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SYNTHESIS OF 2',3'-DIDEOXY-2',3'-DIDEHYDRONUCLEOSIDE ANALOGUES AS POTENTIAL ANTI HIV AGENTS

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Abstract. The 4-substituted pyrimidine 2',3'-dideoxy-2',3'-didehydronucleosides **3** - **10** have been synthesized and the activity of compounds **8** - **10** against HIV evaluated. The synthesis of the 5'-phosphate derivatives **13** - **14** was also reported.

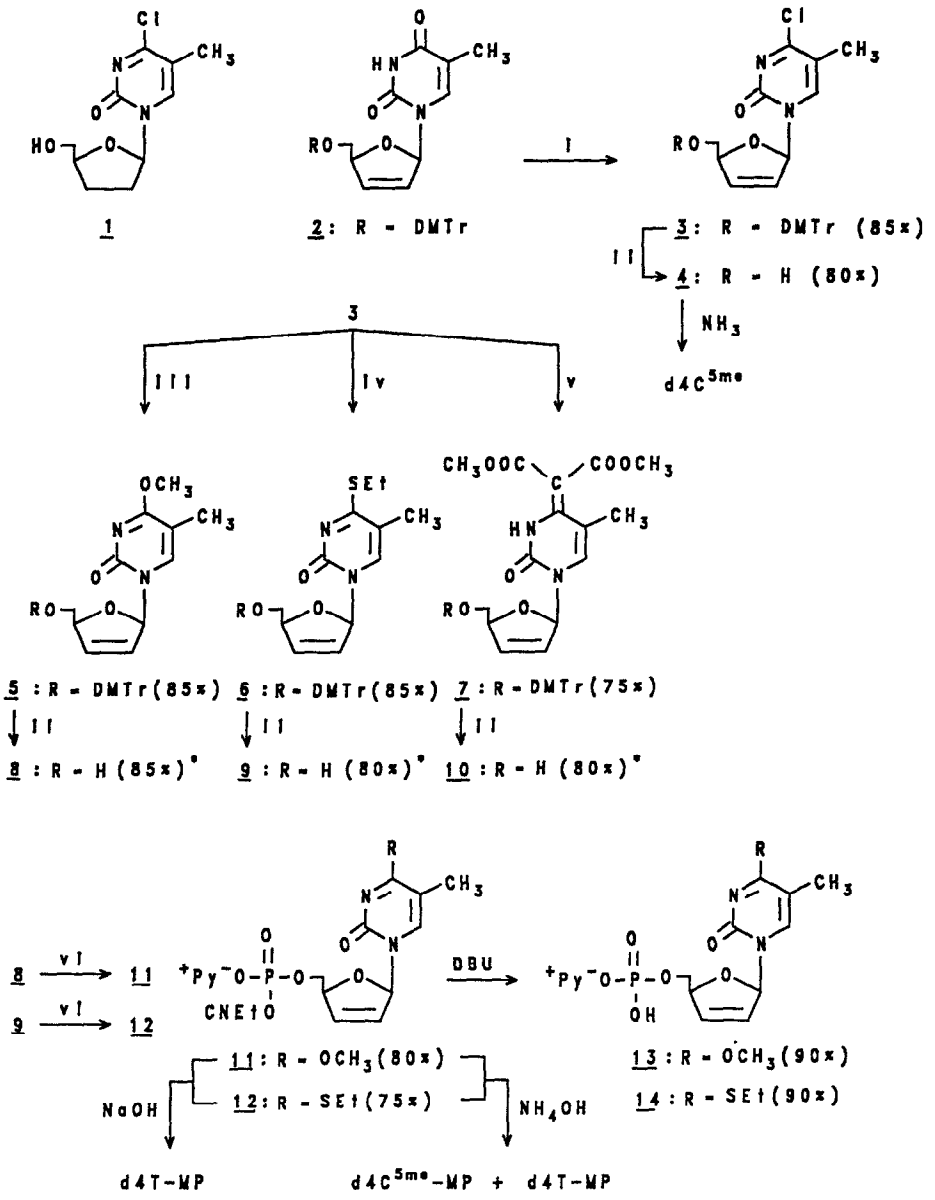
In recent years the interest towards the 2',3'-dideoxy- and 2',3'-dideoxy-2',3'-didehydronucleosides (d2- and d4nucleosides) is increased more and more because some of these compounds have shown promising results as selective inhibitors of the replication of the human immunodeficiency virus (HIV)[1].

