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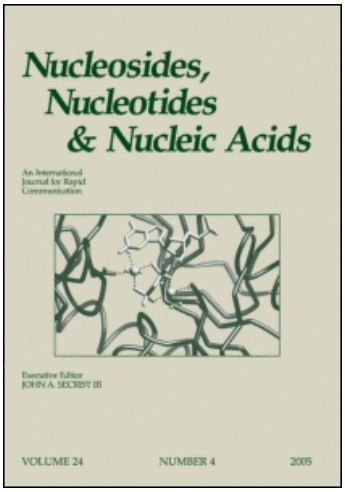

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Synthesis and Antiviral Evaluation of Unnatural β-L-Enantiomers of 3'-Fluoro- and 3'-Azido-2,3'-dideoxyguanosine Derivatives

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NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(1&2), 205–217 (2000)

SYNTHESIS AND ANTIVIRAL EVALUATION OF UNNATURAL β-L-ENANTIOMERS OF 3'-FLUORO- AND 3'-AZIDO-2',3'-DIDEOXYGUANOSINE DERIVATIVES

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Dedicated to the memory of Dr. Gertrude B. Elion

ABSTRACT: 3'-fluoro-2',3'-dideoxy- (**3**) and 3'-azido-2',3'-dideoxy- (**4**) β-L-ribofuranonucleoside derivatives of guanine have been synthesized and their antiviral properties examined. All these derivatives were regioselectively and stereospecifically prepared by glycosylation of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine **5** with a suitable peracylated L-*xylo*-furanose sugar **6**, followed by appropriate chemical modifications. The prepared compounds were tested for their activity against HIV and HBV viruses, but they did not show significant activity.

INTRODUCTION

In the last years, significant progress has been accomplished in the discovery of chemotherapeutic agents against human immunodeficiency virus (HIV).[1] Among them, nucleoside analogs have been demonstrated to be potent drugs in the treatment of HIV infections. These antiretroviral agents target the HIV-encoded reverse transcriptase (RT) enzyme and act, after intracellular triphosphorylation by cellular kinases, as virus-specific RT inhibitors and/or chain terminators.[2] Clinically approved nucleoside analogs include 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxy-

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cytidine (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-cyclopentene-1-methanol (Abacavir). However, inherent drug resistance[3] and toxicity problems[4] encountered with the currently licensed anti-HIV drugs have led to the search of agents possessing more selective antiviral activities. Recently, a number of nucleoside analogs with the unnatural β-L- configuration have been demonstrated to be powerful not only as anti-HIV but also as anti-HBV agents.[5] Among them, 3TC[6,7] was the first of this new generation of nucleoside analogs approved by the Food and Drug Administration for use in Hepatitis B virus (HBV) therapy.

In view of this interesting discovery of β-L-nucleosides as antiviral active compounds, we have recently reported that various adenine β-L-2',3'-dideoxynucleoside analogs, and more particularly β-L-3'-fluoro-2',3'-dideoxyadenosine (3'-fluoro-β-L-ddA) (**1**) and β-L-3'-azido-2',3'-dideoxyadenosine (3'-azido-β-L-ddA) (**2**) (Figure), were selective anti-HBV agents in cell culture experiments.[8]

Consequently, and as a part of our ongoing work on other β-L-nucleoside analogs,[8-17] it was of interest to synthesize in a stereospecific manner and to evaluate the corresponding 3'-fluoro-2',3'-dideoxy- (**3**) and 3'-azido-2',3'-dideoxy- (**4**) β-L-ribofuranonucleoside derivatives of guanine (Figure), both of them being hitherto unknown.

