TSH-Releasing Activity.[22] The same test as described in the previous paper[8] was employed.

Statistics. Statistical comparisons between drug-treated and control groups were performed by using two-tailed Student's *t* test.

Acute Toxicity. Three to 10 male Std/ddY mice (26–28 g) were used in each group. Test compounds dissolved in physiological saline were intravenously (iv) administered to the mice. The animals were kept under observation at 23–24 °C for 1 week, and LD_{50} was determined.[19]

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Synthesis and Antiviral Activity of Monofluoro and Difluoro Analogues of Pyrimidine Deoxyribonucleosides against Human Immunodeficiency Virus (HIV-1)

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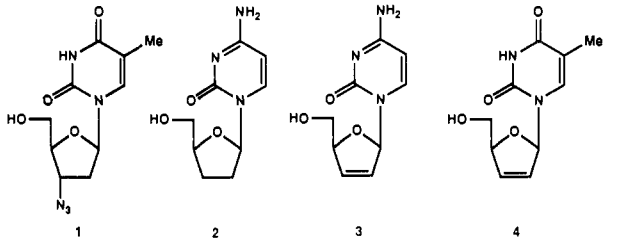
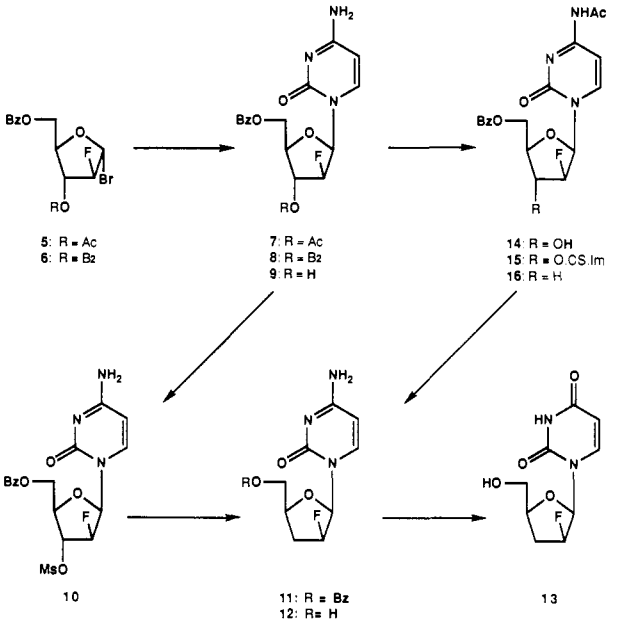
A range of 2′-fluoro and 2′,3′-difluoro analogues of pyrimidine deoxyribonucleosides have been synthesized and evaluated against human immunodeficiency virus (HIV-1) in a human lymphoblastoid cell line. Among these compounds, 1-(2,3-dideoxy-2-fluoro-β-D-threopentofuranosyl)cytosine (**12**), 2′,3′-didehydro-2′,3′-dideoxy-2′-fluorocytidine (**35**), 1-(2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)cytosine (**41**), and 3′-deoxy-2′,3′-didehydro-2′-fluorothymidine (**45**) were found to have significant antiviral activity, with IC_{50} values of 0.65, 10, 10, and 100 μM, respectively. The structure–activity relationships are discussed.

Since the identification of human immunodeficiency virus (HIV) as the etiological agent of acquired immunodeficiency syndrome (AIDS)[1,2] a variety of approaches have been studied in the search for an effective treatment for this disease. Inhibition of the enzyme reverse transcriptase is one approach which has been widely studied both by ourselves and others. This virally encoded enzyme is a DNA polymerase which synthesizes double-stranded DNA from the single-stranded RNA carried in virus particles. Many nucleoside derivatives have been identified which inhibit replication of this virus, particularly 2′,3′-dideoxynucleosides such as 3′-azido-3′-deoxythymidine (Zidovudine, AZT, **1**),[3] 2′,3′-dideoxycytidine (ddC, **2**),[4] 2′,3′-didehydro-2′,3′-dideoxycytidine (d4C, **3**),[5-8] and 3′-deoxy-2′,3′-didehydrothymidine (d4T, **4**).[6-10] A common feature of these compounds is the absence of a 3′-hydroxyl group in the carbohydrate moiety, and their mode of action requires metabolism to the corresponding 5′-triphosphate derivatives which act as inhibitors of reverse transcriptase and/or as chain terminators by incorporation into the growing strand of viral DNA.



1 2 3 4

Scheme I



Since the natural substrates for reverse transcriptase are 2′-deoxynucleotides, it is reasonable to suppose that both

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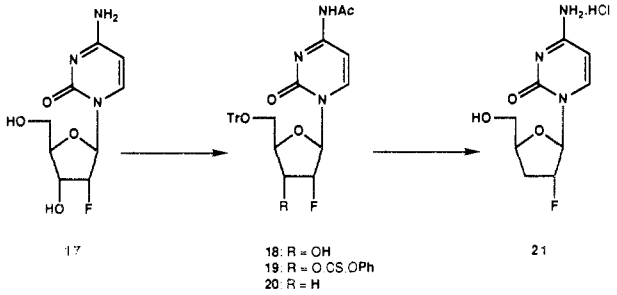
Scheme II



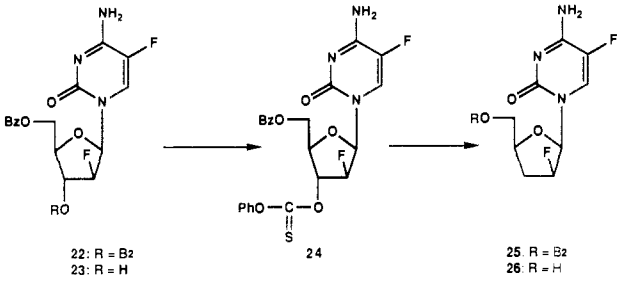
17 18: R = OH; 19: R = O CS OPh; 20: R = H 21

the 3′- and 5′-hydroxyl groups are required for good substrate activity. While the 5′-hydroxyl group must be retained in order to allow phosphorylations to the 5′-triphosphate, the 3′-hydroxyl may be replaced by other functions which mimic that functional group. One of the most favored replacements in carbohydrates is a fluorine atom[11] which is strongly electronegative but sterically undemanding. Since fluorine has approximately the same van der Waals radius as hydrogen,[12] it has been used also to replace hydrogen atoms in a wide range of biologically active molecules[13] including the 2′-hydrogens in 2′-deoxynucleosides. In this paper we report the synthesis and biological properties of some monofluoro and difluoro analogues of dideoxynucleosides.

Chemistry

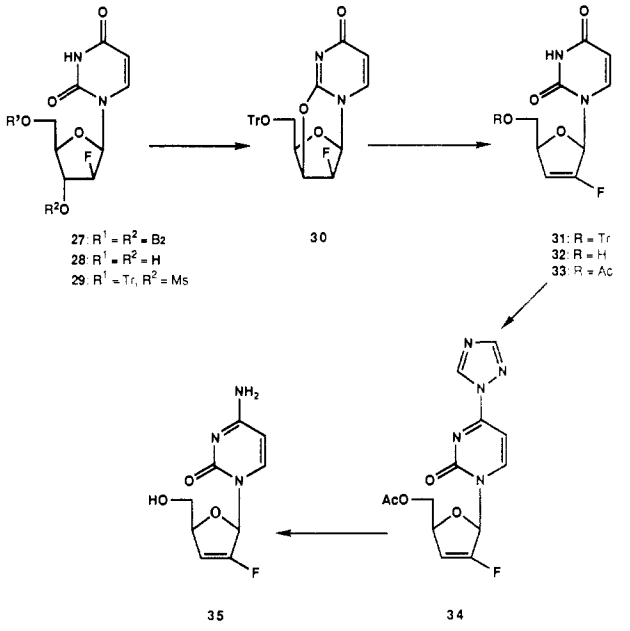
Our first synthesis of the 2′-β-fluoro analogue of ddC was from the bromo sugar **5**[14] as illustrated in Scheme I. Condensation of **5** with the silylated derivative of cytosine following the procedure of Hubbard, Jones, and Walker[15] gave **7**, which on brief treatment with methanolic ammonia gave the 3′-hydroxy derivative **9**. More conveniently, we have used the bromo sugar **6**,[16] which on condensation with silylated cytosine in chloroform gave **8**, which was deprotected with triethylamine in methanol to give **9**. Reaction of **9** with methanesulfonyl chloride in pyridine gave the mesylate **10**, which on treatment with sodium iodide in boiling 2-butanone followed by hydrogenation gave **11**. However, some loss of fluorine occurred during the hydrogenation step and separation of **11** from the desfluoro derivative by preparative HPLC was necessary before treatment with methanolic ammonia to give the desired nucleoside **12**. The preferred procedure from **9** involved

Scheme III



22: R = Bz 23: R = H 24 25: R = Bz 26: R = H

Scheme IV



27: $R^1 = R^2 = Bz$ 28: $R^1 = R^2 = H$ 29: $R^1 = Tr$, $R^2 = Ms$ 30 31: R = Tr 32: R = H 33: R = Ac 35 34

N-acetylation with acetic anhydride in methanol[17] to give **14**, which was treated with thiocarbonyldiimidazole in dimethylformamide[18] to afford **15**. Reduction of **15** with tri-*n*-butyltin hydride[18] gave **16**, which after deprotection with methanolic ammonia gave **12**.[19] Hydrolysis of **12** with aqueous acetic acid, followed by treatment with methanolic ammonia gave the corresponding uridine derivative **13**.

The related 2′-α-fluorodideoxycytidine (**21**) was prepared according to the route in Scheme II. Starting from 2′-deoxy-2′-α-fluorocytidine (**17**), prepared by using the procedure of Mengel and Guschlbauer,[20] N-acetylation with acetic anhydride in methanol and selective tritylation gave **18**. Reaction with phenyl chlorothionoformate gave **19** followed by reduction with tri-*n*-butyltin hydride[21] to give **20**. Removal of the *N*-acetyl group with methanolic ammonia followed by removal of the trityl group with hydrogen chloride in chloroform[22] gave **21** in good overall yield.

