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Thiosugars. Part 5: Synthesis and Biological Activity of 1-(4-Thio-L-arabinofuranosyl)-5-halopyrimidine Nucleosides[†]

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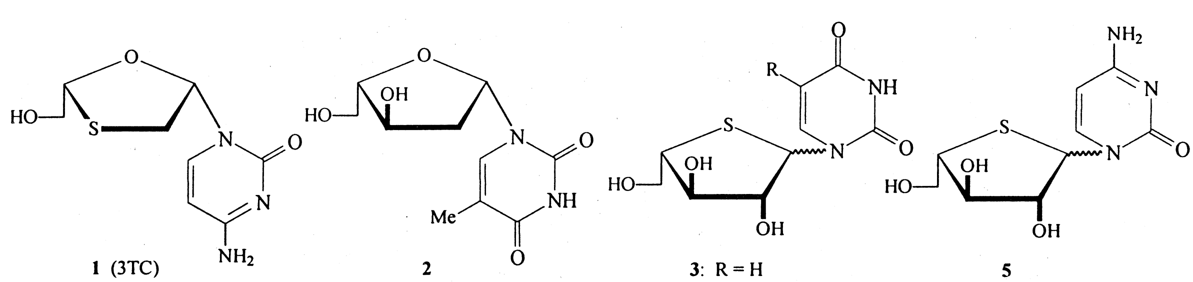
Abstract—1-*O*-Acetyl-2,3,5-tri-*O*-benzyl-4-thio-L-arabinofuranoside (**6**) was transformed in two steps into the 1-(4-thio-L-arabinofuranosyl)-5-halopyrimidine nucleosides **10**, **11** and **12**, obtained as anomeric mixtures which were separable in the case of **10** and **11**. No in vitro antiviral activity against HIV-1 and HIV-2, TK^+- and TK^- VZV and CMV has been found for **10**, **11** and **12**.

4′-Thionucleosides with the natural D-configuration have been of interest for about two decades. Several nucleosides have been prepared and tested for their biological activities.[2] Since the discovery of L-(−)-3TC (**1**) as an antiviral compound L-nucleosides have become compounds of interest. 2′-Deoxy-L-thymidine (**2**) is another good example of an L-nucleoside which shows a weak activity against herpes simplex virus type 1 (HSV-1).[3] Recently we reported[4] the synthesis of 1-(4-thio-L-arabinofuranosyl)uracil (**3**) and thymine (**4**). Independendly, Yoshimura et al.[5] prepared the same thymidine nucleoside **4** and the analogous cytidine nucleoside **5**. They found that the α-anomer of **5** has a moderate anti-HSV-1 and anti-HSV-2 activity. We report here the synthesis of several halogen substituted pyrimidine nucleosides with L-arabino configuration.

Starting from D-xylose we synthesised the benzyl protected 1-*O*-acetyl-4-thio-L-arabinofuranoside **6** in five steps.[4] Glycosidation of **6** with silylated pyrimidine bases[6] in the presence of trimethylsilyl trifluoromethanesulfonate[7] (TMSOTf) in dry MeCN led to anomeric mixtures of the benzyl protected nucleosides **7**, **8** and **9**. In all three cases the α-anomer was the main product. Treatment of these compounds with boron tribromide in CH_2Cl_2 at −80 °C followed by quenching of the reaction mixture with methanol,[8] neutralisation with silver carbonate[4] and silica gel chromatography gave anomeric mixtures