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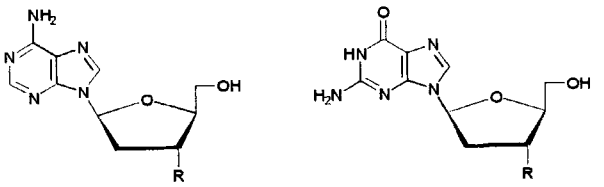
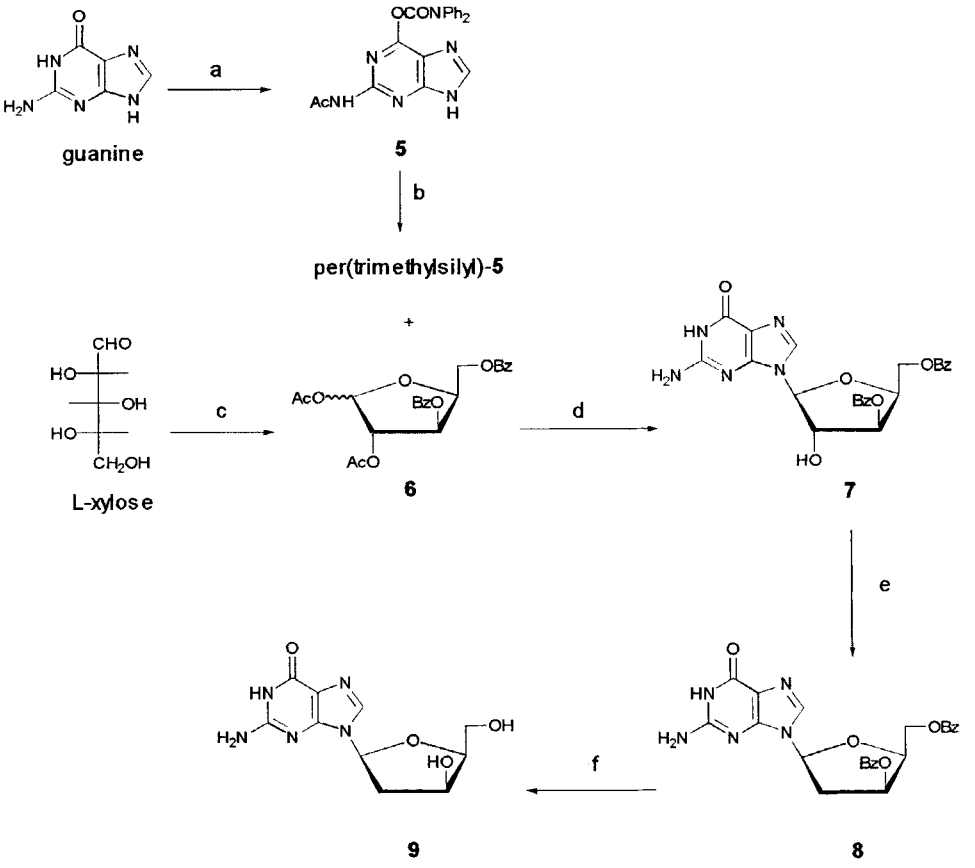
RESULTS AND DISCUSSIONS

A number of methodologies have been reported in the literature for the preparation of dideoxynucleosides and analogues.[18-20] For our part, we chose for the synthesis of the guanine derivatives **3** and **4** to condense first a suitably peracylated L-*xylo*-furanose with a guanine-type base. In accord with Baker's rule[21,22] and owing to 2-*O*-acyl participation during the coupling reaction, we selected as starting sugar 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-*xylo*-furanose (**6**) (Scheme 1).

The starting sugar **6** was readily prepared from commercially available L-xylose following a synthetic pathway previously described by Gosselin et al.[9] Regarding the



FIGURE



SCHEME 1. *Reagents and conditions*: (a) Ref. 23; (b) BSA, DCE, 80°C; (c) Ref. 9; (d) 1) TMSOTf, toluene, 80°C; 2) $H_2NNH_2.H_2O$, AcOH, C_5H_5N, rt; (e) 1) PhO(C=S)Cl, DMAP, CH_3CN, rt; 2) $(Me_3Si)_3SiH$, AIBN, dioxan, reflux; (f) NH_3/MeOH, rt.

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heterocyclic base, we used 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine[23] (**5**) in order to avoid N7/N9 isomeric mixture of nucleosides. Hence, treatment of a suspension of **5** in anhydrous 1,2-dichloroethane (DCE) with bis(trimethylsilyl)acetamide (BSA) at 80°C for 15 min gave per(trimethylsilyl)-**5** which was then coupled with **6** in anhydrous toluene at 80°C for 1 h in the presence of (trimethylsilyl) trifluoromethane sulfonate (TMSOTf) as a catalyst. From the crude coupling product, regioselective 2'-*O*-deacylation and concomitant 6-*O*-(diphenylcarbamoyl) removal with hydrazine hydrate gave 9-(3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)guanine **7** in 60% overall yield after silica gel column chromatography. Structural assignments for **7** were fully established from ^{1}H NMR, ^{13}C NMR and UV spectra. Compound **7** was then reacted with *O*-phenyl chloro(thio)formate (PhOC(=S)Cl) and 4-dimethylaminopyridine (DMAP) in acetonitrile to give the corresponding 2'-*O*-[phenoxy(thiocarbonyl)] intermediate, which was subsequently deoxygenated with tris(trimethylsilyl)silane[15] in dry dioxane in the presence of α,α'-azoisobutyronitrile (AIBN) to afford the 2'-deoxy-β-L-*threo* derivative **8** in 65% overall yield. Deprotection of **8** with methanolic ammonia provided the unprotected 2'-deoxynucleoside **9** as a crystalline solid in 85% yield after purification.

