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Thiosugars. Part 9: Synthesis and Biological Evaluation of Some 4′-Thio-L-arabino Nucleoside Analogues†

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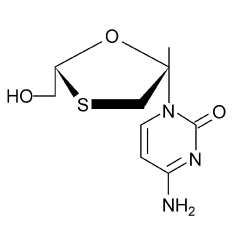
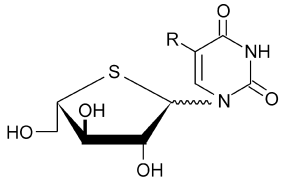
Abstract—1-*O*-Acetyl-2,3,5-tri-*O*-benzyl-4-thio-L-arabinofuranose (**10**) was transformed into the corresponding cytidine derivative **9** and the adenosine derivative **12**. Both nucleosides, as well as the previously reported uridine and thymidine analogues **2** and **3**, were tested for their in vitro antiviral activity.

4′-Thionucleosides with the natural D-configuration of the sugar moiety have been compounds of interest for a period of about 35 years.[1] Several of the synthesised nucleoside analogues exhibit antiviral and antitumour activities.[2] Since the synthesis of 3TC (**1**) and the discovery of its remarkable anti-HIV activity[3] 4′-thionucleosides derived from L-pentofuranoses became interesting targets of synthetic efforts.[4,5] Satoh et al.[6] have reported the synthesis of the 4′-thio-L-arabino nucleosides **3** and **9**. Independently we have published the preparation of **3** via a different route, as well as the synthesis of the uridine derivative **2**.[7] In addition, we have synthesised the 5-halo derivatives of **2** and **4**–**6**, which exhibited, however, neither antiviral activity nor cytotoxicity.[8] In continuation of our investigations in the 4′-thio-L-*arabino* series we report here the synthesis of the cytidine **9** by a route different from that published by Satoh et al. and the first preparation of a purine nucleoside (**12**) of this series. The results of the antiviral testing of these compounds and of **2** and **3** will be given as well.



1 (3TC)



2 3 4 5 6
R = H Me F Cl Br

Starting from D-xylose we prepared the required 1-*O*-acetyl glycosyl donor **10** in six steps[7] according to Dyson, Coe and Walker.[9] Coupling of **10** with silylated cytosine[10] in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf)[11] failed. The preparation of the cytidine derivative **9** was, however, achieved by an alternative route according to a procedure of Uenishi et al.[5] To this end, an anomeric mixture of the uridine **2** (α:β = 2:1)[7] was transformed into the triazolo derivative **7** (49%, α:β = 2:1), which after ammonolysis gave the protected cytidine derivative **8** (70%, α:β = 2:1). Treatment of **8** with boron tribromide at −90 °C,[12] followed by neutralisation of the hydrobromic acid with silver carbonate[7] and reversed phase HPLC gave the deblocked cytidine **9**[13] with a yield of 39%. The product was obtained as a mixture of the anomers (α:β = 5:1) (Scheme 1). In contrast to Satoh et al.,[6] we were not able to separate the anomers on an ODS (octadecyl silane) column.[14]

Reaction of **10** with adenine and TMSOTf, on the other hand, yielded the benzyl protected adenosine derivative **11** as a 3:4 mixture of the anomers (α:β). Cleavage of the protecting groups with boron tribromide and subsequent HPLC[13] led to the separated anomers of the free adenosine **12**[15] with a total yield of 36% (Scheme 2). The ratio of the separated anomers was α:β = 2:1. The α-anomer was crystalline and its structure and

