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1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranose *. A versatile precursor for the synthesis of 3-deoxy-3-fluoro-β-D-xylofuranosyl nucleosides as potential antiviral agents

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ABSTRACT

The title compound has been synthesized from D-xylose for use in the preparation of 3-deoxy-3-fluoro-β-D-xylofuranosyl nucleoside analogues and their 2-deoxy derivatives, as exemplified in the guanine and thymine series.

INTRODUCTION

Purine and pyrimidine nucleosides fluorinated in the sugar moiety[2,3] have been extensively investigated in the search for agents endowed with significant biological properties, and to date some 2′-deoxy-2′-*arabino*-fluoro[4] and 2′,3′-dideoxy-2′-*arabino*-fluoro[5] analogues as well as 2′,3′-dideoxy-3′-fluorothymidine[6] have actually displayed potent anti-herpes and anti-human immunodeficiency virus (anti-HIV) activities, respectively.

However, the synthesis and biological evaluation of 3′-deoxy- and 2′,3′-dideoxy-3′-fluoro analogues of β-D-xylofuranosyl nucleosides have been less explored. Thus, Wright et al. first described the synthesis of (3-deoxy-3-fluoro-β-D-xylofuranosyl)-cytosine[7] and the 9-adenine analogue[8]. The preparation of the latter compound[9,10] and of 1-(3-deoxy-3-fluoro-β-D-xylofuranosyl)uracil[11] have also been reported independently in the literature, but only one 2,3-dideoxy-3-fluoro-β-D-xylofuranosyl nucleoside, namely the adenine derivative[12], has been prepared previously.

We now describe a general approach for the synthesis of 3-deoxy-3-fluoro-β-D-xylofuranosyl nucleoside analogues and their 2′-deoxy derivatives in order to

* Preliminary communications, see refs.

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evaluate their biological properties. The most appropriate synthetic plan to reach such nucleoside analogues appeared to first prepare the suitably deoxyfluoro sugar **9** and to condense it with nucleic acid bases. Subsequent deacylation and/or modifications on the 2′-position would afford the desired compounds.

RESULTS AND DISCUSSION

To date there have been two indirect method for the synthesis of 3-deoxy-3-fluoro-D-xylofuranosyl sugar derivatives, involving either nucleophilic displacement of the sulfonate group from 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-allofuranose[13] or action of potassium hydrogenfluoride on methyl 2,3-anhydro-5-*O*-benzyl-β-D-ribofuranoside[8]. We decided to synthesize the hitherto unknown 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranose (**9**) following a route involving the substitution of a hydroxyl group by fluorine by means of diethylaminosulfur trifluoride (DAST) [for a review, see ref 14].

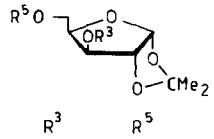
The key precursor of **9** was 1,2-*O*-isopropylidene-α-D-ribofuranose (**5**), which has been previously synthesized either by acetonation of D-ribose (in only 6% yield)[15] or by selective oxidation of the 3-hydroxyl group of 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-xylofuranose (**3**), followed by reduction and subsequent[16] or concomitant[17] debenzoylation. Thus, the 1,2-*O*-isopropylidene derivative **1**, prepared from D-xylose on a large scale as described[18,19], was 5-benzoylated[17,20], the treated with pyridinium chlorochromate in benzene[21] to give **4**. Reduction of **4** with sodium borohydride in aqueous ethanol afforded **5** (43% from **3**, 41% from D-xylose). Attempted selective 5-benzoylation (benzoyl chloride in pyridine at 0°C) of **5** gave a mixture of the 3,5-di-*O*-benzoyl derivative **6** and of compounds monobenzoylated at the 5-position (**7**) and at the 3-position, which were difficult to separate. Alternatively, **5** was treated with an excess of reagent and the resulting **6** was transformed into **7** by selective 3-*O*-debenzoylation with hydrazine hydrate[22] in pyridine.

Fluorination of **7** with DAST was performed following in similar procedure as described for 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[23,24], and compound **8** was isolated in 82% yield.

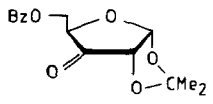
Attempted acetolysis[25] (acetic acid–acetic anhydride–sulfuric acid) of **8** afforded a mixture of **9** (47%) and the penta-*O*-acyl-3-deoxy-3-fluoro-*aldehydo*-D-xylofuranose aldehydrol **10** (45%) as a by-product (data not shown). On the other hand, **8** could be deacetonated in aqueous 85% acetic acid with sulfuric acid, and the resulting 5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranose intermediate was not isolated, but acetylated (acetic anhydride) to afford 72% of crystalline α,β-**9**.

Condensation of **9** with silylated N^2-acetylguanine[26], selective 2′-*O*-deacylation and separation of the resulting β-N-9 **13** and β-N-7 **14** isomers were effected under conditions similar to those used for the synthesis of β-D-xylofuranosyl[27] and α-L-arabinofuranosyl-guanine[28] in our earlier work.

The isolated intermediate **13** was transformed into **17** by a Barton-type[29]



	R^3	R^5
1	Me_2C	
2	H	H
3	H	Bz



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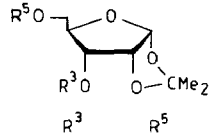
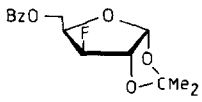


	R^3	R^5
5	H	H
6	Bz	Bz
7	H	Bz



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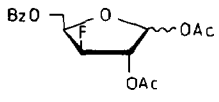
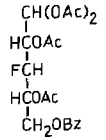