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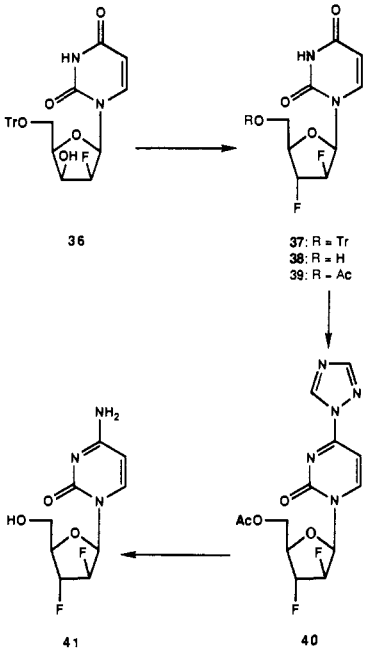
Scheme V



The difluoronucleoside **26** was prepared as outlined in Scheme III. Condensation of the bromo sugar **6** with silylated 5-fluorocytosine gave **22**, which on brief treatment with methanolic ammonia gave **23**. Attempts to selectively N-acetylate **23** were unsuccessful; therefore it was treated with phenyl chlorothionoformate to give **24** with no significant acylation on nitrogen. Reduction of **24** with tri-*n*-butyltin hydride gave **25**, which was deprotected with methanolic ammonia to give **26**.

Compound **35** was prepared as illustrated in Scheme IV. Again starting from the bromo sugar **6**, condensation with silylated uracil afforded **27**, which was treated with methanoic ammonia to give the fully deprotected 2′-deoxyuridine **28**. Treatment with trityl chloride in pyridine followed by methanesulfonyl chloride gave compound **29**, which on brief treatment with aqueous sodium hydroxide gave the anhydronucleoside **30**. Further treatment of **30** with sodium hydroxide gave a mixture of **31** and **36** that was separated by flash chromatography. Compound **31** was deprotected with hydrogen chloride in chloroform to give **32** followed by acetylation with acetic anydride to give **33**. With use of the procedure of Reese,[23] **33** was converted to the triazole **34**, which on treatment with aqueous ammonia followed by methanolic ammonia gave the desired product **35**.

Compound **36** was converted to 1-(2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)cytosine (**41**) by the route illustrated in Scheme V. Thus, treatment of **36** with (diethylamido)sulfur trifluoride (DAST) in dichloromethane gave the difluorouridine **37**. Deprotection with hydrogen chloride in chloroform gave **38** followed by acetylation to give **39**. Transformation to the cytidine derivative by the method described earlier proceeded smoothly via **40** to give **41**.

The 2′-fluoro analogue of d4T was prepared as illustrated in Scheme VI from FMAU (**42**),[24] which was prepared from thymine and the bromo sugar **6** using the procedure described by Howell et al.[25] Treatment of **42** with trityl chloride in pyridine and then methanesulfonyl chloride gave **43**. Rather surprisingly, when treated with sodium hydroxide, **43** gave only compound **44** with no formation of the corresponding lyxo derivative which was obtained with **29** under identical conditions. Finally, deprotection with hydrogen chloride in chloroform gave the desired product **45**.

Scheme VI

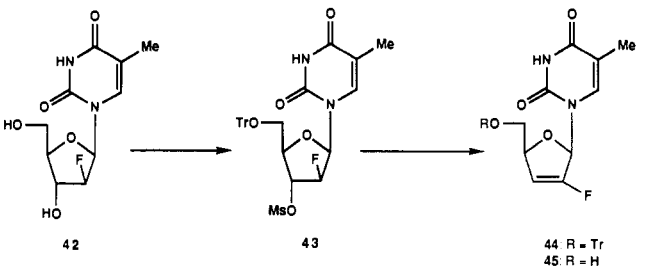


Table I. Antiviral Activity of Pyrimidine Deoxynucleosides on the Replication of HIV-1 and Cytotoxicity in C8166 Cells

compd	IC_{50},[a] μM	CD_{50},[b] μM	SI[f]
1	0.0085[c]	>1000	$>1.2 \times 10^5$
2	0.125[c]	1000	8×10^3
12	0.70[c]	500	7.1×10^2
13	>100[d]	ND[e]	ND
21	>100[d]	ND	ND
26	>100[d]	ND	ND
32	>100[d]	ND	ND
35	10[d]	30	3
38	>100[d]	ND	ND
41	10[d]	>100	>10
45	100[d]	>1000	>10

[a] Concentration of compound that inhibited virus replication by 50%. [b] Concentration of compound that inhibited incorporation of radiolabeled amino acids by 50%. [c] Mean of 12 determinations. [d] Mean of two determinations. [e] ND, not determined. [f] SI, selectivity index.

Antiviral Activity

Compounds were tested against HIV-1 (RF strain) in C8166 cells with a 3-day incubation period. The antiviral activity is expressed as the concentration (IC_{50}) which would reduce virus levels in the culture medium by 50% as measured by an antigen capture ELISA assay (Coulter).[26] This procedure used a primary antiserum with particular reactivity against the virion protein p24 and a horse radish peroxidase detection system. Color generation was measured spectrophotometrically and plotted against the concentration of the compound tested.

Of the compounds tested, AZT (**1**) was the most active against HIV-1 with an IC_{50} value of 0.0085 μM and ddC (**2**) slightly less active with an IC_{50} value of 0.125 μM. The fluorocytidines **12** and **41** also demonstrated significant antiviral activity with IC_{50} values of 0.70 and 10 μM, respectively, whereas compounds **21** and **26** had IC_{50} values above 100 μM, which was the highest concentration tested. The 2′-fluoro analogue of d4C, compound **35**, also had antiviral activity with an IC_{50} value of 10 μM. The only analogue of d4T prepared, compound **45**, had an IC_{50} value of 100 μM against the virus. All of the uridines, compounds **13**, **32**, and **38**, were inactive with IC_{50} values above 100 μM. These compounds were not toxic to the host lymphoblastoid cells at a concentration of 100 μM. The antiviral activities are summarized in Table I.

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Cytotoxicity

Only those compounds that showed an antiviral activity of 100 μM or less were assessed for cytotoxicity. Thus, C8166 cells (2×10^5) were incubated in the presence of test compounds at various concentrations for 3 days. The cells were washed and then incubated for a further 24 h in the presence of ^{14}C protein hydrolysate (Amersham International plc). The cells were harvested and washed, and the incorporation of ^{14}C label was measured by scintillation counting. The radioactivity was plotted against the concentration of test substance and the CD_{50} value calculated.

Structure–Activity Relationships

The presence of a fluorine atom in the 5-position of the pyrimidine moiety of **26** markedly reduced the antiviral activity compared to compound **12**. This was unexpected since it has been reported that the 5-fluoro analogue of ddC has antiviral activity[27] comparable to ddC. Unfortunately, we did not synthesize the 5-fluoro analogue of ddC, and therefore a comparison with ddC and **26** was not possible in our test system. The marked difference in activity between compounds **12** and **21** indicates that a 2′-fluoro substituent in the β-configuration is well tolerated but a 2′-fluoro substituent in the α-configuration is not. This effect was further supported by compound **41**, which also had antiviral activity albeit less than that of compound **12**. The antiviral activity of **45** and **35** are significantly less than that reported for d4T (**4**) and d4C (**3**), respectively, but a true comparison is possible only in the same assay system. All of the uridine derivatives **13**, **32**, and **38** were inactive. While there are some trends and patterns in antiviral activity with the compounds described, in general, structure–activity relationships with nucleoside derivatives are difficult to predict. This is further exemplified by the fact that we found AZT to be more potent than has been cited in the literature.[3,26] However, this result is not so surprising since it has been reported[28] that the antiviral potency of dideoxynucleosides do vary according to cell type, culture medium, cell growth rates, and cell growth phase used in assays. These factors influence the intracellular levels of nucleoside and nucleotide kinases as well as phosphodiesterases which markedly affect the metabolic and catabolic rate of an individual compound and hence its antiviral activity. Furthermore, the observed potency will also depend upon the virus strain, size of inoculum, time of infection, and end point chosen to assess the activity. In this connection studies are in hand to measure the pool size of the mono-, di- and triphosphates of compound **12** relative to AZT (**1**) and ddC (**2**) in various cell lines as well as the affinity for the viral and various cellular polymerases.

Experimental Section

Melting points were determined on a Büchi apparatus in glass capillary tubes and are uncorrected. TLC was performed on silica gel 60 F-254 plates purchased from E. Merck & Co., and flash chromatography was performed on Kieselgel 60, 70–230 mesh ASTM (Merck). Mass spectra were obtained with a Kratos MS902 mass spectrometer in the normal electron impact mode or fitted with a Kratos fast atom bombardment (FAB) source. Positive ion FABMS were generally recorded, but occasionally the negative ion mode was used. Samples were mixed with glycerol on the probe tip from acetone, dimethylformamide, or dimethyl sulfoxide solution. Mass spectra in the chemical ionization mode were recorded on a Finnigan 8430 instrument using isobutane as the reagent gas. ^1H NMR spectra were recorded on either a Bruker AC-250 or a Bruker WM-300 spectrometer, and chemical shifts are presented in ppm from tetramethylsilane as reference. Optical rotations were determined on a Perkin-Elmer 141 MC polarimeter. Elemental analyses were carried out on a Perkin-Elmer Model 240 instrument; where analyses are indicated only by symbols of the elements, the analytical results obtained for those elements were within ±0.4% of the theoretical values.

