Synthesis and Antiviral Evaluation of β-L-*Xylo*-furanosyl Nucleosides of the Five Naturally Occurring Nucleic Acid Bases

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Dedicated to the memory of Professor Roland K. Robins

The β-L-*xylo*-furanosyl analogues of the naturally occurring nucleosides have been synthesized and their antiviral properties examined. All these compounds were hitherto unknown and they were stereospecifically prepared by glycosylation of pyrimidine and purine aglycons with a suitably peracyl-L-*xylo*-furanose (specially synthesized from L-xylose for our present purpose), followed by removal of the protecting groups. All the prepared compounds were tested for their activity against a variety of DNA and RNA viruses (including HIV), but they did not show significant antiviral activity.

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Introduction.

During the last decades there has been some interest in the synthesis and in the biological evaluation of L-nucleoside analogues, but until recently the activities of most nucleosides were associated only with the D-isomers [1]. However, 9-β-L-(+)-adenosine has been reported as occurring in nature and stimulating plant growth [2]. On the other hand, synthetic 2',3'-dideoxy-β-L-cytidine [3] and β-L-thymidine [4] have been shown to exert an antiviral activity in cell cultures against human immunodeficiency virus (HIV) and herpes simplex virus, respectively. Moreover, the unexpected finding that the β-L-isomers of dioxolanyl [5] and oxathiolanyl [6] nucleoside analogues are potent and selective anti-HIV agents provides a strong rationale for studying the mirror images of other D-enantiomers described previously. Among them are the β-*xylo*-furanosyl nucleosides, and in earlier works we have found that 9-β-D-*xylo*-furanosyladenine and -guanine as well as 1-β-D-*xylo*-furanosylcytosine showed marked biological activity [7-9].

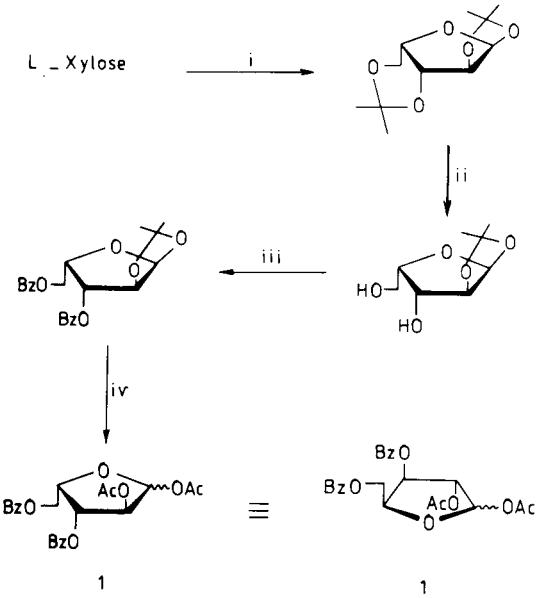
In continuation of our research programme on L-sugar-modified nucleoside analogues [10-14] as potential antiviral agents, we now describe the stereospecific synthesis and biological evaluation of the hitherto unknown β-L-*xylo*-furanosyl nucleosides of the five naturally occurring nucleic acid bases.

Results and Discussion.

Synthesis of Compounds.

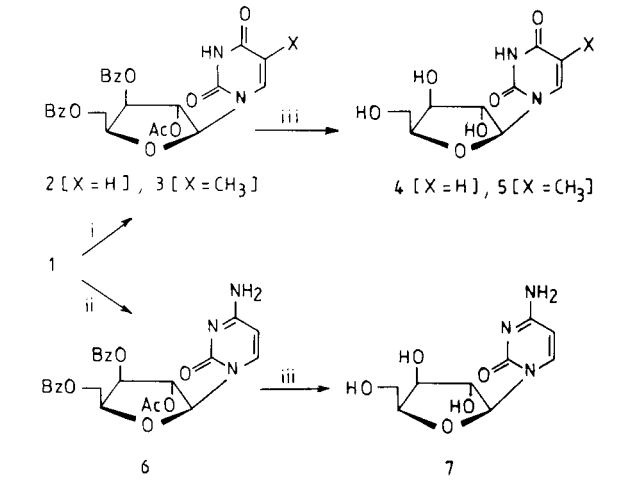
Direct condensation of a suitably protected L-*xylo*-furanose and the purine or pyrimidine bases was employed to prepare the β-L-(*trans*-1',2')-*xylo*-furanosyl nucleosides.

