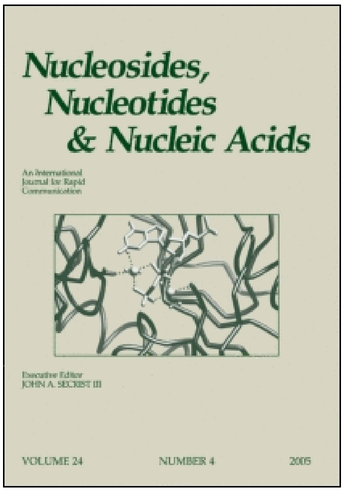

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Synthesis and Antiviral Evaluation of the β-L-Enantiomers of Some Thymine 3'-Deoxypentofuranonucleoside Derivatives

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SYNTHESIS AND ANTIVIRAL EVALUATION OF THE β-L-ENANTIOMERS OF SOME THYMINE 3'-DEOXYPENTOFURANONUCLEOSIDE DERIVATIVES

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Dedicated to the memory of Professor Alexander Krayevsky

ABSTRACT: 3'-Deoxy-β-L-*erythro*- (**3**), 3'-deoxy-β-L-*threo*- (**6**), 2'-fluoro- (**7**) and 2'-azido-2',3'-dideoxy-β-L-*erythro*- (**10**) pentofuranonucleoside derivatives of thymine have been synthesized and their antiviral properties examined. All these derivatives were stereospecifically prepared by glycosylation of thymine with a suitable peracylated 3-deoxy-L-*erythro*-pentofuranose sugar (**1**), followed by appropriate chemical modifications. The prepared compounds were tested for their activity against HIV, but they did not show an antiviral effect.

INTRODUCTION

In the last ten years, significant progress has been accomplished in the search of new therapeutic agents for the treatment of viral diseases,[1] and in this field, nucleoside analogs have gained a decisive place. For instance, to date, six nucleoside analogs, namely, 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), 2',3'-didehydro-3'-deoxythymidine (d_4T), 2',3'-dideoxy-3'-thia-β-L-cytidine (3TC) and (1*S*,4*R*)-4-[2-amino-6-(cyclopropyl)-9*H*-purin-9-yl]-2-

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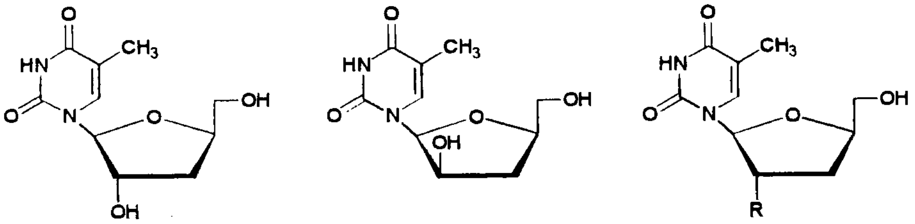


3 **6** **7** (R = F) **10** (R = N_3)