1-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (7). A mixture of cytosine (1.73 g, 15.6 mmol), ammonium sulfate (4 mg), and hexamethyldisilazane (9.5 mL) was stirred under argon and boiled under reflux for 2.5 h to give a clear solution. The solvent was evaporated under reduced pressure to yield bis(trimethylsilyl)cytosine as a white solid. This was twice dissolved in chloroform (25 mL) and the solution evaporated and then taken again in chloroform (40 mL) and treated with a solution of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**5**)[14] (4.7 g, 13 mmol) in chloroform (27 mL). The mixture was stirred under argon and boiled under reflux for 20 h. After cooling, the solution was washed with saturated sodium hydrogen carbonate solution (2×20 mL) and water (20 mL) and then dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated to give the coupled product as a mixture of α- and β-anomers (approximately 1:3 ratio, respectively, determined by ^1H NMR). These were separated by flash chromatography eluting with dichloromethane–methanol (12:1, v/v). Fractions containing solely the less polar anomer, as judged by TLC (dichloromethane–methanol 9:1, v/v), were combined and evaporated to give **7**, 2.46 g as a white foam. Rechromatography of material from intermediate fractions gave a further 0.67 g of pure **7** (total yield 3.13 g, 61%): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.17 (3 H, s, CH_3CO), 4.38 (1 H, m, 4′-CH), 4.69 (2 H, d, J = 5 Hz, 5′-CH_2), 5.24 (1 H, dd, J = 50 Hz, 2 Hz, 2′-CH), 5.36 (1 H, dd, J = 16 Hz, 2 Hz, 3′-CH), 5.73 (1 H, d, J = 8 Hz, 5-CH), 6.3 (1 H, dd, J = 22 Hz, 2 Hz, 1′-CH), 7.40–8.12 (6 H, m, 6-CH and ArH).

Chromatography fractions containing the more polar α-anomer were combined and evaporated to give 1.08 g (21%) of white foam: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.01 (3 H, s, CH_3CO), 4.55 (2 H, m, 5′-CH_2), 4.80 (1 H, m, 4′-CH), 5.39 (1 H, d, J = 49 Hz, 2′-CH), 5.39 (1 H, d, J = 16 Hz, 3′-CH), 5.99 (1 H, d, J = 8 Hz, 5-CH), 6.09 (1 H, d, J = 14 Hz, 1′-CH), 7.12–8.12 (6 H, m, 6-CH and ArH).

1-(3,5-*O*-Dibenzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (8). A solution of bis(trimethylsilyl)cytosine (prepared from 4.4 g (39.6 mmol) of cytosine) in chloroform (100 mL) was treated with a solution of 3,5-*O*-dibenzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**6**)[16] [prepared from 1,3,5-*O*-tribenzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (18 g, 38.8 mmol)] in chloroform (67 mL). The mixture was stirred under argon and boiled under reflux for 20 h. After cooling, the solution was washed with saturated sodium hydrogen carbonate solution (2×100 mL) and water (100 mL) and then dried over anhydrous sodium sulfate, filtered, and evaporated to give the coupled product as a mixture of α- and β-anomers (1:6.4 ratio, respectively, determined by HPLC on a reverse-phase Hypersil 3μ column, using 40% acetonitrile–0.05 M tetraethylammonium phosphate buffer, pH 2.52, at 1 mL/min with UV detection at 254 nm. Retention times were 6.6 and 7.8 min, respectively). A single recrystallization from methanol gave **8** (98% β-anomer by HPLC) as a white solid: 10.7 g (61%); mp 213–215.5 °C; MS m/e (+FAB) 454 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.51 (1 H, m, 4′-CH), 4.77 (2 H, d, J = 4 Hz, 5′-CH_2), 5.43 (1 H, dd, J = 50 Hz, 2 Hz, 2′-CH), 5.60 (1 H, dd, J = 17 Hz, 3 Hz, 3′-CH), 5.72 (1 H, d, J = 7 Hz, 5-CH), 6.41 (1 H, dd, J = 22 Hz, 2 Hz, 1′-CH), 7.4–8.12 (11 H, m, 6-CH and ArH). Anal. ($C_{23}H_{20}FN_3O_6$) C, H, N.

1-(5-*O*-Benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-cytosine (9). (a) A solution of **7** (3.6 g, 9.21 mmol) in 2 M methanolic ammonia solution (19 mL) was stirred at room temperature for 2 h. The solution was immediately evaporated to dryness and the residue purified by flash chromatography eluting with dichloromethane–methanol (9:1, v/v) to give **9** as a colorless foam, 2.5 g (78%).

(b) A suspension of **8** (24.9 g, 55 mmol) in methanol (500 mL) and triethylamine (250 mL) was stirred at room temperature for 16 h. The resulting solution was evaporated under reduced

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pressure and the residue coevaporated with toluene (2 × 250 mL) to remove final traces of triethylamine. The residual mixture of partially and fully debenzoylated products was separated by flash chromatography eluting initially with dichloromethane to remove methyl benzoate and then with dichloromethane–methanol (9:1, v/v) to give, after evaporation, **9** as a white solid, 11.9 g (62%), pure enough for further use. Recrystallization of a sample from ethyl acetate (or acetonitrile) gave analytically pure material: mp 172–176 °C; MS *m/e* (EI) 349 $(M)^+$; ^1H NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ 4.38 (1 H, m, 4′-CH), 4.40 (1 H, dd, *J* = 23 Hz, 2 Hz, 3′-CH), 4.60 (2 H, m, 5′-CH_2), 5.11 (1 H, dd, *J* = 50 Hz, 3 Hz, 2′-CH), 5.74 (1 H, d, *J* = 7 Hz, 5-CH), 6.29 (1 H, dd, *J* = 22 Hz, 2 Hz, 1′-CH), 7.4–8.1 (6 H, m, 6-CH and ArH). Anal. ($C_{16}H_{16}FN_3O_5$) C, H, N.

Further elution with methanol of the column used above gave, after evaporation of the eluate, fully debenzoylated material as a white foam, 5.2 g (38%). This was redissolved in methanol (25 mL) and the solution treated with 4 M hydrogen chloride in methanol (6 mL). A crystalline white precipitate separated. After cooling to −20 °C, the solid was filtered off and washed with methanol and ether to give 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine hydrochloride: 4.9 g, mp 241–242 °C dec; $[\alpha]^{20}_D$ +115.1° (*c* = 1% in water) [lit.[29] mp 240–242 °C dec; $[\alpha]^{20}_D$ +108° (*c* = 0.2% in water)]; ^1H NMR (D_2O, 300 MHz) δ 3.58–3.81 (2 H, m, 5′-CH_2), 3.96 (1 H, m, 4′-CH), 4.27 (1 H, dm, *J* = 20 Hz, 3′-CH), 5.07 (1 H, dm, *J* = 50 Hz, 2′-CH), 6.09 (1 H, d, *J* = 7 Hz, 5-CH), 6.12 (1 H, dd, *J* = 17 Hz, 4 Hz, 1′-CH), 7.88 (1 H, d, *J* = 7 Hz, 6-CH). Anal. ($C_9H_{12}FN_3O_4$·HCl) C, H, N.

1-[5-*O*-Benzoyl-2-deoxy-2-fluoro-3-*O*-(methylsulfonyl)-β-D-arabinofuranosyl]cytosine (10). A suspension of **9** (1.7 g, 4.87 mmol) in dry pyridine (30 mL) was stirred under argon and cooled to 5 °C. Methanesulfonyl chloride (1.12 g, 9.78 mmol) was added dropwise and the mixture stirred at 0 °C for 18 h to give an orange solution. Water (0.34 mL) was added and stirring continued at 0 °C for 1 h, and the mixture was then poured onto ice/water (100 mL) and extracted with ethyl acetate (3 × 50 mL). Combined extracts were washed with brine (50 mL) and then dried over anhydrous magnesium sulfate, filtered, and evaporated. The residual syrup was purified by flash chromatography eluting with dichloromethane–methanol (19:1, v/v) to give **10** as a white foam: 1.6 g (76%); MS *m/e* (+FAB) 429 $(M + H)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.19 (2 H, s, CH_3SO_2), 4.56 (1 H, m, 4′-CH), 4.69 (2 H, d, *J* = 5 Hz, 5′-CH_2), 5.33 (1 H, dd, *J* = 16 Hz, 3 Hz, 3′-CH), 5.40 (1 H, dd, *J* = 50 Hz, 3 Hz, 2′-CH), 5.77 (1 H, d, *J* = 8 Hz, 5-CH), 6.30 (1 H, dd, *J* = 22 Hz, 3 Hz, 1′-CH), 7.4–8.1 (6 H, m, 6-CH and ArH). Anal. ($C_{17}H_{18}FN_3O_7S$) C, H, N.

1-(5-*O*-Benzoyl-2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (11). A mixture of **10** (1.55 g, 3.63 mmol), sodium iodide (2.7 g, 18 mmol), and 2-butanone (36 mL) was stirred under argon and boiled under reflux for 18 h. The solvent was evaporated under reduced pressure and the residue partitioned between water (50 mL) and ethyl acetate (3 × 50 mL). The ethyl acetate extract was dried over anhydrous magnesium sulfate, filtered, and evaporated. The residual foam was purified by flash chromatography eluting with dichloromethane–methanol (19:1, v/v) to give recovered methanesulfonate (**10**), 0.36 g, and 1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-3-iodo-β-D-arabinofuranosyl)cytosine, 0.78 g (61% based on unrecovered methanesulfonate), as a pale brown foam: MS *m/e* (EI) 459 $(M)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.31 (1 H, dq, *J* = 23 Hz, 3′-CH), 4.52 (2 H, d, *J* = 4.5 Hz, 5′-CH_2), 4.78 (1 H, q, 4′-CH), 5.43 (1 H, dm, *J* = 53 Hz, 2′-CH), 5.80 (1 H, d, *J* = 7 Hz, 5-CH), 6.40 (1 H, dd, *J* = 18 Hz, 3 Hz, 1′-CH), 7.34–8.0 (6 H, m, 6-CH and ArH).