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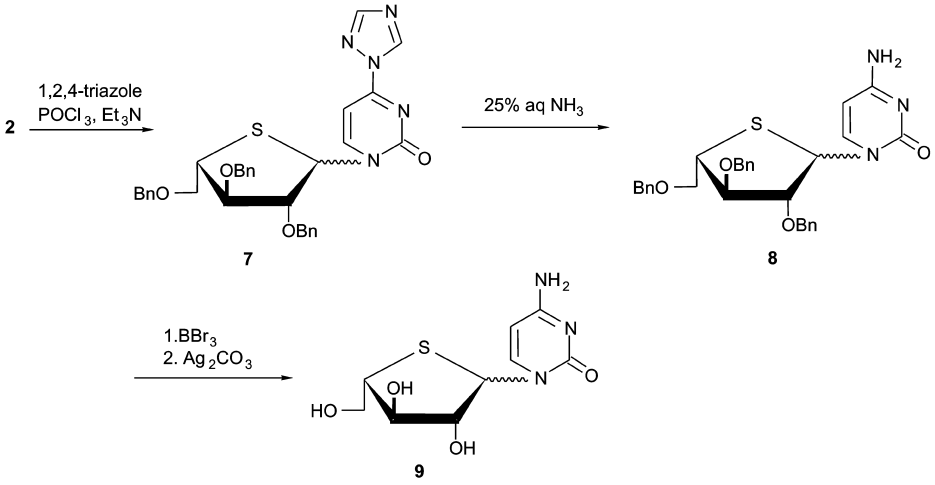
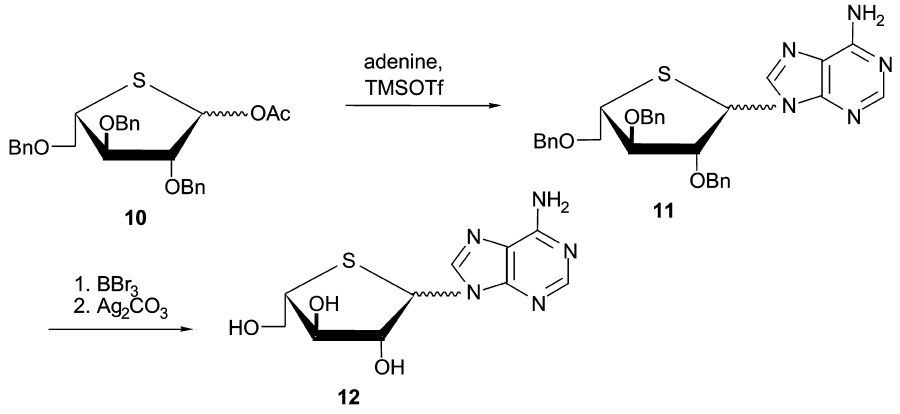


Scheme 1.



Scheme 2.

configuration was confirmed by an X-ray diffraction analysis, which revealed an envelope (E_3) conformation[16] of the thiofuranose ring (cf. Fig. 1).[17]

The α- and β-anomers of **2**, **3** and **12** and the anomeric mixture of **9** were tested for antiviral activity against HIV-1, HIV-2, HCMV, VZV, HSV-1, HSV-2, Vaccinia virus, Vesicular stomatitis virus, Coxsackie B4 virus, Respiratory syncytial virus, Parainfluenza-3 virus, Reovirus-1, Sindbis virus and Punta Toro virus. The minimum inhibitory concentration required to reduce the virus-induced cytopathogenicity by 50% was higher than 240 or 400 μg/mL in all but three cases. A minimum concentration of 48 μg/mL was found for α-**2** against HSV-1 (KOS), for β-**3** against HSV-1 (KOS and TK$^-$ VMW 1837) and for α-**12** against Reovirus-1. These test results for **3** and **9** correspond with those of Satoh et al.[6] None of the nucleosides was cytotoxic at the highest concentration level applied (200–400 μM).

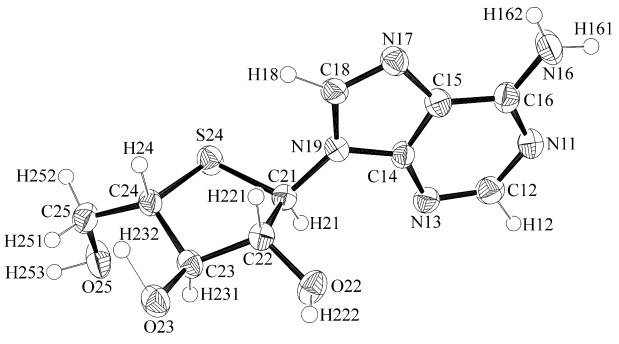


Figure 1. ORTEP view of the α-**12** molecule.[17]