1 (3TC) 2 3: R = H 4: R = Me 5

[†]Part 4: ref 1; Part 2: ref 4
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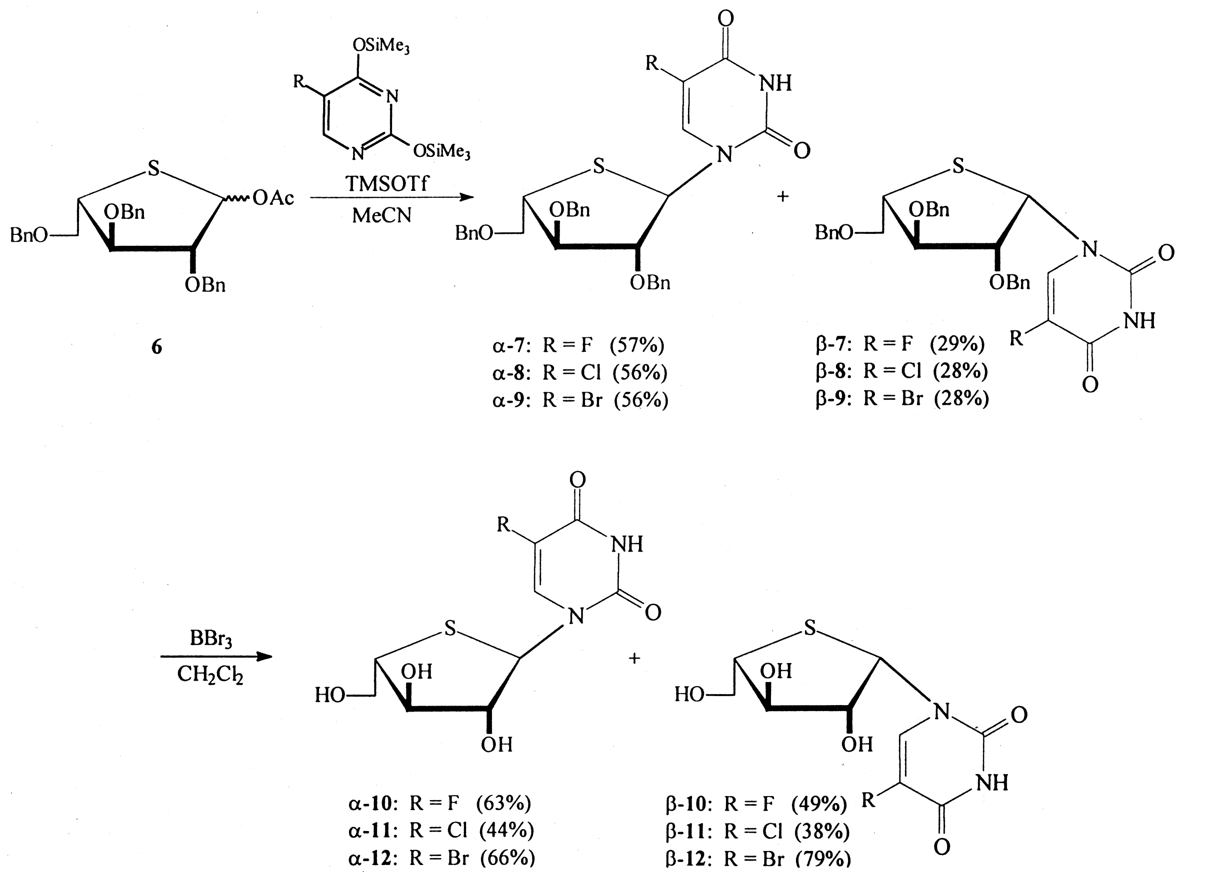

Scheme 1.

of the unprotected nucleosides **10**[9] (α:β 13:5), **11**[10] (α:β 12:5) and **12**[11] (α:β 10:6) (Scheme 1). Reversed phase HPLC[12] yielded the pure anomers of **10** and **11**. The anomeric mixture of **12** could not be separated.

No in vitro antiviral activity against HIV-1 and HIV-2, TK^+ VZV (YS strain and OKA strain), TK^- VZV (07/1 strain and YS/R strain) and CMV (AD-169 strain and Davis strain) has been found for **10**, **11** and **12**.

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9. α-**10**: $[\alpha]_D^{20}$ −81.4 (*c* 1.0, MeOH); mp 210 °C; IR (KBr) ν 3409, 3062, 2930, 2819, 1702, 1477, 1390, 1248, 1097, 1027, 916, 824, 672, 563, 486 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.39 (1H, ddd, $J_{4',5'a}=8.0$, $J_{5'a,5'b}=10.9$, $J_{5'a,OH}=5.4$ Hz, H-5′$_a$), 3.57 (1H, ddd, $J_{3',4'}=7.8$, $J_{4',5'a}=8.0$, $J_{4',5'b}=4.1$ Hz, H-4′), 3.67 (1H, ddd, $J_{2',3'}=7.4$, $J_{3',4'}=7.8$, $J_{3',OH}=4.6$ Hz, H-3′), 3.83 (1H, ddd, $J_{4',5'b}=4.1$, $J_{5'a,5'b}=10.9$, $J_{5'b,OH}=4.7$ Hz, H-5′$_b$), 4.01 (1H, ddd, $J_{1',2'}=7.1$, $J_{2',3'}=7.4$, $J_{2',OH}=5.4$ Hz, H-2′), 4.92 (1H, dd, $J_{5'a,OH}=5.4$, $J_{5'b,OH}=4.7$ Hz, 5′-OH), 5.54 (1H, d, $J_{3',OH}=4.6$ Hz, 3′-OH), 5.72 (1H, d, $J_{2',OH}=5.4$ Hz, 2′-OH), 5.75 (1H, dd, $J_{1',2'}=7.1$, $J_{1',F}=1.8$, H-1′), 8.39 (1H, d, $J_{6,F}=7.4$ Hz, H-6), 11.83 (1H, d, $J_{F,NH}=5.1$ Hz, NH) ppm;