In accord with Baker's rule [15], and owing to 2-*O*-acyl participation during the condensation, we selected as starting sugar the dissymmetric peracylated 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-L-*xylo*-furanose (**1**). This hitherto unknown sugar was readily prepared from commercial L-xylose in four steps (Scheme 1), following a similar route as described previously in the D-series [16-17].

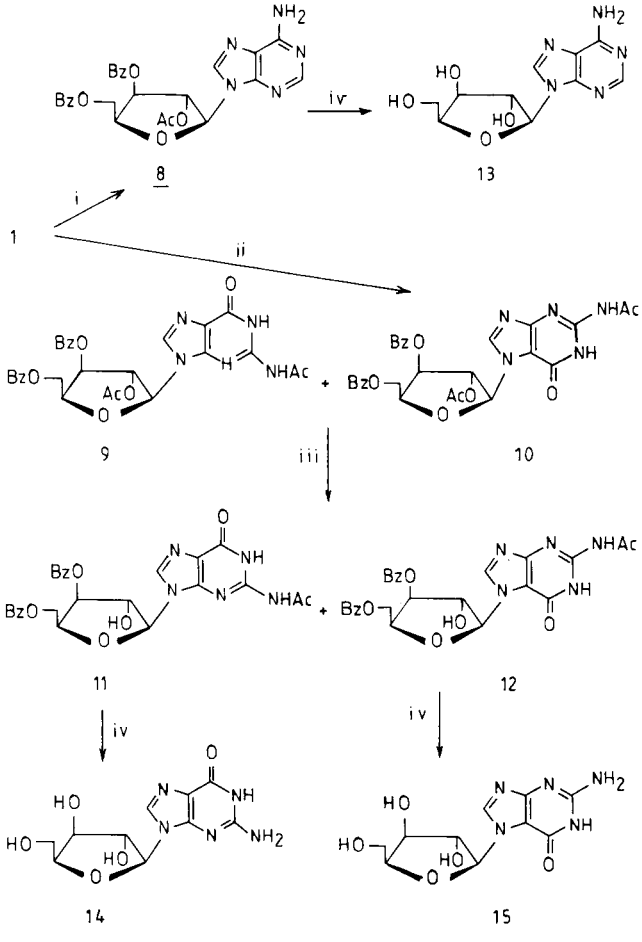


Scheme 1: i) $(CH_3)_2CO$, H_2SO_4, $CuSO_4$, then NH_4OH; ii) HCl/H_2O, then $NaHCO_3/H_2O$; iii) C_6H_5COCl/C_5H_5N-$CHCl_3$; iv) CH_3CO_2H, $(CH_3CO)_2O$, H_2SO_4.

Glycosylations were effected by various procedures which, except for the guanine series, did not require prior protection of the heterocyclic bases. Thus, the protected nucleosides of uracil, thymine, and cytosine were obtained by slightly modified Vorbruggen procedures [18-19]. Removal of the *O*-acetyl and -benzoyl protecting groups from compounds **2, 3** and **6** with methanolic ammonia afforded the desired β-L-*xylo*-furanosylpyrimidine nucleosides **4, 5** and **7** (Scheme 2).



Scheme 2: i) uracil or thymine, $(CH_3)_3SiNHSi(CH_3)_3$, $(CH_3)_3SiCl$, $SnCl_4/CH_3CN$; ii) silylated cytosine, $CF_3SO_3Si(CH_3)_3/ClCH_2CH_2Cl$; iii) NH_3/CH_3OH.



Scheme 3: i) adenine, $SnCl_4/CH_3CN$; ii) silylated N^2-acetylguanine, $CF_3SO_3Si(CH_3)_3/CH_3CN$; iii) $NH_2\text{-}NH_2\cdot H_2O/CH_3CO_2H\text{-}C_5H_5N$; iv) NH_3/CH_3OH.