A solution of the above iodide (0.75 g, 1.63 mmol) in ethanol (30 mL) was treated with a solution of sodium hydrogen carbonate (0.15 g, 1.79 mmol) in water (7.5 mL) and then hydrogenated at room temperature and atmospheric pressure in the presence of 10% palladium on carbon catalyst (0.2 g) for 19 h. The catalyst was removed by filtration and washed with methanol. The filtrate was evaporated and the residue purified initially by flash chromatography eluting with dichloromethane–methanol (19:1, v/v) to give crude product (0.36 g) which was homogeneous on TLC (dichloromethane–methanol 9:1, v/v) but was a mixture of desired product **11** and 5′-*O*-benzoyl-2′,3′-dideoxycytidine (2:1 ratio determined by HPLC on a normal-phase Hypersil 5μ column, using 5% methanol–dichloromethane at 1.7 mL/mm with UV detection at 254 nm. Retention times were 2.93 and 3.68 min, respectively). This mixture was separated on a preparative HPLC column under the same conditions to give, after evaporation of appropriate fractions, **11** as a colorless foam, 0.17 g (31%): MS *m/e* (EI) 333 $(M)^+$; ^1H NMR ($CDCl_3$, 250 MHz) δ 2.31 (1 H, m, 3′-CH), 2.6 (1 H, m, 3′-CH), 4.52 (2 H, m, 5′-CH_2), 4.59 (1 H, m, 4′-CH), 5.34 (1 H, dm, *J* = 53 Hz, 2′-CH), 5.74 (1 H, d, *J* = 17 Hz, 5-CH), 6.13 (1 H, dd, *J* = 20 Hz, 2 Hz, 1′-CH), 7.39–8.12 (6 H, m, 6-CH and ArH).

***N*-Acetyl-1-(5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (14).** A solution of **9** (11.8 g, 33.8 mmol) in methanol (1180 mL) was stirred and heated to boiling under reflux. The solution was treated with six portions of acetic anhydride (12 mL) at hourly intervals. After 6 h the solution was evaporated to dryness and the residue coevaporated with toluene (2 × 300 mL) and then redissolved in methanol (1000 mL) and treated again at reflux with three further portions of acetic anhydride (12 mL) at hourly intervals. The solution was evaporated to dryness and the residue dissolved in ethyl acetate. The solution washed with ice-cold 1 M hydrochloric acid (2 × 100 mL), water (100 mL), saturated sodium hydrogen carbonate solution (100 mL), and brine (100 mL) and then dried over anhydrous sodium sulfate, filtered, and evaporated to give **14**, 12.1 g (91%), sufficiently pure for further use. Recrystallization from ethyl acetate gave analytically pure material: mp 151–153 °C; MS *m/e* (+FAB) 392 $(M + H)^+$; ^1H NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ 2.22 (3 H, s, CH_3CO), 4.42 (1 H, m, 4′-CH), 4.46 (1 H, dd, *J* = ∼20 Hz, 2 Hz, 3′-CH), 4.60 (2 H, m, 5′-CH_2), 5.23 (1 H, dd, *J* = 50 Hz, 3 Hz, 2′-CH), 6.31 (1 H, dd, *J* = 21 Hz, 3 Hz, 1′-CH), 7.4–8.1 (7 H, m ArH). Anal. ($C_{18}H_{18}FN_3O_6$) C, H, N.

***N*-Acetyl-1-[5-*O*-benzoyl-2-deoxy-2-fluoro-3-*O*-[(1-imidazolyl)thiocarbonyl]-β-D-arabinofuranosyl]cytosine (15).** A solution of **14** (3.0 g, 7.61 mmol) and thiocarbonyldiimidazole (3.67 g, 20.6 mmol) in *N*,*N*-dimethylformamide (15 mL) was stirred at room temperature under argon for 18 h to give a yellow suspension. The mixture was evaporated under reduced pressure and the residue dissolved in dichloromethane (300 mL). The yellow solution was washed with ice-cold water (2 × 50 mL) and then dried over anhydrous sodium sulfate, filtered, and evaporated. The solid residue was slurried with ethyl acetate, filtered, and dried in vacuo to give **15**, 3.47 g (90%), as a white solid: mp 204 °C dec. Recrystallization from 1,2-dichloroethane gave analytically pure product: mp 208 °C dec; MS *m/e* (CI) 502 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.29 (3 H, s, CH_3CO), 4.73 (1 H, m, 4′-CH), 4.83 (2 H, m, 5′-CH_2), 5.69 (1 H, dd, *J* = 49 Hz, 3 Hz, 2′-CH), 6.13 (1 H, dd, *J* = 15 Hz, 2 Hz, 3′-CH), 6.42 (1 H, dd, *J* = 20 Hz, 3 Hz, 1′-CH), 7.10 (1 H, s, imidazole 4-CH), 7.4–8.1 (8 H, m, imidazole 3-CH and ArH), 8.59 (1 H, s, imidazole 2-CH), 9.33 (1 H, br s, NH). Anal. ($C_{22}H_{20}FN_5O_6S$) C, H, N.

***N*-Acetyl-1-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (16).** A suspension of **15** (3.4 g, 6.79 mmol) in dry toluene (68 mL) was stirred and heated at reflux. Dry argon gas was bubbled through the mixture for 10 min to remove oxygen. A solution of tributyltin hydride (3.33 g, 11.44 mmol) and azobisisobutyronitrile (0.14 g) in dry toluene was added dropwise to the refluxing mixture during 20 min. The resulting clear solution was stirred and boiled under reflux for 1 h and then cooled and evaporated to dryness. The residue was dissolved in dichloromethane (100 mL) and the solution washed with water (2 × 50 mL), dried over anhydrous sodium sulfate, and evaporated. The residue was triturated with hexane (100 mL) and the pale yellow solid product filtered off and washed with hexane to give **16**: 2.51 g (99%); mp 174–177 °C. Recrystallization from ethanol gave analytically pure material: mp 193–196 °C; MS *m/e* (+FAB) 751 $(2M + H)^+$, 376 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (3 H, s, CH_3CO), 2.39 (1 H, m, 3′-CH), 2.63 (1 H, m, 3′-CH), 4.56 (2 H, m, 5′-CH_2), 4.68 (1 H, m, 4′-CH), 5.43 (1 H, dm, *J* = 53 Hz, 2′-CH), 6.11 (1 H, dd, *J* = 19 Hz, 3 Hz, 1′-CH), 7.4–8.11 (7 H, m, 5-CH, 6-CH, and ArH), 9.49 (1 H, br s, NH). Anal. ($C_{18}H_{18}FN_3O_5$) C, H, N.

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1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (12). (a) A mixture of 11 (0.13 g, 0.4 mmol) and a saturated solution of ammonia in methanol (6 mL) was stirred at room temperature for 18 h. The solution was evaporated and the residue dissolved in distilled water (10 mL). The solution was washed with ethyl acetate (3 × 5 mL) and then evaporated on a freeze drier. The residue was redissolved in water (10 mL) and lyophilized again to ensure removal of benzamide. This gave **12** (69 mg, 76%) as a white powder which hardened after exposure to the atmosphere, mp 192–195 °C.

(b) A mixture of **16** (1.6 g, 4.27 mmol) and a saturated solution of ammonia in methanol (80 mL) was stirred at room temperature for 18 h to give a clear solution. The solution was evaporated and the residue triturated with ethyl acetate (50 mL) until crystalline. The pale yellow solid was filtered and washed with ethyl acetate to give crude product, 0.96 g. Recrystallization from ethanol gave **12** as colorless crystals: 0.79 g (80%); mp 205–208 °C; $[\alpha]^{20}_D$ +168.7° (c = 0.5% in water); MS m/e (+FAB) 230 (M + H)$^+$; ^{1}H NMR (D_2O, 300 MHz) δ 2.0 (1 H, m, 3′-CH), 2.46 (1 H, m, 3′-CH), 3.60 (2 H, m, 5′-CH_2), 4.20 (1 H, m, 4′-CH), 5.20 (1 H, dm, J = 53 Hz, 2′-CH), 5.88 (1 H, d, J = 8 Hz, 5-CH), 5.91 (1 H, dd, J = 19 Hz, 3 Hz, 1′-CH), 7.69 (1 H, dd, J = 8 Hz, 1 Hz, 6-CH). Anal. ($C_9H_{12}FN_3O_3$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)uracil (13). A solution of **12** (250 mg, 1.1 mmol) in 80% acetic acid (10 mL) was heated under reflux for 4 days. The resulting brown solution was evaporated to dryness, residual solvent was removed azeotropically by evaporation of toluene (2 × 10 mL), and the resulting material was taken up in methanol (10 mL). The methanol solution was cooled in ice, saturated with ammonia, and stirred at room temperature for 24 h. The solution was again evaporated to dryness under reduced pressure and the residue purified by flash chromatography eluting with dichloromethane–methanol (9:1, v/v). Recrystallization from ethyl acetate gave the product **13** 92 mg (36%): mp 159–160 °C; MS m/e (+FAB) 231 (M + H)$^+$; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.97–2.15 (1 H, m, 3′-CH_2), 2.38–2.57 (1 H, m, 3′-CH_2), 3.55 (2 H, m, 5′-CH_2), 4.10 (1 H, m, 4′-CH), 5.03 (1 H, t, J = 6 Hz, 5′-OH), 5.30 (1 H, m, 2′-CH), 5.14 (1 H, d, J = 8 Hz, 5-H), 5.98 (1 H, m, 1′-CH), 7.76 (1 H, m, 6-H), 11.45 (1 H, br s, NH). Anal. ($C_9H_{11}FN_2O_4$) C, H, N.

