration was achieved by a double inversion. Pyridinium chlorochromate oxidation of the D-*arabino* sugar (5) to the 3-ketone, followed by reduction with sodium borohydride, gave exclusively the D-*lyxo* sugar (6), $[\alpha]_D^{20}$ +7.9 (c, 1.20)[8] [Lit.[9] for L-isomer -5.0 (c, 1.2)] in 93% yield over the two steps. Esterification of (6) with triflic anhydride afforded the divergent intermediate (7) in 95% yield.

Synthesis of azidolactones and reaction with potassium carbonate in methanol. Treatment of D-*lyxo* triflate (7) with sodium azide in DMF gave the *arabino* azide (8), [m.p. 37-39°C, $[\alpha]_D^{20}$ +10.3 (c, 1.30)] in 87% yield. The protecting groups were removed with aqueous trifluoroacetic acid and the lactol was oxidised to an azido lactone with bromine in buffered aqueous dioxane. The primary position was then reprotected using *tert*-butylchlorodiphenylsilane with imidazole as base, to give the silyl lactone (2), {$[\alpha]_D^{20}$ +20.9 (c, 1.20 in $CHCl_3$)} in 44% yield over the 3 steps.[10] Treatment of (2) with triflic anhydride in dichloromethane in the presence of pyridine gave the ester (9) which, when subjected to potassium carbonate in methanol underwent elimination to give the unsaturated β-azidolactone (10);[11] no azidooxetanes were isolated.



a) PCC / CH_2Cl_2 / 4A Sieves; b) $NaBH_4$ / EtOH; c) Tf_2O / pyridine / CH_2Cl_2; d)NaN_3 / DMF; e) aq. TFA; f) aq. dioxane / Br_2 / Ba $(OCOPh)_2$; g) *tert*-$BuPh_2SiCl$ / imidazole / DMF; h) MeOH / K_2CO_3.

The analogous *ribo* lactone (15) was synthesised from the protected azido *allo*furanose (11)[12] in seven steps. Removal of the exocyclic acetonide with aqueous acetic acid furnished the monoacetonide (12) in 82% yield [m.p.73-75°C, $[\alpha]_D^{20}$ +76.0 (c, 1.02 in acetone), Lit.[13] m.p.76-77°C, $[\alpha]_D^{20}$ +111 (c, 1.5)]. The diol (12) was cleaved using sodium periodate in aqueous ethanol; the resulting aldehyde was reduced with sodium borohydride

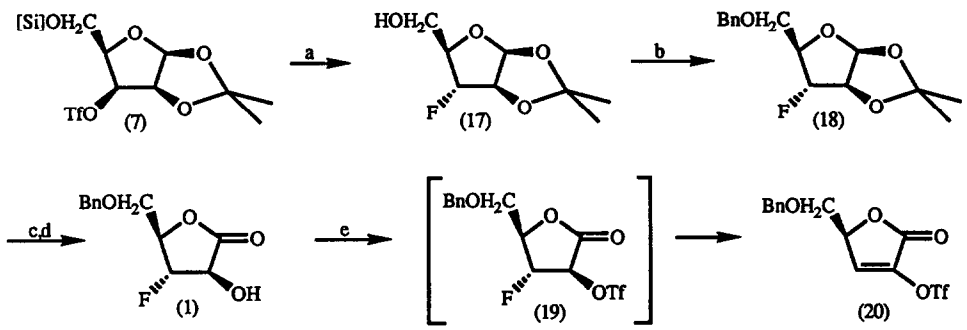


a) aq AcOH; b) $NaIO_4$ / aq EtOH then $NaBH_4$ / EtOH; c) aq. TFA then aq. dioxane / Br_2 / Ba $(OCOPh)_2$; d) $^tBuPh_2SiCl$, imidazole / DMF; e) Tf_2O / pyridine / CH_2Cl_2; f) K_2CO_3 / MeOH; g) $NaOCOCF_3$ / DMF then MeOH / wet SiO_2; h) $NaBH_4$ / EtOH.

to give the azidoribofuranose (13), [(m.p. 46-47°C, $[\alpha]_D^{20}$ +130.4 (c, 0.97), Lit.[14] an oil - no rotation quoted] in 80% yield over the two steps. Hydrolysis of the remaining acetonide group using aqueous trifluoroacetic acid was followed by oxidation of the lactol with bromine in a buffered aqueous dioxane solution affording the hydroxylactone (14) {$[\alpha]_D^{20}$ +156.7 (c, 1.54 in acetone)} in quantitative yield.