9



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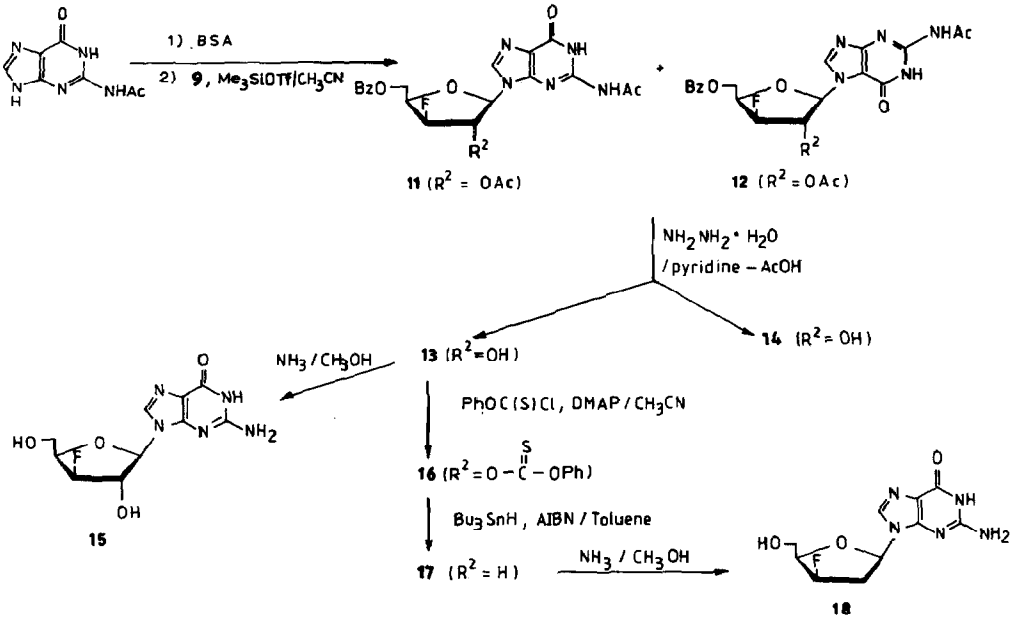
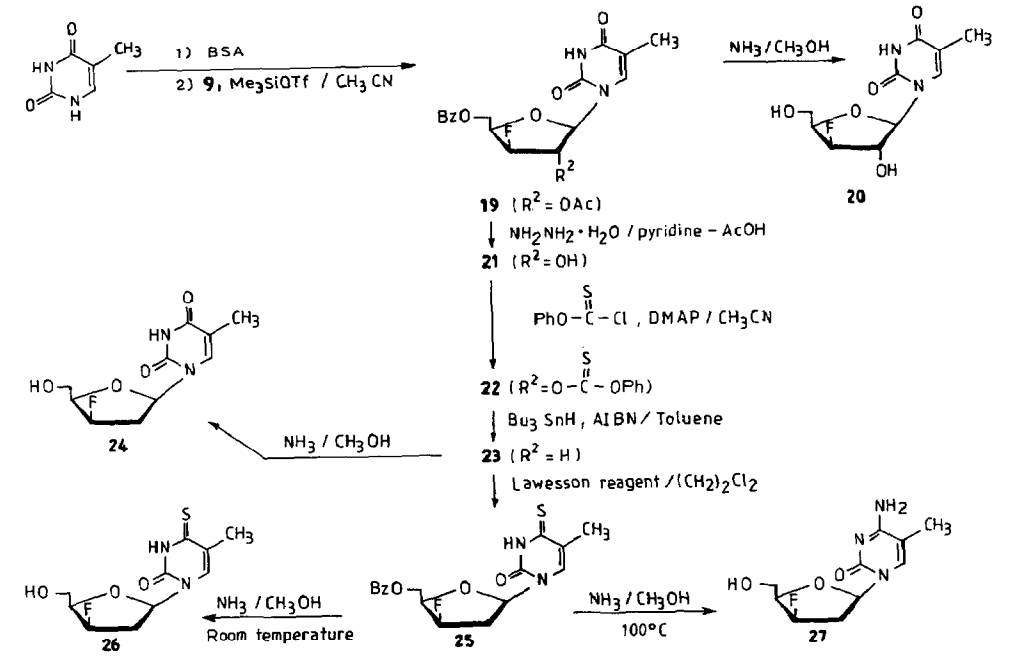
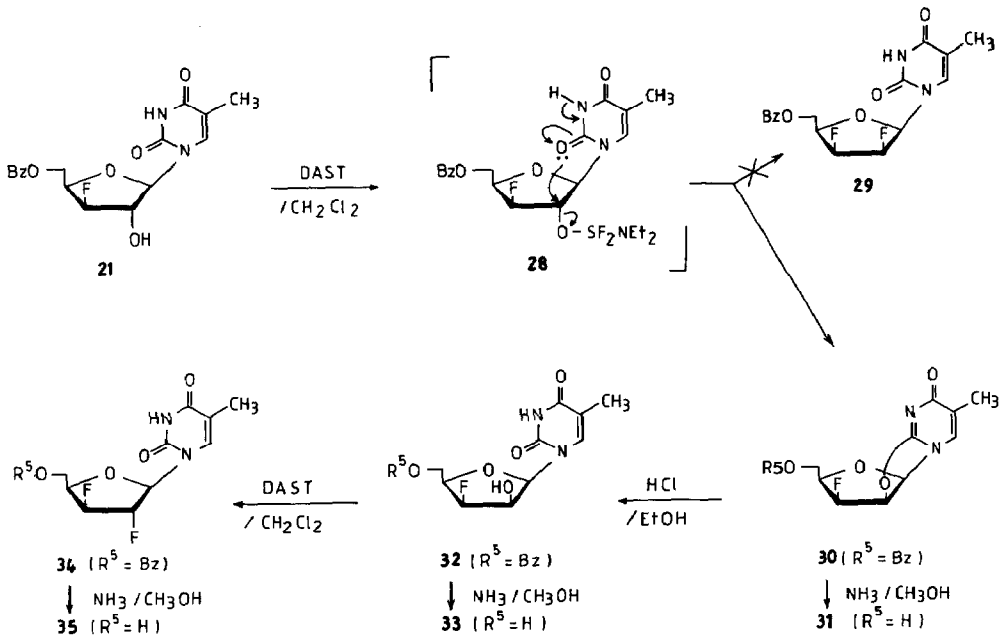
reductive 2′-deoxygenation. Thus, reaction of **13** with phenyl chlorothionocarbonate[30] and 4-(dimethylamino)pyridine in acetonitrile gave the corresponding 2′-*O*-(phenoxythiocarbonyl) derivative **16**, which was treated with tributyltin hydride and α,α'-azobis(isobutyronitrile) in toluene to afford, after column chromatography, compound **17**. Deacylation of **13** and **17** with methanolic ammonia afforded 9-(3-deoxy-3-fluoro-β-D-xylofuranosyl)guanine (**15**) and its 2′-deoxy derivative **18**, respectively.

On the other hand, condensation of **9** and silylated thymine with minor modifications of a Vorbrüggen procedure[31] gave the fully-protected nucleoside **19** which was either deprotected with methanolic ammonia (to afford **20**) or 2′-*O*-deacetylated with hydrazine hydrate in buffered acetic acid–pyridine[32] (to give **21**). As in the guanine series, **21** was converted into a 2′-thiocarbonate ester derivative **22** which was subjected to a Barton-type deoxygenative hydrogenolysis[29] to afford **23**. Subsequently, **23** was deprotected to give **24** or converted to its thioamide derivative **25** by treatment with Lawesson's reagent in refluxing dichloromethane, following an approach previously developed in a uridine series[33]. Compound **25** was treated with methanolic ammonia either at room temperature or at 100°C to afford the deprotected thioamide **26** and 4-amino derivatives **27**, respectively.

Fluorodehydroxylation at the 2′-position of **21** was next examined. However, treatment of **21** with DAST resulted in the formation of the O^2,2′-anhydro compound **30** with no detectable 2′,3′-vicinal difluoro product **29**. This result is in accord with the previously observed[11] facile formation of the O^2,2′-anhydro bond during the reaction of pyrimidine nucleosides with DAST. Treatment of **30** with hydrochloric acid in aqueous ethanol, followed by neutralization with a Dowex (OH^-) ion-exchange resin afforded the lyxoside **32**, which, after purification, was treated with DAST to give the expected *xylo*-difluoro nucleoside **34** in 89% yield.


1) BSA
2) 9, Me3SiOTf/CH3CN
11 (R2 = OAc)
12 (R2 = OAc)
NH2NH2 • H2O
/pyridine – AcOH
13 (R2=OH)
14 (R2 = OH)
NH3 / CH3OH
15
PhOC(S)Cl, DMAP / CH3CN
16 (R2 = O – C(=S) – OPh)
Bu3SnH, AIBN / Toluene
17 (R2 = H)
NH3 / CH3OH
18


1) BSA
2) 9, Me3SiOTf / CH3CN
NH3/CH3OH
19 (R2 = OAc)
20
NH2NH2 • H2O / pyridine – AcOH
21 (R2 = OH)
PhO–C(=S)–Cl, DMAP / CH3CN
22 (R2 = O – C(=S) – OPh)
Bu3SnH, AIBN / Toluene
23 (R2 = H)
NH3 / CH3OH
24
Lawesson reagent / (CH2)2Cl2
NH3 / CH3OH
Room temperature
26
25
NH3 / CH3OH
100°C
27



Finally, the fluorinated nucleosides **30**, **32**, and **34** were deprotected with methanolic ammonia to the corresponding free nucleosides **31**, **33**, and **35**.

Structural assignments for the compounds reported were based on elemental analysis and physical constants. For the four compounds **3–5** and **7** described previously, unless otherwise noted the data accorded with those in the literature.

The hitherto unknown fluorinated nucleosides **15**, **18**, **20**, **24**, **26**, **27**, **31**, **33**, and **35** were tested for their in vitro inhibitory effects on the replication of a number of DNA and RNA viruses (including HIV) in several cell systems. With the exception of **24**, none of the other compounds showed a marked antiviral effect or produced any detectable alteration of host-cell morphology at the highest concentration tested (generally 10^{-4} M). 1-(2,3-Dideoxy-3-fluoro-β-D-xylofuranosyl)thymine (**24**) produced 50% inhibition of replication of HIV-1 at $8 \cdot 10^{-6}$ and 10^{-5} M in MT-4 and CEM cells, respectively, with a selective index ≥ 10. However, the exhibited anti-HIV activity of **24** is markedly lower than the activity of 2′,3′-dideoxy-3′-azidothymidine (AZT).

EXPERIMENTAL

General methods.—General procedures and instrumentation used are described in ref 35. ^{19}F NMR spectra were recorded at ambient temperature with a Bruker WM-250 WB spectrometer using $CFCl_3$ as internal reference.

5-O-Benzoyl-1,2-O-isopropylidene-α-D-xylofuranose (**3**).—To a cooled (ice-bath) solution of 1,2-*O*-isopropylidene-α-D-xylofuranose[18,19] (**2**) (30.0 g, 158 mL) in anhyd

pyridine (150 mL) was added BzCl (19.2 mL, 166 mmol) dropwise with stirring. The mixture was stirred for 0.5 h at room temperature with the exclusion of moisture. Water (1 mL) was added, stirring was continued for 0.5 h, and the mixture was concentrated to low volume, diluted with CH_2Cl_2, washed with satd aq $NaHCO_3$ and water, dried (Na_2SO_4), filtered and concentrated to dryness, and toluene was evaporated three times from residue which was crystallized from diethyl ether. Filtration provided **3** (33.4 g); concentration of the mother liquor yielded additional **3** (2.8 g, 78% overall yield); mp 83–85°C; lit.[18] mp 83.5–84.5°C. ^{1}H NMR data ($CDCl_3$): δ 1.30 and 1.50 (2s, each 3 H, CMe_2), 3.55 (d, 1H, HO-3), 4.2–4.7 (m, 5 H, H-2,3,4,5,5′), 5.95 (d, 1 H, *J* 3.7 Hz, H-1), and 7.3–8.2 (m, 5H, Ph).