In the purine series (Scheme 3), the method of Saneyoshi [20,21] was successful with adenine, while application of the procedure of Wright and Dudycz [22,23] to N^2-acetylguanine [24] afforded an unseparable mixture of the two β-L-9-N **9** and β-L-7-N **10** isomers. Treatment of this mixture with hydrazine hydrate resulted in the 2′-*O*-deacylated derivatives **11, 12** which could be easily isolated separately by silica gel column chromatography. Removal of the acyl protecting groups from **8, 11** and **12** with methanolic ammonia afforded the β-L-*xylo*-furanosyl purine nucleosides **13, 14** and **15**.

Structural assignments for the compounds were based on elemental analysis and physical constants. Their ^1H nmr and mass spectra were identical to those of their D-isomer and their optical rotation data agreed with their L-configuration.

Biological Evaluation.

All the prepared β-L-*xylo*-furanosyl nucleosides **4, 5, 7** and **13-15** were tested for their *in vitro* inhibitory effects on the replication of a number of DNA viruses (*i.e.*, human cytomegalovirus, herpes simplex virsus type 1 and type 2, vaccinia virus) and RNA viruses (parainfluenza virus type III, respiratory syncytial virus, Sindbis virus, Coxsackie virus B3 and polio virus-1) in three cell systems (MRC-5, Vero and KB cells). None of these compounds showed marked antiviral effects or detectable alteration of host cell morphology at the highest concentration tested (generally 10^{-4} *M*). When evaluated in two anti-HIV assays, none of the tested compounds showed significant antiviral effect at a concentration less than 10 fold lower than the minimal concentration causing a detectable alteration of MT-4 and CEM host cell viability ($\geq 10^{-4}$ *M*).

Conclusion.

From the present work, and in contrast to the β-D-*xylo*-furanose configuration, it is obvious that a β-L-*xylo*-furanose structure in nucleoside analogues does not induce inhibition of virus multiplication. Among the several hypotheses than can explain this lack of activity, the unability of these compounds to enter cells, to serve as substrate for the enzymes catalysing triphosphorylation or to inhibit enzymes involved in the metabolism of nucleic acids can be proposed. Further research is needed to test these hypotheses. However that may be, the present data obtained with β-L-*xylo*-furanosyl nucleosides do not preclude novel studies on other L-nucleoside series and experiments related to this topic are currently in progress in our laboratory.

EXPERIMENTAL

L-Xylose was purchased from Interchim, France and was used without further purification. General procedures and instrumentation used have been described previously [25].

1,2-Di-*O*-acetyl-3,5-di-*O*-benzoyl-L-*xylo*-furanose (**1**).

This compound was prepared as described for the D-enantiomer [17] in four steps from L-xylose without purification of the intermediates. The anomeric mixture of **1** was obtained as a pale-yellow syrup and recrystallization from ethanol afforded the pure α anomer (26% overall yield), mp 104-107°; ^{1}H nmr (DMSO-d$_6$): δ 2.06 and 2.10 (2s, 3H each, 2 COC*H*$_3$), 4.50 (m, 2H, 5,5'-H), 4.85 (m, 1H, 4-H), 5.54 (dd, 1H, 2-H, J = 4.6 and 5.9 Hz), 5.79 (t, 1H, 3-H, J = 6.3 Hz), 6.43 (d, 1H, 1-H, J = 4.6 Hz), 7.5-8.0 (m, 10H, 2 COC$_6$*H*$_5$); $[\alpha]_D^{20}$ −125.2° (c 1.3, CHCl$_3$); ms: (FAB >0, matrix 3-nitrobenzyl alcohol) m/z 443 [M + H]$^+$, 383 [M − CH_3CO_2]$^+$, 105 [$C_6H_5C\equiv O$]$^+$.

Anal. Calcd. for $C_{23}H_{22}O_9$ (442.41): C, 62.44; H, 5.01. Found: C, 62.28; H, 5.04.

1-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)uracil (**2**) and 1-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)thymine (**3**).