Improved syntheses of d4nucleosides have been recently proposed[2] and, with the aim of obtaining new chemotherapeutically viable derivatives, some structurally correlated analogues, both sugar[3] and base modified[4], have been synthesized.

As a part of our program concerning the synthesis of new pyrimidine nucleoside analogues[5], we wish to report here the syntheses of compounds **3** - **10**. In addition the 5'-phosphorylation of compounds **8** and **9** using a slightly modified Tener's procedure[6] is described.

Recently we reported the synthesis of **1**[5c] using the adduct of triphenylphosphine (PPh_3) and CCl_4[7] as chlorinating agent of the C-4 of the base. We also reported that the conventional chlorination conditions[8] to prepare **1** were unsuitable, occurring the concomitant cleavage of the N-glycosidic bond, which in d2T and d4T is less stable than in dT[9]. In this paper the use of the adduct PPh_3/CCl_4 is extended to the chlorination of the C-4 of the d4T in order to synthesize a useful reactive intermediate for the synthesis of base modified d4nucleosides. The treatment of 5'-O-(4,4'-dimethoxytrityl)-3'-deoxy-2',3'-didehydrothymidine (**2**, DMTr-d4T)[10] with PPh_3/CCl_4 led, in essentially neutral conditions, to the formation of the 4-chloro derivative **3** in 85 % yield.

Compound **3**, left in contact with a solution of methanol/triethylamine (9:1) or with ethanethiol/triethylamine (9:1) afforded **5** and **6** respectively, in almost quantitative yields. Analogously, treating **3** with sodium dimethylmalonate in tetrahydrofuran the derivative **7**[11] was obtained.



Reagents and conditions: i, PPh_3 (1.2 eq), CCl_4, 1 h reflux; ii, HCl, (0.7 eq), $CHCl_3$, 15 min, 0 °C; iii, CH_3OH/Et_3N (9:1) 8 h, room temp.; iv, $EtSH/Et_3N$ (9:1), 5 h, room temp.; v, sodiumdimethylmalonate (1.2 eq) in THF,10 min, room temp.; vi,2-cyanoethylphosphate (pyridinium salt, 2 eq) in pyridine, 4 h, room temp..

* Based on consumed starting material.

In order to remove the 5'-DMTr group from compounds **3**,**5**,**6**,**7** we tried the commonly used acid reagents on d2- and d4nucleosides (i.e. 80% aqueous acetic acid or $ZnBr_2$/dioxane), unfortunately observing extensive deglycosylations. The goal was reached using hydrogen chloride in chloroform[12] thus obtaining the derivatives **4**, **8**, **9**, **10**. Nucleoside **4** reacted (15 min, 0 °C) with methanolic ammonia to give $d4C^{5me}$ in almost quantitative yield. It should be noted that the preparation of $d4C^{5me}$ following the steps **2**→**3**→**4**→**5** (overall yield 61 %) furnishes a valuable alternative to the already reported synthesis[13].

Compounds **8** and **9** were converted into diesters **11** and **12** using as phosphorylating reagent 2-cyanoethylphosphate[6] (pyridinium salt) in the presence of dicyclohexylcarbodiimide (DCCI). The conventional treatments to remove the 2-cyanoethyl (CNEt) group from **11** (**12**) with NaOH aq. (1 M, 1 h, room temp.) or NH_4OH conc. (1 h, 50 °C) afforded respectively d4T-5'-monophosphate (d4T-MP) or a mixture of $d4C^{5me}$-MP and d4T-MP. We succeeded to convert, in high yields, **11** and **12** into **13** and **14** respectively using 1,8--diazabicyclo[5.4.0]undec-7-ene (DBU, 6-7 h, room temperature).

^1H, ^{13}C NMR and CI mass spectra confirmed the structures of all the synthesized compounds[16].

Compounds **8**, **9** and **10** were tested against HIV C8166 cells. None of these compounds, tested at conc. varying from 5 to 50μM, displayed any significative antiviral activity.