In view of the preparation of the target nucleosides **3** and **4**, the compound **9** was selectively converted into the 5'-*O*-(*tert*-butyldimethylsilyl) key derivative **10** which was isolated as a crystalline solid in 95% yield (Scheme 2). Fluorination reaction was accomplished by treatment of **10** with (diethylamino)sulphur trifluoride (DAST) in anhydrous dichloromethane at 0°C,[24] and subsequent desilylation with tetrabutylammonium fluoride (TBAF) on silica gel in tetrahydrofuran (THF) provided 3'-fluoro-β-L-2',3'-dideoxyguanosine (**3**) in low yield. On the other hand, we chose for the preparation of 3'-azido-β-L-2',3'-dideoxyguanosine (**4**) to synthesize from **10**, the corresponding 3'-*O*-mesylate derivative, followed by displacement with azide ion.[25] However, treatment of **10** with mesyl chloride in a pyridine-DMF mixture did not afford the corresponding 3'-*O*-mesylate but exclusively and in good yield the 2-*N*-(dimethylamino)methylene derivative **11**. Several attempts were unsuccessful in order to obtain the 3'-*O*-mesylate derivative of **10** (or **11**). Nevertheless, reaction of **11** under Misunobu conditions[26] with diethylazodicarboxylate (DEAD), triphenyl phosphine (PPh_3) in dry THF and diphenylphosphoryl azide (DPPA), followed by treatment with acetic acid in aqueous EtOH provided **4** in moderate yield.

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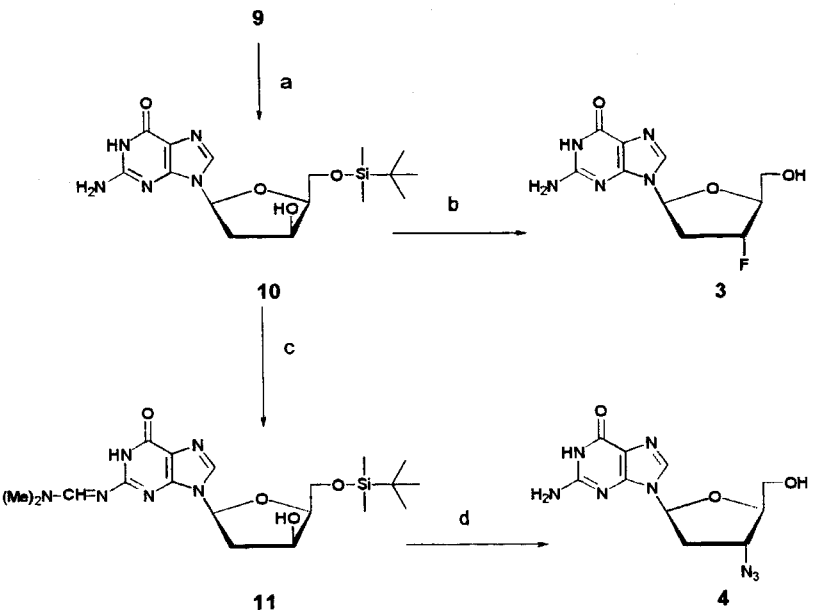

SCHEME 2. *Reagents and conditions*: (a) TBDMSCl, imidazole, DMF, 5°C; (b) 1) DAST, CH_2Cl_2, 0°C; 2) TBAF on silica gel, THF, rt; (c) MsCl, DMF, C_5H_5N, rt; (d) 1) DPPA, PPh_3, DEAD, THF, rt; 2) AcOH, EtOH, H_2O, rt.