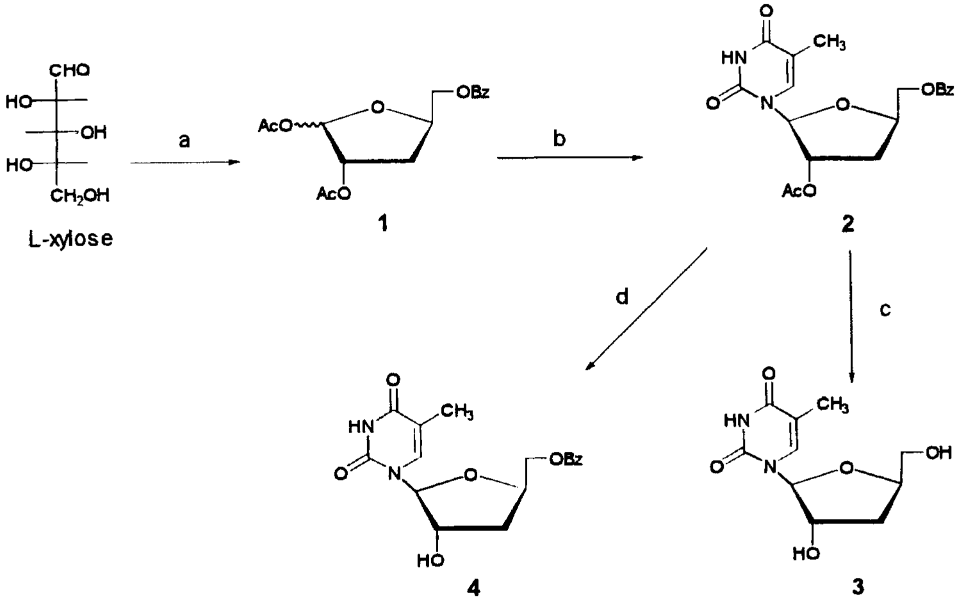
FIGURE

cyclopentene-1-methanol (Abacavir) have been approved by the Food and Drug Administration (FDA) for the treatment of human immunodeficiency virus (HIV) infection. All these nucleoside derivatives act as chain terminators and/or virus-specific reverse transcriptase inhibitors[2] after intracellular triphosphorylation by cellular kinases. However, the clinical use of the currently licensed anti-HIV nucleosides is hampered by drug resistance[3] and toxicity problems.[4] These limitations have led to the search of new agents possessing more selective antiviral activities. In this regard, recently, a number of nucleoside analogs with the unnatural β-L- configuration have emerged as powerful not only anti-HIV but also anti-HBV agents.[5]

In view of this interesting breakthrough of β-L-nucleosides as potential antiviral drugs, and as a part of our ongoing work on such unnatural enantiomers,[6-16] we present in this report the stereospecific synthesis and the anti-HIV evaluation of 3'-deoxy-β-L-*erythro*- (**3**) and 3'-deoxy-β-L-*threo*- (**6**) pentofuranosylthymine as well as 2'-fluoro- (**7**) and 2'-azido- (**10**) 2',3'-dideoxy-β-L-*erythro*-pentofuranosylthymine, all of them being hitherto unknown except for 7.[17]

RESULTS AND DISCUSSION

Several methodologies have been reported in the literature for the preparation of 2'-deoxy- and 2',3'-dideoxynucleoside analogues.[18-20] For our part, we chose to condense a suitably protected 3-deoxy-L-sugar derivative with thymine as the heterocyclic base to prepare the nucleosides **3**, **6**, **7** and **10**. In accordance with Baker's rule[21,22] and owing to 2-*O*-acyl participation during the coupling reaction, we selected 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-L-*erythro*-pentofuranose (**1**) as a starting sugar (Scheme 1).



SCHEME 1. *Reagents and conditions*: (a) Ref. 23; (b) silylated thymine/TMSOTf/ DCE, rt; (c) NH_3/MeOH, rt; (d) MeONa/THF, rt.

The starting sugar **1** was readily prepared from commercially available L-xylose following a synthetic pathway previously described.[23] Glycosylation reaction of thymine with **1** was carried out under Vorbrügen conditions using (trimethylsilyl) trifluoromethane sulfonate (TMSOTf) as a catalyst in anhydrous 1,2-dichloroethane (DCE) and afforded 1-(2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-β-L-*erythro*-pentofuranosyl)-thymine (**2**) in 79% yield after silica gel column chromatography. Complete deprotection of **2** with methanolic ammonia gave the desired nucleoside **3** as a crystalline solid in 81% yield after purification, while, regioselective 2'-*O*-deacylation of compound **2** with solid sodium methoxide in suspension in tetrahydrofuran (THF) afforded the 5'-*O*-