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11. Within the detection limit of ^1H and ^{13}C NMR, spectral data indicate **10** as the sole tautomeric form present.
12. 0.7 eq. of HCl in $CHCl_3$ (0 °C, 15 min) were used on the respect of DMTr--product. Approximately 50% of the unchanged starting compound was recovered in each case and has been recycled.
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16. ^1H (270 MHz), ^{13}C (67.9 MHz) NMR and mass (CI) spectral data are the following: **4**,(acetone-d_6), ^1H NMR δ: 8.46 (bs,1H) H-6; 6.88 (m,1H) H-1' 6.40 (dt,1H,) H-3'; 6.01 (m,1H) H-2'; 4,97 (m,1H) H-4'; 3.84 (m,2H) H_2-5' 2.08 (bs,3H) CH_3-5. ^{13}C NMR δ: 171.8(C-4); 156.4 (C-2); 145.1 (C-6); 135.2 (C-3'); 127.5 (C-2'); 112.2 (C-5); 92.7 (C-1'); 89.5 (C-4'); 63.2 (C-5'); 15.6 (CH_3-5). Ions at m/z: 243 $(MH)^+$,144 $(B+H)^+$. UV (CH_3OH) λ_{max} 316 nm (5500); m.p 104-105 °C. **8**, (CD_3OD), ^1H NMR, δ: 8.07 (bs,1H) H-6; 7.00 (m,1H) H-1'; 6.38 (dt,1H) H-3'; 6.00 (m,1H) H-2'; 4.92 (m,1H) H-4'; 3.97 (s,3H) OCH_3; 3.78 (m,2H) H_2-5'; 1.93 (bs,3H) CH_3-5. ^{13}C NMR δ:173.0 (C-4); 159.0 (C-2) 143.2 (C-6); 135.6 (C-3'); 128.3 (C-2'); 106.9 (C-5); 92.9 (C-1'); 89.7 (C-4'); 64.0 (C-5'); 55.4 (OCH_3); 12.4 (CH_3-5). Ions at m/z: 239 $(MH)^+$, 141 $(B+2H)^+$. UV (CH_3OH) λ_{max} 282 nm (5100); m.p. 120--122 °C. **9**, (CD_3OD), ^1H NMR, δ: 8.01 (bs,1H) H-6; 6.97 (m,1H) H-1'; 6.38 (dt, 1H) H-3'; 5.99 (m,1H) H-2'; 4.95 (m,1H) H-4'; 3.79 (m,2H) H_2-5'; 3.21 (q,2H) SCH_2; 2.01 (bs,3H) CH_3-5; 1.35 (t,3H) $CH_2\underline{C}H_3$. ^{13}C NMR, δ: 180.7 (C-4); 156.8 (C-2); 140.5 (C-6); 135.7 (C-3'); 120.1 (C-2'); 114.5 (C-5); 93.4 (C-1'); 90.0 (C-4'); 64.0 (C-5'); 25.4 ($\underline{C}H_2CH_3$); 14.8 and 14.4 (CH_3-5 and CH_2-$\underline{C}H_3$). Ions at m/z: 269 $(MH)^+$,171 $(B+2H)^+$. UV (CH_3OH) λ_{max} 308 nm (10500), 274 nm (10100); m.p. 190-193 °C. **10**, ($CDCl_3$), ^1H NMR, δ: 12.06 (bs,1H) N-H; 7.10 (bs,1H) H-6; 6.95 (m,1H) H-1'; 6.30 (dt,1H) H-3'; 5.82 (m,1H) H-2'; 4.90 (m,1H) H-4'; 3.94 (m,2H) H_2-5'; 3.77 and 3.74 (s's,3H each) 2 OCH_3; 1.81 (bs, 3H) CH_3-5. ^{13}C NMR, δ:168.1 and 167.9 (2 $\underline{C}OOCH_3$); 149.9, 148.2 (C-2, C-4); 134.5, 134.2 (C-6, C-3'); 126.7 (C-2'); 107.1 (C-5); 92.7 [$\underline{C}(COOCH_3)_2$]; 89.7, 86.8 (C-1', C-4'); 63.5 (C-5'); 52.3 and 51.8 (2 OCH_3); 15.5 (CH_3-5). Ions at m/z: 339 $(MH)^+$, 241 $(B+2H)^+$. UV ($CHCl_3$) λ_{max} 339 nm (12800), 250 nm (6000); **13**, ^1H NMR (D_2O), significative protons at δ: 7.84 (m,1H) H-6; 4.07 (m,2H) H_2-5'; 3,99 (s,3H) OCH_3. **14**, ^1H NMR (D_2O) significative protons at δ: 7.90 (m,1H) H-6; 4.07 (m,2H) H_2-5'; 3.18 (q,2H) SCH_2; 1.35 (t,3H) $CH_2\underline{C}H_3$.