To a mixture of uracil (1.27 g, 11.33 mmoles) or thymine (1.43 g, 11.34 mmoles) and the protected sugar **1** (5.0 g, 11.30 mmoles) in anhydrous acetonitrile (170 ml) was added consecutively hexamethyldisilazane (1.9 ml, 9.01 mmoles), trimethylchlorosilane (1.15 ml, 9.06 mmoles) and tin(IV) chloride (1.59 ml, 13.59 mmoles). For uracil, the resulting clear solution was stirred at room temperature for 24 hours, for thymine it was refluxed for 1.5 hours. The reaction mixtures were concentrated to a small volume, diluted with chloroform (150 ml), then twice washed with the same volume of saturated aqueous sodium hydrogen carbonate solution and finally with water. The organic layers were dried over sodium sulfate, filtered through Celite, and evaporated. The resulting crude materials were purified by silica gel column chromatography [eluent: stepwise gradient of methanol (0-4%) in methylene chloride] to give pure **2** (3.70 g, 66%) and **3** (3.69 g, 64%).

Compound **2**.

This compound had mp 95-98° (precipitated from petroleum ether); uv (95% ethanol): λ max 260 nm (ε 9,500), 230 nm (ε 26,500); λ min 251 nm (ε 9,300); ^{1}H nmr (DMSO-d$_6$): δ 2.12 (s, 3H, COC*H*$_3$), 4.65 (m, 2H, 5',5''-H), 4.80 (m, 1H, 4'-H), 5.49 (dd, 1H, 2'-H, J = 2.3 and 3.4 Hz), 5.63 (d, 1H, 5-H, J = 8.1 Hz), 5.75 (dd, 1H, 3'-H, J = 2.3 and 4.6 Hz), 5.99 (d, 1H, 1'-H, J = 3.4 Hz), 7.6-8.0 (m, 11H, 6-H and 2 COC$_6$*H*$_5$), 11.4 (br s, 1H, 3-HN); $[\alpha]_D^{20}$ −66.4° (c 1.0, DMSO); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 495 [M + H]$^+$, 383 [s]$^+$, 105 [$C_6H_5C\equiv O$]$^+$; (FAB <0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 493 [M − H]$^-$, 451 [M − CH_3CO]$^-$, 111 [B]$^-$.

Anal. Calcd. for $C_{25}H_{22}N_2O_9$ (494.48): C, 60.72; H, 4.49; N, 5.67. Found: C, 61.12; H, 4.82; N, 5.32.

Compound **3**.

This compound had mp 88-91° (crystallized from a petroleum ether-benzene mixture); uv (95% ethanol): λ max 254 nm (ε 9,000), 229 nm (ε 24,300); λ min 241 nm (ε 7,700); ^{1}H nmr (DMSO-d$_6$): δ 1.68 (s, 3H, 5-C*H*$_3$), 2.11 (s, 3H, COC*H*$_3$), 4.65 (m, 2H, 5',5''-H), 4.75 (m, 1H, 4'-H), 5.46 (dd, 1H, 2'-H, J = 2.3 and 3.4 Hz), 5.76 (dd, 1H, 3'-H, J = 2.3 and 4.3 Hz), 6.04 (d, 1H, 1'-H, J = 3.4 Hz), 7.4-8.0 (m, 11H, 6-H and 2 COC$_6$*H*$_5$), 11.4 (br s, 1H, 3-HN); $[\alpha]_D^{20}$ −47.1° (c 1.0, DMSO); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 509 [M + H]$^+$, 449 [M − CH_3CO_2]$^+$, 383 [s]$^+$, 105 [$C_6H_5C\equiv O$]$^+$; (FAB <0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 507 [M − H]$^-$, 465 [M − CH_3CO]$^-$, 125 [B]$^-$.

Anal. Calcd. for $C_{26}H_{24}N_2O_9 \cdot 1.0C_6H_6$ (586.58): C, 65.52; H, 5.16; N, 4.78. Found: C, 65.50; H, 5.11; N, 4.70.

General Procedure for the Preparation of Unprotected β-L-*Xylo*-furanosyl Nucleosides.

A solution of the protected nucleoside in methanolic ammonia (previously saturated at −10° and tightly stoppered) (*ca.* 30 ml/mmole) was stirred overnight at room temperature. The solution was evaporated to dryness under reduced pressure and the residue was co-evaporated under reduced pressure several times with methanol. The crude material obtained was dissolved in water and the resulting solution was washed five times with chloroform. The aqueous layer was evaporated and the product was usually purified by direct crystallization.

1-β-L-*Xylo*-furanosyluracil (**4**).