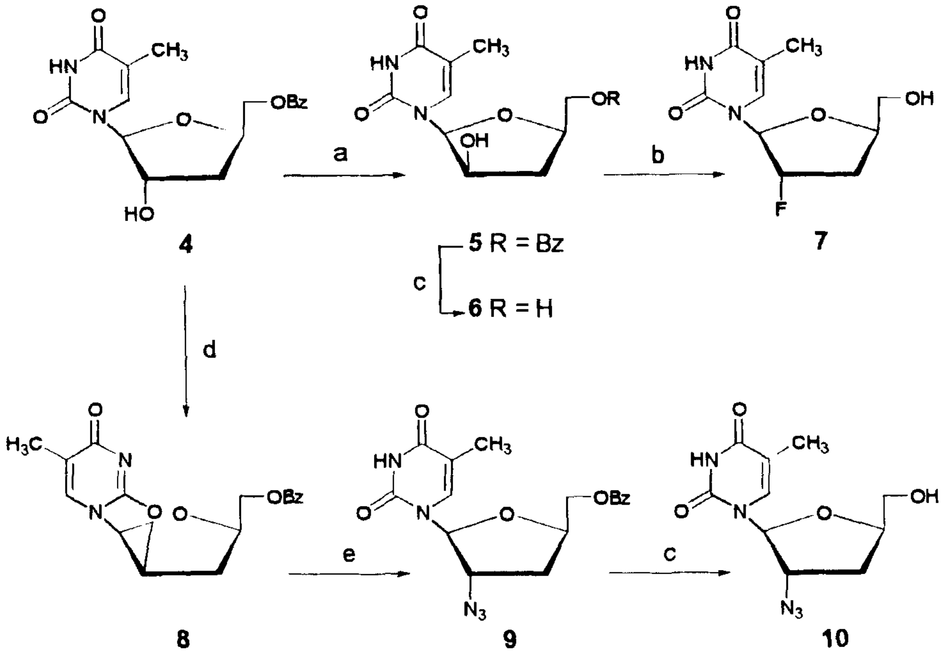
benzoyl derivative **4** (68% after silica gel column chromatography). This key derivative **4** was used subsequently for the preparation compounds **6**, **7** and **10**.

Compound **4** was first converted into the 5'-*O*-benzoyl-3'-deoxy-β-L-*threo* derivative **5** which was isolated as a crystalline solid in 60% yield (Scheme 2). Such an inversion of configuration at the 2'-position of **4** was achieved in two steps *via* an oxidation-reduction process.[24] Thus, treatment of **4** with a dimethyl sulfoxide (DMSO)/benzene mixture in the presence of dicyclohexyl carbodiimide (DCC), dichloroacetic acid and pyridine afforded the 2'-keto intermediate which was stereoselectively reduced *in situ* with sodium borohydride. In accord with their structures, the ^{1}H NMR spectra of nucleosides **4** and **5** exhibited differences. In particular, the spectrum of **5** showed the H-1' proton as a doublet with the coupling constant ($J_{1',2'}$ = 4.5 Hz) expected for the arabinose configuration of the 2'-hydroxy group.[25] Debenzoylation of **5** with methanolic ammonia provided the 3'-deoxy-β-L-*threo*-pentofuranonucleoside **6**. Next, fluorination reaction was accomplished by treatment of **5** with (diethylamino)sulphur trifluoride (DAST)[26] in a dichloromethane-pyridine mixture at 0°C, and subsequent deprotection with methanolic ammonia gave 2'-fluoro-2',3'-dideoxy-β-L-thymidine (**7**) in 80% overall yield from **5**.

Compound **4** was also used for the preparation of 2'-azido-2',3'-dideoxy-β-L-thymidine (**10**). Thus, under Mitsunobu reaction conditions with diethylazodicarboxylate (DEAD) and triphenyl phosphine (PPh_3) in dry THF, formation of the anhydro-nucleoside **8** was almost quantitative. Introduction of the azido group to the 2'-position was then carried out by generation of lithium azide *in situ* from azidotrimethylsilane (Me_3SiN_3) and lithium fluoride in the presence of tetramethyl ethylenediamine (TMEDA) in dimethyl formamide (DMF).[27] Under these conditions **9** was obtained in 95% yield after purification, and removal of the benzoyl group with methanolic ammonia afforded **10** as crystalline solid in 80% yield after silica gel column chromatography.

ANTI-HIV EVALUATION

All the unprotected nucleosides **3**, **6**, **7** and **10** were tested for their *in vitro* inhibitory effects on the replication of HIV-1 in CEM-SS and MT-4 cell systems.



SCHEME 2. *Reagents and conditions*: (a) 1) DCC/DMSO/Cl_2CHCO_2H/C_6H_6/C_5H_5N, rt; 2) $NaBH_4/C_6H_6$/absolute EtOH, rt; (b) 1) DAST, C_5H_5N-CH_2Cl_2, 0°C→ rt; 2) NH_3/MeOH, rt; (c) NH_3/MeOH, rt; (d) PPh_3, DEAD, THF, rt; (e) Me_3SiN_3/LiF/DMF/TMEDA, reflux.

However, none of these compounds showed an antiviral effect or detectable alteration of host-cell morphology at the highest concentration tested (generally 100 μM).

