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Acyclic Nucleoside Analogues from Thymine-Substituted Thymidines and Related Compounds

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Abstract

Hydrolysis of 3'-deoxy-3'-(thymin-1-yl)thymidine, 3'-deoxy-3'-(uracil-1-yl)thymidine, and related furanoses with two nucleobases has been investigated. 3'-β-Substituted analogues, but not the 3'-α-substituted ones, afford isomeric pyranose nucleosides as intermediates, which have been isolated (**6c** and **6d**). Reduction of the hydrolysis products with sodium borohydride afford the corresponding acyclic compounds (2'-deoxy-D-ribitol or D-ribitol derivatives), which have been fully characterised as their peracetates. © 1999 Elsevier Science Ltd. All rights reserved.

Keywords: Nucleosides; Uridines; Hydrolysis

In a previous work [1] we reported on the synthesis of eight novel nucleosides (the pentofuranose derivatives with two nucleobases summarised in Figure 1), in six or seven high-yielding steps from thymidine or uridine, respectively. In principle, many related molecules may be similarly prepared from other 2'-deoxy-D-ribofuranosides and D-ribofuranosides.

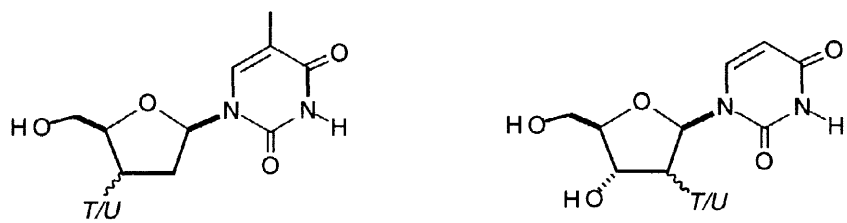

Figure 1. *T* = thymin-1-yl, *U* = uracil-1-yl

Among the possible uses of these compounds, we envisaged that, if the cleavage of the anomeric bond was feasible, they could be converted into different series of modified nucleosides in a stereoselective way. For instance, several substances belonging to the iso-nucleoside family, a set of analogues of growing interest [2–12], might be obtained from appropriate thymidine-derived nucleosides (Fig. 1, left), either by hydrolysis, followed by replacement of the anomeric OH group, or by elimination of the nucleobase at $C_{1'}$ [13,14], followed by reduction. Moreover, from these or other suitable derivatives, by hydrolysis

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and/or ring-opening reactions, several acyclic carbonucleosides should be attainable; as known, the importance of antiherpetic agents acyclovir and ganciclovir ("seco-guanosines"), of phosphonomethoxyalkyl purines and pyrimidines, and of polyhydroxyalkyl purines (eg, buciclovir) has attracted the attention of many laboratories, as shown by the number of citations in recent reviews [15–18] and papers [19,20]. In this context, we report here studies on *(i) the relative stability of representative substrates under hydrolysis conditions and (ii) the preparation of acyclic nucleoside analogues from the reduction of the hydrolysis products.* Although these studies are not exhaustive, as only cases in which the nucleobases are thymine or uracil rings have been evaluated, it is reasonable to believe that the results could be extrapolated to other substrates.

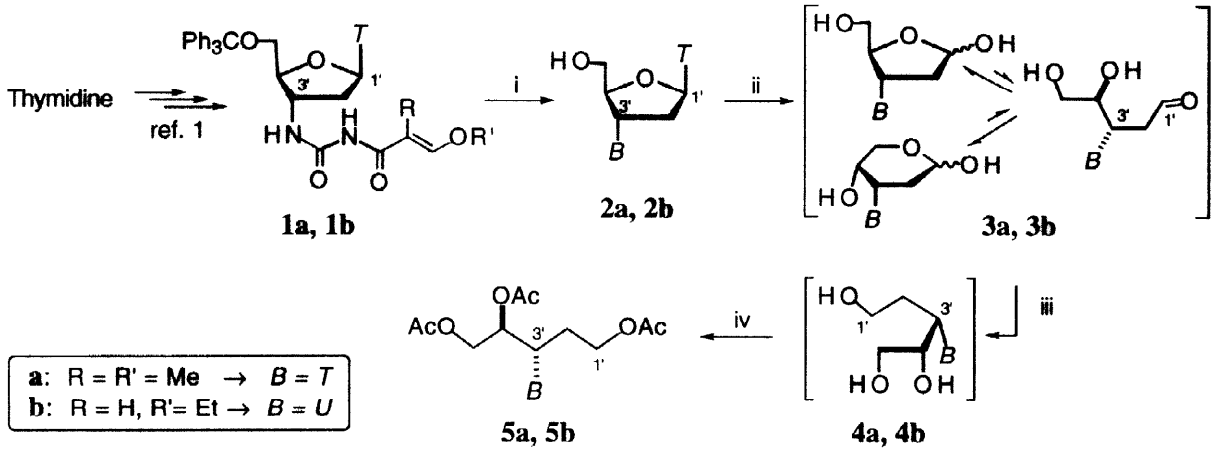
Results and Discussion

From thymidine we prepared the precursors **1a–d**, as previously reported [1], which were cyclised in dilute sulfuric acid and dioxan [21] to the desired 3'-deoxy-3'-(thymin-1-yl)thymidine (**2a**), 3'-deoxy-3'-(uracil-1-yl)thymidine (**2b**), 1-[2,3-dideoxy-3-(thymin-1-yl)-β-D-*threo*-pentofuranosyl]thymine (**2c**), and 1-[2,3-dideoxy-3-(uracil-1-yl)-β-D-*threo*-pentofuranosyl]thymine (**2d**). Uridine-derived compounds were also synthesised as previously reported [1].