BIOLOGICAL EVALUATION

All the unprotected nucleosides **3**, **4** and **9** were tested for their *in vitro* inhibitory effects on the replication of HIV-1 in CEM-SS and MT-4 cell systems. However, none of these compounds showed marked antiviral effects or detectable alteration of host-cell morphology at the highest concentration tested (generally 100 μM). When evaluated in anti-HBV assays in HepG2 cells, none of the tested compounds showed antiviral effect (up to a concentration of 10 μM) nor cytotoxicity (up to a concentration of 200 μM).

CONCLUSION

From the present work, and in contrast to the adenine β-L-nucleoside analogs (3'-fluoro-β-L-ddA and 3'-azido-β-L-ddA),[8] it appears that 3'-fluoro- and 3'-azido-2',3'-dideoxy-β-L-nucleoside analogs of guanine do not induce inhibition of HIV and HBV virus 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

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enzymes catalyzing phosphorylations or to inhibit viral polymerases by their triphosphate forms, can be proposed. Further research would be needed to support these hypotheses. However that may be, the present data obtained with β-L-guanosine derivatives do not preclude novel studies on other L-nucleoside series and experiments related to this topic 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. 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).

2-*N*-Acetyl-9-(3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)guanine 7

BSA (17.6 ml, 72 mmol) was added to a suspension of 2-*N*-acetyl-6-*O*-(diphenylcarbamoyl)guanine **5**[23] (13.9 g, 36 mmol) in dry DCE (250 ml), and stirring was continued at 80 °C for 15 minutes. After evaporation of the clear solution, the residue was dissolved in dry toluene (150 ml) and TMSOTf (9.30 ml, 48 mmol) and a

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solution of 2-*O*-acetyl-3,5-di-*O*-benzoyl-L-*xylo*-furanose **6**[9] (13.3 g, 30 mmol) in dry toluene (150 ml) were added. The solution was stirred at 80 °C for 1 hour and cooled, and ethyl acetate (1000 ml) was added. The organic phase was washed with a saturated solution of sodium hydrogen carbonate (2 x 800 ml), water (1000 ml), dried over sodium sulfate and evaporated to dryness. The resulting crude material was dissolved in a mixture of pyridine and acetic acid (4:1, v/v, 390 ml) and hydrazine hydrate was added (98%, 21 ml, 300 mmol). After 45 minutes stirring, acetone was added (300 ml) and stirring was continued for 2 hours. The solvents were removed and the residue was dissolved in chloroform (300 ml) and the organic layer was washed with a saturated solution of sodium hydrogen carbonate (2 x 500 ml), water (1000 ml), dried over sodium sulfate 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* **7** as a white foam (9.59 g, 60% overall yield from **6**): $[\alpha]_D^{20}$ -49.0 (*c* 0.99 in Me_2SO) [Lit.[9] $[\alpha]_D^{20}$ –53.0 (*c* 0.8 in Me_2SO)]; λ_{max} (95% EtOH)/nm 282 (sh, ε 13000), 274 (ε 14000), 260 (ε 18000), 255 (sh, ε 17700), 232 (ε 29300), λ_{min} 270 (ε 13500), 249 (ε 16700); $\delta_H[(CD_3)_2SO]$ 2.16 (s, 3H, $CH_3C(O)N$), 4.69 (m, 2H, H-5' and H-5"), 4.88 (m, 2H, H-2' and H-4'), 5.60 (dd, 1H, H-3', $J_{2',3'}$ = 2.6 Hz, $J_{3',4'}$ = 4.6 Hz), 5.92 (d, 1H, H-1', $J_{1',2'}$ = 2.9 Hz), 6.45 (br s, 1H, OH-2'), 7.89-7.46 (m, 10H, 2x *Ph*C=O), 8.23 (s, 1H, H-8), 11.78 (br s, 1H, N_2-H), 12.01 (br s, 1H, N_2-H); $\delta_C[(CD_3)_2SO]$ 24.7 ($CH_3C(O)N$), 63.3 (C-5'), 78.2 (C-2' or C-4'), 78.4 (C-3'), 78.8 (C-2' or C-4'), 89.7 (C-1'), 121.2 (C-5), 129.6-134.7 (*Ph*C=O), 138.0 (C-8), 149.0 (C-4), 149.3 (C-2), 155.7 (C-6), 166.3 and 165.6 (2x PhC=O), 174.4 ($CH_3C(O)N$); m/z (FAB > 0, G-T) 534 $(M + H)^+$, 341 $(S)^+$, 194 $(BH_2)^+$, 152 $(B\text{-}Ac+3H)^+$, 105 $(PhC{=}O)^+$, 77 $(C_6H_5)^+$; m/z (FAB < 0, G-T) 1598 $(3M-H)^-$, 1065 $(2M-H)^-$, 532 $(M-H)^-$, 192 $(B)^-$, 121 $(PhCO_2)^-$. Anal. Calcd for $C_{26}H_{23}N_5O_8$: C, 58.53; H, 4.35; N, 13.13. Found : C, 58.12; H, 4.51; N, 12.97.