^{13}C NMR (DMSO-d_6) δ 50.54 (C-4′), 60.42 (C-1′), 61.58 (C-5′), 73.58 (C-3′), 78.19 (C-2′), 124.71 (d, $J_{6,F}$ = 34.5 Hz, C-6), 138.13 (d, $J_{5,F}$ = 230.9 Hz, C-5), 147.92 (2-CO), 155.08 (d, $J_{4,F}$ = 26.3 Hz, 4-CO) ppm.; FAB MS m/z 279 [M + H]; MS (70 eV) m/z (%) 278 (0.3) [M^+], 260 (11) [M^+- H_2O], 201 (5), 161 (10), 131 (100) [$C_5H_7O_2S^+$], 103 (42), 87 (54), 57 (61), 45 (50); HRMS calcd 260.0267 ($M^+ - H_2O$); found 260.0268. β-**10**: $[\alpha]_D^{20}$ −54.4 (c 1.0, MeOH); mp 228 °C; IR (KBr) ν 3405, 3039, 2985, 2909, 2811, 1700, 1662, 1493, 1393, 1257, 1107, 1059, 1044, 944, 878, 834, 757, 670, 579, 531, 483 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.15 (1H, ddd, $J_{3',4'}$ = 5.1, $J_{4',5'a}$ = 5.2, $J_{4',5'b}$ = 5.2 Hz, H-4′), 3.67.76 (2H, m, H-5′$_a$, H-5′$_b$), 3.95 (1H, ddd, $J_{2',3'}$ = 6.2, $J_{3',4'}$ = 5.1, $J_{3',OH}$ = 4.9 Hz, H-3′), 4.01 (1H, ddd, $J_{1',2'}$ = 5.8, $J_{2',3'}$ = 6.2, $J_{2',OH}$ = 5.8 Hz, H-2′), 5.29 (1H, dd, $J_{5'a,OH}$ = 5.1, $J_{5'b,OH}$ = 5.1 Hz, 5′-OH), 5.44 (1H, d, $J_{3',OH}$ = 4.9 Hz, 3′-OH), 5.76 (1H, d, $J_{2',OH}$ = 5.8 Hz, 2′-OH), 6.06 (1H, dd, $J_{1',2'}$ = 5.8, $J_{1',F}$ = 1.8 Hz, H-1′), 8.39 (1H, d, $J_{6,F}$ = 7.7 Hz, H-6), 11.82 (1H, d, $J_{F,NH}$ = 5.1 Hz, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 53.58 (C-4′), 61.09 (C-1′), 64.41 (C-5′), 73.58 (C-3′), 77.86 (C-2′), 127.93 (d, $J_{6,F}$ = 35.4 Hz, C-6), 139.07 (d, $J_{5,F}$ = 228.9 Hz, C-5), 150.12 (2-CO), 157.31 (d, $J_{4,F}$ = 25.5 Hz, 4-CO) ppm.; FAB MS m/z 279 [M + H]; MS (70 eV) m/z (%) 278 (1) [M^+], 260 (13) [M^+- H_2O], 201 (8), 161 (9), 131 (100) [$C_5H_7O_2S^+$], 103 (36), 87 (59), 57 (72), 45 (42); HRMS calcd 278.0373 (M^+), 260.0267 (M^+- H_2O); found 278.0377, 260.0270.