The stability to hydrolysis of **2a** and **2b** was investigated first. Their hydrolysis in 1 M H_2SO_4–dioxan 1:1 (ie, under the conditions in which **1a** and **1b** cyclise to **2a** and **2b**, respectively) was extremely low, since after refluxing for 2–3 days only one third of the starting material was hydrolysed. However, when **2a** and **2b** were independently refluxed in 4 M H_2SO_4–dioxan 1:1, they were completely hydrolysed within 24 h. Similarly, heating at 100 °C in 6 M HCl and dioxan was also effective to promote this transformation in *ca.* 20 h.

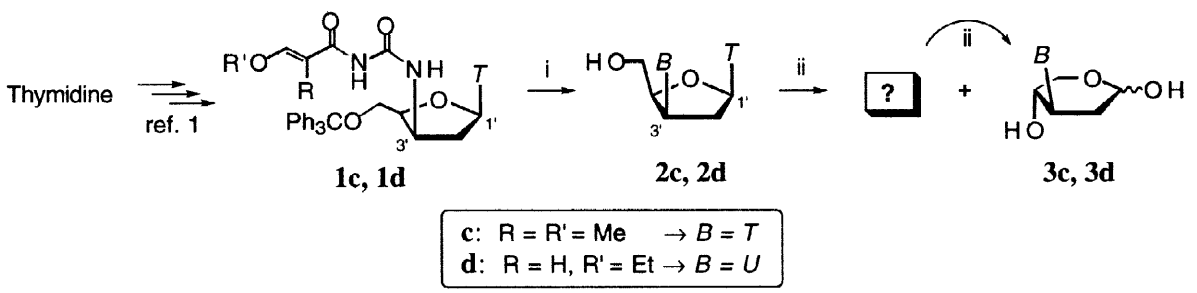
These results suggested that the acid-catalysed cyclisation of each acriloylurea (with removal of the trityl group) and the cleavage of the nucleosidic bond could be performed in one pot, to shorten the synthetic sequence from thymidine. In fact, when **1a** and **1b** were independently heated at 100 °C in a 1:1 mixture of 4 M H_2SO_4 and dioxan, formation of the pyrimidine ring at $C_{3'}$ and removal of the thymine ring at $C_{1'}$ was complete in 24 h.

After neutralisation and evaporation to dryness of the above reaction mixtures, the hydrolysis products were purified by flash chromatography to give a mixture of tautomers (indicated as **3a** and **3b**, see Scheme 1), in 70–75% crude yields. The ^1H NMR spectrum in CD_3OD of **3a**, for instance, shows the presence of at least three anomeric protons and of four signals corresponding to thymine H_6 protons. After reduction of **3a** and **3b** with $NaBH_4$ in MeOH (to triols **4a** and **4b**, insoluble in organic solvents, not purified), followed by treatment with acetic anhydride in pyridine, tri-*O*-acetyl-derivatives **5a** and **5b** (which could be fully characterised) were obtained, in 34% and 21% overall yields from **1a** and **1b**, respectively.



Scheme 1. (i) 1 M H_2SO_4–dioxan 1:1, Δ, 4 h; (ii) 4 M H_2SO_4–dioxan 1:1, Δ, 20–24 h; (iii) $NaBH_4$, MeOH, 0 °C, 20 min; (iv) Ac_2O, pyridine, rt, 7 h, 34% overall yield of **5a** from **1a**, 21% overall yield of **5b** from **1b**

When **1c** and **1d** (or when **2c** and **2d**, see Scheme 2) were subjected to the above-mentioned hydrolysis conditions, the starting materials also disappeared within 24 h, with formation of the desired compounds **3c** and **3d**, respectively; however, *in both cases another product* of intermediate R_f *was also noted.* These two unexpected compounds were resistant to hydrolysis: even after heating for three days small amounts were still detected in the corresponding hydrolysis mixtures.



Scheme 2. (i) 1 M H_2SO_4–dioxan 1:1, Δ, 4 h; (ii) 4 M H_2SO_4–dioxan 1:1, Δ, 24–72 h, 46% overall yield of **3c** from **1c**, 36% overall yield of **3d** from **1d**

The ^1H NMR spectra of both these novel nucleoside analogues showed clearly the presence of two nucleobases and their ^{13}C NMR spectra indicated that they were pyranose isomers ($C_{4'}$ appearing at *ca.* δ 70 ppm, which is typical of pyranoside nucleosides, while a chemical shift around δ 85 ppm is to be expected for furanoside nucleosides) [22]. Moreover, the β configuration at $C_{1'}$ was deduced from the main $^3J_{HH}$ values (see Figure 2), which were practically identical for the two compounds. Therefore, structures **6c** and **6d**, respectively, were attributed to them.