5-O-Benzoyl-1,2-O-isopropylidene-α-D-erythro-pentofuranos-3-ulose (**4**).—To a solution of **3** (35.0 g, 119 mmol) in benzene (540 mL) was added pyridinium chlorochromate (42.0 g, 195 mmol)[21]. The mixture was vigorously stirred and boiled under reflux for 4 h. More pyridinium chlorochromate (4.2 g, 19.5 mmol) was added and stirring and boiling were continued for 2 h. The mixture was filtered through Celite, and the reaction vessel and Celite were washed with hot toluene (3 × 200 mL). The combined filtrates were concentrated to dryness, the residue was dissolved in a minimum amount of hot heptane and filtered. On cooling to room temperature, a part of the compound crystallized, and filtration provided pure **4** (15.4 g). The mother liquor was concentrated in vacuo and column chromatography of the residue on silica gel, using a stepwise gradient of MeOH (0–4%) in CH_2Cl_2 gave additional **4** (7.3 g, 65% overall yield); mp 94–95°C; lit[36] 86–89°C; lit.[17,39] 93–95°C; lit.[37] 93.5–94.5°C; lit.[38] 96–97°C; lit.[40] 98–99°C.

1,2-O-Isopropylidene-α-D-ribofuranose (**5**).—To a solution of **4** (22.0 g, 75.3 mmol) in a mixture of EtOH (750 mL) and water (350 mL) was added a solution of $NaBH_4$ (13.3 g, 352 mmol) in water (200 mL) dropwise with stirring. The mixture was stirred for 4 h at room temperature, and then EtOAc (200 mL) was added and the stirring was continued for 2 h. After concentration to dryness, the resulting residue was chromatographed on a column of silica gel using a stepwise gradient of MeOH (0–12%) in CH_2Cl_2 to afford pure **5** (12.1 g, 85%); mp 83–85°C [from petroleum ether (boiling range 40–65°C)–ethyl ether]; lit.[17] 85–86°C; lit.[15] 86–87°C. ^{1}H NMR data ($CDCl_3$): δ 1.35 and 1.55 (2s, each 3 H, CMe_2), 2.9 (m, 2 H, HO-3,5), 3.6–4.0 (m, 4 H, H-3,4,5,5′), 4.5 (t, 1 H, *J* 4.0 Hz, H-2), and 5.75 (d, 1 H, *J* 3.9 Hz, H-1).

5-O-Benzoyl-1,2-O-isopropylidene-α-D-ribofuranose (**7**).—To a cooled (ice-bath) solution of **5** (12.0 g, 63.1 mmol) in dry pyridine (80 mL) was added BzCl (16.4 mL, 142 mmol) dropwise with stirring. The mixture was stirred for 1 h at room temperature, then partially concentrated in vacuo, diluted with CH_2Cl_2, washed with satd aq $NaHCO_3$ and water, dried (Na_2SO_4), filtered, and concentrated to dryness. The resulting oil was dissolved in pyridine (320 mL) and treated with hydrazine hydrate (≈ 80% in water; 6.3 mL) at room temperature for 60 h. Acetone (200 mL) was added and the stirring was continued for 3 h. The mixture

was concentrated to dryness and toluene was evaporated three times from the oil, which was chromatographed on a silica gel column using a stepwise gradient of MeOH (0–8%) in CH_2Cl_2 to afford **7** slightly contaminated by benzoic acid. Crystallisation from 6:1 cyclohexane–ethyl ether, gave pure **7** (7.6 g). The mother liquor was successively washed with aq 0.01 M HCl, 5% $NaHCO_3$ and water, dried (Na_2SO_4), filtered, and concentrated to dryness. Chromatography of the residue on a column of silica gel, using a stepwise gradient of MeOH (0–2%) in CH_2Cl_2 gave, after crystallisation, additional pure **7** (3.9 g, 62% overall yield); mp 77–78°C; lit.[22] 76.5–77.5°C; lit.[41] 78–79°C; lit.[16] 81–82°C. ^{1}H NMR data ($CDCl_3$): δ 1.35 and 1.50 (2s, each 3 H, CMe_2), 3.8–4.3 (m, 3 H), 4.3–4.8 (m, 3 H), 5.75 (d, 1 H, J 4.2 Hz, H-1), and 7.2–8.2 (m, 5 H, Ph).

5-O-Benzoyl-3-deoxy-3-fluoro-1,2-O-isopropylidene-α-D-xylofuranose (**8**).—Compound **7** (6.82 g, 23.2 mmol) and 4-dimethylaminopyridine (DMAP, 5.66 g, 46.3 mmol) were dissolved in anhyd CH_2Cl_2 (270 mL) cooled to −10°C, and DAST (6.12 mL, 46.3 mmol) was slowly added during 5 min to the stirred solution under N_2. The mixture was slowly warmed to room temperature, and, after 18 h, cooled to 0°C; MeOH (20 mL) was added to decompose the excess of reagent. The solution was evaporated to dryness, and the resulting oil was chromatographed on a column of silica gel using CH_2Cl_2 as eluent to afford pure **8** (5.66 g, 82%) as an oil. ^{1}H NMR data ($CDCl_3$): δ 1.34 and 1.51 (2 s, each 3 H, CMe_2), 4.48–4.76 (m, 3 H, H-4,5,5′), 4.74 (dd, 1 H, $J_{2,F}$ 10.9, $J_{2,1}$ 3.7 Hz, H-2), 5.05 (dd, 1 H, $J_{3,F}$ 50.6, $J_{3,4}$ 1.4 Hz, H-3), 6.04 (d, 1 H, J 3.7 Hz, H-1), 7.4–8.1 (m, 5 H, Ph); ^{19}F NMR ($CDCl_3$): δ −214.4 (ddd, $J_{F,2}$ 10.9, $J_{F,3}$ 50.6, $J_{F,4}$ 32.0 Hz). Anal. Calcd for $C_{15}H_{17}FO_5$: C, 60.80; H, 5.79; F, 6.41. Found: C, 61.05; H, 5.80; F, 6.38.

1,2-Di-O-acetyl-5-O-benzoyl-3-deoxy-3-fluoro-D-xylofuranose (**9**).—A solution of **8** (5.38 g, 18.2 mmol) and H_2SO_4 (0.18 mL, 3.4 mmol) in aq 85% AcOH (18.2 mL) was stirred and heated for 9 h at 45°C. The mixture was concentrated in vacuo to ≈ 9 mL, then diluted with pyridine (3.6 mL). Acetic anhydride (22.8 mL, 241 mmol) was added dropwise with stirring at 45°C, and stirring was continued for 45 min at 45°C. After cooling to room temperature, the mixture was concentrated in vacuo, diluted with CH_2Cl_2, washed with aq 5% $NaHCO_3$ and water, dried (Na_2SO_4), filtered, and concentrated to dryness, and toluene was evaporated three times from the residue followed by $CHCl_3$ to afford crude **9**. Chromatography on a column of silica gel, using a stepwise gradient of EtOAc (0–10%) in 1:1 CH_2Cl_2–cyclohexane gave the pure α,β anomers **9** (4.45 g, 72%) which crystallised from 5:1 heptane–ethyl ether; mp 63–64°C. ^{1}H NMR data (Me_2SO-d_6): δ 2.04 and 2.07 (2s, 3 H, Ac, 2.04 ppm, Ac for the β anomer), 2.11 (s, 3 H, Ac), 4.40–4.74 (m, 3 H, H-4,5,5′), 5.24 and 5.40 [d and dt, 1 H, H-2; H-2β ($J_{2,F}$ 12.6 Hz) and H-2α ($J_{2,F}$ 23.3, $J_{2,3} = J_{1,2} = 4.9$ Hz)], 5.43 and 5.56 [dd and dt, 1 H, H-3; H-3β ($J_{3,F}$ 49.4, $J_{3,4}$ 4.0 Hz) and H-3α ($J_{3,F}$ 53.0, $J_{2,3}$ 4.9 Hz)], 6.11 and 6.42 [s and d, 1 H, H-1; H-1β ($J_{1,2}$ 0 Hz) and H-1α ($J_{1,2}$ 4.9 Hz), α/β-ratio ≃ 5:1], and 7.5–8.0 (m, 5 H, Ph). ^{19}F NMR (Me_2SO-d_6): δ −202.35 (dt, $J_{F,2} \simeq J_{F,4} = 22.6$, $J_{F,3}$ 53.0 Hz, F-3α), −202.9

(ddd, $J_{F,2}$ 12.6, $J_{F,3}$ 50.0, $J_{F,4}$ 24.7 Hz, F-3β). Anal. Calcd for $C_{16}H_{17}FO_7$: C, 56.47; H, 5.04; F, 5.58. Found: C, 56.24; H, 5.08; F, 5.45.

