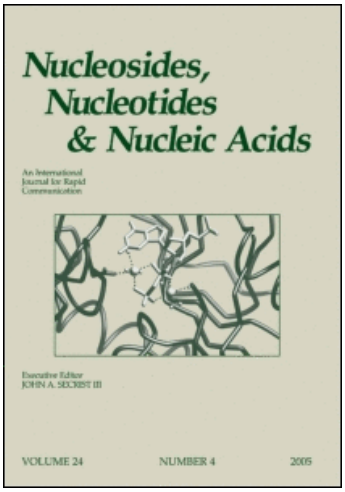

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4'-*C*-HYDROXYMETHYL-2'-FLUORO- D-ARABINOFURANOSYLPURINE NUCLEOSIDES

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF 4′-*C*-HYDROXYMETHYL-2′-FLUORO-D-ARABINOFURANOSYLPURINE NUCLEOSIDES

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ABSTRACT

A series of 4′-*C*-hydroxymethyl-2′-fluoro-D-arabinofuranosylpurine nucleosides was prepared and evaluated for cytotoxicity. The details of a convenient synthesis of the carbohydrate precursor 4-*C*-hydroxymethyl-3,5-di-*O*-benzoyl-2-fluoro-α-D-arabinofuranosyl bromide **(13)** are presented. Proof of the structure and configuration at all chiral centers of the sugars and the nucleosides were obtained by proton NMR. All five target nucleosides were evaluated for cytotoxicity in human tumor cell lines. The 4′-*C*-hydroxymethyl clofarabine analogue (**16**β) showed slight cytotoxicity in CCRF-CEM leukemia cells.

INTRODUCTION

In recent years, pursuit of the synthesis of new nucleosides has continued because of their demonstrated utility as anticancer and as antiviral agents. The incorporation of various groups at *C*-4′ of a normal nucleoside structure has received renewed interest recently[1–8]. It has been shown by several investigators that such a modification in most cases can be tolerated with retention or even enhancement of the biological activity[4,5,8]. The

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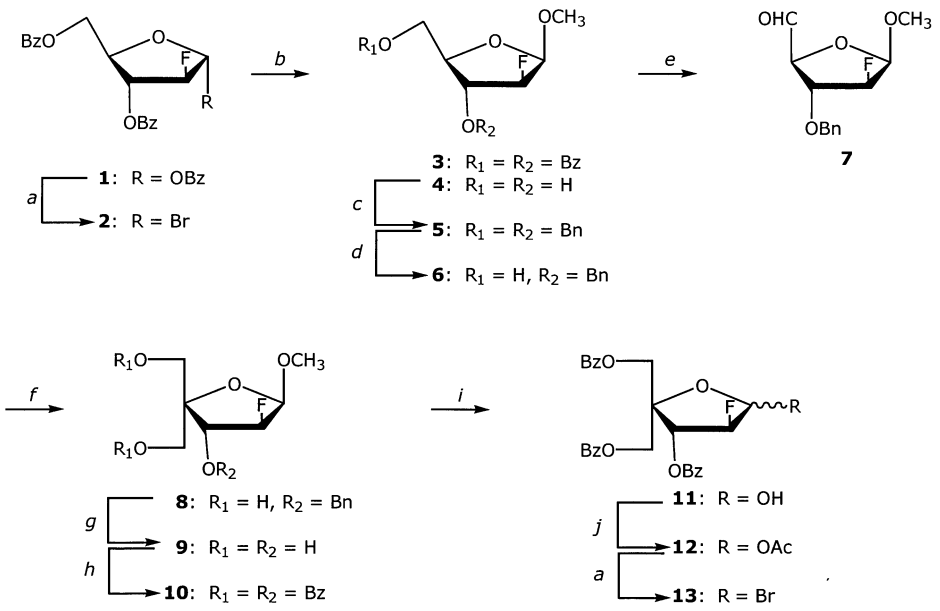
observed biological activity suggests that metabolism to the triphosphate is likely occurring. Our laboratory has continued its investigations of new nucleosides as potential anticancer agents in recent years. Fludarabine phosphate, which was developed in our laboratory[9], has been approved by FDA for the treatment of refractory lymphocytic leukemia. Clofarabine (2-chloro-2′-fluoro-ara-A), also developed in our laboratory[10], is currently in clinical trials. Expanding upon its structure, with a 2′-fluorine in the *arabino* configuration, we have initiated a program to examine certain other carbohydrate modifications in the system, especially at the 4′-position.