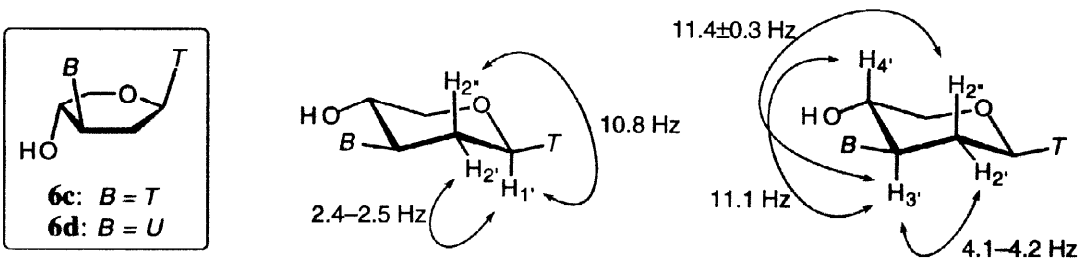
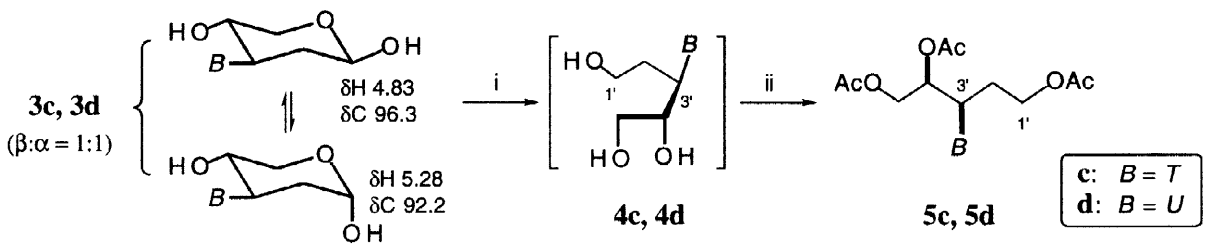


Figure 2. $^3J_{HH}$ values for both **6c** and **6d**

Formation of compounds **6c** and **6d** supports a hydrolysis mechanism in which the $C_{1'}$–O bond of **2c** and **2d** is cleaved first, *via* protonation of the oxygen atom in the furanose ring [23]. The intermediates formed in this way may then undergo hydrolysis to the desired products (**3c** and **3d**) or may equilibrate to other isomers, among which **6c** and **6d**, that are much more slowly hydrolysed. This last fact is understandable taking into account the β configuration of these glycosides and the equatorial arrangement in a chair conformation of the three substituents.

Compounds **3c** and **3d** could also be characterized by NMR spectroscopy. Each one turned out to be a 1:1 mixture of the α and β pyranose isomers. Unlike **3a** and **3b**, no furanose forms were observed in the solvent utilised. Reduction of **3c** and **3d** with $NaBH_4$ in MeOH to **4c** and **4d**, respectively (which were not isolated), followed by treatment with acetic anhydride in pyridine afforded tri-*O*-acetyl derivatives **5c** and **5d** (Scheme 3), in 38% and 21% overall yields from **1c** and **1d**, respectively.



Scheme 3. (i) $NaBH_4$, MeOH, 0 °C, 20 min; (ii) Ac_2O, pyridine, rt, 7 h, 39% overall yield of **5c** from **1c**, 21% overall yield of **5d** from **1d**

Compounds **3a–d** can be related to those obtained (as a mixture) from the direct reaction of 2-deoxy-D-ribose with purines [24] and with pyrimidines, in connection with studies about the possibility of spontaneous nucleic acid syntheses [25], or with guanines in the presence of $P_4O_{10}/H_2O/Bu_3N$ [26].

It is well known [23] that uridine derivatives are much less prone to hydrolysis at the anomeric center than thymidine derivatives and, in general, than $C_{2'}$-unsubstituted nucleosides. Nevertheless, for the sake of comparison, we investigated the behaviour under hydro-

lysis conditions of the uridine-derived pentofuranoses with two nucleobases (see Figure 1, right formulae). When 2'-deoxy-2'-(thymin-1-yl)uridine [1] was subjected to the above-mentioned conditions (sulfuric acid at different concentrations and dioxan), decomposition to uracil and thymine occurred before complete hydrolysis of the starting material could be observed. With this and other uridine-derived substrates (Figure 1, right formulae), we also tried alternative reaction conditions [Me_3SiOTf/lutidine, $(Me_3Si)_2NH/Me_3SiCl$] aimed at cleaving the $C_{1'}$–N bond, ie to remove selectively the nucleobase at the anomeric carbon atom, without success. Apparently, elimination of the nucleobase at position 2' is as rapid as the loss of the nucleobase at $C_{1'}$.

In summary, we have disclosed a strategy for obtaining isonucleosides and acyclonucleosides from thymidine derivatives with an additional nucleobase at $C_{3'}$; however, it cannot be applied at present to uridine derivatives with an additional nucleobase at $C_{2'}$.