Protection of the primary alcohol of (14) by *tert*-butylchlorodiphenylsilane and imidazole in dimethyl formamide gave the hydroxylactone (3) [m.p. 30°C, $[\alpha]_D^{20}$ +63.3 (c, 1.90)] in 53% yield.[15] Esterification of the 2-position was effected with trifluoromethanesulphonic anhydride and pyridine in dichloromethane forming (15) as an unstable oil. On treatment with potassium carbonate in methanol, this *ribo* triflate (15) gave principally the same elimination product (10) as the *arabino* triflate (9), arising from base induced elimination of triflic acid. However, the ring contracted material (4)[16] $[\alpha]_D^{20}$ +35.4 (c, 1.25) was also isolated [10% yield]. The stereochemistry of the oxetane (4) was determined by elaboration to the bis-silyl ether (16)[17] by reduction of the ester function followed by silylation. The bis-silyl ether (16), $[\alpha]_D^{20}$ +8.6 (c, 1.45), was shown to be unsymmetrical both by the number of lines in its ^{13}C spectrum and by its non-zero optical rotation, proof that this product arises from ring contraction with *inversion* of configuration at C-2 of the lactone (11). The lactone (2) was also synthesised by epimerisation of lactone (3); reaction of triflate (11) with sodium trifluoroacetate in dimethyl formamide, followed by workup with methanol and silica, afforded the lactone (2), identical spectroscopically to that produced from D-arabinose.

Synthesis of the fluorolactone (1) and reaction with potassium carbonate in methanol. Treatment of (7) with tetrabutylammonium fluoride in tetrahydrofuran resulted in displacement of triflate by fluoride and simultaneous removal of the silyl protecting group to give (17), [m.p. 65-67°C, $[\alpha]_D^{20}$ +18.1 (c, 0.95)]. The primary hydroxyl group in (17) was reprotected as a benzyl ether by reaction with benzyl bromide and sodium hydride in tetrahydrofuran to give the fluoro-arabinose (18), $[\alpha]_D^{20}$ 3.1 (c, 1.50) in 90 % yield over the two steps. Hydrolysis of the acetonide group in (18) with aqueous trifluoroacetic acid, followed by oxidation of the resulting lactol with bromine afforded the lactone (1), [m.p. 46-48.5°C, $[\alpha]_D^{20}$ +8.0 (c, 0.85)] in 83% yield.[18] All attempts to synthesise the α-triflate ester (19) resulted in an *in situ* elimination to the stable crystalline enol triflate (20), [m.p. 44-45°C, $[\alpha]_D^{20}$ -42.6 (c, 0.90)] in 88% yield;[19] no ring contracted products were isolated.



a) NBu_4F / THF; b) BnBr / DMF / NaH; c) aq. TFA; d) Br_2 / barium benzoate / aq. dioxan; e) Tf_2O / pyridine / CH_2Cl_2.

In summary, the β-azido lactone triflates (9) and (15) mainly undergo elimination of triflic acid on treatment with potassium carbonate in methanol whereas the β-fluoro lactone (19) eliminates hydrogen fluoride to give a stable enol triflate; at best, only very low yields of oxetanes were obtained in these reactions. Alternative approaches to the synthesis of fluoro- and azido-oxetane nucleosides are being explored.[20]

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8. *Specific rotations in this paper were determined in chloroform unless stated otherwise; all stable new* compounds reported here have satisfactory spectral data and, excepting (10) which could not be isolated pure, all have satisfied microanalysis.

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10. Data for (2): ^{1}H NMR ($CDCl_3$) δ 1.08 (9H, s, ^{t}Bu), 3.19 (1H, br s, OH), 3.80-4.05 (2H, dq, H,H'-5, $J_{H,H'}$ 12.3 Hz, $J_{4,5}$ 2.4 Hz, $J_{4,5'}$ 2.9 Hz), 4.13 (1H, m, H-4), 4.44 (1H, dd, H-3, $J_{2,3}$ 9.0 Hz, $J_{3,4}$ 8.1 Hz), 4.51 (1H, d, H-2), 7.45-7.68 (10H, m, $SiPh_2$); ^{13}C NMR δ 19.1 (s, $Me_3\underline{C}$), 26.7 (q, Me_3C), 61.0 (t, C-5), 62.8 (d, C-4), 73.4, 79.3 (2d, C-3, C-2), 128.1, 130.2, 132.0 (3d, C-ArH), 135.8 (s, C-Ar), 173.8 (s, C=O); ν_{max} (film) 3450 (br, OH), 2940, 2110 (N_3) and 1800 (C=O) cm^{-1}.