10. α-**11**: $[\alpha]_D^{20}$ −89.1 (c 1.0, MeOH); mp 226 °C (under decomposition); IR (KBr) ν 3469, 3024, 2949, 2892, 2803, 1700, 1462, 1433, 1387, 1346, 1257, 1104, 1073, 1040, 983, 921, 871, 831, 752, 669, 569 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.39 (1H, ddd, $J_{4',5'a}$ = 8.0, $J_{5'a,5'b}$ = 10.8, $J_{5'a,OH}$ = 5.7 Hz, H-5′$_a$), 3.60 (1H, ddd, $J_{3',4'}$ = 7.6, $J_{4',5'a}$ = 8.0, $J_{4',5'b}$ = 4.3 Hz, H-4′), 3.69 (1H, ddd, $J_{2',3'}$ = 7.1, $J_{3',4'}$ = 7.6, $J_{3',OH}$ = 4.6 Hz, H-3′), 3.83 (1H, ddd, $J_{4',5'b}$ = 4.3, $J_{5'a,5'b}$ = 10.8, $J_{5'b,OH}$ = 4.7 Hz, H-5′$_b$), 4.06 (1H, ddd, $J_{1',2'}$ = 6.7, $J_{2',3'}$ = 7.1, $J_{2',OH}$ = 5.3 Hz, H-2′), 4.93 (1H, dd, $J_{5'a,OH}$ = 5.7, $J_{5'b,OH}$ = 4.7 Hz, 5′-OH), 5.52 (1H, d, $J_{3',OH}$ = 4.6 Hz, 3′-OH), 5.74 (1H, d, $J_{2',OH}$ = 5.3 Hz, 2′-OH), 5.75 (1H, d, $J_{1',2'}$ = 6.7 Hz, H-1′), 8.42 (1H, s, H-6), 11.85 (1H, ws, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 55.55 (C-4′), 65.52 (C-1′), 66.06 (C-5′), 78.28 (C-3′), 82.97 (C-2′), 109.98 (C-5), 142.26 (C-6), 152.89 (2-CO), 161.57 (4-CO) ppm; FAB MS m/z 295 [M + H]; MS (70 eV) m/z 276 (7) [$M^+ - H_2O$], 146 (40) [$C_4H_3ClN_2O_2^+$], 131 (100) [$C_5H_7O_2S^+$], 103 (90), 76 (42), 57 (95), 40 (92); HRMS calcd 295.0155 ($M^+ + H$), 275.9972 ($M^+ - H_2O$); found 295.0158, 275.9966. β-**11**: $[\alpha]_D^{20}$ −22.0 (c 1.0, MeOH); decomposes at 245 °C; IR (KBr) ν 3469, 3155, 3097, 3027, 2972, 2917, 2860, 2820, 1703, 1640, 1477, 1418, 1393, 1341, 1319, 1175, 1146, 1091, 1062, 1041, 957, 844, 817, 756, 637, 519 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.17 (1H, ddd, $J_{3',4'}$ = 5.1, $J_{4',5'a}$ = 5.1, $J_{4',5'b}$ = 5.1 Hz, H-4′), 3.66.74 (2H, m, H-5′$_a$, H-5′$_b$), 3.96 (1H, ddd, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 5.1, $J_{3',OH}$ = 4.9 Hz, H-3′), 4.01 (1H, ddd, $J_{1',2'}$ = 5.6, $J_{2',3'}$ = 5.8, $J_{2',OH}$ = 5.8 Hz, H-2′), 5.31 (1H, dd, $J_{5'a,OH}$ = 5.0, $J_{5'b,OH}$ = 5.0 Hz, 5′-OH), 5.45 (1H, d, $J_{3',OH}$ = 4.9 Hz, 3′-OH), 5.78 (1H, d, $J_{2',OH}$ = 5.8 Hz, 2′-OH), 6.08 (1H, d, $J_{1',2'}$ = 5.6 Hz, H-1′), 8.46 (1H, s, H-6), 11.78 (1H, ws, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 54.41 (C-4′), 61.84 (C-1′), 61.90 (C-5′), 76.13 (C-3′), 78.22 (C-2′), 106.49 (C-5), 142.29 (C-6), 151.10 (2-CO), 159.79 (4-CO) ppm; FAB MS m/z 295 [M + H]; MS (70 eV) m/z 276 (5) [M^+- H_2O], 146 (40) [$C_4H_3ClN_2O_2^+$], 131 (100) [$C_5H_7O_2S^+$], 103 (78), 76 (54), 57 (90), 40 (93); HRMS calcd 275.9972 (M^+- H_2O); found 275.9975.