Experimental

Melting points were determined with a Büchi melting point apparatus and are uncorrected. For flash chromatographic separations, 0.040–0.063 mesh silica gel was used, and for analytical TLC Merck silica gel plates with F-254 indicator. Specific rotations were obtained at 20 °C on a Perkin-Elmer 241MC polarimeter. Infrared spectra were run on a Perkin Elmer 681 spectrometer or a Nicolet 510 FT-IR spectrometer. NMR spectra were recorded on Varian Gemini-200 or Varian 300 Unity Plus spectrometers, in either $CDCl_3$ or CD_3OD (as indicated in each case); chemical shifts are reported in ppm relative to TMS; coupling constants (J) are given in Hz. Mass spectra were obtained on HP 5988A or VG-Quattro spectrometers. High-resolution mass spectra were registered at C.A.C.T.I., Universidade de Vigo. Microanalyses were performed by the C.I.D. (C.S.I.C., Barcelona). Compounds **1a–d** and **2a–d** were prepared as previously reported [1].

(2*S*,3*S*)-1,2,5-Tri-*O*-acetyl-3-(thymin-1-yl)-1,2,5-pentanetriol (5a). Compound **1a** (256 mg, 0.41 mmol) was dissolved in 3 mL of dioxan and 3 mL of 4 M H_2SO_4. After stirring for 24 h at 100 °C, the reaction mixture was neutralised by addition of solid $NaHCO_3$ and the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2–MeOH 90:10) of the residue afforded 69 mg of a complex mixture (70% crude yield) which was dissolved in 2 mL of MeOH and cooled to 0 °C. Sodium borohydride (69 mg) was then added in small portions. After stirring for 20 min, CO_2 gas was bubbled through the reaction mixture for 5 min and pH was adjusted to 7.0 by addition of 2 M HCl. The solvent was then evaporated under reduced pressure and the resulting residue was suspended, under N_2 atmosphere, in 2 mL of anhydrous pyridine. Acetic anhydride (250 μL) was then added at 0 °C and stirring was continued for 7 h at rt. The reaction was quenched with 1 mL of MeOH and the solvent was evaporated under reduced pressure. Flash chromatography (EtOAc–hexanes 85:15) of the resulting residue afforded 52 mg (34% from **1a**) of **5a** as a white solid: mp 124–125 °C (EtOAc–hexanes); R_f (CH_2Cl_2–MeOH 95:5) 0.27; $[\alpha]_D = -37.4$ (c 1.0, CH_2Cl_2); IR (film) 1740, 1680; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.95 (d, 3 H, J=1.2, Me-C_5), 2.02 (s, 3 H, CH_3CO), 2.06 (s, 3 H, CH_3CO), 2.13 (s, 3 H, CH_3CO), 4.03–4.09 (m, 3 H, $H_{1'}+H_{1''}+H_{5'}$), 4.26 (dd, 1 H, $J_{5'5''}$=12.3, $J_{4'5''}$=3.0, $H_{5''}$), 4.83 (broad signal, 1 H, $H_{3'}$), 5.32 (br s, 1 H, $H_{4'}$), 6.97 (q, 1 H, J=1.2, H_6), 8.97 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ 12.4 (Me-C_5), 20.5 (CH_3CO), 20.6 (CH_3CO), 20.7 (CH_3CO), 27.6 ($C_{2'}$), 52.5 ($C_{3'}$), 60.4, 62.1 ($C_{1'}$ and $C_{5'}$), 71.4 ($C_{4'}$), 111.7 (C_5), 136.5 (C_6), 151.1 (C_2), 163.5 (C_4), 169.9 (CH_3CO), 170.3 (CH_3CO), 170.6 (CH_3CO); MS (CI, NH_3) 371 ($[M+1]^+$, 19%), 388 ($[M+NH_4]^+$, 100%). Anal. Calcd for $C_{16}H_{22}N_2O_8$: C: 51.89%, H: 5.99%, N: 7.56%. Found: C: 51.79%, H: 5.98%, N: 7.49%.

(2*S*,3*S*)-1,2,5-Tri-*O*-acetyl-3-(uracil-1-yl)-1,2,5-pentanetriol (5b). When **1b** (269 mg, 0.43 mmol) was treated as described above for **1a**, 32 mg of **5b** (21% from **1b**) were obtained as a gum: R_f (CH_2Cl_2–MeOH 95:5) 0.27; $[\alpha]_D$ = –36.5 (*c* 1.2, CH_2Cl_2); IR (film) 1740, 1690; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (s, 3 H, CH_3CO), 2.07 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO), 2.16 (m, 2 H, $H_{2'}$+$H_{2''}$), 4.06 (dd, 1 H, $J_{5'5''}$=12.3, $J_{4'5''}$=5.4, $H_{5'}$), 4.08 (t, 2 H, $J_{1'2'}$=6.3, methylene protons $H_{1'}$ and $H_{1''}$), 4.29 (dd, 1 H, $J_{5'5''}$=12.3, $J_{4'5''}$=3.6, $H_{5''}$), 4.85 (br s, 1 H, $H_{3'}$), 5.33 (br s, 1 H, $H_{4'}$), 5.78 (d, 1 H, *J*=7.8, H_5), 7.16 (d, 1 H, *J*=7.8 H_6), 8.88 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.6 (CH_3CO), 20.7 (CH_3CO), 20.8 (CH_3CO), 27.4 ($C_{2'}$), 53.4 ($C_{3'}$), 60.4, 62.0 ($C_{1'}$ and $C_{5'}$), 71.4 ($C_{4'}$), 103.0 (C_5), 141.4 (C_6), 150.9 (C_2), 162.6 (C_4), 169.8 (CH_3CO), 170.3 (CH_3CO), 170.7 (CH_3CO); MS (CI, NH_3) 357 ([M+1]$^+$, 10%), 374 ([M+NH_4]$^+$, 100%); HRMS (EI) M^+ found 356.12097, $C_{15}H_{20}N_2O_8$ requires 356.12197.