N^2-Acetyl-9 and 7-(5-O-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)guanine (**13** *and* **14**).—A suspension of N^2-acetylguanine[26] (1.70 g, 8.82 mmol) in anhyd MeCN (30 mL) was treated with bis(trimethylsilyl)acetamide (BSA, 8.72 mL, 35.3 mmol) during 15 min under reflux. To the resulting solution was added the sugar **9** (2.50 g, 7.35 mmol) in MeCN (38 mL), followed by addition of trimethylsilyl triflate (Me_3SiOTf; 2.0 mL, 11.0 mmol). The solution was heated under reflux for 9 h. After cooling to room temperature, the mixture was evaporated to dryness, and to the residue were added CH_2Cl_2 and satd aq $NaHCO_3$. The organic phase was separated, washed with water, dried (Na_2SO_4) and filtered. The residue obtained by evaporation of the organic solution was dissolved in 1:4 AcOH–pyridine (50 mL) and treated with hydrazine hydrate ($\approx$ 80% in water, 1.35 mL) with stirring at room temperature for 5 h. The reaction was quenched by acetone (100 mL) with stirring at room temperature for 1 h. The mixture was evaporated to dryness, and toluene was evaporated four times from the residue. Chromatography on a column of silica gel of the residue, using a stepwise gradient of MeOH (0–7%) in CH_2Cl_2, gave the N-7 isomer **14** (0.6 g, 19%; slightly contaminated by **11**) and the pure N-9 isomer **13** (1.84 g, 58%).

Compound **14** had mp 133–135°C (after trituration with EtOAc and filtration); λ_{max} (95% EtOH) 280 nm (ϵ, 13600); λ_{min} 248 nm (ϵ, 11000); ^{1}H NMR data (Me_2SO-d_6): δ 2.18 (s, 3 H, Ac), 4.60–4.85 (m, 4 H, H-2′,4′,5′,5″), 5.26 (d, 1 H, $J_{3',F}$ 52.0 Hz, H-3′), 6.26 (d, 1 H, $J_{1',2'}$ 2.5 Hz), 6.4 (br s, 1 H, N^2-H), 7.5–8.0 (m, 5 H, Ph), 8.29 (s, 1 H, H-8), and 11.7 (br s, 1 H, NH-1); ^{19}F NMR (Me_2SO-d_6): δ −199.8 (ddd, $J_{F,2'}$ 14.0, $J_{F,3'}$ 52.1, $J_{F,4'}$ 31.3 Hz). FAB-mass spectrum (matrix, glycerol): m/z 432 $(M + H)^+$.

Compound **13** had mp 142–144°C; λ_{max} (95% EtOH) 258 nm (ϵ, 14300) and 234 nm (ϵ, 13800); λ_{min} 245 nm (ϵ, 12600); ^{1}H NMR data (Me_2SO-d_6): δ 2.19 (s, 3 H, Ac), 4.6–4.8 (m, 4 H, H-2′,4′,5′,5″), 5.29 (d, 1 H, $J_{3',F}$ 51.6 Hz, H-3′), 6.88 (d, 1 H, $J_{1',2'}$ 2.4 Hz, H-1′), 6.4 (br s, 1 H, N^2-H), 7.5–8.0 (m, 5 H, Ph), 8.03 (s, 1 H, H-8), and 12.0 (br s, 1 H, NH-1); ^{19}F NMR (Me_2SO-d_6): δ −199.49 (ddd, $J_{F,2'}$ 15.4, $J_{F,3'}$ 51.6, $J_{F,4'}$ 30.2 Hz). FAB-mass spectrum (matrix, glycerol): m/z 432 $(M + H)^+$. Anal. Calcd for $C_{19}H_{18}FN_5O_6$: C, 52.90; H, 4.21; F, 4.41. Found: C, 52.98; H, 4.50; F, 4.42.

9-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)guanine (**15**).—A solution of **13** (0.20 g, 0.46 mmol) in methanolic ammonia (previously saturated at −10°C and tightly stoppered; 7 mL) was stirred for 48 h at room temperature. The solution was evaporated to dryness and the residue was co-evaporated under reduced pressure several times with MeOH. Crystallisation from water afforded pure **15** (81 mg, 61%) in two crops; mp 240°C (dec.); λ_{max} (H_2O) 254 nm (ϵ 12800); λ_{min} 225 nm; ^{1}H NMR data (Me_2SO-d_6): δ 3.70 (m, 2 H, H-5′,5″), 4.23 (m, 1 H, $J_{4',F}$ 26.0 Hz, H-4′), 4.60 (dm, 1 H, $J_{2',F}$ 15.8 Hz, H-2′), 5.03 (t, 1 H, HO-5′), 5.05 (d, 1 H, $J_{3',F}$ 51.7 Hz, H-3′), 5.72 (d, 1 H, $J_{1',2'}$ 2.1 Hz, H-1′), 6.2 (br s, 1 H, HO-2′), 6.6 (br s, 2

H, NH_2), 7.63 (s, 1 H, H-8), and 10.7 (br s, 1 H, NH-1); ^{19}F NMR (Me_2SO-d_6): δ −200.16 (ddd, $J_{F,2'}$, 16.0, $J_{F,3'}$ 52.0, $J_{F,4'}$ 29.0 Hz). FAB-mass spectrum (matrix glycerol): m/z 571 $(2M + H)^+$, 378 $(M + \text{glycerol} + H)^+$, and 286 $(M + H)^+$.

N^2-Acetyl-9-(5-O-benzoyl-2,3-dideoxy-3-fluoro-β-D-xylofuranosyl)guanine (**17**).—To a solution of **13** (0.91 g, 2.11 mmol) in anhyd MeCN (60 mL) were added O-phenyl chlorothiocarbonate (0.31 mL, 2.22 mmol) and DMAP (2.06 g, 16.9 mmol). The solution was stirred overnight at room temperature, and then the solvent was removed under reduced pressure. Dichloromethane (100 mL) and water (100 mL) were added. The organic phase was separated and washed successively with ice-cold 0.1 M aq HCl, water, satd aq $NaHCO_3$ and water, then dried (Na_2SO_4), filtered and evaporated to dryness. The residue was dissolved in dry toluene, the solution was evaporated under reduced pressure, and this process was repeated three times to give the crude thiocarbonate **16** which was directly dissolved in dry toluene (100 mL) and treated with tributyltin hydride (1.12 mL, 4.22 mmol) and α,α′-azobisisobutyronitrile (AIBN; 6.9 mg, 0.042 mmol) at 80°C for 2 h under Ar. The solvent was evaporated to leave crude **17** which was precipitated from hexane. Purification was accomplished by chromatography on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–6%) in CH_2Cl_2. Pooling and evaporation of the appropriate fractions as indicated by TLC gave pure **17** (0.22 g, 25%) as an amorphous powder; mp 120–125°C; λ_{max} (95% EtOH) 259 nm (ε, 14500) and 243 nm (ε, 14000); λ_{min} 246 nm (ε, 12700); ^1H NMR data (Me_2SO-d_6): δ 2.17 (s, 3 H, Ac), 2.82 (m, 1 H, $J_{2',2''}$ 16, $J_{2',F}$ 23 Hz, H-2′), 2.99 (m, 1 H, $J_{2'',1'}$ 7.7, $J_{2'',2'}$ 16, $J_{2'',F}$ 42 Hz, H-2″), 4.4–4.7 (m, 3 H, H-4′,5′,5″), 5.59 (d, 1 H, $J_{3',F}$ 54.1 Hz, H-3′), 6.27 (d, 1 H, $J_{1',2''}$ 7.7 Hz, H-1′), 7.5–8.0 (m, 5 H, Ph), 8.02 (s, 1 H, H-8), and 12.0 (br s, 1 H, NH-1); ^{19}F NMR (Me_2SO-d_6): δ −191.4 (dddd, $J_{F,2'}$ 42.2, $J_{F,2''}$ 23.0, $J_{F,3'}$ 53.5, $J_{F,4'}$ 30.8 Hz). FAB-mass spectrum (matrix, glycerol) m/z 416 $(M + H)^+$.