CONCLUSION

From the present work it appears that 3'-deoxy-β-L-*erythro*- (**3**) and 3'-deoxy-β-L-*threo*- (**6**) pentofuranosylthymine, as well as 2'-fluoro- (**7**) and 2'-azido- (**10**) 2',3'-dideoxy-β-L-*erythro*-pentofuranosylthymine do not induce inhibition of HIV replication. Among the several hypotheses that can explain this lack of antiviral activity, the inability of these compounds to enter cells, to serve as substrate for the enzymes catalyzing phosphorylations or to inhibit viral reverse transcriptase by their triphosphate forms, can be proposed. Further research would be needed to support these hypotheses. However that may be, the present data do not preclude not only an activity of **3**, **6**, **7** and **10** against other viruses, but also the pursuit of studies on other β-L-nucleoside series as potential antiviral drugs. Experiments related to these topics are currently in progress in our laboratory.

EXPERIMENTAL

Evaporation of solvents was carried out on a rotary evaporator under reduced pressure. Melting points were determined in open capillary tubes on a Gallenkamp MFB-595-010 M apparatus and are uncorrected. UV spectra were recorded on an Uvikon 931 (Kontron) spectrophotometer. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz in $(CD_3)_2SO$ at ambient temperature with a Brüker DRX 400. The ^{19}FNMR spectrum was recorded at 250 MHz in $(CD_3)_2SO$ at ambient temperature with a Brüker AC 250 with $CFCl_3$ as internal reference. Chemical shifts are given in δ-values, $(CD_3)CD_2H)SO$ being set at δ_H 2.49 and δ_C 39.5 as a reference. Deuterium exchange and COSY experiments were performed in order to confirm proton assignments. Coupling constants, J, are reported in Hertz. 2D ^{1}H-^{13}C heteronuclear COSY were recorded for the attribution of ^{13}C signals. FAB mass spectra were recorded in the positive-ion or negative-ion mode on a JEOL SX 102. The matrix was a mixture (50 :50, v/v) of glycerol and thioglycerol (G-T). Specific rotations were measured on a Perkin-Elmer Model 241 spectropolarimeter (path length 1 cm), and are given in units of 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out by the Service de Microanalyses du CNRS, Division de Vernaison (France). Thin layer chromatography was performed on precoated aluminium sheets of Silica Gel 60 F_{254} (Merck, Art. 5554), visualization of products being accomplished by UV absorbance followed by charring with 10% ethanolic sulphuric acid and heating. Column chromatography was carried out on Silica Gel 60 (Merck, Art. 9385).

1-(2-*O*-Acetyl-5-*O*-benzoyl-3-deoxy-β-L-*erythro*-pentofuranosyl)thymine (2). A mixture of thymine (352 mg, 2.79 mmol), hexamethyldisilazane (21 ml) and a catalytic amount of ammonium sulfate was refluxed under argon for 18h. The clear solution obtained was concentrated to dryness under reduced pressure. TMSOTf (0.675 ml, 3.72 mmol) was added to a solution of sugar **1**[23] (600 mg, 1.86 mmol) and silylated base in dry DCE (28 ml).The reaction mixture was stirred for 1h under argon, poured into saturated $NaHCO_3$ solution (30 ml) and stirred for 15 min. The organic phase was washed with water (2 × 50 ml), dried (Na_2SO_4) and evaporated to dryness. Column chromatography of the residue on silica gel using a stepwise gradient of methanol (0-4%) in dichloromethane afforded the *title compound* **2** as a white foam (574 mg, 79%) which was crystallized from carbon tetrachloride: m.p. 80-81°C, $[\alpha]_D^{20}$ + 20 (*c* 1.05 in Me_2SO); λ_{max} (95% EtOH)/nm 267 (ε 9200), 228 (ε 12200), λ_{min} 248 (ε 5000); δ_H 1.62 (d, 3H, CH_3-5, J = 0.7 Hz) 2.06 (s, 3H, CH_3CO), 2.1-2.2 (m, 1H, H-3'), 2.4 (m, 1H, H-3"), 4.4-4.6 (m, 3H, H-4', H-5' and H-5"), 5.3 (m, 1H, H-2'), 5.80 (d, 1H, H-1', $J_{1',2'}$ = 2.4 Hz), 7.40 (d, 1H, H-6, J = 1.1 Hz), 7.5-8.0 (m, 5H, C_6H_5CO), 11.36 (s, 1H, NH-3); m/z (FAB > 0, G-T) 389 $(M + H)^+$, 263 $(S)^+$, 127 $(BH_2)^+$, 105 $(PhC{=}O)^+$; m/z (FAB < 0, G-T) 387 $(M-H)^-$, 125 $(B)^-$, 121 $(PhCO_2)^-$. Anal. Calcd for $C_{19}H_{20}N_2O_7$.1/6 CCl_4: C, 55.62; H, 4.87; N, 6.77. Found: C, 55.97; H, 5.14; N, 6.27.