11. Data for (10): ^{1}H NMR ($CDCl_3$) δ 1.05 (9H, s, ^{t}Bu), 3.86-3.92 (2H, m, H-5,5'), 5.02 (1H, m, H-4), 6.50 (1H, m, H-1), 7.44-7-69 (10H, m, Ar); ν_{max} (film) 2940, 2120 (N_3) and 1770 (C=O) cm^{-1}.

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15. Data for (3): ^{1}H NMR ($CDCl_3$) δ 1.06 (9H, s, ^{t}Bu), 3.37 (1H, br s, OH), 3.78, 3.91 (2H, 2dq, H,H'-5, $J_{H,H'}$ 12.1 Hz, $J_{4,5(5')}$ 2.9 Hz), 4.34 (1H, m, H-4), 4.43 (1H, d, H-3, $J_{2,3}$ 6.4 Hz), 5.04 (1H, d, H-2), 7.42-7.58 (10H, m, $SiPh_2$); ^{13}C NMR δ 18.9 (s, $Me_3\underline{C}$), 26.6 (q, Me_3), 63.4 (t, C-5), 61.3 (d, C-4), 69.7, 82.5 (2d, C-3, C-2), 128.2, 130.4, 131.5, 132.2 (4d, C-ArH), 135.6, 135.7 (2s, C-Ar), 175.3 (s, C=O); ν_{max} (film) 3450 (br, OH), 3025, 2130 (N_3) and 1790 (C=O) cm-^{1}.

16. Data for (4): ^{1}H NMR ($CDCl_3$) δ 1.13 (9H, s, ^{t}Bu), 3.87 (2H, 2dd, H-4,4'), 3.91 (3H, s, CH_3O), 4.71-4.76 (1H, m, H-3), 4.98 (1H, dd, H-2, $J_{1,2}$ 7.6 Hz, $J_{2,3}$ 5.3 Hz), 5.27 (1H, d, H-1, $J_{1,2}$ 7.6 Hz), 7.38-7.75 (10H, m, Ar).

17. Data for (16): $[\alpha]_D^{20}$ +8.6 (c, 1.45 in $CHCl_3$); ^{13}C NMR ($CDCl_3$) δ 19.07, 19.14 (2s, Si-$\underline{C}$), 26.66, (q, Me), 57.00 (d, C-2), 63.17, 64.34, (2t, C-1, C-5), 81.64, 85.67 (2d, C-2, C-4), 127.87, 127.96, 129.88, 129.99 (4d, Ar-H), 133.03, 133.29, 133.46 (3s Ar).

18. Data for (1): ^{1}H NMR ($CDCl_3$) δ 3.79 (2H, m, H,H'-5), 4.15 (1H, br s, OH), 4.50-4.70 (4H, m,, H-2, H-4, $C\underline{H}_2Ar$), 5.17 (1H, dt, H-3, $J_{3,F}$ 53.2 Hz, $J_{2,3}$ 4.4 Hz, $J_{3,4}$ 4.2 Hz), 7.30-7.40 (5H, m, H-Ph); ^{13}C NMR δ 67.8 (t, C-5), 74.0 (t, $C\underline{H}_2Ph$), 76.2 (dd, C-3, $J_{3,F}$ 379.2 Hz), 91.8, 95.5 (2d, C-2, C-4), 128.2, 128.6, 129.0 (3d, C-ArH), 136.6, (s, C-Ar), 173.6 (s, C=O); ν_{max} (film) 3388 (br, OH), 2950 and 1794 (C=O) cm-^{1}.

19. Data for (20): ^{1}H NMR ($CDCl_3$) δ 3.75 (2H, d, H-5,5',$J_{4,5}$ 5.0 Hz), 4.54 (2H, s, $ArC\underline{H}_2$), 5.21 (1H, m, H-4), 7.25-7.43 (5H, m, Ar); ^{13}C NMR δ 68.4 (t, C-5), 73.9 (t, $C\underline{H}_2Ph$), 77.8 (d, C-4), 118.6 (q, CF_3) 127.9, 128.3, 128.7, 136.3 (4d), 137.1 (s), 138.0 (s); 164.0 (s, C-1). ν_{max} (KBr): 1790 (C=O) cm-^{1}.

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