9-(2,3-Dideoxy-3-fluoro-β-D-xylofuranosyl)guanine (**18**).—A solution of **17** (0.17 g, 0.40 mmol) in methanolic ammonia (11 mL) was stirred for 36 h at room temperature. The solution was evaporated to dryness, and to the residue water was added. The aqueous phase was washed twice with ethyl ether and then evaporated to dryness to afford pure **18** which was crystallised from water (66 mg, 61% in two crops); mp 235°C (dec); λ_{max} (H_2O) 254 nm (ε, 13000); λ_{min} 224 nm; ^1H NMR data (Me_2SO-d_6): δ 2.58 (ddd, 1 H, $J_{2',1'}$ 2.0, $J_{2',2''}$ 16.0, $J_{2',F}$ 25.1 Hz, H-2′), 2.84 (dddd, 1 H, $J_{2'',1'}$ 7.5, $J_{2'',2'}$ 16.0, $J_{2'',3'}$ 4.5, $J_{2'',F}$ 42.3 Hz, H-2″), 3.8–3.6 (m, 2 H, H-5′,5″), 5.05 (ddt, 1 H, $J_{4',3'}$ 2.5, $J_{4',5'}$ 6.3, $J_{4',F}$ 29.9 Hz, H-4′), 4.98 (t, 1 H, J 5.6 Hz, HO-5′), 5.36 (ddd, 1 H, $J_{3',2''}$ 4.0, $J_{3',4'}$ 2.7, $J_{3',F}$ 53.2 Hz, H-3′), 6.14 (dd, 1 H, $J_{1',2'}$ 2.0, $J_{1',2''}$ 7.5 Hz, H-1′), 6.5 (br s, 2 H, NH_2), 7.64 (s, 1 H, H-8), and 10.64 (s, 1 H, NH-1); ^{19}F NMR (Me_2SO-d_6): δ −191.5 (dddd, $J_{F,2'}$ 23.8, $J_{F,2''}$ 42.5, $J_{F,3'}$ 54.0, $J_{F,4'}$ 30.0 Hz). FAB-mass spectrum (matrix, glycerol) m/z 270 $(M + H)^+$. Anal. Calcd for $C_{10}H_{12}FN_5O_3$: C, 44.61; H, 4.49; F, 7.06; N, 26.01. Found: C, 44.62; H, 4.47; F, 6.82; N, 25.72.

1-(2-O-Acetyl-5-O-benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)thymine (**19**).—A

suspension of thymine (3.14 g, 24.9 mmol) in anhyd MeCN (107 mL) was treated with BSA (25 mL, 102.2 mmol) during 15 min under reflux. To the resulting solution was added the sugar **9** (7.06 g, 20.8 mmol) in MeCN (107 mL), followed by addition of Me_3SiOTf (5.7 mL, 31.4 mmol). The solution was heated under reflux for 1 h. After cooling to 0°C, the solution was neutralized by carefully adding aq 5% $NaHCO_3$, then concentrated in vacuo. Dichloromethane (300 mL) was added, the organic phase was separated, washed twice with water, dried (Na_2SO_4), filtered and evaporated to dryness. Chromatography on a column of silica gel using as eluent stepwise gradients first of EtOAc (0–60%) in CH_2Cl_2 and then of MeOH (1–2%) in EtOAc gave pure **19** (5.1 g, 60%) as a foam; mp 71–76°C (lyophilized from dioxane); λ_{max} (95% EtOH) 264 nm (ϵ, 10000) and 228 nm (ϵ, 15300); λ_{min} 247 n (ϵ, 6900); $[\alpha]_D^{20}$ + 8.2° (*c* 1.0, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.73 (s, 3 H, Me), 2.10 (s, 3 H, Ac), 4.48–4.77 (m, 3 H, H-4′,5′,5″), 5.32 (dd, 1 H, $J_{2',1'}$ 3.4, $J_{2',F}$ 18.0 Hz, H-2′), 5.46 (d, 1 H, $J_{3',F}$ 50.7 Hz, H-3′), 6.00 (d, 1 H, $J_{1',2'}$ 3.4 Hz, H-1′), 7.32 (s, 1 H, H-6), 7.5–8.0 (m, 5 H, Ph), and 11.46 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −200.3 (ddd, $J_{F,2'}$ 19.9, $J_{F,3'}$ 50.9, $J_{F,4'}$ 29.7 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 813 $(2M + H)^+$, 407 $(M + H)^+$, 281 $(s)^+$, and 127 $(BH_2)^+$; negative mode *m/z* 811 $(2M - H)^-$, 405 $(M - H)^-$, and 125 $(B)^-$. Anal. Calcd for $C_{19}H_{19}FN_2O_7 \cdot 1/4H_2O$: C, 55.54; H, 4.79; F, 4.62; N, 6.82. Found: C, 55.49; H, 4.85; F, 4.87; N, 6.80.

1-(3-Deoxy-3-fluoro-β-D-xylofuranosyl)thymine (**20**).—A solution of **19** (0.31 g, 0.76 mmol) in methanolic ammonia (24 mL) was stirred for 16 h at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on a column of silica gel using as eluent a stepwise gradient of MeOH (0–9%) in CH_2Cl_2 to afford pure **20** (0.16 g, 91%) as a foam; mp 45–47°C (lyophilized from a 9:1 dioxane–water mixture); λ_{max} (95% EtOH) 265 nm (ϵ 10400); λ_{min} 233 nm (ϵ, 2300); $[\alpha]_D^{20}$ −51.4° (*c* 1.1, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.76 (d, 3 H, *J* 1.0 Hz, Me), 3.7 (m, 2 H, H-5′,5″), 4.2 (dm, 1 H, $J_{4',F}$ 32.5 Hz, H-4′), 4.3 (dm, 1 H, $J_{2',F}$ 17.4 Hz, H-2′), 5.0 (m, 1 H, HO-5′), 5.4 (dm, 1 H, $J_{3',F}$ 52 Hz, H-3′), 5.73 (d, 1 H, $J_{1',2'}$ 2.5 Hz, H-1′), 6.12 (d, 1 H, *J* 3.2 Hz, HO-2′), 7.29 (d, 1 H, *J* 1.0 Hz, H-6), and 11.40 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −200.0 (ddd, $J_{F,2'}$ 15.9, $J_{F,3'}$ 51.9, $J_{F,4'}$ 29.3 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 261 $(M + H)^+$ and 127 $(BH_2)^+$; negative mode *m/z* 519 $(2M - H)^-$, 259 $(M - H)^-$, and 125 $(B)^-$. Anal. Calcd for $C_{10}H_{13}FN_2O_5 \cdot 1/8H_2O$: C, 45.00; H, 5.35; F, 6.78; N, 10.00. Found: C, 45.28; H, 5.23: F, 6.55; N, 10.32.

1-(5-O-Benzoyl-3-deoxy-3-fluoro-β-D-xylofuranosyl)thymine (**21**).—To a solution fo **19** (2.86 g; 7.04 mmol) in 1:4 AcOH–pyridine (66 mL) was added hydrazine hydrate (≃ 80% in water; 1.1 mL). The solution was stirred for 11 h at room temperature. Acetone (25 mL) was added and the stirring was continued for 12 h. Dichloromethane (200 mL) and water (150 mL) were added. The organic phase was separated and washed with satd aq $NaHCO_3$ and water, dried (Na_2SO_4), filtered, evaporated and co-evaporated with toluene. The residue was chro-

matographed on a column of silica gel, using a stepwise gradient of MeOH (0–4%) in CH_2Cl_2, to give pure **21** (2.15 g, 84%) as a foam; mp 98–99°C; λ_{max} (95% EtOH) 264 nm (ϵ, 11000) and 227 nm (ϵ, 16000); λ_{min} 241 nm (ϵ, 7300); $[\alpha]_D^{20}$ +4.1° (*c* 1.0, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.71 (s, 3 H, Me), 4.40 (d, 1 H, $J_{2',F}$ 17.9 Hz, H-2'), 4.56 (dm, 1 H, $J_{4',F}$ 34.1 Hz, H-4'), 4.6 (m, 2 H, H-5',5''), 5.16 (dm, 1 H, $J_{3',F}$ 52.4 Hz, H-3'), 5.80 (d, 1 H, $J_{1',2'}$ 2.7 Hz, H-1'), 6.28 (s, 1 H, HO-2'), 7.31 (d, 1 H, *J* 1.2 Hz, H-6), 7.5–8.0 (m, 5 H, Ph), and 11.41 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −199.3 (ddd, $J_{F,2'}$ 12.0, $J_{F,3'}$ 52.0, $J_{F,4'}$ 29.2 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 365 $(M + H)^+$, 239 $(s)^+$ and 127 $(BH_2)^+$; negative mode *m/z* 363 $(M - H)^-$ and 127 $(B)^-$. Anal. Calcd for $C_{17}H_{17}FN_2O_6$: C, 56.04; H, 4.71; F, 5.22; N, 7.69. Found: C, 56.23; H, 4.69; F, 4.95; N, 7.71.