1-(3-Deoxy-β-L-*erythro*-pentofuranosyl)thymine (3).

A solution of **2** (400 mg, 1.02 mmol) in methanolic ammonia (previously saturated at - 10 °C and tightly stoppered) (25 ml) was stirred for 18 h at room temperature, then evaporated to dryness. The residue was purified by silica gel column chromatography using a stepwise of methanol (0-10%) in dichloromethane to afford the *title compound* **3** (200 mg, 81%), which was crystallized from ethanol: m.p. 90-92 °C [Lit.[28] m.p. 96 °C for the D-enantiomer]; $[\alpha]_D^{20}$ + 13.4 (*c* 1.04 in Me_2SO) [Lit.[28] $[\alpha]_D^{20}$ - 1.84 (*c* 2.17 in MeOH) for the D-enantiomer]; λ_{max} (95% EtOH)/nm 267 (ε 9200); δ_H 1.8 (m, 4H, H-3' and CH_3-5), 2.0 (m, 1H, H-3"), 3.51 (m, 1H, H-5'), 3.72 (m, 1H, H-5"), 4.2-4.4 (m, 2H, H-2'and H-4'), 5.09 (m, 1H, OH-5'), 5.49 (d, 1H, OH-2', J = 3.7 Hz), 5.63 (d, 1H, H-1', $J_{1',2'}$ = 2.1 Hz), 7.82 (s, 1H, H-6), 11.24 (br s, 1H, NH-3); m/z (FAB > 0, G-T) 243 $(M + H)^+$, 127 $(BH_2)^+$; m/z (FAB < 0, G-T) 241 $(M-H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{10}H_{14}N_2O_5.H_2O$: C, 46.15; H, 6.20; N, 10.76. Found : C, 46.23; H, 6.53; N, 10.77.

1-(5-*O*-Benzoyl-3-deoxy-β-L-*erythro*-pentofuranosyl)thymine (4).

To a stirred solution of **2** (6.2 g, 15.9 mmol) in THF (127 ml) (previously passed on a sintered funnel covered with Al_2O_3) was added solid sodium methoxide (948 mg, 17.5 mmol). The resulting suspension was stirred for 2h at room temperature, then neutralized by addition of resin Dowex 50W×2 (H^+ form). The resin was washed several times with boiling methanol and the combined filtrates were evaporated to dryness. Column chromatography of the residue on silica gel using a stepwise gradient of methanol (0-6%) in dichloromethane afforded the *title compound* **4** (3.74 g, 68%) which was crystallized from cyclohexane/dichloromethane: m.p. 79-81°C; $[\alpha]_D^{20}$ + 34.9 (*c* 1.03 in Me_2SO); λ_{max} (95% EtOH)/nm 267 (ε 9300), 228 (ε 11200), λ_{min} 248 (ε 5200); δ_H 1.56 (d, 3H, CH_3-5, J = 0.7 Hz), 1.9-2.0 (m, 1H, H-3'), 2.1-2.2 (m, 1H, H-3"), 4.3 (m, 1H, H-2'), 4.4 (m, 1H, H-5'), 4.5-4.6 (m, 2H, H-4'and H-5"), 5.60 (d, 1H, OH-2', J = 4.4 Hz), 5.69 (d, 1H, H-1', $J_{1',2'}$ = 2.5 Hz), 7.33 (d, 1H, H-6, J = 0.9 Hz), 7.5-8.0 (m, 5H, C_6H_5CO), 11.32 (s, 1H, NH-3); m/z (FAB > 0, G-T) 347 $(M + H)^+$, 127 $(BH_2)^+$; m/z (FAB < 0, G-T) 345 $(M-H)^-$. Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found : C, 58.44; H, 5.08; N, 7.85.