(2*S*,3*R*)-1,2,5-Tri-*O*-acetyl-3-(thymin-1-yl)-1,2,5-pentanetriol (5c). Compound **1c** (214 mg, 0.34 mmol) was dissolved in 3 mL of dioxan and 3 mL of 4 M H_2SO_4 and heated at 100 °C for 67 h. After cooling, the mixture was neutralised by addition of solid $NaHCO_3$, and the solvent was evaporated under reduced pressure. Flash chromatography (CH_2Cl_2–MeOH 90:10) of the residue afforded 14 mg (12%) of **6c** and 38 mg (46%) of **3c**. **1-[2,3-Dideoxy-3-(thymin-1-yl)-β-D-*threo*-pentopyranosyl]thymine (6c)**: white solid; mp 228 °C (dec.); R_f (CH_2Cl_2–MeOH 85:15) 0.39; $[\alpha]_D$ = +14.3 (*c* 0.9, MeOH); IR (film) 3420 (br), 1695; ^1H NMR (CD_3OD, 300 MHz) δ 1.89 (d, 3 H, *J*=1.2, Me), 1.90 (d, 3 H, *J*=1.2, Me), 2.08 (ddd, 1 H, $J_{2'2''}$=12.3, $J_{2'3'}$=4.2, $J_{1'2'}$=2.4, $H_{2'}$), 2.37 (pseudo q, 1 H, $J_{2'2''}$=12.3, $J_{2''3'}$=11.7, $J_{1'2''}$=10.8, $H_{2''}$), 3.44 (dd, 1 H, *J*=10.8, *J*=9.6, $H_{5'}$), 4.03–4.16 (m, 2 H, $H_{4'}$+$H_{5''}$), 4.49–4.56 (m, 1 H, $H_{3'}$), 5.79 (dd, 1 H, $J_{1'2''}$=10.8, $J_{1'2'}$=2.4, $H_{1'}$), 7.57 (q, 1 H, *J*=1.2, H_6), 7.58 (q, 1 H, *J*=1.2, H_6); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 12.4 (2 × Me), 34.5 ($C_{2'}$), 60.1 ($C_{3'}$), 66.7 ($C_{5'}$), 71.1 ($C_{4'}$), 81.9 ($C_{1'}$), 111.6 (C_5), 111.9 (C_5), 137.6 (C_6), 140.2 (C_6), 153.2 (C_2), 166.4 (C_4), 167.5 (C_4); MS (FAB$^+$) 351.0 [M+1]$^+$; HRMS (EI) M^+ found 350.12291, $C_{15}H_{18}N_4O_6$ requires 350.12264. **2,3-Dideoxy-3-(thymin-1-yl)-D-*threo*-pentopyranose (3c, mixture of anomers)**: R_f (CH_2Cl_2–MeOH 85:15) 0.27; IR (film) 3345 (br), 1690; ^1H NMR (CD_3OD, 300 MHz) δ 1.88 (d, 3 H, *J*=1.2, Me), 1.89 (d, 3 H, *J*=1.2, Me), 1.90–1.96 (m, 2 H, $H_{2'}$ of both anomers), 2.04 (ddd, 1 H, $J_{2'2''}$=12.5, $J_{2''3'}$=4.5, $J_{1'2''}$=2.3, $H_{2''}$, anomer β), 2.10 (dd, 1 H, $J_{2'2''}$=13.1, $J_{1'2''}$=3.4, $H_{2''}$, anomer α), 3.67 (dd, 1 H, $J_{5'5''}$=10.6, $J_{4'5''}$=5.6, $H_{5''}$, anomer α), 3.88 (t, $J_{4'5''}$=$J_{5'5''}$=10.4, $H_{5''}$, anomer β), 3.91–4.03 (m, 3 H, $H_{4'}$ of anomer α + $H_{4'}$ of anomer β + $H_{5''}$ of anomer α), 4.40 (ddd, 1 H, *J*=12.6, *J*=9.7, *J*=4.5, $H_{3'}$, anomer β), 4.70–4.80 (m, 1 H, $H_{3'}$, anomer α), 4.83 ($H_{1'}$ of anomer β, obscured by solvent signals), 5.28 (dd, 1 H, $J_{1'2''}$=3.4, $J_{1'2'}$=1.2, $H_{1'}$, anomer α), 7.49 (q, 1 H, *J*=1.2, H_6), 7.51 (q, 1 H, *J*=1.2, H_6), assignments corroborated by COSY; ^{13}C NMR (CD_3OD, 75.4 MHz) δ 12.3 (2 × Me), 36.0 ($C_{2'}$), 37.8 ($C_{2'}$), 57.2 ($C_{3'}$), 59.8 ($C_{3'}$), 63.9 ($C_{5'}$), 67.2 ($C_{4'}$), 67.9 ($C_{4'}$), 68.6 ($C_{5'}$), 92.2 ($C_{1'}$), 96.3 ($C_{1'}$), 111.4 (C_5), 111.5 (C_5), 140.0 (C_6), 140.3 (C_6), 153.3 (C_2), 166.4 (C_4); MS (FAB$^+$) 242.9 [M+1]$^+$.