***N*-Acetyl-2′-deoxy-2′-fluoro-5′-*O*-tritylcytidine (18).** Acetic anhydride (6 × 2.5 mL) was added portionwise over 5 h to a refluxing solution of 2′-deoxy-2′-fluorocytidine[20] (2.38 g, 9.7 mmol) in methanol (250 mL). After a final 1 h of heating, the reaction mixture was allowed to cool to room temperature and the solvent evaporated under reduced pressure. The residue was then taken up in dry pyridine (50 mL), trityl chloride (2.79 g, 10 mmol) was added, and the solution was heated on an oil bath at 100 °C for 2.5 h. The mixture was then evaporated to dryness and the residue partitioned between water (75 mL) and dichloromethane (75 mL). The organic phase was washed with saturated aqueous copper(II) sulfate solution (25 mL), dried, and evaporated. Flash chromatography eluting with ethyl acetate–hexane (1:1, v/v) gave the product **18** 1.57 g (30%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.05 (3 H, s, CH_3CO), 3.55–3.65 (3 H, m, 5′-CH_2 and 3′-OH), 4.18 (1 H, br d, J = 7 Hz, 4′-CH), 4.54 (1 H, m, 3′-CH), 5.16 (1 H, m, 2′-CH), 6.03 (1 H, d, J = 16 Hz, 1′-CH), 7.15 (1 H, d, J = 8 Hz, 6-CH), 7.25–7.46 (15 H, m, ArH), 8.41 (1 H, d, J = 8 Hz, H-5), 9.50 (1 H, br s, NH).

***N*-Acetyl-2′-deoxy-2′-fluoro-3′-*O*-[phenoxy(thiocarbonyl)]-5′-*O*-tritylcytidine (19).** Phenyl chlorothionocarbonate (516 mg, 3.0 mmol) was added to an ice-cooled solution of **18** (1.27 g, 2.40 mmol) and 4-(dimethylamino)pyridine (2.30 g, 19.0 mmol) in acetonitrile (60 mL), and the mixture was allowed to warm to room temperature and stirred for 1 h under argon. The acetonitrile was then evaporated under reduced pressure, the residue taken up in water (50 mL), and the product extracted with dichloromethane (3 × 50 mL). The extracts were combined, washed with saturated aqueous copper(II) sulfate, dried over magnesium sulfate, and evaporated. Purification of the crude product by flash chromatography eluting with ethyl acetate gave **19**: 1.14 g (72%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.07 (3 H, s, CH_3CO), 3.57–3.73 (2 H, m, 5′-CH_2), 4.61 (1 H, br d, J = 8 Hz, 4′-CH), 5.5 (1 H, m, 2′-CH), 5.93 (1 H, m, 3′-CH), 6.20 (1 H, d, J = 16 Hz, 1′-CH), 7.10 (1 H, d, J = 8 Hz, 6-CH), 7.22–7.50 (20 H, m, ArH), 8.37 (1 H, d, J = 8 Hz, 5-CH), 9.65 (1 H, br s, NH).

***N*-Acetyl-2′,3′-dideoxy-2′-fluoro-5′-*O*-tritylcytidine (20).** A solution of **19** (1.14 g, 1.73 mmol), tributyltin hydride (0.76 g, 2.6 mmol), and azobisisobutyronitrile (5 mg) in freshly distilled toluene (100 mL) was deoxygenated by bubbling nitrogen through the solution for 30 min and then heated on an oil bath at 90 °C for 1 h. At this point TLC (ethyl acetate, UV) showed only partial conversion to product, further azobisisobutyronitrile (10 mg) was added and the solution again deoxygenated. After an additional 2 h of heating, the TLC still showed some starting material to be present. Further portions of azobisisobutyronitrile (10 mg) and tributyltin hydride (0.76 g, 2.6 mmol) were added, and after deoxygenation, heating was continued for a further 3 h. At this point the reaction appeared complete by TLC. The solvent was evaporated under reduced pressure and the product purified by flash chromatography eluting with ethyl acetate to give **20**: 0.56 g (61%); MS m/e (+FAB) 514 (M + H)$^+$; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.08–2.38 (2 H, m, 3′-CH_2), 2.29 (3 H, s, CH_3CO), 3.43–3.74 (2 H, m, 5′-CH_2), 4.63 (1 H, m, 4′-CH), 5.75 (1 H, d, J = 52 Hz, 2′-CH), 6.11 (1 H, d, J = 17 Hz, 1′-CH), 7.16 (1 H, d, J = 8 Hz, 6-H), 7.27–7.48 (15 H, m, ArH), 8.43 (1 H, d, J = 8 Hz, 5-H), 9.70 (1 H, br s, NH).

2′,3′-Dideoxy-2′-fluorocytidine Hydrochloride Salt (21). Ice-cooled methanol (60 mL), saturated with gaseous ammonia, was added to **20** (556 mg, 1.09 mmol) and the mixture stirred overnight at room temperature. The solution was evaporated to dryness and the resulting white solid redissolved in chloroform (60 mL). This solution was cooled in an ice bath and a solution of hydrogen chloride in chloroform added portionwise over 30 min (2 × 6.5 mL of 0.42 M solution). The reaction mixture was stirred for an additional 1 h at room temperature and then evaporated to dryness under reduced pressure. The residue was taken up in water (50 mL), washed with dichloromethane (3 × 20 mL), and freeze-dried. Recrystallization from moist ethanol gave the product **21**: 85 mg (29%); mp 219–220 °C; MS m/e (–FAB) 264 (M + Cl)$^-$; ^{1}H NMR (D_2O, 300 MHz) δ 1.93–2.37 (2 H, m, 3′-CH_2), 3.77–4.02 (2 H, m, 5′-CH_2), 4.59 (1 H, m, 4′-CH), 5.48 (1 H, m, 2′-CH), 6.02 (1 H, d, J =17 Hz, 1′-CH), 6.19 (1 H, d, J = 8 Hz, 6-H), 8.15 (1 H, d, J = 8 Hz, 5-H). Anal. ($C_9H_{12}FN_3O_3$·HCl) C, H, N, Cl.

1-(3,5-*O*-Dibenzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorocytosine (22). A mixture of 5-fluorocytosine (2.93 g, 22.7 mmol), ammonium sulfate (6 mg), and hexamethyldisilazane (13.5 mL) was stirred under argon and boiled under reflux for 2.5 h to give a clear solution. The solvent was evaporated under reduced pressure and the residue twice dissolved in chloroform (30 mL) and the solution evaporated. The residue was again taken in dry chloroform (58 mL) and the solution filtered into a solution of 3,5-*O*-dibenzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide (**6**) (9.5 g, 22.5 mmol) in dry chloroform (39 mL). The solution was stirred under argon and boiled under reflux for 48 h. After cooling, the solution was washed with saturated sodium hydrogen carbonate solution (2 × 30 mL) and water (30 mL) and then dried over anhydrous sodium sulfate and filtered, and the solvent was evaporated to give the coupled product **22** 9.6 g (90%). Recrystallization from acetonitrile gave analytically pure material: mp 196–199 °C; MS m/e (EI) 471 (M)$^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.46 (1 H, m, 4′-CH), 4.80 (2 H, m, 5′-CH_2), 5.42 (1 H, dd, J = 50 Hz, 2.5 Hz, 2′-CH), 5.52 (1 H, br s, NH), 5.61 (1 H, dd, J = 17 Hz, 2.5 Hz, 3′-CH), 6.35 (1 H, dm, J = 21 Hz, 1′-CH), 6.97 (1 H, br s, NH), 7.4–8.15 (11 H, m, 6-CH and ArH). Anal. ($C_{23}H_{19}F_2N_3O_6$) C, H, N.

1-(5-*O*-Benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorocytosine (23). A solution of **22** (8.73 g, 18.5 mmol) in a saturated solution of ammonia in methanol (87 mL) was stirred at room temperature for 1.5 h. The solution was evaporated to dryness under reduced pressure and the residue crystallized from ethanol (100 mL) to give **23**, 2.9 g, mp 220–224 °C. Further material was obtained by evaporation of the recrystallization mother liquors and purification of the residue by flash chromatography eluting with dichloromethane–methanol (19:1, v/v). Total yield was 4.49 g (66%). A second recrystallization from ethanol gave analytically pure material: mp 224–226 °C; MS m/e (+FAB) 735 (2M + H)$^+$; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 4.19 (1 H, q, J = 5 Hz, 4′-CH), 4.36 (1 H, dm, J = 17 Hz, 3′-CH), 4.60 (2 H, d, J = 5 Hz, 5′-CH_2), 5.04 (1 H, dm, J = 52

Hz, 2'-CH), 6.10 (1 H, d, J = 5 Hz, OH), 6.15 (1 H, dm, J = 26 Hz, 1'-CH), 7.5–8.04 (6 H, m, 6-CH and ArH), 7.92 (2 H, br s, NH_2). Anal. ($C_{16}H_{15}F_2N_3O_5$) C, H, N.

1-[5-*O*-Benzoyl-2-deoxy-2-fluoro-3-*O*-[phenoxy(thiocarbonyl)]-β-D-arabinofuranosyl]-5-fluorocytosine (24). A suspension of **23** (2.5 g, 6.81 mmol) and 4-(dimethylamino)pyridine (6.22 g, 51 mmol) in dry acetonitrile (60 mL) was stirred under argon and cooled to 5 °C while phenyl chlorothionocarbonate (1.23 g, 7.13 mmol) was added dropwise. The mixture was stirred at 5 °C under argon for 2 h and then evaporated and the residue dissolved in dichloromethane (200 mL). The solution was washed with water (100 mL), 2 M hydrochloric acid (2 × 100 mL), water (100 mL), saturated sodium hydrogen carbonate solution (100 mL), and water (100 mL) and then dried over anhydrous sodium sulfate, filtered, and evaporated to give **24** as a pale yellow solid, 2.68 g (78%), which was used without further purification. A pure sample was obtained by flash chromatography eluting with ethyl acetate–cyclohexane (1:1, v/v): ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.70 (1 H, m, 4'-CH), 4.80 (2 H, m, 5'-CH_2), 5.47 (1 H, dd, J = 50 Hz, 2 Hz, 2'-CH), 5.90 (1 H, dd, J = 15 Hz, 2 Hz, 3'-CH), 6.36 (1 H, d, J = 22 Hz, 1'-CH), 7.05–8.2 (11 H, m, 6-CH and ArH).