1-(5-O-Benzoyl-2,3-dideoxy-3-fluoro-β-D-xylofuranosyl)thymine (**23**).—This compound was prepared by a route analogous to that employed for the synthesis of **17**. Thus, **21** (2.15 g, 5.90 mmol) was reacted with O-phenyl chlorothiocarbonate (1.71 mL, 12.36 mmol) and DMAP (2.18 g, 17.84 mmol) in anhyd CH_2Cl_2 (58 mL) to give, after usual workup, crude **22** which was treated with tributyltin hydride (4.06 mL, 15.32 mmol) and AIBN (0.16 g, 0.97 mmol) in toluene (125 mL) at 80°C for 2 h under Ar. Precipitation from cyclohexane and purification of the precipitate by chromatography on a column of silica gel, using a stepwise gradient of MeOH (0–4%) in CH_2Cl_2, gave pure **23** (1.62 g, 79%) which was crystallised from MeOH; mp 152–153°C; λ_{max} (95% EtOH) 265 nm (ϵ, 9000) and 227 nm (ϵ, 13900); λ_{min} 247 nm (ϵ, 6200); $[\alpha]_D^{20}$ +26.6° (*c* 0.9, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.75 (s, 3 H, Me), 2.28 (ddd, 1 H, $J_{2',F}$ 26.0 Hz, H-2'), 2.80 (dddd, 1 H, $J_{2'',1'}$ 8.3, $J_{2'',2'}$ 15.9, $J_{2'',3'}$ 4.9, $J_{2'',F}$ 42.7, $J_{2',2''}$ 16.0, $J_{2',1'}$ 9.8 Hz, H-2''), 4.3 (dm, 1 H, $J_{4',F}$ 29.8 Hz, H-4'), 4.5–4.7 (m, 2 H, H-5',5''), 5.44 (dm, 1 H, $J_{3',F}$ 59.0 Hz, H-3'), 6.21 (dd, 1 H, $J_{1',2'}$ 2.3, $J_{1',2''}$ 8.3 Hz, H-1'), 7.34 (s, 1 H, H-6), 7.5–8.0 (m, 5 H, Ph), and 11.37 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −189.2 (dddd, $J_{F,2'}$ 26.8, $J_{F,2''}$ 41.2, $J_{F,3'}$ 55.4, $J_{F,4'}$ 27.6 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 441 $(M + glycerol + H)^+$, 349 $(M + H)^+$, 127 $(BH_2)^+$, and 105 $(PhC{\equiv}O)^+$; negative mode *m/z* 347 $(M - H)^-$ and 125 $(B)^-$. Anal. Calcd for $C_{17}H_{17}FN_2O_5$: C, 58.61; H, 4.92; F, 5.46; N, 8.04. Found: C, 58.39; H, 4.64; F, 5.48; N, 8.22.

1-(2,3-Dideoxy-3-fluoro-β-D-xylofuranosyl)thymine (**24**).—A solution of **23** (0.16 g, 0.46 mmol) in methanolic ammonia (14 mL) was stirred for 16 h at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–10%) in CH_2Cl_2, to afford pure **24** (0.10 g, 89%) which was crystallised from water; mp 131–132°C; λ_{max} (95% EtOH) 265 nm (ϵ, 10700); λ_{min} 233 nm (ϵ, 2400); $[\alpha]_D^{20}$ −22.1° (*c* 1.0, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.76 (d, 3 H, *J* 1.0 Hz, Me), 2.20 (ddd, 1 H, $J_{2',2''}$ 16.0 Hz, $J_{2',F}$ 28.7, $J_{2',1'}$, 2.7 Hz, H-2'), 2.73 (dddd, 1 H, $J_{2'',F}$ 42.0, $J_{2'',2'}$ 16.0, $J_{2'',1'}$ 8.4, $J_{2'',3'}$ 4.8 Hz, H-2''), 3.7 (m, 2 H, H-5',5''), 3.96 (dm, 1 H, $J_{4',F}$ 28.9 Hz, H-4'), 5.0 (br s, 1 H, HO-5'), 5.3 (ddd, 1 H,

$J_{3',2''}$ 4.5, $J_{3',4'}$ 2.4, $J_{3',F}$ 55.3 Hz, H-3'), 6.14 (dd, 1 H, $J_{1',2'}$ 2.1, $J_{1',2''}$ 8.4 Hz, H-1'), 7.29 (d, 1 H, J 1.0 Hz, H-6), and 11.33 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −189.8 (dddd, $J_{F,2'}$ 25.1, $J_{F,2''}$ 42.1, $J_{F,3'}$ 54.7, $J_{F,4'}$ 29.8 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode m/z 245 $(M+H)^+$ and 127 $(BH_2)^+$; negative mode m/z 243 $(M-H)^-$ and 125 $(B)^-$, Anal. Calcd for $C_{10}H_{13}FN_2O_4$: C, 49.18; H, 5.36; F, 7.78; N, 11.47. Found: C, 49.18; H, 5.37; F, 7.62; N, 11.49.

1-(5-O-Benzoyl-2,3-dideoxy-3-fluoro-β-D-xylofuranosyl)-4-thiothymine (**25**).—To a solution of **23** (0.50 g, 1.44 mmol) in anhyd CH_2Cl_2 (15 mL) was added Lawesson's reagent (Aldrich, Art. 22, 743-9; 0.35 g, 0.87 mmol). The mixture was refluxed for 110 min under N_2, then evaporated to dryness. The residue was chromatographed on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–2%) in CH_2Cl_2 to afford pure **25** (0.48 g, 91%) which was crystallised from MeOH; mp 126–127°C; λ_{max} (95% EtOH) 333 nm (ϵ, 18 400) and 230 nm (ϵ, 15 100); λ_{min} 288 nm (ϵ, 3 900); $[\alpha]_D^{25}$ +113° (c 1.0, Me_2SO); ^{1}H NMR data (Me_2SO-d_6): δ 1.95 (d, 3 H, J 0.8 Hz, Me), 2.38 (ddd, 1 H, $J_{1',2'}$ 2.3, $J_{2',2''}$ 16.0, $J_{2',F}$ 24.6 Hz, H-2'), 2.81 (dddd, 1 H, $J_{2'',1'}$ 8.2, $J_{2'',2'}$ 16.0, $J_{2'',3'}$ 4.7, $J_{2'',F}$ 42.4 Hz, H-2''), 4.41 (ddt, 1 H, $J_{4',3'}$ 2.5, $J_{4',5'}$ 5.5, $J_{4',F}$ 30.0 Hz, H-4'), 4.69 (d, 2 H, J 5.2, H-5',5''), 5.47 (ddd, 1 H, $J_{3',2''}$ 4.2, $J_{3',4'}$ 2.5, $J_{3',F}$ 54.2 Hz, H-3'), 6.14 (dd, 1 H, $J_{1',2'}$ 2.0, $J_{1',2'}$ 8.0 Hz, H-1'), 7.51 (d, 1 H, J 0.8 Hz, H-6), 7.5–8.0 (m, 5 H, Ph), and 12.77 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −189.9 (dddd, $J_{F,2'}$ 24.6, $J_{F,2''}$ 42.3, $J_{F,3'}$ 54.5, $J_{F,4'}$ 29.9 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode m/z 365 $(M+H)^+$, 143 $(BH_2)^+$, and 105 $(PhC\equiv O)^+$; negative mode m/z 363 $(M-H)^-$, 343 $(M-HF-H)^-$, and 141 $(B)^-$. Anal. Calcd for $C_{17}H_{17}FN_2SO_4$: C, 56.03; H, 4.70; F, 5.21; N, 7.69; S, 8.80. Found: C, 56.08; H, 4.59; F, 5.09; N, 7.74; S, 9.02.

1-(2,3-Dideoxy-3-fluoro-β-D-xylofuranosyl)-4-thiothymine (**26**).—A solution of **25** (0.20 g, 0.55 mmol) in methanolic ammonia (17 mL) was stirred for 16 h at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–4%) in CH_2Cl_2, to afford pure **26** (0.11 g, 77%) which was lyophilized from dioxane; mp 54–58°C; λ_{max} (95% EtOH) 332 nm (ϵ, 20 400) and 244 nm (ϵ, 5 500); λ_{min} 281 nm (ϵ, 3 800) and 223 nm (ϵ, 3 100); $[\alpha]_D^{20}$ +46.4° (c 1.0, Me_2SO); ^{1}H NMR data (Me_2SO-d_6): δ 1.97 (d, 3 H, J 0.9 Hz, Me), 2.31 (ddd, 1 H, $J_{2',1'}$ 2.2, $J_{2',2''}$ 15.9, $J_{2',F}$ 23.6 Hz, H-2'), 2.65 (dddd, 1 H, $J_{2'',1'}$ 8.0, $J_{2'',2'}$ 15.9, $J_{2'',3'}$ 4.6, $J_{2'',F}$ 42.9 Hz, H-2''), 3.8 (m, 2 H, H-5',5''), 4.03 (ddt, 1 H, $J_{4',3'}$ 2.4, $J_{4',5'}$ 6.2, $J_{4',F}$ 30.5 Hz, H-4'), 5.03 (t, 1 H, J 5.5 Hz, HO-5'), 5.28 (ddd, 1 H, $J_{3',2''}$ 4.2, $J_{3',4'}$ 2.5, $J_{3',F}$ 54.3 Hz, H-3'), 6.08 (dd, 1 H, $J_{1',2'}$ 1.8, $J_{1',2''}$ 8.0 Hz, H-1'), 7.45 (d, 1 H, J 0.9 Hz, H-6) and 12.72 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −190.4 (dddd, $J_{F,2'}$ 23.8, $J_{F,2''}$ 42.7, $J_{F,3'}$ 54.0, $J_{F,4'}$ 30.4 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode m/z 261 $(M+H)^+$ and 143 $(BH_2)^+$; negative mode m/z 519 $(2M-H)^-$, 259 $(M-H)^-$, and 141 $(B)^-$. Anal. Calcd for $C_{10}H_{13}FN_2SO_3 \cdot 1.4C_4H_8O_2$: C, 46.98; H, 5.34; N, 9.89; S, 11.32. Found: C, 46.75; H, 5.21; N, 9.87; S, 11.49.