Compound **3c** (38 mg, 0.16 mmol) was dissolved in 1 mL of MeOH, cooled to 0 °C, and 40 mg of $NaBH_4$ were then added in small portions. After stirring for 15 min, CO_2 gas was bubbled through the reaction mixture for 5 min and the pH was adjusted to 7.0 by addition of 2 M HCl. The solvent was then evaporated under reduced pressure and the residue was suspended, under nitrogen atmosphere, in 1 mL of anhydrous pyridine. Acetic anhydride (300 μL) was added at 0 °C and stirring was continued for 7 h at rt. The reaction was quenched with 1 mL of MeOH and the solvent was evaporated under reduced pressure. Flash chromatography (EtOAc–hexanes 85:15) of the resulting residue afforded 49 mg (39% from **1c**) of **5c** as a white solid: mp 86–88 °C; R_f (CH_2Cl_2–MeOH 95:5) 0.26; $[\alpha]_D$ = +65.3 (*c* 2.3, CH_2Cl_2); IR (film) 1735, 1685; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.95 (d, 3 H, *J*=1.2, *Me*–C_5), 2.03 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 2.12 (s, 3 H, CH_3CO), 3.98 (dd, 1 H, $J_{5'5''}$=12.0, $J_{4'5'}$=6.0, $H_{5'}$), 4.08 (t, 2 H, $J_{1'2'}$=6.2, $H_{1'}$ and $H_{1''}$), 4.40 (dd, 1 H, $J_{5'5''}$=12.0, $J_{4'5''}$=4.2, $H_{5''}$), 5.12 (br s, 1 H, $H_{3'}$), 5.40 (br s, 1 H, $H_{4'}$), 7.11 (q, 1 H, *J*=1.2, H_6), 9.67 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 12.7 (*Me*–C_5), 20.6 (CH_3CO), 20.7 (CH_3CO), 20.7 (CH_3CO), 28.9 ($C_{2'}$), 51.3 ($C_{3'}$), 60.1, 62.4 ($C_{1'}$ and $C_{5'}$), 71.4 ($C_{4'}$), 111.2 (C_5), 136.8 (C_6), 151.4 (C_2), 163.4 (C_4), 169.4 (CH_3CO), 170.2 (CH_3CO), 170.6 (CH_3CO); MS (CI, NH_3) 371 ([M+1]$^+$, 15%), 388 ([M+NH_4]$^+$, 100%). Anal. Calcd for $C_{16}H_{22}N_2O_8$: C: 51.89%, H: 5.99%, N: 7.56%. Found: C: 51.39%, H: 5.88%, N: 7.44%.