1-(5-*O*-Benzoyl-2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-5-fluorocytosine (25). A suspension of **24** (2.68 g, 5.32 mmol) and azobisisobutyronitrile (0.2 g) in dry toluene (100 mL) was stirred at room temperature. Dry argon was bubbled through the mixture and tributyltin hydride (2.2 g, 7.6 mmol) was added dropwise over 5 min. The mixture was stirred at room temperature for 15 min and then heated at 75 °C for 1.5 h. The resulting solution was evaporated to dryness and the residue dissolved in dichloromethane (50 mL). The solution was washed with water (2 × 25 mL) and then dried over anhydrous sodium sulfate, filtered, and evaporated. The residue was purified by flash chromatography on silica gel eluting the dichloromethane–methanol (49:1, v/v) to give **25** as a white solid, 1.07 g (57%). Recrystallization from ethyl acetate gave analytically pure material: mp 165–167 °C; MS m/e (+FAB) 703 $(2M + H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (1 H, m, 3'-CH), 2.60 (1 H, m, 3'-CH), 4.44–4.67 (3 H, m, 4'-CH and 5'-CH_2), 5.15 (1 H, dm, J = 53 Hz, 2'-CH), 5.45 (1 H, br s, NH), 6.10 (1 H, dm, J = 20 Hz, 1'-CH), 6.80 (1 H, br s, NH), 7.42–8.11 (6 H, m, 6-CH and ArH). Anal. ($C_{16}H_{15}F_2N_3O_4$) C, H, N.

1-(2,3-Dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)-5-fluorocytosine (26). A solution of **25** (1.0 g, 2.85 mmol) in a saturated solution of ammonia in methanol (100 mL) was stirred at room temperature for 18 h. The solution was evaporated and the residue dissolved in water (15 mL). The aqueous solution was washed with diethyl ether (3 × 5 mL) and then evaporated. The residue was recrystallized from water to give **26** as colorless crystals: 0.53 g (76%); mp 195–196 °C; MS m/e (+FAB) 495 $(2M + H)^+$; ^{1}H NMR (D_2O, 300 MHz) δ 2.00 (1 H, m, 3'-CH), 2.45 (1 H, m, 3'-CH), 3.64 (2 H, m, 5'-CH_2), 4.22 (1 H, m, 4'-CH), 5.21 (1 H, dm, J = 55 Hz, 2'-CH), 5.90 (1 H, dm, J = 18 Hz, 1'-CH), 7.84 (1 H, dd, J = 7 Hz, 1 Hz, 6-CH). Anal. ($C_9H_{11}F_2N_3O_3 \cdot 0.27H_2O$) C, H, N, H_2O.

1-(3,5-*O*-Dibenzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (27). A suspension of uracil (4.59 g, 41 mmol) and ammonium sulfate (1 mg) in hexamethyldisilazane (25 mL) was stirred and refluxed under nitrogen for 3 h. The solvent was evaporated and the residue was taken up in chloroform (80 mL) and evaporated. This process was repeated, and the residue was dissolved in chloroform (80 mL) and a solution of 3,5-*O*-dibenzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl bromide [prepared from 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranose (19.0 g, 41 mmol)] in chloroform (80 mL) was added. The mixture was refluxed under nitrogen for 24 h and then cooled and diluted with chloroform (100 mL). The solution was washed with saturated sodium hydrogen carbonate solution (2 × 150 mL), dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was suspended in ethyl acetate (30 mL), cooled to 0 °C, and filtered to give **27**: 14.55 g (78%); mp 185–187 °C; MS m/e (+FAB) 455 $(M + H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.52, (1 H, m, 4'-CH), 4.77 (2 H, d, J = 5 Hz, 5'-CH_2), 5.35 (1 H, dd, J = 50 Hz, 3 Hz, 2'-CH), 5.65 (1 H, dd, J = 17 Hz, 3 Hz, 3'-CH), 5.70 (1 H, dd, J = 8 Hz, 2 Hz, 5-CH), 6.33 (1 H, dd, J = 20 Hz, 3 Hz, 1'-CH), 7.45–7.70 (7 H, m, 6-CH and ArH), 8.03–8.10 (4 H, m, ArH), 8.83 (1 H, br s, NH). Anal. ($C_{23}H_{19}FN_2O_7$) C, H, N.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (28). A solution of **27** (14.55 g, 32 mmol) in saturated methanolic ammonia solution (450 mL) was stood at room temperature in a stoppered flask for 24 h. The solvent was evaporated and the residue partitioned between ethyl acetate (75 mL) and water (100 mL). Layers were separated, and the aqueous solution was washed with ethyl acetate (75 mL). The combined ethyl acetate solutions were extracted with water (30 mL) and the combined aqueous extracts were evaporated to a syrup. This was freeze-dried to give **28** as a white solid: 6.95 g (88%); mp 133–154 °C (lit.[30] mp 162 °C from 2-propanol–diethyl ether); ^{1}H NMR (D_2O, 250 MHz) δ 3.38–4.03 (2 H, m, 5'-CH_2), 4.10 (1 H, m, 4'-CH), 4.36 (1 H, dm, J = 13 Hz, 3'-CH), 4.43 (1 H, dm, J = 37 Hz, 2'-CH), 5.43 (1 H, d, J = 5 Hz, 5-CH), 5.73 (1 H, dd, J = 13 Hz, 3 Hz, 1'-CH), 6.86 (1 H, d, J = 5 Hz, 6-CH).

1-[2-Deoxy-2-fluoro-3-*O*-(methylsulfonyl)-5-*O*-trityl-β-D-arabinofuranosyl]uracil (29). A solution of the uridine **28** (6.25 g, 25.4 mmol) and trityl chloride (8.62 g, 31 mmol) in dry pyridine (125 mL) was stirred under nitrogen at 100–110 °C for 2 h. The solution was then cooled to 0 °C and methanesulfonyl chloride (4.82 mL, 7.13 g, 62 mmol) was added. The mixture was stirred at 0 °C for 72 h and then further methanesulfonyl chloride (2.4 mL, 3.55 g, 31 mmol) was added and the mixture stirred at room temperature for 5 h. Water (2 mL) was added and the mixture was stirred at 0 °C for 40 min and then poured on to ice–water (500 mL). The mixture was extracted with dichloromethane (3 × 200 mL), and the combined extracts were washed with water (2 × 250 mL), dried over anhydrous sodium sulfate, and evaporated. The resulting oil was purified by flash chromatography eluting with ethyl acetate–hexane (1:1, v/v) to give the product **29**, 12.32 g (86%), as a colorless glass. A sample was crystallized from ethyl acetate–hexane to give white crystals: mp 185–187 °C; MS m/e (EI) 566 $(M)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.05 (3 H, s, SO_2CH_3), 3.52 (2 H, d, J = 5 Hz, 5'-CH_2), 4.20 (1 H, q, J = 5 Hz, 4'-CH), 5.27 (1 H, dm, J = 35 Hz, 2'-CH), 5.38 (1 H, d, J = 4 Hz, 3'-CH), 5.59 (1 H, d, J = 8 Hz, 5-CH), 6.24 (1 H, dd, J = 17 Hz, 3 Hz, 1'-CH), 7.24–7.46 (15 H, m, ArH), 7.50 (1 H, dd, J = 8 Hz, 1 Hz, 6-CH), 9.20 (1 H, br s, NH). Anal. ($C_{29}H_{27}FN_2O_7S$) C, H, N.

2',3'-Dideoxy-2',3'-didehydro-3'-fluoro-5'-*O*-trityluridine (31) and 1-(2-Deoxy-2-fluoro-5-*O*-trityl-β-D-lyxofuranosyl)uracil (36). A solution of sodium hydroxide (220 mg, 5.5 mmol) in water (20 mL) was added to a solution of **29** (2.83 g, 5.0 mmol) in ethanol (60 mL). The mixture was refluxed for 75 min, cooled, and adjusted to pH 7 with 2 M hydrochloric acid. Ethanol was removed by evaporation and the mixture was diluted with water (20 mL) and filtered. The solid was washed with water (20 mL) and dried to give the anhydronucleoside **30** as a white solid: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.44 (2 H, d, J = 6 Hz, 5'-CH_2), 4.38 (1 H, m, 4'-CH), 5.10 (1 H, t, J = 2 Hz, 3'-CH), 5.40 (1 H, m, 1'-CH), 5.42 (1 H, dt, J = 50 Hz, 4 Hz, 2'-CH), 6.05 (1 H, d, J = 8 Hz, 5-CH), 7.06 (1 H, d, J = 8 Hz, 6-CH), 7.20–7.45 (15 H, m, ArH). This was dissolved in ethanol (55 mL) and a solution of sodium hydroxide (550 mg, 13.8 mmol) in water (50 mL) added. The mixture was refluxed for 75 min and then cooled and adjusted to pH 7 with 2 M hydrochloric acid. Ethanol was removed by evaporation, and the mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 50 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated. The residue was suspended in ethyl acetate (15 mL), cooled to 0 °C, and filtered to give **31** as a white solid, 0.98 g. The filtrate was evaporated and the residue was purified by flash chromatography eluting with ethyl acetate–hexane (2:1, v/v) to give a further 0.30 g of **31**: total yield 1.28 g (54% over two steps); mp 230–231 °C; MS m/e (+FAB) 471 $(M + H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.45 (2 H, d, J = 3 Hz, 5'-CH_2), 4.90 (1 H, br s, 4'-CH), 5.06 (1 H, dd, J = 9 Hz, 3 Hz, 5-CH), 5.62 (1 H, s, 3'-CH), 6.89 (1 H, m, 1'-CH), 7.25–7.40 (15 H, m, ArH), 7.93 (1 H, d, J = 9 Hz, 6-CH), 8.35 (1 H, br s, NH). Anal. ($C_{28}H_{23}FN_2O_4$) C, H, N.