1-(2,3-Dideoxy-3-fluoro-β-D-xylofuranosyl)-5-methylcytosine (**27**).—A solution of **25** (0.20 g, 0.55 mmol) in methanolic ammonia (2 mL) was heated at 100°C for 6 h in a sealed stainless-steel bomb. The mixture was cooled, evaporated to dryness, and water and CH_2Cl_2 were added. The aqueous phase was separated, twice washed with CH_2Cl_2 and evaporated to dryness. The residue was chromatographed on column of a silica gel, using as eluent a stepwise gradient of MeOH (0–20%) in CH_2Cl_2, to afford pure **27** (0.11 g, 83%) which was lyophilized from water; mp 64–66°C; λ_{max} (95% EtOH) 272 nm (ϵ, 10900) and 242 nm (ϵ, 8200); λ_{min} 251 nm (ϵ, 8100) and 231 nm (ϵ, 8000); $[\alpha]_D^{20}$ 0° (*c* 0.8, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.83 (d, 3 H, *J* 0.98 Hz, Me), 2.07 (dddd, 1 H, $J_{2',1'}$ 2.6, $J_{2',2''}$ 15.8, $J_{2',F}$ 24.6 Hz, H-2'), 2.69 (dddd, 1 H, $J_{2'',1'}$ 8.2, $J_{2'',2'}$ 15.8, $J_{2'',3'}$ 4.7, $J_{2'',F'}$ 40.3 Hz, H-2''), 3.7 (m, 2 H, H-5', 5''), 3.97 (ddt, 1 H, $J_{4',3'}$ 2.3, $J_{4',5'}$ 6.2, $J_{4',F}$ 30.3 Hz, H-4'), 4.99 (t, 1 H, *J* 5.6 Hz, HO-5'), 5.23 (dddd, 1 H, $J_{3',2''}$ 4.4, $J_{3',4'}$ 2.4, $J_{3',F}$ 54.4 Hz, H-3'), 6.09 (dd, 1 H, $J_{1',2'}$ 2.1, $J_{1',2''}$ 8.2 Hz, H-1'), 6.8 (br s, 1 H, 0.5 NH_2), 7.27 (d, 1 H, *J* 0.9 Hz, H-6), and 7.3 (br s, 1 H, 0.5 NH_2); ^{19}F NMR (Me_2SO-d_6): δ −190.2 (dddd, $J_{F,2'}$ 24.9, $J_{F,2''}$ 42.4, $J_{F,3'}$ 54.9, $J_{F,4'}$ 30.0 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 244 $(M + H)^+$ and 126 $(BH_2)^+$; negative mode *m/z* 242 $(M - H)^-$ and 124 $(B)^-$.

2,2'-Anhydro-1-(5-O-benzoyl-3-deoxy-3-fluoro-β-D-lyxofuranosyl)thymine (**30**).—A solution of **21** (0.96 g, 2.63 mmol) and DAST (0.66 mL, 5.38 mmol) in anhyd CH_2Cl_2 (24 mL) was refluxed for 20 min with stirring. After cooling to room temperature, sat aq $NaHCO_3$ was added until pH ≃ 8.0. Dichloromethane (300 mL) was added, and the organic phase was separated, washed with water, dried (Na_2SO_4), filtered and concentrated to dryness. Chromatography on a column of silica gel of the residue, using a stepwise gradient of MeOH (0–7%) in CH_2Cl_2 afforded pure **30** (0.58 g, 64%) which crystallised from MeCN; mp 216–219°C; λ_{max} (95% EtOH) 255 nm (sh; ϵ, 12600) and 230 nm (ϵ, 21000); $[\alpha]_D^{20}$ −13.7° (*c* 1.0, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.76 (s, 3 H, CH_3), 4.4 and 4.6 (2m, each 1 H, H-5',5''), 4.6 (dm, 1 H, $J_{4',F}$ 30.1 Hz, H-4'), 5.6 (dm, 1 H, $J_{3',F}$ 52.0 Hz, H-3'), 5.7 (m, 1 H, H-2'), 6.18 (d, 1 H, $J_{1',2'}$ 5.9 Hz, H-1'), and 7.45–7.98 (m, 6 H, Ph and H-6); ^{19}F NMR (Me_2SO-d_6): δ −213.5 (ddd, $J_{F,2'}$ 13.1, $J_{F,3'}$ 52.2, $J_{F,4'}$ 26.9 Hz). FAB-mass spectrum (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 347 $(M + H)^+$ and 105 $(PhC \equiv O)^+$. Anal. Calcd. for $C_{17}H_{15}FN_2O_5$: C, 58.96; H, 4.37; F, 5.49; N, 8.09. Found: C, 59.19; H, 4.41; F, 5.56; N, 8.21.

2,2'-Anhydro-1-(3-deoxy-3-fluoro-β-D-lyxofuranosyl)thymine (**31**).—A solution of **30** (0.14 g, 0.40 mmol) in methanolic ammonia (12 mL) was stirred for 16 h at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–15%) in CH_2Cl_2 to afford pure **31** (62 mg, 64%) which was crystallised from MeOH; mp 187°C; λ_{max} (95% EtOH) 249 nm (ϵ, 8700) and 228 nm (ϵ, 7300); λ_{min} 232 nm (ϵ, 7200); $[\alpha]_D^{20}$ −68.5° (*c* 0.9, H_2O); ^1H NMR data (Me_2SO-d_6): δ 1.78 (d, 3 H, *J* 1.2 Hz, Me), 3.4–3.7 (m, 2 H, H-5',5''), 4.20 (ddt, 1 H, $J_{4',3'}$ 3.1, $J_{4',5'} = J_{4',5''} = 9.2$, $J_{4',F}$ 26.0 Hz, H-4'), 5.04 (t, 1 H, *J* 5.0 Hz, HO-5'), 5.38 (ddd, 1

H, $J_{3',2'}$ 5.1, $J_{3',4'}$ 3.1, $J_{3',F}$ 52.7 Hz, H-3'), 5.62 (ddd, 1 H, $J_{2',1'}$ 6.3, $J_{2',3'}$ 5.1, $J_{2',F}$ 12.5 Hz, H-2'), 6.11 (d, 1 H, $J_{1',2'}$ 6.3 Hz, H-1'), and 7.74 (d, 1 H, J 1.2 Hz, H-6); ^{19}F NMR (Me_2SO-d_6): δ −214.4 (dddd, $J_{F,2'}$ 12.5, $J_{F,3'}$ 52.8, $J_{F,4'}$ 26.1, J 1.4 Hz). FAB-mass spectrum (matrix, 1:1 glycerol–thioglycerol): positive mode m/z 243 $(M + H)^+$

1-(5-O-Benzoyl-3-deoxy-3-fluoro-β-D-lyxofuranosyl)thymine (**32**).—A solution of **30** (0.58 g, 1.68 mmol) in 95% EtOH (58 mL) containing fuming HCl (37%, 0.46 mL) was refluxed for 1 h. After cooling to room temperature, the pH of the solution was adjusted to ca. 8.0 by addition of Dowex 1 × 2 (OH^-) ion-exchange resin. The resin was filtered and the filtrate was evaporated to dryness. Column chromatography of the residue, using a stepwise gradient of MeOH (0–6%) in CH_2Cl_2 gave pure **32** (0.58 g, 95%) which crystallised from 95% EtOH; mp 179°C; λ_{max} (95% EtOH) 265 nm (ϵ, 9900) and 227 nm (ϵ, 14900); λ_{min} 249 nm (ϵ, 6600); $[\alpha]_D^{20}$ +41.0° (*c* 1.0, Me_2SO); ^{1}H NMR data (Me_2SO-d_6): δ 1.72 (d, 3 H, J 1 Hz, Me), 4.3 (dm, 1 H, $J_{4',F}$ 29.2 Hz, H-4'), 4.6 (m, 3 H, H-2',5',5''), 5.2 (dm, 1 H, $J_{3',F}$ 56.8 Hz, H-3'), 5.95 (d, 1 H, J 6.1 Hz, HO-2'), 6.20 (d, 1 H, $J_{1',2'}$ 7.3 Hz, H-1'), 7.27 (d, 1 H, J 1 Hz, H-6), 7.5–8.0 (m, 5 H, Ph), and 11.29 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −212.9 (dt, $J_{F,2'} \simeq J_{F,4'} = 27.8$, $J_{F,3'}$ 55.5 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode m/z 729 $(2M + H)^+$, 457 $(M + \text{glycerol} + H)^+$, 365 $(M + H)^+$, 239 (s)$^+$, 127 $(BH_2)^+$, and 105 $(PhC \equiv O)^+$; negative mode m/z 727 $(2M - H)^-$, 455 $(M + \text{glycerol-H})^-$, 363 $(M - H)^-$, and 125 $(B)^-$. Anal. Calcd. for $C_{17}H_{17}FN_2O_6 \cdot 1/2\ H_2O$: C, 55.81; H, 5.17; F, 4.91; N, 7.23. Found: C, 56.04; H, 5.31, F, 4.63; N, 7.09.