(2*S*,3*R*)-1,2,5-Tri-*O*-acetyl-3-(uracil-1-yl)-1,2,5-pentanetriol (5d). Compound **1d** (226 mg, 0.36 mmol) was dissolved in 2.5 mL of dioxan and 2.5 mL of 4 M H_2SO_4 and the mixture was heated for 64 h at 100 °C. After neutralisation with solid $NaHCO_3$, column chromatography as in the case of **1c** and evaporation of the solvent afforded 13 mg (11%) of **6d** and 30 mg of a mixture that was purified again on silica gel to afford **3d**. **1-[2,3-Dideoxy-3-(uracil-1-yl)-β-D-*threo*-pentopyranosyl]thymine (6d)**: white solid; mp 160 °C (dec.); R_f (CH_2Cl_2– MeOH 85:15) 0.35; $[\alpha]_D$ = –82.3 (*c* 0.9, MeOH); IR (film) 1685; ^1H NMR (CD_3OD, 300 MHz) δ 1.88 (d, 3 H, *J*=1.2, Me), 2.11 (ddd, 1 H, $J_{2'2''}$=12.5, $J_{2'3'}$=4.1, $J_{1'2'}$=2.5, $H_{2'}$), 2.37 (pseudo q, 1 H, $J_{2'2''}$= 12.5, $J_{2''3'}$=11.1, $J_{1'2''}$=10.8, $H_{2''}$), 3.45 (dd, 1 H, *J*=11.0, *J*=9.8, $H_{5'}$), 4.04–4.16 (m, 2 H, $H_{4'}$+$H_{5''}$), 4.52 (td, 1 H, $J_{2''3'}$=$J_{3'4'}$=11.1, $J_{2'3'}$=4.1, $H_{3'}$), 5.71 (d, 1 H, *J*=8.1, H_5), 5.79 (dd, 1 H, $J_{1'2''}$=10.8, $J_{1'2'}$=2.5, $H_{1'}$), 7.56 (q, 1 H, *J*=1.2, $H_6{}^T$), 7.71 (d, 1 H, *J*=8.1, $H_6{}^U$); ^{13}C NMR (CD_3OD, 75.4 MHz) δ 12.3 (Me), 34.5 ($C_{2'}$), 60.7 ($C_{3'}$), 66.6 ($C_{5'}$), 71.1 ($C_{4'}$), 82.0 ($C_{1'}$), 102.7 ($C_5{}^U$), 111.9 ($C_5{}^T$), 137.5 ($C_6{}^T$), 144.6 ($C_6{}^U$), 151.9 (C_2), 153.0 (C_2), 166.1 (C_4); MS (FAB$^+$) 337.1 $[M+1]^+$; HRMS (EI) M^+ found 336.10696, $C_{14}H_{16}N_4O_6$ requires 336.10698. **2,3-Dideoxy-3-(uracil-1-yl)-D-*threo*-pentopyranose (3d, mixture of anomers)**: R_f (CH_2Cl_2–MeOH 85:15) 0.21; IR (film) 3370, 1685; ^1H NMR (CD_3OD, 300 MHz) δ 1.84–1.90 (m, 1 H, $H_{2'}$, anomer β), 1.94 (ddd, 1 H, $J_{2'2''}$=12.6, $J_{2'3'}$=4.4, $J_{1'2'}$=1.3, $H_{2'}$, anomer α), 2.06 (ddd, 1 H, $J_{2'2''}$=12.5, $J_{2''3'}$=4.4, $J_{1'2''}$= 2.3, $H_{2''}$, anomer β), 2.13 (dd, 1 H, $J_{2'2''}$=12.6, $J_{1'2''}$=3.3, $H_{2''}$, anomer α), 3.67 (dd, 1 H, $J_{5'5''}$=10.6, $J_{4'5''}$= 5.5, $H_{5'}$, anomer β), 3.88 (t, $J_{4'5''}$=$J_{5'5''}$=10.5, $H_{5''}$, anomer β), 3.89–4.01 (m, 3 H, $H_{4'}$ of anomer α + $H_{4'}$ of anomer β + $H_{5''}$ of anomer α), 4.39 (ddd, 1 H, *J*=12.7, *J*=10.1, *J*=4.4, $H_{3'}$, anomer β), 4.69–4.79 (m, 1 H, $H_{3'}$, anomer α), 4.83 ($H_{1'}$ of anomer β, obscured by solvent), 5.28 (dd, 1 H, $J_{1'2''}$=3.1, $J_{1'2''}$= 2.3, $H_{1'}$, anomer α), 5.68 (d, 1 H, *J*=8.1, H_5), 5.69 (d, 1 H, *J*=8.1, H_5), 7.65 (d, 1 H, *J*=8.1, H_6), 7.66 (d, 1 H, *J*=8.1, H_6), assignments confirmed by COSY; ^{13}C NMR (CD_3OD, 75.4 MHz) δ 36.0 ($C_{2'}$), 37.8 ($C_{2'}$), 57.6 ($C_{3'}$), 60.2 ($C_{3'}$), 64.0 ($C_{5'}$), 67.3 ($C_{4'}$), 67.9 ($C_{4'}$), 68.6 ($C_{5'}$), 92.2 ($C_{1'}$), 96.3 ($C_{1'}$), 102.5 (C_5), 102.6 (C_5), 144.5 (C_6), 144.7 (C_6), 153.2 (C_2), 166.4 (C_4); MS (FAB$^+$) 228.9 $[M+1]^+$.

A sample of **3d** (30 mg) was dissolved in 1 mL of MeOH and cooled to 0 °C. Sodium borohydride (30 mg) was then added and stirring was continued for 15 min. Carbon dioxide was bubbled through the reaction mixture for 5 min and the pH was then adjusted to 7.0 by addition of 2 M HCl. After evaporation of the solvent, the residue was suspended, under nitrogen atmosphere, in 1 mL of anhydrous pyridine, and 300 μL of acetic anhydride were added at 0 °C. Stirring at rt was continued for 6 h and afterwards the reaction was quenched by addition of 1 mL of MeOH. Evaporation of the solvent under reduced pressure and separation by flash chromatography afforded 27 mg (21% from **1d**) of **5d** as a gum: R_f (CH_2Cl_2–MeOH 95:5) 0.28; IR (film) 1740, 1675; $[\alpha]_D$= +66.0 (*c* 1.3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.04 (s, 3 H, CH_3CO), 2.04 (s, 3 H, CH_3CO), 2.13 (s, 3 H, CH_3CO), 3.98 (dd, 1 H, $J_{5'5''}$=12.3, $J_{4'5'}$=5.5, $H_{5'}$), 4.09 (t, 2 H, $J_{1'2'}$=6.0, methylene protons $H_{1'}$ and $H_{1''}$), 4.40 (dd, 1 H, $J_{5'5''}$=12.3, $J_{4'5''}$=4.2, $H_{5''}$), 5.10 (br s, 1 H, $H_{3'}$), 5.40 (br s, 1 H, $H_{4'}$), 5.78 (d, 1 H, *J*=7.8, H_5), 7.31 (d, 1 H, *J*=7.8, H_6), 9.59 (br s, 1 H, NH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 20.6 (CH_3CO), 20.7 (CH_3CO), 20.7 (CH_3CO), 29.0 ($C_{2'}$), 51.4 ($C_{3'}$), 60.0, 62.3 ($C_{1'}$ and $C_{5'}$), 71.3 ($C_{4'}$), 102.3 (C_5), 141.2 (C_6), 151.3 (C_2), 162.9 (C_4), 169.5 (CH_3CO), 170.3 (CH_3CO), 170.7 (CH_3CO); MS (CI, NH_3) 357 ($[M+1]^+$, 10%), 374 ($[M+NH_4]^+$, 100%); HRMS (EI) M^+ found 356.12261, $C_{15}H_{20}N_2O_8$ requires 356.12197.