11. IR (KBr, anomeric mixture): ν 3421, 3048, 2928, 2828, 1693, 1622, 1453, 1380, 1253, 1099, 1051, 904, 801, 758, 637, 559, 439 cm^{-1}; α-**12**: ^1H NMR (DMSO-d_6) δ 3.39 (1H, ddd, $J_{4',5'a}$ = 7.8, $J_{5'a,5'b}$ = 10.8, $J_{5'a,OH}$ = 5.6 Hz, H-5′$_a$), 3.61 (1H, ddd, $J_{3',4'}$ = 7.7, $J_{4',5'a}$ = 7.8, $J_{4',5'b}$ = 4.4 Hz, H-4′), 3.65.74 (1H, m, H-3′), 3.83 (1H, ddd, $J_{4',5'b}$ = 4.4, $J_{5'a,5'b}$ = 10.8, $J_{5'b,OH}$ = 4.9 Hz, H-5′$_b$), 4.07 (1H, ddd, $J_{1',2'}$ = 6.7, $J_{2',3'}$ = 6.7, $J_{2',OH}$ = 5.3 Hz, H-2′), 4.93 (1H, dd, $J_{5'a,OH}$ = 5.6, $J_{5'b,OH}$ = 4.9 Hz, 5′-OH), 5.51 (1H, d, $J_{3',OH}$ = 4.6 Hz, 3′-OH), 5.74 (1H, d, $J_{2',OH}$ = 5.3 Hz, 2′-OH), 5.75 (1H, d, $J_{1',2'}$ = 6.7 Hz, H-1′), 8.47 (1H, s, H-6), 11.81 (1H, ws, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 51.79 (C-4′), 59.86 (C-1′), 62.21 (C-5′), 74.48 (C-3′), 79.17 (C-2′), 94.69 (C-5), 140.80 (C-6), 149.23 (2-CO), 157.85 (4-CO) ppm; β-**12**: ^1H NMR (DMSO-d_6) δ 3.17 (1H, ddd, $J_{3',4'}$ = 5.2, $J_{4',5'a}$ = 5.0, $J_{4',5'b}$ = 5.0 Hz, H-4′), 3.65.74 (2H, m, H-5′$_a$, H-5′$_b$), 3.96 (1H, ddd, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 5.2, $J_{3',OH}$ = 5.0 Hz, H-3′), 4.01 (1H, ddd, $J_{1',2'}$ = 5.6, $J_{2',3'}$ = 5.5, $J_{2',OH}$ = 5.8 Hz, H-2′), 5.31 (1H, dd, $J_{5'a,OH}$ = 5.0, $J_{5'b,OH}$ = 5.0 Hz, 5′-OH), 5.46 (1H, d, $J_{3',OH}$ = 5.0 Hz, 3′-OH), 5.79 (1H, d, $J_{2',OH}$ = 5.8 Hz, 2′-OH), 6.08 (1H, d, $J_{1',2'}$ = 5.6 Hz, H-1′), 8.53 (1H, s, H-6), 11.81 (1H, ws, NH) ppm; ^{13}C NMR (DMSO-d_6) δ 52.40 (C-4′), 59.81 (C-1′), 61.74 (C-5′), 74.10 (C-3′), 76.22 (C-2′), 92.98 (C-5), 140.83 (C-6), 149.33 (2-CO), 157.95 (4-CO) ppm; FAB MS (anomeric mixture) m/z 341 [M + H, for ^{81}Br], 339 [M + H, for ^{79}Br]; MS (70 eV, anomeric mixture) m/z 322 (7) [$M^+ - H_2O$, for ^{81}Br], 320 (7) [$M^+ - H_2O$, for ^{79}Br], 192 (52) [$C_4H_3BrN_2O_2^+$, for ^{81}Br], 190 (50) [$C_4H_3BrN_2O_2^+$, for ^{79}Br], 149 (98), 147 (79), 131 (100) [$C_5H_7O_2S^+$], 120 (54), 85 (23), 57 (89), 45 (57); HRMS (anomeric mixture) calcd 340.9630 ($M^+ + H$, for ^{81}Br), 338.9650 ($M^+ + H$, for ^{79}Br), 321.9446 ($M^+ - H_2O$, for ^{81}Br), 319.9466 ($M^+ - H_2O$, for ^{79}Br); found 340.9643, 338.9648, 321.9437, 319.9458.

12. Reversed phase HPLC was performed on an ODS column with MeCN/H_2O as eluent. **10**: 10:90; **11**: 9:91; **12**: 7:93.