Initially, we focused our attention on the synthesis of the 4′-*C*-hydroxymethyl analogue of clofarabine and related compounds, hoping to discover good biological activity as well as to learn more about structure activity relationships for compounds with this modification. Very few 4′-*C*-hydroxymethyl nucleosides have been reported in the literature, and most of the work has been limited to the synthesis of ribonucleosides and 2′-deoxynucleosides[11–13]. 4′-*C*-hydroxymethylthymidine has been synthesized[12], and derivatives of it have been described[14–16]. No 4′-*C*-hydroxymethyl-arabino or 2′-fluoroarabinonucleosides, however, have been reported in the literature. Toward that goal, we have developed a route to a 4-*C*-hydroxymethyl-2-fluoroarabinofuranose derivative and utilized it in the synthesis of certain purine nucleosides containing that carbohydrate moiety. All these nucleosides have been characterized, and their anomeric configurations were determined by proton NMR. Final deblocked nucleosides and their α-anomers have been evaluated for cytotoxicity against human tumor cell lines. We herein report the details of a convenient synthesis of this 4-*C*-hydroxymethyl-2-fluoroarabinofuranose intermediate, its conversion to a series of purine nucleoside analogues, and the results from their *in vitro* testing[17].

CHEMISTRY

Carbohydrate Synthesis. Our route (Scheme 1) to this series appeared to be best accomplished by preparing the blocked 4-*C*-hydroxymethyl derivative **13**, which can be synthesized from α-bromo sugar **2**[18] (easily obtained from commercially available 1). Compound **2** was converted to **3** by the careful addition of $NaOCH_3$ in MeOH at 0 °C. When bromide displacement was complete, more $NaOCH_3$ was added with the reaction continuing at room temperature to provide deprotected **4**. Benzylation of **4** to **5** followed by the selective removal of the primary benzyl ether[19] gave alcohol **6**. The 5-hydroxyl of **6** failed to oxidize to the aldehyde **7** using 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) hydrochloride[5] or aqueous sodium periodate[11]. Oxidation of **6** with DMSO/acetic anhydride[20] afforded impure **7**, which, when condensed with formaldehyde in base[11],

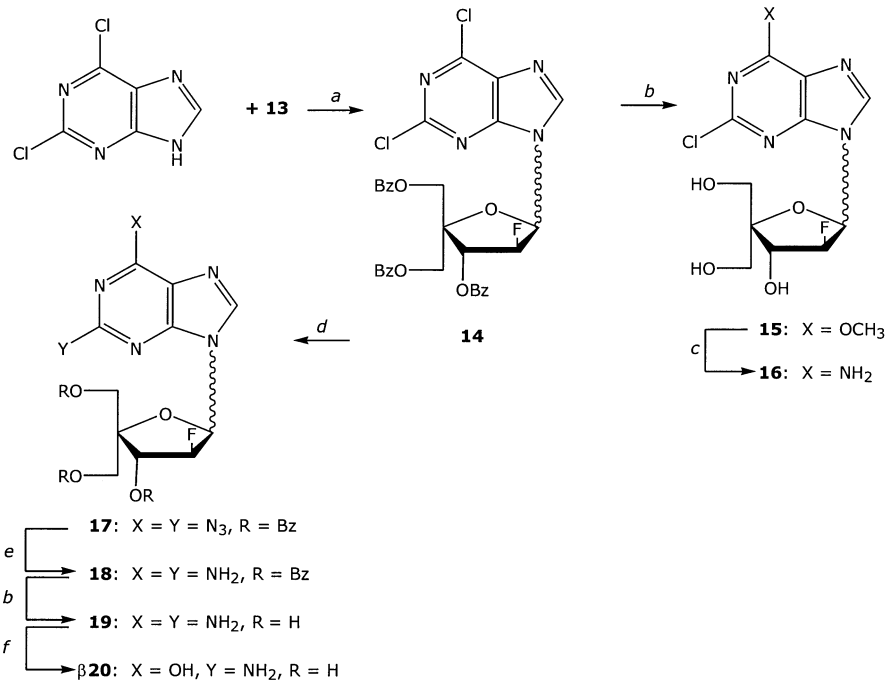


Scheme 1. Conditions: (a) HBr/HOAc; (b) $NaOCH_3$/MeOH, 0 °C then R.T; (c) BnCl/KOH, THF; (d) 10% Pd/C, H2, 50 psi, 1 : 1 MeOH/HOAc, pyridine; (e) PCC, 4A sieve, CH_2Cl_2; (f) 37%, HCHO, NaOH, THF/H_2O; (g) 10% Pd/C, H_2, 50 psi, 1 : 1 MeOH/HOAc; (h) BzCl/pyridine; (i) TFA/H_2O, 55 °C; (j) Ac_2O/pyridine.

produced <15% of diol **8**. The yield of **8** was increased to 61% by a molecular sieve catalyzed pyridinium chlorochromate oxidation[21] of **6** to **7** followed by reaction with formaldehyde as above. The remaining benzyl group was removed, and the product **9** was benzoylated to give **10**. Acidic hydrolysis of the methyl group of **10** provided **11** as an anomeric mixture ($2\alpha : 1\beta$), which was acetylated to afford **12** ($3\alpha : 1\beta$)[22]. Treatment of **12** with excess HBr in acetic acid gave the target 4-*C*-hydroxymethyl bromo sugar **13** ($6\alpha : 1\beta$) suitable for subsequent coupling reactions.