1-(5-*O*-Benzoyl-3-deoxy-β-L-*threo*-pentofuranosyl)thymine (5).

To a stirred solution of **4** (4.2 g, 12.1 mmol) in a benzene/DMSO mixture (6:4, 180 ml) were added successively DCC (7.48 g, 36.3 mmol), dichloroacetic acid (0.5 ml, 6.06 mmol) and dry pyridine (1 ml). After 4h, ethyl acetate (EtOAc) (600ml) and oxalic acid (3.2 g, 36.3 mmol) in methanol (9 ml) were added. The resulting suspension was stirred for 1h, then filtered. The filtrate was washed with brine (2×300 ml), 5% $NaHCO_3$ (2×300 ml), water (2×300 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The resulting crude material was coevaporated with absolute EtOH, then dissolved in a benzene/absolute EtOH mixture (1:2, 100 ml). After cooling to 0°C, $NaBH_4$ (686 mg, 18.1 mmol) was added. The solution was stirred for 30 min, diluted with EtOAc (300 ml). The resulting suspension was stirred further for 20 min , then filtered. The filtrate was washed with brine (2×200 ml), water (2×200 ml), dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography using a stepwise gradient of methanol (0-6%) in dichloromethane to afford the *title compound* **5** (2.5 g, 60%) which was crystallized from methanol/dichloromethane: m.p. 82-84 °C; $[\alpha]_D^{20}$ - 44.4 (*c* 1.0 in Me_2SO); λ_{max} (95% EtOH)/nm 267 (ε 9400), 228 (ε 11400), λ_{min} 248 (ε 5300); δ_H 1.63 (d, 3H, CH_3-5, J = 0.8 Hz), 1.8-1.9 (m, 1H, H-3'), 2.4 (m, 1H, H-3"), 4.3 (m, 2H, H-2' and H-5'), 4.4 (m, 1H, H-5"), 4.6 (m, 1H, H-4'), 5.44 (d, 1H, OH-2', J = 4.3 Hz), 5.91 (d, 1H, H-1', $J_{1',2'}$ =

4.5 Hz), 7.37 (d, 1H, H-6, J = 1.2 Hz), 7.5-8.0 (m, 5H, C_6H_5CO), 11.24 (s, 1H, NH-3); m/z (FAB > 0, G-T) 347 $(M + H)^+$, 127 $(BH_2)^+$; m/z (FAB < 0, G-T) 345 $(M-H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found : C, 58.59; H, 5.25; N, 8.02.

1-(-3-Deoxy-β-L-*threo*-pentofuranosyl)thymine (6).

A solution of **5** (386 mg, 1.11 mmol) in methanolic ammonia (25 ml) was stirred for 18 h at room temperature, then evaporated to dryness. The residue was purified by silica gel column chromatography using a stepwise of methanol (0-10%) in dichloromethane to afford the *title compound* **6** (210 mg, 80%), which was crystallized from toluene/methanol: m.p. 162-164°C; $[\alpha]_D^{20}$ - 78.2 (c 1.01 in Me_2SO); λ_{max} (95% EtOH)/nm 267 (ε 9500) [Lit.[25] λ_{max} (EtOH)/nm 268 (ε 9600) for the D-enantiomer]; δ_H 1.75 (m, 4H, H-3' and CH_3), 2.2 (m, 1H, H-3"), 3.6-3.8 (m, 2H, H-5' and H-5"), 3.95 (m, 1H, H-4'), 4.3 (m, 1H, H-2'), 5.08 (t, 1H, OH-5', J = 5.4 Hz), 5.31 (d, 1H, OH-2', J = 5.2 Hz), 5.84 (d, 1H, H-1', $J_{1',2'}$ = 5.0 Hz), 7.62 (d, 1H, H-6, J = 0.9 Hz), 11.19 (s, 1H, NH-3); δ_C 13.2 (CH_3-5), 34.9 (C-3'), 63.3 (C-5'), 70.3 (C-2'), 78.4 (C-4'), 86.2 (C-1'), 107.9 (C-5), 138.9 (C-6), 151.4 (C-2), 164.8 (C-4); m/z (FAB > 0, G-T) 243 $(M + H)^+$, 127 $(BH_2)^+$; m/z (FAB < 0, G-T) 241 $(M-H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{10}H_{14}N_2O_5$: C, 49.58; H, 5.83; N, 11.56. Found : C, 49.63; H, 5.83; N, 11.30.