2-*N*-Acetyl-9-(3,5-di-*O*-benzoyl-2-deoxy-β-L-*threo*-pentofuranosyl)guanine 8

To a stirred solution of **7** (1.50 g, 2.80 mmol) in dry acetonitrile (40 ml), DMAP (3.08 g, 25.2 mmol) and phenoxythiocarbonylchloride (0.775 ml, 5.60 mmol) were added successively. After 1.5 h, the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (60 ml) and the organic layer was washed with 0.5 N hydrochloric acid (2 x 50 ml), dried over sodium sulfate and evaporated to dryness. The

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resulting crude material was coevaporated with dry dioxan, then dissolved in the same solvent (50 ml) and α,α'-azoisobutyronitrile (0.153 g, 0.93 mmol) and tris(trimethylsilyl)silane (1.05 ml, 3.40 mmol) were added. The resultant solution was heated under reflux for 1 h. After cooling to room temperature the solvent was removed under reduced pressure. Chromatography of the residue on silica gel column using as eluent a stepwise gradient of methanol (0-4%) in dichloromethane afforded the *title compound* **8** (0.95 g, 65%) which was crystallized from isopropyl alcohol: m.p. 134-135 °C; $[\alpha]_D^{20}$ -31.0 (*c* 0.98 in Me_2SO); λ_{max} (95% EtOH)/nm 255 (ε 17700), 249 (ε 16700), λ_{min} 232 (ε 29300); δ_H[$(CD_3)_2SO$] 2.15 (s, 3H, $CH_3C(O)N$), 2.87 (m, 1H, H-2'), 3.70 (m, 1H, H-2"), 4.68 (m, 3H, H-3', H-5' and H-5"), 5.85 (br s, 1H, H-3'), 6.29 (dd, 1H, H-1', $J_{1',2'}$ = 2.9 Hz, $J_{1',2''}$ = 7.4 Hz), 7.47-7.89 (m, 10H, 2x *Ph*C=O), 8.25 (s, 1H, H-8), 11.73 (br s, 1H, N_2-H), 12.00 (br s, 1H, N_2-H); δ_C[$(CD_3)_2SO$] 24.6 ($CH_3C(O)N$), 38.7 (C-2'), 63.4 (C-5'), 74.2 (C-3'), 80.9 (C-4'), 84.2 (C-1'), 121.3 (C-5), 129.6-134.6 (*Ph*C=O), 137.9 (C-8), 148.7 (C-4), 149.0 (C-2), 155.7 (C-6), 166.3 and 165.7 (2x Ph*C*=O), 174.4 ($CH_3C(O)N$); m/z (FAB > 0, G-T) 518 $(M + H)^+$, 325 (S) $^+$, 194 $(BH_2)^+$, 152 (B-Ac+3H)$^+$, 105 $(PhC{=}O)^+$, 77 $(C_6H_5)^+$; m/z (FAB < 0, G-T) 1550 $(3M-H)^-$, 1033 $(2M-H)^-$, 516 $(M-H)^-$, 192 $(B)^-$, 121 $(PhCO_2)^-$. Anal. Calcd for $C_{26}H_{23}N_5O_7$: C, 60.34; H, 4.48; N, 13.53. Found : C, 59.86; H, 4.65; N, 13.23.

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9-(2-Deoxy-β-L-*threo*-pentofuranosyl)guanine 9

A solution of **8** (3.50 g, 6.75 mmol) in methanolic ammonia (previously saturated at - 10 °C and tightly stoppered) (135 ml) was stirred for 24 h at room temperature, then evaporated to dryness. The resulting crude material was dissolved in water (100 ml) and the solution was washed with chloroform (2 x 50 ml). The aqueous layer was evaporated under reduce pressure and the residue was subjected to a RP 18 silica gel column chromatography, with a gradient of methanol (0-15%) in water to afford the *title compound* **9** (1.53 g, 85%) which was crystallized from water. The physicochemical properties were identical to those previously reported for the D-enantiomer.[27] $[\alpha]_D^{20}$ +89.0 (*c* 1.02 in Me_2SO). Anal. Calcd for $C_{10}H_{13}N_5O_4.1/2\ H_2O$: C, 43.48; H, 5.11; N, 25.35. Found : C, 43.36; H, 5.13; N, 24.86.