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13. IR (KBr, anomeric mixture) ν 3340, 3206, 2923, 2873, 1650, 1528, 1493, 1400, 1284, 1186, 1102, 1044, 833, 789, 588 cm^{-1}; FAB MS (*m*NBA, anomeric mixture) *m*/*z* 260 [M + H]; FAB HRMS (*m*NBA, anomeric mixture) calcd 260.0705 ($C_9H_{14}N_3O_4S$); found 260.0707.
14. Column used for semipreparative HPLC: LiChroCART 250-10 with Lichrosphere 100-10 RP 18 (10 μM) filling material. HPLC was performed with MeCN/H_2O as eluent; **9**: 7:93; **12**: 8:92.
15. α-**12**: $[\alpha]_D^{20}$ −47.3 (*c* 0.5, MeOH); mp 249 °C (decomp.); IR (KBr) ν 3393, 3276, 2927, 2887, 1708, 1616, 1572, 1481, 1425, 1303, 1253, 1217, 1186, 1109, 1037, 914, 814, 791, 650, 613, 546 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.43 (1H, ddd, $J_{5'a,4'}$ = 8.0, $J_{5'a,5'b}$ = 10.9, $J_{5'a,OH}$ = 6.0 Hz, H-5′$_a$), 3.66 (1H, ddd, $J_{4',3'}$ = 8.0, $J_{4',5'b}$ = 5.5 Hz, H-4′), 3.75 (1H, ddd, $J_{3',2'}$ = 7.6, $J_{3',OH}$ = 5.2 Hz, H-3′), 3.89 (1H, ddd, $J_{5'b,OH}$ = 4.5 Hz, H-5′$_b$), 4.56 (1H, ddd, $J_{2',1'}$ = 7.2, $J_{2',OH}$ = 5.9 Hz, H-2′), 4.93 (1H, dd, 5′-OH), 5.60 (1H, d, 3′-OH), 5.73 (1H, d, H-1′), 5.78 (1H, d, 2′-OH), 7.23 (2H, ws, NH_2), 8.15 (1H, s, $H_{adenine}$), 8.40 (1H, s, $H_{adenine}$) ppm; ^{13}C NMR (DMSO-d_6) δ 50.97 (C-4′), 58.71 (C-1′), 62.00 (C-5′), 74.84 (C-3′), 79.07 (C-2′), 117.65 ($C_{adenine}$), 138.74 ($CH_{adenine}$), 148.17 ($C_{adenine}$), 151.03 ($CH_{adenine}$), 154.62 ($C_{adenine}$) ppm; FAB MS (*m*NBA) *m*/*z* 284 [M + H]; FAB HRMS (*m*NBA) calcd 284.0817 ($C_{10}H_{14}N_5O_3S$); found 284.0802; β-**12**: $[\alpha]_D^{20}$ +12.8 (*c* 1.0, MeOH); mp 229–231 °C (decomp.); IR (KBr) ν 3382, 3205, 2923, 2873, 1645, 1606, 1577, 1477, 1417, 1338, 1303, 1245, 1201, 1104, 1054, 910, 817, 689, 647, 587 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.25 (1H, ddd, $J_{4',3'}$ = 6.2, $J_{4',5'a}$ = 5.9, $J_{4',5'b}$ = 4.4 Hz, H-4′), 3.75 (1H, ddd, $J_{5'a,5'b}$ = 11.1, $J_{5'a,OH}$ = 5.3 Hz, H-5′$_a$), 3.86 (1H, ddd, $J_{5'b,OH}$ = 4.7 Hz, H-5′$_b$), 4.10–4.16 (2H, m, H-2′, H-3′), 5.19 (1H, dd, 5′-OH), 5.50 (1H, d, $J_{OH,3'}$ = 4.7 Hz, 3′-OH), 5.71 (1H, d, $J_{OH,2'}$ = 3.5 Hz, 2′-OH), 6.06 (1H, d, $J_{1',2'}$ = 5.2 Hz, H-1′), 7.21 (2H, ws, NH_2), 8.13 (1H, s, $H_{adenine}$), 8.36 (1H, s, $H_{adenine}$) ppm; ^{13}C NMR (DMSO-d_6) δ 51.30 (C-4′), 56.48 (C-1′), 61.00 (C-5′), 74.42 (C-3′), 76.30 (C-2′), 117.23 ($C_{adenine}$), 139.66 ($CH_{adenine}$), 148.91 ($C_{adenine}$), 151.15 ($CH_{adenine}$), 154.84 ($C_{adenine}$) ppm; FAB MS (*m*NBA) *m*/*z* 284 [M + H]; FAB HRMS (*m*NBA) calcd 284.0805 ($C_{10}H_{14}N_5O_3S$); found 284.0802.
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17. Crystallographic details of α-**12** have been deposited with the Cambridge Crystallographic Data Centre and may be obtained, on request, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Tel. +44-1223-336408, fax +44-1223-336033, e-mail: deposit@ccdc.cam.ac.uk. Deposition number: CCDC 153055.