Compound **2** (2.4 g, 4.85 mmoles) provided 1.0 g of **4** (84% yield) mp 156-156° (crystallized from methanol); uv (95% ethanol): λ max 260 nm (ε 10,000); λ min 229 nm (ε 2,200); ^{1}H nmr (DMSO-d$_6$): δ 3.6-3.8 (m, 2H, 5',5''-H), 3.90 (br s, 1H, 3'-H; d, J = 1.1 Hz after deuterium oxide exchange), 3.93 (br d, 1H, 2'-H; d, J = 1.0 Hz after deuterium oxide exchange), 4.10 (1H, m, 4'-H), 4.75 (t, 1H, 5'-HO, J = 5.3 Hz), 5.42 (d, 1H, 3'-HO, J = 3.1 Hz), 5.61 (d, 1H, 5-H, J = 8.1 Hz), 5.64 (d, 1H, 1'-H, J = 1.0 Hz), 5.76 (d, 1H, 2'-HO, J = 4.1 Hz), 7.75 (d, 1H, 6-H, J = 8.1 Hz), 11.3 (br s, 1H, 3-HN); $[\alpha]_D^{20}$ −28.1° (c 0.96, water); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 489 [2M + H]$^+$, 245 [M + H]$^+$, 113 [BH_2]$^+$; (FAB <0, matrix, 3-nitrobenzyl alcohol) m/z 243 [M − H]$^-$, 111 [B]$^-$.

Anal. Calcd. for $C_9H_{12}N_2O_6 \cdot 1.0H_2O$ (262.22): C, 41.22; H, 5.38; N, 10.69. Found: C, 41.40; H, 5.32; N, 10.97.

1-β-L-*Xylo*-furanosylthymine (**5**).

Compound **3** (0.92 g, 1.81 mmoles) provided 0.36 g of **5** (77% yield) as a white foam, mp 151-155°; uv (95% ethanol): λ max 266 nm (ε 9,700); λ min 234 nm (ε 2,200); ^{1}H nmr (DMSO-d$_6$): δ 1.74 (s, 3H, 5-C*H*$_3$), 3.6-3.8 (m, 2H, 5'-5''-H), 3.85-3.95 (m, 2H, 2',3'-H), 4.05 (m, 1H, 4'-H), 4.74 (t, 1H, 5'-HO, J = 5.6 Hz), 5.40 (d, 1H, 2'- or 3'-HO, J = 3.6 Hz), 5.65 (d, 1H, 1'-H, J = 1.5 Hz), 5.73 (d, 1H, 2'- or 3'-HO, J = 4.1 Hz), 7.63 (d, 1H, 6-H, J = 1.1 Hz), 11.3 (br s, 1H, 3-HN); $[\alpha]_D^{20}$ 0° (c 1.0, water); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 259 [M + H]$^+$, 127 [BH_2]$^+$; (FAB <0, matrix, 3-nitrobenzyl alcohol) m/z 257 [M − H]$^-$, 125 [B]$^-$.

Anal. Calcd. for $C_{10}H_{14}N_2O_6 \cdot \frac{1}{4}H_2O$ (262.74): C, 45.71; H, 5.56; N, 10.66. Found: C, 45.48; H, 5.59; N, 10.56.

1-β-L-*Xylo*-furanosylcytosine (**7**).

A suspension of cytosine (3.7 g, 33.3 mmoles) in a mixture of hexamethyldisilazane (100 ml) and pyridine (40 ml) containing ammonium sulfate (40 mg, 0.3 mmole) was heated under reflux for 1 hour. After cooling, the excess of hexamethyldisilazane and pyridine was removed *in vacuo* and by codistillation with anhydrous xylene. Silylated cytosine was dissolved in anhydrous 1,2-dichloroethane (100 ml). A solution of sugar **1** (15.0 g, 33.9 mmoles) in 1,2-dichloroethane (35 ml) and trimethylsilyl triflate (9.24 ml, 47.8 mmoles) were added. The reaction mixture was heated under reflux for 2 hours and then cooled to room temper-