9-(5-*O*-*tert*-Butyldimethylsilyl-2-deoxy-β-L-*threo*-pentofuranosyl)guanine 10

To a stirred solution of 9-(2-deoxy-β-L-*threo*-pentofuranosyl)guanine **9** (0.6 g, 2.20

mmol) and imidazole (0.6 g, 8.80 mmol) in dry DMF (22 ml) was added *tert*-butyldimethylsilyl chloride (0.365 g, 2.42 mmol). The reaction mixture was stirred at 0°C for 45 minutes then quenched with methanol (0.5 ml). The solvent was removed under reduced pressure and the residue was stirred with cold water (40 ml). The white precipitate was collected, washed with water and crystallization from 95% ethanol afforded the *title compound* **10** (0.801 g; 95%): m.p. 248 °C; $[\alpha]^{20}$ +56.0 (*c* 0.97 in Me_2SO); λ_{max} (95% EtOH)/nm 254 (ε 13500); $\delta_H[(CD_3)_2SO]$ 0.01 (s, 6H, $(CH_3)_2Si$), 0.84 (s, 9H, $(CH_3)_3C$), 2.13 (m, 1H, H-2'), 2.66 (septuplet, 1H, H-2", $J_{2",1'}$ = 2.1 Hz, $J_{2",3'}$ = 5.4 Hz, $J_{2",2'}$ = 14.2 Hz), 3.74 (m, 1H, H-5'), 3.90 (m, 2H, H-4' and H-5"), 4.30 (m, 1H, H-3'), 5.43 (d, 1H, OH-3', $J_{3',OH}$ = 4.3 Hz), 6.01 (dd, 1H, H-1', $J_{1',2'}$ = 8.4 Hz), 6.46 (br s, 2H, NH_2), 7.90 (s, 1H, H-8), 10.62 (br s, 1H, N_1-H); $\delta_C[(CD_3)_2SO]$ – 4.4 ($(CH_3)_2Si$), 18.9 ($(CH_3)_3C$), 26.7 ($(CH_3)_3C$), 41.7 (C-2'), 63.0 (C-5'), 69.8 (C-3'), 82.7 (C-1'), 85.7 (C-4'), 117.2 (C-5), 136.9 (C-8), 151.4 (C-4), 154.5 (C-2), 157.6 (C-6); m/z (FAB > 0, G-T) 763 $(2M + H)^+$; 382 $(M + H)^+$; 152 $(BH_2)^+$; m/z (FAB < 0, G-T) 761 $(2M - H)^-$; 380 $(M-H)^-$; 150 $(B)^-$. Anal. Calcd for $C_{16}H_{27}N_5O_4Si.5/4\ H_2O$: C, 47.56; H, 7.36; N, 17.33. Found : C, 47.48; H, 7.53; N, 17.33.

9-(3-Fluoro-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)guanine 3

DAST (0.21 ml, 1.56 mmol) was added to a solution of nucleoside **10** (0.400 g, 1.04 mmol) in dry dichloromethane (20 ml) at 0 °C under argon and stirring was continued for 15 minutes. The mixture was then poured into a saturated solution of sodium hydrogen carbonate (50 ml) at 0 °C. The organic phase was washed with water (2 x 50 ml), dried over sodium sulfate and evaporated to dryness. The resulting crude material was directly dissolved in dry THF (15 ml) and 1.1 mmol F^-/g TBAF on silica gel (2.83 g, 3.12 mmol) was added. The resulting suspension was stirred for 30 minutes at room temperature, then filtered. The resin was washed several times with methanol and the combined filtrates were evaporated to dryness. The residue was subjected to a silica gel column chromatography, with a stepwise gradient of methanol (0-8%) in chloroform to afford the *title compound* **3** (0.03 g, 12% overall yield from **10**) which was crystallized from water. The physicochemical properties were identical to those previously reported for the D-enantiomer.[28] HRMS calcd for $C_{10}H_{13}FN_5O_3$: 270.1002, found 270.0944.