Further elution of the column with the same solvent gave the lyxo nucleoside **36** as a white solid: 0.873 g (36% over two steps); mp 205–209 °C; MS m/e (+FAB) 489 $(M + H)^+$; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.25 (1 H, br s, OH), 3.51 (1 H, dd, J = 10 Hz, 5 Hz, 5'-CH), 3.65 (1 H, dd, J = 10 Hz, 5 Hz, 5'-CH), 4.20 (1 H, m, 3'-CH or 4'-CH), 4.50 (1 H, m, 3'-CH or 4'-CH), 5.14 (1 H, dt, J = 50 Hz, 5 Hz, 2'-CH), 5.62 (1 H, d, J = 9 Hz, 5-CH), 6.25 (1 H, dd,

J = 12 Hz, 5 Hz, 1'-CH), 7.20–7.50 (15 H, m, ArH), 7.68 (1 H, d, 6-CH), 9.57 (1 H, br s, NH). Anal. ($C_{28}H_{25}FN_2O_5$) C, H, N.

2',3'-Dideoxy-2',3'-didehydro-3'-fluorouridine (32). A solution of **31** (1.20 g, 2.6 mmol) in chloroform (50 mL) was stirred at 0 °C, and 0.3 M hydrogen chloride in chloroform (8 mL) was added. The solution was stirred at 0 °C for 30 min and then evaporated to dryness. The crude product was purified by flash chromatography eluting with ethyl acetate to give the product **32** as a colorless gum, 373 mg (64%). A sample was crystallized from ethyl acetate–hexane to give a white solid: mp 162–163 °C; MS m/e (+FAB) 229 $(M + H)^+$; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.55–3.63 (2 H, m, 5'-CH_2), 4.80 (1 H, m, 4'-CH), 5.13 (1 H, t, J = 5 Hz, 5'-OH), 5.70 (1 H, d, J = 9 Hz, 5-CH), 5.98 (1 H, m, 3'-CH), 6.78 (1 H, m, 1'-CH), 8.00 (1 H, d, J = 9 Hz, 6-CH), 11.50 (1 H, br s, NH). Anal. ($C_9H_9FN_2O_4$) C, H, N.

5'-*O*-Acetyl-2',3'-dideoxy-2',3'-didehydro-3'-fluorouridine (33). A solution of **32** (373 mg, 1.6 mmol) in a mixture of pyridine (6.0 mL) and acetic anhydride (0.35 mL, 380 mg, 3.3 mmol) was stored at 0 °C for 18 h. The mixture was diluted with water (50 mL) and extracted with dichloromethane (3 × 30 mL). The combined extracts were washed with saturated sodium hydrogen carbonate solution (30 mL), dried over anhydrous sodium sulfate, and evaporated to give the product **33** as light brown crystals, 409 mg (93%). A sample was recrystallized from ethyl acetate–hexane to give a white crystalline solid: mp 172–173 °C; MS m/e (+FAB) 271 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (3 H, s, CH_3CO), 4.24 (1 H, d, J = 11 Hz, 5'-CH), 4.34 (1 H, dd, J = 11 Hz, 4 Hz, 5'-CH), 5.05 (1 H, m, 4'-CH), 5.70 (1 H, s, 3'-CH), 5.80 (1 H, dd, J = 8 Hz, 1 Hz, 5-CH), 6.90 (1 H, m, 1'-CH), 7.52 (1 H, d, J = 8 Hz, 6-CH), 8.62 (1 H, br s, NH). Anal. ($C_{11}H_{11}FN_2O_5$) C, H, N.

1-(5-*O*-Acetyl-2,3-dideoxy-2-fluoro-β-D-*glycero*-pent-2-enofuranosyl)-4-(1,2,4-triazol-1-yl)-2-pyrimidinone (34). Phosphoryl chloride (89 μL, 1 mmol) was added to a solution of triazole (311 mg, 4.5 mmol) in acetonitrile (2.6 mL). The mixture was cooled to 0 °C and triethylamine (0.6 mL, 4.3 mmol) was added over 1 min, followed by a solution of **33** (135 mg, 0.5 mmol) in acetonitrile (2 mL). The mixture was stirred for 1 h at room temperature, and then triethylamine (0.4 mL) and water (0.1 mL) were added. The mixture was stirred for 10 min and then evaporated to dryness. The residue was partitioned between dichloromethane (20 mL) and saturated sodium hydrogen carbonate solution (20 mL), and the organic solution was dried over anhydrous sodium sulfate and evaporated to give the product **34** 150 mg (93%). A sample was recrystallized from ethyl acetate–hexane to give white crystals: mp 161–163 °C; MS m/e 321 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.14 (3 H, s, CH_3CO), 4.25 (1 H, dt, J = 12 Hz, 2 Hz, 5'-CH), 4.46 (1 H, dd, J = 12 Hz, 3 Hz, 5'-CH), 5.16 (1 H, m, 4'-CH), 5.72 (1 H, s, 3'-CH), 7.10 (1 H, d, J = 6 Hz, 5-CH), 7.13 (1 H, m, 1'-CH), 8.15 (1 H, s, ArH), 8.25 (1 H, d, J = 6 Hz, 6-CH), 9.30 (1 H, s, ArH). Anal. ($C_{13}H_{12}FN_5O_4$) C, H, N.

2',3'-Dideoxy-2',3'-didehydro-2'-fluorocytidine (35). Concentrated aqueous ammonia solution (0.33 mL) was added to a solution of **34** (150 mg, 0.47 mmol) in dioxane (2 mL), and the mixture was kept at room temperature in a sealed vessel for 18 h. The solution was evaporated to dryness and the residue was taken up in saturated methanolic ammonia (4 mL) and the solution kept at room temperature for 7 h. The solvent was evaporated and the crude product was purified by flash chromatography eluting with dichloromethane–methanol (9:1, v/v) to give the product as a colorless gum, 33 mg. This was crystallized from ethyl acetate to give **35** as a white crystalline solid: 20 mg (19%); mp 157–159 °C; MS m/e (+FAB) 228 $(M + H)^+$; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.55 (2 H, m, 5'-CH_2), 4.76 (1 H, m, 4'-CH), 5.03 (1 H, t, J = 5 Hz, 5'-OH), 5.78 (1 H, d, J = 6 Hz, 5-CH), 5.92 (1 H, m, 3'-CH), 6.85 (1 H, m, 1'-CH), 7.30 (2 H, br d, NH_2), 7.85 (1 H, d, J = 6 Hz, 6-CH). Anal. ($C_9H_{10}FN_3O_3$) C, H, N.

In a subsequent run the acetate **33** was converted to **35** without purification of the intermediate **34** to give **35** in overall yield of 47% over three steps (two pots).

1-(2,3-Dideoxy-2,3-difluoro-5-*O*-trityl-β-D-arabinofuranosyl)uracil (37). A solution of **36** (761 mg, 1.56 mmol) in dichloromethane (35 mL) was stirred at −78 °C and (diethylamido)sulfur trifluoride (2.0 mL, 15 mmol) was added during 1 min. The mixture was allowed to warm up to room temperature, stirred for a further 1.5 h, and then poured on to ice–water (500 mL). The organic solution was dried over anhydrous sodium sulfate and evaporated. The crude product was chromatographed on a flash column eluting with ethyl acetate–hexane (5:2, v/v) to give the product **37** 450 mg (59%) as a colorless gum. A sample was crystallized from ethyl acetate–hexane to give white crystals: mp 93–106 °C dec; MS m/e (+FAB) 491 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.46 (2 H, d, J = 5 Hz, 5'-CH_2), 4.10 (1 H, dm, $J_{HF3'}$ = 27 Hz, 4'-CH), 5.10–5.35 (2 H, m, J_{HF} = 50 Hz in each case, 2'-CH and 3'-CH), 5.62 (1 H, dd, J = 9 Hz, 3 Hz, 5-CH), 6.26 (1 H, dm, $J_{HF2'}$ = 20 Hz, 1'-CH), 7.25–7.48 (16 H, m, ArH and 6-CH), 8.84 (1 H, br s, NH). Anal. ($C_{28}H_{24}F_2N_2O_4$) C, H, N.

1-(2,3-Dideoxy-2,3-difluoro-β-D-arabinofuranosyl)uracil (38). A solution of **37** (130 mg, 0.27 mmol) in chloroform (5 mL) was stirred at 0 °C and 0.3 M hydrogen chloride in chloroform (0.7 mL) was added. The solution was stirred at 0 °C for 45 min and then evaporated to dryness. The crude product was purified by flash chromatography eluting with ethyl acetate to give the product **38** 57 mg (87%) as a white crystalline solid: mp 169–170 °C; MS m/e (+FAB) 249 $(M + H)^+$; ^1H NMR (CD_3OD, 300 MHz) δ 3.75–3.86 (2 H, m, 5'-CH_2), 4.22 (1 H, dm, $J_{HF3'}$ = 24 Hz, 4'-CH), 5.26 (1 H, dm, $J_{HF2'}$ = 16 Hz, $J_{HF3'}$ = 51 Hz, 3'-CH), 5.36 (1 H, dm $J_{HF2'}$ = 50 Hz, $J_{HF3'}$ = 13 Hz, 2'-CH), 5.70 (1 H, d, J = 8 Hz, 5-CH), 6.22 (1 H, dm, $J_{HF2'}$ = 19 Hz, 1'-CH), 7.78 (1 H, dd, J = 8 Hz, 2 Hz, 6-CH). Anal. ($C_9H_{10}F_2N_2O_4$) C, H, N.