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References

[1] Costa AM, Faja M, Farràs J, Vilarrasa J. *Tetrahedron Lett.* **1998**, *39*, 1835–1838. [Preliminary accounts: XXV Reunión Bienal de la Real Sociedad Española de Química, Vitoria (Euzkadi, Spain), Sept. 1994. Costa AM. Síntesi de 3'-pirimidinil-nucleòsids (Graduation Thesis). Universitat de Barcelona, 1995.]

[2] Nair V, Nuesca ZM. *J. Am. Chem. Soc.* **1992**, *114*, 7951–7953.

[3] Sujino K, Sugimura H. *J. Chem. Soc., Chem. Commun.* **1994**, 2541–2542 (and ref. 1–8 therein).

[4] Kakefuda A, Shuto S, Nagahata T, Seki J, Sasaki T, Matsuda A. *Tetrahedron* **1994**, *50*, 10167–10182.

[5] Verheggen I, Van Aerschot A, Van Meervelt L, Rozenski J, Wiebe L, Snoeck R, Andrei G, Balzarini J, Claes P. *J. Med. Chem.* **1995**, *38*, 826–835.

[6] Scheuer-Larsen C, Pfundheller HM, Wengel J. *J. Org. Chem.* **1995**, *60*, 7298–7303 (and ref. 6 therein).

[7] Prévost N, Rouessac F. *Tetrahedron Lett.* **1997**, *38*, 4215–4218.

[8] Prévost N, Rouessac F. *Synth. Commun.* **1997**, *27*, 2325–2335.

[9] Yang ZJ, Yu HW, Min JM, Ma LT, Zhang LH. *Tetrahedron:Asymmetry* **1997**, *8*, 2739–2747.

[10] Talekar RR, Wightman RH. *Tetrahedron* **1997**, *53*, 3831–3842.

[11] Jung ME, Nichols CJ. *J. Org. Chem.* **1998**, *63*, 347–355.

[12] Hossain N, van Halbeek H, De Clercq E, Herdewijn P. *Tetrahedron* **1998**, *54*, 2209–2226.

[13] Larsen E, Jorgensen PT, Sofan MA, Pedersen EB. *Synthesis* **1994**, 1037–1038.

[14] Cameron MA, Cush SB, Hammer RP. *J. Org. Chem.* **1997**, *62*, 9065–9069.

[15] Perigaud C, Gosselin G, Imbach JL. *Nucleosides & Nucleotides* **1992**, *11*, 903–945.

[16] El Ashry ESH, El Kilany Y. *Adv. Heterocycl. Chem.* **1997**, *67*, 391–438.

[17] El Ashry ESH, El Kilany Y. *Adv. Heterocycl. Chem.* **1997**, *68*, 1–88.

[18] El Ashry ESH, El Kilany Y. *Adv. Heterocycl. Chem.* **1998**, *69*, 129–215.

[19] Hirota K, Monguchi Y, Kitade Y, Sajiki H. *Tetrahedron* **1997**, *53*, 16683–16698.

[20] Schultze LM, Chapman HH, Dubree NJP, Jones RJ, Kent KM, Lee TT, Louie MS, Postich MJ, Prisbe EJ, Rohloff JC, Yu RH. *Tetrahedron Lett.* **1998**, *39*, 1853–1856.

[21] Shaw G,Warrener RN. *J. Chem. Soc.* **1958**, 153–161.

[22] See, eg, Breitmaier E, Voelter W. In Carbon-13 NMR spectroscopy. Weinheim:VCH, 1989:379-394.

[23] For a discussion on the hydrolysis mechanisms of standard nucleosides, see for instance: Ueda T. Synthesis and reactions of pyrimidine nucleosides. In Townsend LB, editor. Chemistry of nucleosides and nucleotides. New York: Plenum Press, 1988:93-95. Also see: Cadet J, Teoule R. *J. Am. Chem. Soc.* **1974**, *96*, 6517-6519.

[24] Carbon JA. *J. Am. Chem. Soc.* **1964**, *86*, 720–725.

[25] Nelsestuen GL. *Biochemistry* **1979**, *18*, 2843–2846.

[26] Petersen H, Pedersen EB, Nielsen CM. *Chem. Scripta* **1989**, *29*, 375–378.