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2-*N*,*N*-Dimethylaminomethylene-9-(5-*O*-*tert*-butyldimethylsilyl-2-deoxy-β-L-*threo*-pentofuranosyl)guanine 11

Methanesulfonyl chloride (0.48 ml, 6.20 mmol) was added to a stirred solution of **10** (1.02 g, 2.69 mmol) in a pyridine – DMF mixture (4:1, 50 ml) at 0°C under argon. After 5.5 hours, water was added (3 ml) and the solvents were removed under reduced pressure. Dichloromethane (30 ml) was added and the organic phase was washed with a saturated solution of sodium hydrogen carbonate (2 x 20 ml), water (30 ml), dried over sodium sulfate and evaporated to dryness. Column chromatography of the residue on silica gel using a stepwise gradient of methanol (0-8%) in dichloromethane afforded the *title compound* **11** as a white foam (1.00 g, 85%), which was crystallized from ethyl acetate: m.p. 159-160 °C; $[\alpha]_D^{20}$ +88.0 (*c* 0.97 in Me_2SO); λ_{max} (95% EtOH)/nm 303 (ε 21200); 236 (ε 15000); δ_H[$(CD_3)_2SO$] 0.01 (s, 6H, $(CH_3)_2Si$), 0.84 (s, 9H, $(CH_3)_3C$), 2.17 (m, 1H, H-2'), 2.71 (septuplet, 1H, H-2", $J_{2",1'}$ = 2.2 Hz, $J_{2",3'}$ = 5.5 Hz, $J_{2",2'}$ = 14.4 Hz), 3.01 and 3.13 (2s, 6H, CH_3-N), 3.73 (m, 1H, H-5'), 3.91 (m, 2H, H-4' and H-5"), 4.32 (br.s, 1H, H-3'), 5.62 (d, 1H, OH-3', $J_{3',OH}$ = 3.8 Hz), 6.17 (dd, 1H, H-1', $J_{1',2'}$ = 8.6 Hz), 8.05 (s, 1H, H-8), 11.32 (br s, 1H, N_1-H); δ_C[$(CD_3)_2SO$] –4.5 ($(CH_3)_2Si$), 18.9 ($(CH_3)_3C$), 26.6 ($(CH_3)_3C$), 35.5 and 41.5 (2 x CH_3-N), 41.7 (C-2'), 63.1 (C-5'), 69.8 (C-3'), 82.6 (C-1'), 85.6 (C-4'), 119.9 (C-5), 138.4 (C-8), 150.3 (C-4), 158.2 (C-2), 158.5 (C-6); m/z (FAB > 0, G-T) 437 $(M + H)^+$; 207 $(BH_2)^+$; m/z (FAB < 0, G-T) 435 $(M-H)^-$; 205 $(B)^-$. Anal. Calcd for $C_{19}H_{32}N_6O_4Si$. 1/2 H_2O : C, 51.21; H, 7.46; N, 18.86. Found : C, 51.27; H, 7.63; N, 18.81.

9-(3-Azido-2,3-dideoxy-β-L-*erythro*-pentofuranosyl)guanine 4

DEAD (0.466 ml, 2.96 mmol) and DPPA (0.64 ml, 2.96 mmol) in dry THF (5 ml) were added to a solution of nucleoside **11** (0.43 g, 0.986 mmol) and triphenylphosphine (0.775 g, 2.96 mmol) in dry THF (10 ml) at 0 °C under argon, and stirred for 30 minutes at room temperature. Solvent was removed and the residue was subjected to a silica gel column chromatography with a stepwise gradient of methanol (0-5%) in dichloromethane. The appropriate fractions were pooled and directly treated with a acetic acid-water-ethanol (1:1:1, 9 ml) mixture for 20 h. Evaporation to dryness and column chromatography on RP 18 silica gel using a gradient of methanol (0-20%) in water afforded the *title compound* **4** (0.06 g, 20% overall yield from **11**) which was

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crystallized from methanol. The physicochemical properties were identical to those previously reported for the D-enantiomer.[28] HRMS calcd for $C_{10}H_{13}N_8O_3$: 293.1111, found 293.1151.

Biological Methods.– The anti-HIV and anti-HBV assays on cell culture were performed by following previously established procedures as described in ref. 29.

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