ature. After dilution with 1,2-dichloroethane, the solution was poured into ice-cold saturated aqueous sodium hydrogen carbonate. The organic phase was separated, twice washed with water, dried over sodium sulfate and evaporated. Chromatography of the residue on a silica gel column [eluent:methanol (0-10%) in methylene chloride] led, after evaporation of the appropriate fractions, to the isolation of compound **6**. This compound was directly dissolved in methanolic ammonia (500 ml) and stirred overnight at room temperature. After standard workup, crystallization from methanol afforded 4.1 g of pure **7** (51% yield), mp 238-240°; uv (95% ethanol): λ max 272 nm (ε 10,600); λ min 250 nm (ε 7,300); ^{1}H nmr (DMSO-d_6): δ 3.6-3.8 (m, 2H, 5',5''-H), 3.8-3.9 (m, 2H, 2',3'-H), 4.05 (m, 1H, 4'-H), 4.72 (t, 1H, 5'-HO, J = 5.6 Hz), 5.29 (d, 1H, 2'- or 3'-HO, J = 3.6 Hz), 5.61 (d, 1H, 1'-H, J = 0.9 Hz), 5.63 (d, 1H, 2'- or 3'-HO, J = 4.1 Hz), 5.67 (d, 1H, 5-H, J = 7.4 Hz), 7.00 and 7.10 (2 br s, 1H each, NH_2), 7.68 (d, 1H, 6-H, J = 7.4 Hz); $[\alpha]_D^{20}$ + 15.2° (c 1.1, DMSO); ms: (FAB >0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 244 $[M + H]^+$, 112 $[BH_2]^+$.

Anal. Calcd. for $C_9H_{13}N_3O_5$ (243.21): C, 44.44; H, 5.39; N, 17.28. Found: C, 44.20; H, 5.34; N, 16.98.

9-(2-*O*-Acetyl-3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)adenine (**8**).

Adenine (4.7 g, 34.8 mmoles) was suspended in a solution of the sugar **1** (15.0 g, 33.9 mmoles) in anhydrous acetonitrile (450 ml). Tin(IV) chloride (7.97 ml, 68.1 mmoles) in acetonitrile (200 ml) was added, and the mixture was stirred at room temperature for 20 hour with exclusion of moisture. The reaction mixture was concentrated, diluted with chloroform, and cooled with an ice bath. A saturated aqueous sodium hydrogen carbonate solution (500 ml) was carefully added with stirring. When the evolution of carbon dioxide had ceased, the mixture was evaporated to dryness. The residue was then triturated with boiling chloroform, filtered through a sintered funnel covered with Celite, and this operation was repeated three times. The combined filtrates were washed with water, dried over sodium sulfate, and evaporated. Chromatography of the residue on a silica gel column [eluent: stepwise gradient of methanol (0-4%) in methylene chloride] led, after evaporation of the appropriate fractions, to the isolation of pure **8** (10.9 g, 61%), mp 114-117° (crystallized from methanol or diethyl ether); uv (95% ethanol): λ max 259 nm (ε 15,600), 231 nm (ε 28,300); λ min 250 nm (ε 14,000); ^{1}H nmr (DMSO-d_6): δ 2.11 (s, 3H, $COCH_3$), 4.65 (m, 2H, 5',5''-H), 4.86 (m, 1H, 4'-H), 5.85 (dd, 1H, 3'-H, J = 2.4 and 4.8 Hz), 6.18 (m, 1H, 2'-H), 6.25 (d, 1H, 1'-H, J = 3.7 Hz), 7.35 (s, 2H, NH_2), 7.40-7.95 (m, 10H, 2 COC_6H_5), 7.97 and 8.36 (2s, 1H each, 2-H and 8-H); $[\alpha]_D^{20}$ −57.3° (c 1.0, chloroform); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 518 $[M + H]^+$, 383 $[s]^+$, 136 $[BH_2]^+$, 105 $[C_6H_5C\equiv O]^+$; (FAB <0, matrix: glycerol-thioglycerol, 1:1, v/v) 516 $[M - H]^-$, 134 $[B]^-$.

Anal. Calcd. for $C_{26}H_{23}N_5O_7 \cdot \frac{1}{4}H_2O$ (521.99): C, 59.82; H, 4.54; N, 13.42. Found: C, 59.47; H, 4.51; N, 13.41.

N^2-Acetyl-9-(3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)guanine (**11**) and N^2-Acetyl-7-(3,5-di-*O*-benzoyl-β-L-*xylo*-furanosyl)guanine (**12**).