1-(5-*O*-Acetyl-2,3-dideoxy-2,3-difluoro-β-D-arabinofuranosyl)uracil (39). A solution of **38** (378 mg, 1.5 mmol) in a mixture of pyridine (5.6 mL) and acetic anhydride (0.33 mL) was stored at 4 °C for 48 h. The mixture was poured into ice–water (50 mL) and extracted with dichloromethane (3 × 30 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated to yield a sticky crystalline solid. This was recrystallized from ethyl acetate–hexane to give **39**, 350 mg (79%), as white needles: mp 155–156 °C; MS m/e (+FAB) 291 $(M + H)^+$; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.12 (3 H, s, CH_3CO), 4.28–4.53 (3 H, m, 4'-CH and 5'-CH_2), 5.17 (1 H, dd, J = 50 Hz, 12 Hz, 2'-CH or 3'-CH), 5.26 (1 H, ddd, J = 50 Hz, 10 Hz, and 4 Hz, 2'-CH or 3'-CH), 5.80 (1 H, dd, J = 8 Hz, 3 Hz, 5-CH), 6.26 (1 H, dm, $J_{HF2'}$ = 20 Hz, 1'-CH), 7.50 (1 H, dd, J = 8 Hz, 2 Hz, 6-CH), 9.08 (1 H, br s, NH). Anal. Found: C, 45.5; H, 4.0; N, 9.1. $C_{11}H_{12}F_2N_2O_5$ requires: C, 45.5; H, 4.2; N, 9.65.

1-(2,3-Dideoxy-2,3-difluoro-β-D-arabinofuranosyl)cytosine (41). Phosphoryl chloride (184 μL, 2.1 mmol) was added to a cold solution of triazole (643 mg, 9.3 mmol) in acetonitrile (7 mL). The mixture was stirred at 0 °C and triethylamine (1.24 mL, 8.9 mmol) was added over 1 min, followed by a solution of **39** (300 mg, 1.0 mmol) in acetonitrile (4.5 mL). The mixture was stirred for 2 h at room temperature, and then triethylamine (0.83 mL) and water (0.21 mL) were added. The mixture was stirred for 10 min and then evaporated to dryness. The residue was partitioned between dichloromethane (40 mL) and saturated sodium hydrogen carbonate solution (40 mL), and the organic solution was dried over anhydrous sodium sulfate and evaporated to give a white solid, 595 mg. This was dissolved in dioxane (6.5 mL) and concentrated aqueous ammonia solution (1.1 mL) was added. The mixture was kept at room temperature for 7 h and then evaporated to dryness. The residue was dissolved in saturated methanolic ammonia (14 mL) and the solution kept at room temperature for 18 h and then evaporated to dryness. The crude product was purified by flash chromatography eluting with dichloromethane–methanol (9:1, v/v), and the product was crystallized from methanol–ethyl acetate to give 41, 80 mg (31% over three steps), as a white crystalline solid: mp 187–191 °C; MS m/e (+FAB) 248 $(M + H)^+$; ^1H NMR (DMSO-d_6, 300 MHz) δ 3.65 (2 H, d, J = 5 Hz, 5'-CH_2), 4.15 (1 H, dm, $J_{HF3'}$ = 25 Hz, 4'-CH), 5.29 (1 H, dd, J = 50 Hz, 15 Hz, 3'-CH), 5.41 (1 H, ddm, J = 50 Hz, 12 Hz, 2'-CH), 5.78 (1 H, d, J = 8 Hz, 5-CH), 6.17 (1 H, dm, $J_{HF2'}$ = 19 Hz, 1'-CH), 7.30 (2 H, br d, NH_2), 7.62 (1 H, d, J = 8 Hz, 6-CH). Anal. ($C_9H_{11}F_2N_3O_3 \cdot 0.3H_2O$) C, H, N.

1-(2-Deoxy-2-fluoro-3-*O*-(methylsulfonyl)-5-*O*-trityl-β-D-arabinofuranosyl)thymine (43). A solution of **42**[24] (0.55 g, 2.1 mmol) and trityl chloride (612 mg, 2.2 mmol) were dissolved in dry pyridine (20 mL) and heated under reflux under an atmosphere of argon for 4 h. The mixture was cooled in an ice bath, methanesulfonyl chloride (170 μL, 252 mg, 2.2 mmol) was added,

and the mixture was stirred at room temperature for 18 h.

Water (0.5 mL) was added and the mixture stirred for an additional 30 min to hydrolyze the excess sulfonyl chloride. The pyridine and water were then removed by evaporation under reduced pressure, final traces being removed by azeotroping with toluene (2 × 5 mL). The residue was partitioned between dichloromethane (20 mL) and water (20 mL), the layers were separated, and the organic phase was washed with saturated aqueous copper(II) sulfate solution, dried over magnesium sulfate, and evaporated. Purification of the resulting material by flash chromatography eluting with ethyl acetate–hexane (1:1, v/v) gave **43**: 812 mg (69%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.75 (3 H, d, J = 2 Hz, 5-CH_3), 3.52 (2 H, m, 5′-CH_2), 4.20 (1 H, m, 4-CH), 5.30 (1 H, m, 2′-CH), 5.44 (1 H, m, 3′-CH), 6.30 (1 H, m, 1′-CH), 7.24–7.50 (16 H, m, ArH and 6-CH), 9.96 (1 H, s, NH).

3′-Deoxy-2′,3′-didehydro-2′-fluoro-5′-*O*-tritylthymidine (44). A solution of sodium hydroxide (150 mg, 3.8 mmol) in water (1.5 mL) was added to a solution of **43** (712 mg, 1.27 mmol) in ethanol (50 mL), and the mixture was heated under reflux for 2.5 h. After the mixture cooled to room temperature, the solvent was removed under reduced pressure and the residue taken up in water (30 mL). The product was extracted with dichloromethane (3 × 30 mL), and the extracts were combined, dried over magnesium sulfate, and evaporated. Purification by flash chromatography eluting with hexane–ethyl acetate (2:1, v/v) gave **44**: 312 mg (55%); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 1.32 (3 H, s, 5-CH_3), 3.40 (2 H, m, 5′-CH_2), 4.95 (1 H, br s, 4′-CH), 5.72 (1 H, s, 3′-CH), 6.98 (1 H, br s, 1′-CH), 7.28–7.50 (16 H, m, ArH and 6-CH), 9.15 (1 H, s, NH).

3′-Deoxy-2′,3′-didehydro-2′-fluorothymidine (45). A solution of hydrogen chloride in chloroform (0.31 M, 2.4 mL, 0.75 mmol) was added to an ice-cooled solution of **44** (312 mg, 0.7 mmol) in chloroform (20 mL). After 30 min the solvent was evaporated under reduced pressure and the residue purified by flash chromatography eluting with ethyl acetate to give the product **45**, 130 mg (78%). A sample was recrystallized from ethyl acetate to give white crystals; mp 152–154 °C; MS m/e (+FAB) 243 $(M + H)^+$; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (3 H, s, 5-CH_3), 3.75–3.82 (1 H, m, 5′-CH_2), 3.91–3.99 (1 H, m, 5′-CH_2), 4.93 (1 H, m, 4′-CH), 5.72 (1 H, s, 3′-CH), 6.88 (1 H, m, 1′-CH), 7.58 (1 H, s, 6-CH), 8.30 (1 H, br s, NH). Anal. ($C_{10}H_{11}FN_2O_4$) C, H, N.

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Synthesis and Anti-HIV-1 Activity of 2′-"Up"-Fluoro Analogues of Active Anti-AIDS Nucleosides 3′-Azido-3′-deoxythymidine (AZT) and 2′,3′-Dideoxycytidine (DDC)[1,†]

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1-(3-Azido-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)thymine (**6**, F-AZT) and 1-(2,3-dideoxy-2-fluoro-β-D-*threo*-pentofuranosyl)cytosine (**12**, F-DDC) were synthesized from the potent antiherpes virus nucleosides 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)thymine (**1**, FMAU) and 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (FIAC) in the hope that introduction of a 2′-"up"-fluoro substituent might potentiate the anti-HIV activity of AZT and DDC. FMAU (**1**) was converted in three steps into 2,3′-anhydro-1-(2-fluoro-2-deoxy-5-*O*-trityl-β-D-lyxofuranosyl)thymine (**4**), which when treated with NaN_3 followed by detritylation afforded **6**. F-DDC was prepared by two methods. Tritylation of FIAC followed by treatment of the product with thiocarbonyldiimidazole afforded the 5′-*O*-trityl-3′-*O*-(imidazolyl)thiocarbonyl nucleoside **9**. Upon radical reduction of **9** with Bu_3SnH and AIBN, 5′-*O*-trityl-DDC **10** was obtained. Compound **10** was detritylated to give **12**, which (when obtained by this procedure) resisted crystallization, but the diacetate **12′** was obtained in crystalline form. Alternatively, FAC (**14**) was converted into N^4,O^5-dibenzoyl derivative **15**, which was treated with thiocarbonyldiimidazole. Reduction of **16** with Bu_3SnH/AIBN followed by debenzoylation afforded **12**, which was obtained in crystalline form. F-AZT did not exhibit any significant activity against the human immunodeficiency virus (HIV) in vitro. F-DDC, however, showed activity against HIV-1, but the therapeutic index is much inferior to that of AZT.

Our previous studies with uracil and cytosine nucleosides bearing 2′-fluoro substituents in the "up" (arabino) configuration provided a host of potent agents against many DNA viruses.[2-5] Most notable among these are 2′-fluoro-5-iodo-ara-C (FIAC, Figure 1) and 2′-fluoro-5-methyl-ara-U (FMAU), both of which are effective in vitro and in vivo against Herpes simplex viruses types 1 and 2 (HSV-1 and HSV-2), and Varicella zoster virus (VZV). Both compounds inhibited human cytomegalovirus (HCMV)[5-7] in vitro, as well as Epstein-Barr virus (EBV).[8]

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