1-(2-Fluoro-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)thymine (7).

DAST (0.45 ml, 3.45 mmol) was added to a solution of nucleoside **5** (478 mg, 1.38 mmol) in dry dichloromethane (20 ml) and pyridine (0.7 ml) at 0 °C under argon. Stirring was continued for 18h at room temperature, and the reaction mixture was poured into a saturated $NaHCO_3$ solution (25 ml). The organic phase was washed with water (2 x 50 ml), dried (Na_2SO_4) and evaporated to dryness. The residue was subjected to a silica gel column chromatography using a stepwise gradient of methanol (0-6%) in dichloromethane. The appropriate fractions were pooled, and directly treated with methanolic ammonia for 18h. After evaporation to dryness under reduced pressure, the residue was purified by silica gel column chromatography using a stepwise gradient of methanol (0-6%) in dichloromethane to afford the *title compound* **7** (270 mg, 80%

overall yield from **5**) which was crystallized from methanol: m.p. 188-190°C [Lit.[17] m.p. 186-188°C], [Lit.[29] m.p. 186-187°C for the D-enantiomer]; $[\alpha]_D^{20}$ - 6.4 (*c* 1.1 in Me_2SO); λ_{max} (95% EtOH)/nm 267 (ε 9500) [Lit.[29] λ_{max} (MeOH)/nm 266 (ε 9450) for the D-enantiomer]; δ_H 1.73 (d, 3H, CH_3-5, J = 0.8 Hz), 2.0-2.1 (m, 2H, H-3' and H-3''), 3.6 (m, H, H-5') 3.8 (m, 1H, H-5''), 4.4 (m, 1H, H-4'), 5.2-5.4 (m, 2H, H-2' and OH-5'), 5.87 (d, 1H, H-1', $J_{1',F}$ = 18.5 Hz), 7.85 (d, 1H, H-6, J = 1.0 Hz), 11.36 (s, 1H, NH-3); δ_F - 178 (m); δ_C 13.1 (CH_3-5), 32.0 (d, C-3', $J_{C\text{-}3',F}$ = 20.4 Hz), 61.4 (C-5'), 82.1 (C-4'), 90.2 (C-1', $J_{C\text{-}1',F}$ = 36.7 Hz), 86.2 (d, C-2', $J_{C\text{-}2',F}$ = 177.1 Hz),. 109.5 (C-5), 136.7 (C-6), 151.1 (C-2), 164.7 (C-4); m/z (FAB > 0, G-T) 245 $(M + H)^+$, 127 $(BH_2)^+$; m/z (FAB < 0, G-T) 243 $(M\text{-}H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{10}H_{13}N_2O_4F$: C, 49.18; H, 5.37; N, 11.47; F, 7.78. Found : C, 49.33; H, 5.31; N, 11.46; F, 7.57.

1-(5-*O*-Benzoyl-2,2'-anhydro-3-deoxy-β-L-*arabino*-furanosyl)thymine (8).

A mixture of **4** (700 mg, 2.02 mmol) and triphenyl phosphine (634 mg, 2.42 mmol) was stirred in dry THF (15 ml) and treated with diethyl azodicarboxylate (0.35 ml, 2.42 mmol). The reaction mixture was stirred for 15 min, concentrated to half volume and allowed to crystallize. The white crystals were collected by filtration to afford the *title compound* **8** (600 mg, 90%): m.p. 158-160°C; $[\alpha]_D^{20}$ - 9 (*c* 0.99 in Me_2SO); δ_H 1.72 (d, 3H, CH_3-5, J = 0.9 Hz), 2.1 (m, 1H, H-3'), 2.6 (m, 1H, H-3''), 3.8-4.0 (m, 2H, H-5' and H-5''), 4.5 (m, 1H, H-4'), 5.4 (m, 1H, H-2'), 6.0 (d, 1H, H-1', $J_{1',2'}$ = 5.5 Hz), 7.2-7.7 (m, 6H, H-6 and C_6H_5CO); m/z (FAB > 0, G-T) 329 $(M + H)^+$, 105 $(PhC{=}O)^+$; m/z (FAB < 0, G-T) 327 $(M\text{-}H)^-$, 121 $(PhCO_2)^-$. Anal. Calcd for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found : C, 62.00; H, 4.91; N, 8.15.