A suspension of N^2-acetylguanine [24] (5.0 g, 25.88 mmoles) in anhydrous acetonitrile (110 ml) was treated with bis(trimethylsilyl)acetamide (25.3 ml, 102.4 mmoles) during 15 minutes under reflux. To the resulting solution was added starting sugar **1** (9.55 g, 21.59 mmoles) in acetonitrile (100 ml), followed by addition of trimethylsilyl triflate (5.9 ml, 30.53 mmoles). The solution was heated under reflux for 6 hours. After cooling to room temperature, the reaction mixture was evaporated to dryness and to the residue were added chloroform (600 ml) and water (300 ml). The cloudy biphasic mixture was filtered by using Watman phase separator. The organic phase was separated, washed four times with water, dried over sodium sulfate, and evaporated to dryness to afford a crude mixture (12.3 g) of N-9 and N-7 full-protected isomers **9** and **10**. A solution of this crude mixture in a pyridine-acetic acid mixture (4:1, v/v, 220 ml) was treated with hydrazine hydrate [16] (≅80% in water, 2.9 ml) with stirring at room temperature for 3 hours. Reaction was quenched by acetone (52 ml) with stirring at room temperature. After 1 hour, the mixture was partially evaporated *in vacuo* and extracted from water (300 ml) into chloroform (2 x 200 ml). The combined organic phases were washed several times first with aqueous saturated sodium hydrogen carbonate then with water, dried over sodium sulfate, and evaporated to dryness. Chromatography of the residue (11.1 g) on a silica gel column using as eluent a stepwise gradient of methanol (0-7%) in methylene chloride led to the isolation of the N-7 isomer **12** (1.2 g, contaminated by some impurities as ascertained by ^{1}H nmr) and of the pure N-9 isomer **11** (5.1 g, 44% from **1**).

Compound **11**.

This compound had mp 150-153° (precipitated from petroleum ether); uv (95% ethanol): λ max 282 nm (sh, ε 23,000), 274 nm (ε 24,100), 260 nm (ε 27,700), 254 nm (sh; ε 27,100), 231 nm (ε 41,600); λ min 270 nm (ε 23,900), 248 nm (ε 25,700); ^{1}H nmr (DMSO-d_6): δ 2.16 (s, 3H, $COCH_3$), 4.68 (d, 2H, 5',5''-H, J = 5.7 Hz), 4.90 (m, 2H, 2',4'-H), 5.60 (dd, 1H, 3'-H, J = 2.5 and 4.4 Hz), 5.92 (d, 1H, 1'-H, J = 2.8 Hz), 6.45 (br s, 1H, 2'-HO), 7.4-7.9 (m, 10H, 2 COC_6H_5), 8.23 (s, 1H, 8-H), 11.7 and 12.0 (2 br s, 1H each, 1-HN and H-N^2); $[\alpha]_D^{20}$ −53.0° (c 0.8, DMSO); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 534 $[M + H]^+$, 341 $[s]^+$, 194 $[BH_2]^+$, 105 $[C_6H_5C\equiv O]^+$; (FAB <0, matrix, 3-nitrobenzyl alcohol) m/z 532 $[M - H]^-$, 490 $[M - CH_3CO]^-$, 192 $[B]^-$.

Anal. Calcd. for $C_{26}H_{23}N_5O_8 \cdot \frac{1}{2}H_2O$ (542.49): C, 57.56; H, 4.46; N, 12.91. Found: C, 57.46; H, 4.62; N, 12.74.

9-β-L-*Xylo*-furanosyladenine (**13**).

Compound **8** (0.5 g, 0.97 mmole) was deacylated by treatment with methanolic ammonia (15 ml) for a night following the general procedure used for the preparation of compounds **4**, **5** and **7**. Direct crystallization from methanol afforded pure **13** (0.2 g, 75%), mp 143-146°; uv (95% ethanol): λ max 258 nm (ε 14,700); λ min 228 nm (ε 2,500); ^{1}H nmr (DMSO-d_6): δ 3.65 and 3.75 (2m, 1H each, 5' and 5''-H), 4.05 (m, 1H, 3'-H), 4.15 (m, 1H, 4'-H), 4.31 (br s, 1H, 2'-H), 4.73 (t, 1H, 5'-HO, J = 5.6 Hz), 5.80 (d, 1H, 3'-HO, J = 5.0 Hz), 5.85 (m, 2H, 1'-H and 2'-HO, 5.85 ppm, d, 1H, 1'-H, J = 1.5 Hz after deuterium oxide exchange), 7.27 (s, 2H, NH_2), 8.14 and 8.25 (2s, 1H each, 2-H and 8-H); $[\alpha]_D^{20}$ +40.8° (c 0.8, water); ms: (FAB >0, matrix, 3-nitrobenzyl alcohol) m/z 268 $[M + H]^+$, 137 $[BH_2]^+$.