1-(3-Deoxy-3-fluoro-β-D-lyxofuranosyl)thymine (**33**).—A solution of **32** (0.20 g, 0.55 mmol) in methanolic ammonia (16 mL) was stirred for 16 h at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–13%) in CH_2Cl_2 to give pure **33** (0.12 g, 84%) which was lyophilized from 9:1 dioxane–water; mp 45–47°C; λ_{max} (95% EtOH) 265 nm (ϵ, 8100); λ_{min} 233 nm (ϵ, 2100); $[\alpha]_D^{20}$ 0° (*c* 0.9, Me_2SO); ^{1}H NMR data (Me_2SO-d_6): δ 1.74 (s, 3 H, Me), 3.7 (m, 2 H, H-5',5''), 3.95 (ddt, 1 H, $J_{4',3'}$ 1.9, $J_{4',5'}$ 5.6, $J_{4',F}$ 29.8 Hz, H-4'), 4.58 (dm, 1 H, $J_{2',F}$ 27.7 Hz, H-2'), 4.98 (dm, 1 H, $J_{3',F}$ 56.0 Hz, H-3'), 5.02 (t, 1 H, J 5.5 Hz, HO-5'), 5.83 (d, 1 H, J 6.1 Hz, HO-2'), 6.13 (d, 1 H, J 7.3 Hz, H-1'), 7.21 (s, 1 H, H-6), and 11.28 (s, 1 H, NH-3); ^{19}F NMR (Me_2SO-d_6): δ −213.2 (dt, $J_{F,2'} \simeq J_{F,4'} = 28.5$, $J_{F,3'}$ 56.5 Hz). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode m/z 261 $(M + H)^+$ and 127 $(BH_2)^+$; negative mode m/z 259 $(M - H)^-$ and 125 $(B)^-$. Anal. Calcd. for $C_{10}H_{13}FN_2O_5 \cdot 1/4C_4H_8O_2 \cdot 1/2H_2O$: C, 45.36; H, 5.50; F, 6.53; N, 9.62. Found: C, 45.48; H, 5.41; F, 6.43; N, 9.70.

1-(5-O-Benzoyl-2,3-dideoxy-2,3-difluoro-β-D-xylofuranosyl)thymine (**34**).—Compound **32** (0.20 g, 0.55 mmol) was dissolved in anhyd CH_2Cl_2 (2.3 mL) containing pyridine (0.23 mL, 2.85 mmol). After cooling to 0°C, DAST (0.10 mL, 0.82 mmol) was added dropwise to the stirred solution under N_2. The mixture was warmed to

room temperature, stirred for 16 h, then cooled again to 0°C and more DAST (0.10 mL, 0.82 mmol) was added. The mixture was warmed to room temperature, stirred for 3 h, cooled to 0°C, and MeOH (0.42 mL) was added. The solution was evaporated to dryness and the residue was chromatographed on a column of silica gel, using as eluent a stepwise gradient of MeOH (0–3%) in CH_2Cl_2, to give pure **34** (0.18 g, 89%) which was lyophilized from dioxane; mp 61–63°C; λ_{max} (95% EtOH) 263 nm (ϵ, 10800) and 228 nm (ϵ, 17100); λ_{min} 247 nm (ϵ, 8300); $[\alpha]_D^{20}$ +6.9° (*c* 1.0, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.71 (d, 3 H, *J* 1.1 Hz, Me), 4.7 (m, 3 H, H-4′,5′,5″), 5.57 (ddm, 1 H, $J_{2',(F-2')}$ 48.0, $J_{2',(F-3')}$ 15.0 Hz, H-2′), 5.62 (ddm, 1 H, $J_{3',(F-2')}$ 11.2, $J_{3',(F-3')}$ 50.0 Hz, H-3′), 6.11 (dd, 1 H, $J_{1',2'}$ 1.9, $J_{1',(F-2')}$ 20.6 Hz, H-1′), 7.28 (d, 1 H, *J* 1.1 Hz, H-6), 7.5–8.0 (m, 5 H, Ph), and 11.51 (s, 1 H, NH-3); ^{19}F NMR. data (Me_2SO-d_6): δ −192.6 (ddt, 1 F, $J_{(F-2'),2'}$ 47.9, $J_{(F-2'),1'}$ 20.6, $J_{(F-2'),3'} \simeq J_{(F-2'),(F-3')} = 10.1$ Hz, F-2′), −206.4 (dddd, 1 F, $J_{(F-3'),2'}$ 14.0, $J_{(F-3'),3'}$ 49.5, $J_{(F-3'),4'}$ 32.1, $J_{(F-3'),(F-2')}$ 10.5 Hz, F-3′). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 733 $(2M + H)^+$, 459 $(M + \text{glycerol} + H)^+$, 367 (M + H) +, 241 (s)$^+$, 127 $(BH_2)^+$, and 105 $(PhC \equiv O)^+$; negative mode *m/z* 365 $(M - H)^-$ and 125 $(B)^-$. Anal. Calcd for $C_{17}H_{16}F_2N_2O_5$: C, 55.74; H, 4.40; N, 7.65. Found: C, 55.90; H, 4.41; N, 7.42.

1-(2,3-Dideoxy-2,3-difluoro-β-D-xylofuranosyl)thymine (**35**).—A solution of **34** (0.18 g, 0.49 mmol) in methanolic ammonia (15 mL) was stirred for 16 h at room temperature. The solution was evaporated to dryness, and the residue was chromatographed on a column of silica gel using as eluent a stepwise gradient of MeOH (0–5%) in CH_2Cl_2, to give pure **35** (0.11 g, 86%) which was crystallised from water; mp 181–182°C; λ_{max} (95% EtOH) 262 nm (ϵ, 9500); λ_{min} 233 nm (ϵ, 2600); $[\alpha]_D^{20}$ −41.7° (*c* 1.0, Me_2SO); ^1H NMR data (Me_2SO-d_6): δ 1.77 (d, 3 H, *J* 1.2 Hz, Me), 3.8 (m, 2 H, H-5′,5″), 4.25 (dm, 1 H, $J_{4',(F-3')}$ 29.1 Hz), 5.2 (br s, 1 H, HO-5′), 5.42 (ddd, 1 H, $J_{3',4'}$ 2.7, $J_{3',(F-2')}$ 12.3, $J_{3',(F-3')}$ 49.8 Hz, H-3′), 5.48 (ddm, 1 H, $J_{2',(F-2')}$ 49.1, $J_{2',(F-3')}$ 14.6 Hz, H-2′), 6.03 (dd, 1 H, $J_{1',2'}$ 2.1, $J_{1',(F-2')}$ 20.5 Hz, H-1′), 7.28 (d, 1 H, *J* 1.2 Hz, H-6), and 11.50 (s, 1 H, NH-3); ^{19}F NMR data (Me_2SO-d_6): δ −192.6 (dddt, 1 F, $J_{(F-2'),1'}$ 20.8, $J_{(F-2'),2'}$ 47.9, $J_{(F-2'),3'} \simeq J_{(F-2'),(F-3')} =$ 10.3, $J_{(F-2'),4'}$ 2.2 Hz, F-2′), −207.3 (ddt, 1 F, $J_{(F-3'),2'} \simeq J_{(F-3'),(F-2')} = 12.1$, $J_{(F-3'),3'}$ 49.7, $J_{(F-3'),4'}$ 29.2 Hz, F-3′). FAB-mass spectra (matrix, 1:1 glycerol–thioglycerol): positive mode *m/z* 525 $(2M + H)^+$, 355 $(M + \text{glycerol} + H)^+$, 263 $(M + H)^+$, and 127 $(BH_2)^+$;negative mode *m/z* $(M + \text{glycerol-H})^-$, 261 $(M\text{-H})^-$, 241 $(M\text{-HF} - H)^-$ and 125 $(B)^-$. Anal. Calcd for $C_{10}H_{12}F_2N_2O_4$: C, 45.80; H, 4.61; F, 14.49; N, 10.69. Found: C, 46.07; H, 4.65; F, 14.07; N, 10.59.

Biological methods.—The broad antiviral assays on cell culture and the anti-HIV assays were performed following previously established procedures as described in refs 28 and 34.

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