1-(5-*O*-Benzoyl-2-azido-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)thymine (9).

To a suspension of LiF (156 mg, 6.03 mmol) in dry DMF (10 ml) and TMEDA (3.1 ml, 20.4 mmol) was added azidotrimethylsilane (0.85 ml, 6.4 mmol). The reaction was heated at 105°C for 2.5h, then compound **8** (1.1 g, 3.35 mmol) was added. After heating for 18h at the same temperature, the reaction was cooled and the solvents were evaporated to dryness. The residue was subjected to silica gel column chromatography using a stepwise gradient of methanol (0-3%) in dichloromethane to afford the title compound **9** (1.2 g, 95%) which was crystallized from absolute EtOH: m.p. 130-132°C; $[\alpha]_D^{20}$ + 41 (*c* 1.0 in Me_2SO); λ_{max} (95% EtOH)/nm 267 (ε 9400), 228 (ε 11000), λ_{min} 248 (ε 5100); δ_H 1.55 (d, 3H, CH_3-5, J = 0.8 Hz), 2.0-2.1 (m, 1H, H-3'), 2.2-2.3 (m, 1H, H-3"), 4.4-4.6 (m, 4H, H-2', H-4', H-5' and H-5"), 5.77 (d, 1H, H-1', $J_{1',2'}$ = 2.5 Hz), 7.37 (d, 1H, H-6, J = 1.3 Hz), 7.5-8.0 (m, 5H, C_6H_5CO), 11.41 (s, 1H, NH-3); m/z (FAB > 0, G-T) 372 $(M + H)^+$, 246 $(S)^+$, 127 $(BH_2)^+$, 105 $(PhC{=}O)^+$; m/z (FAB < 0, G-T) 370 $(M-H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{17}H_{17}N_5O_5$: C, 54.98; H, 4.61; N, 18.86. Found : C, 54.43; H, 4.68; N, 18.17.

1-(2-Azido-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)thymine (10).

A solution of **9** (400 mg, 1.06 mmol) in methanolic ammonia (25 ml) was stirred for 18h at room temperature, then evaporated to dryness. Chromatography of the residue on a silica gel column using as eluent a stepwise gradient of methanol (0-8%) in dichloromethane afforded the title compound **10** (228 mg, 80%) which was crystallized from acetone/hexane: m.p. 167-168°C [Lit.[30] m.p. 167-168°C for the D-enantiomer]; $[\alpha]_D^{20}$ + 45.6 (*c* 1.03 in Me_2SO) [Lit.[30] $[\alpha]_D^{20}$ - 43.5 (*c* 0.92 in Me_2SO) for the D-enantiomer]; λ_{max} (95% EtOH)/nm 267 (ε 9800) [Lit.[30] λ_{max} (MeOH) 268 (ε 10050) for the D-enantiomer]; δ_H 1.74 (d, 3H, CH_3-5, J = 0.8 Hz), 1.8-1.9 (m, 1H, H-3'), 2.1-2.2 (m, 1H, H-3"), 3.53 (m, 1H, H-5'), 3.75 (m, 1H H-5"), 4.18 (m, 1H, H-4'), 4.44 (m, 1H, H-2'), 5.21 (t, 1H, OH-5', J = 5.2 Hz), 5.73 (d, 1H, H-1', $J_{1',2'}$ = 2.1 Hz), 7.86 (d, 1H, H-6, J = 1.0 Hz), 11.36 (s, 1H, NH-3); δ_C 13.1 (CH_3-5), 31 (C-3'), 61.8 (C-5'), 66.3 (C-2'), 81.9 (C-4'), 89.8 (C-1'), 109.5 (C-5), 136.4 (C-6), 151.1 (C-2), 164.7 (C-4) ;m/z (FAB > 0, G-T) 268 $(M + H)^+$, 127 $(BH_2)^+$; m/z (FAB < 0, G-T) 266 $(M-H)^-$, 125 $(B)^-$. Anal. Calcd for $C_{10}H_{13}N_5O_4$: C, 44.94; H, 4.90; N, 26.21. Found : C, 44.82; H, 4.96; N, 25.95.

Biological Methods.- The anti-HIV assays on cell culture were performed by following previously established procedures as described in ref. 31.

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