Anal. Calcd. for $C_{10}H_{13}N_5O_4 \cdot \frac{1}{2}H_2O$ (276.25): C, 43.47; H, 5.11; N, 25.35. Found: C, 43.43; H, 5.12; N, 24.90.

9-β-L-*Xylo*-furanosylguanine (**14**).

Compound **11** (1.0 g, 1.87 mmoles) was deacetylated by treatment with methanolic ammonia (60 ml) for 48 hours following the general procedure used for the preparation of compounds **4**, **5** and **7**. Direct crystallization from water afforded pure **14** (0.34 g, 64%), mp 242° (start of decomposition); uv (95% ethanol): λ max 273 nm (sh, ε 12,700), 254 nm (ε 17,400); λ min 223 nm (ε 3,400);

^{1}H nmr (DMSO-d_6): δ 3.6-3.8 (m, 2H, 5'-5''-H), 4.00 (m, 1H, 3'-H), 4.10 (m, 1H, 4'-H), 4.20 (m, 1H, 2'-H), 4.71 (t, 1H, 5'-HO, J = 5.6 Hz), 5.56 (d, 1H, 3'-HO, J = 4.3 Hz), 5.66 (d, 1H, 1'-H, J = 1.6 Hz), 5.80 (d, 1H, 2'-HO, J = 4.2 Hz), 6.49 (s, 2H, NH_2), 7.84 (s, 1H, 8-H), 10.6 (br s, 1H, 1-HN); $[\alpha]_D^{20}$ +60.6° (c 1.0, DMSO); ms: (FAB >0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 284 $[M + H]^+$, 152 $[BH_2]^+$.

Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot 1.0H_2O$ (301.26): C, 39.87; H, 5.02; N, 23.24. Found: C, 40.08; H, 4.99; N, 23.25.

7-β-L-*Xylo*-furanosylguanine (**15**).

Compound **12** (0.5 g) was deacylated by treatment with methanolic ammonia (30 ml) for 48 hour following the general procedure used for the preparation of compounds **4**, **5** and **7**. Direct crystallization from water afforded pure **15** (0.11 g, 4% from **1**), mp 256° start of decomposition; uv (95% ethanol): λ max 284 nm (ε 9,300), 242 nm (ε 7,600); λ min 259 nm (ε 4,900), 236 nm (ε 7,500); ^{1}H nmr (DMSO-d_6): δ 3.6-3.8 (m, 2H, 5',5''-H), 3.95 (m, 1H, 3'-H), 4.15 (m, 1H, 4'-H), 4.20 (m, 1H, 2'-H), 4.72 (t, 1H, 5'-HO, J = 5.6 Hz), 5.43 (d, 1H, 3'-HO, J = 4.3 Hz), 5.78 (d, 1H, 2'-HO, J = 4.2 Hz), 6.06 (d, 1H, 1'-H, J = 1.3 Hz), 6.17 (s, 2H, NH_2), 8.09 (s, 1H, 8-H), 10.9 (br s, 1H, 1-HN); $[\alpha]_D^{20}$ +28.3° (c 1.0, DMSO); ms: (FAB >0, matrix, glycerol-thioglycerol, 1:1, v/v) m/z 284 $[M + H]^+$, 152 $[BH_2]^+$.

Anal. Calcd. for $C_{10}H_{13}N_5O_5 \cdot \frac{1}{2}H_2O$ (292.25): C, 41.09; H, 4.83; N, 23.97. Found: C, 41.04; H, 4.83; N, 23.56.

Biological Methods.

The broad antiviral assays on cell culture and the anti-HIV assays were performed by following previously established procedures as described in refs [13] and [14].

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