The anomeric configurations of compounds **11**, **12**, and **13** were assigned by comparison of the ^1H NMR spectra. The α anomers had $J_{1,2} = 0$ Hz, confirming that H-1 and H-2 were trans to each other. Similarly, the beta anomers had $J_{1,F} = 0$ Hz, which confirmed that H-1 and 2-F were in a trans relationship[23].

Nucleoside Synthesis. Our route (Scheme 2) to the purine nucleosides began with the coupling of 2,6-dichloropurine and **13** using the sodium salt glycosylation procedure[24]. An 82% total yield of 9-isomers **14** was obtained after column chromatography with only minor amounts of suspected 7-isomers observed in later fractions. Separation of **14**β and **14**α was achieved on small scale only, so enriched anomeric mixtures were used in ensuing steps.



Scheme 2. Conditions: (*a*) NaH, MeCN, R.T., 18 h; (*b*)$NaOCH_3$/MeOH; (*c*) EtOH, NH_3, 80 °C, 16 h; (*d*) NaN_3, EtOH, 1/2 h; (*e*) 5% Pd/C, H_2, 1 atm, 2 : 1 EtOH/DMAc 16 h; (*f*) adenosine deaminase.

Treatment of **14** with $NaOCH_3$/MeOH removed the benzoyl groups and replaced the 6-chloro with a methoxy group to give **15**. Preparative TLC resolved **15**β and **15**α, which were reacted separately with ethanolic ammonia at 80 °C to provide 2-Cl-6-NH_2 analogues **16**β and **16**α.

Conversion of **14** to 2,6-diazido derivative **17** was carried out by treatment with NaN_3 in refluxing EtOH. When the reaction mixture was cooled, **17**β crystallized and **17**α remained in solution. After isolation, the separate anomers were hydrogenated at atmospheric pressure with 5% Pd/C to give intermediates **18**β and **18**α. Deprotection with $NaOCH_3$/MeOH led to 2,6-diamino products **19**β and **19**α. Deamination of **19**β occurred slowly with calf intestinal adenosine deaminase in water to produce guanosine analogue **20**β. Under the same conditions, **19**α appeared not to be a substrate for the enzyme and was recovered unchanged.

The anomeric configurations of **14**–**20**β were determined by comparison of the ^{1}H NMR spectra of the individual anomers. All β anomers showed 5-bond coupling between H-8 and 2′-F, $^5J_{H\text{-}8,2'F}$ between 1.0 and 3.1 Hz[25]. In the α anomers, H-8 showed no coupling with the 2′-F. The anomeric configurations were further confirmed by NOE difference

spectroscopy. The β nucleoside **14**β gave NOE's between H-8 and H-3′ of 2–3%, and the α anomer **14**α gave NOE's between H-1′ and H-3′ of 1–2%.

The assignments of H-5′ and H-6′ for **14**–**20**β were determined by NOE's of 1–2% between H-3′ and H-5′ and/or by the long range 5-bond coupling of one of the H-5′ hydrogens with the 2′-F, $^5J_{H\text{-}5',2'F}$ between 0.6 and 1.6 Hz.

BIOLOGICAL RESULTS

The 4′-*C*-hydroxymethyl nucleosides (**16**α, **16**β, **19**α, **19**β, **20**β) were examined *in vitro* against a spectrum of human tumor systems: **SNB-7 (CNS), DLD-1 (colon), NCI-H23 (lung), ZR-75-1 (mammary), LOX IMVI (melanoma), PC-3 (prostate), CAK-1 (renal)**, and **CCRF-CEM (leukemia)**. All the compounds were found to be noncytotoxic at the highest level tested (60 μg/mL) except **16**β. This clofarabine analogue (**16**β) exhibited an IC_{50} value at 5 μg/mL (~13 μM) in CCRF-CEM cells. In this cell line, clofarabine has an IC_{50} of 0.05 μm[10]. No further toxicity for **16**β was observed in any of the other cell lines.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Nicolet NT-300 NB spectrometer operating at 300.635 MHz (^{1}H). Chemical shifts are expressed in parts per million downfield from tetramethylsilane. UV absorption spectra were determined with a Perkin-Elmer Lambda 9 spectrometer by dissolving each compound in methanol or water and diluting 10-fold with 0.1 N HCl, pH 7 buffer, or 0.1 N NaOH. Numbers in parentheses are extinction coefficients ($\times 10^{-3}$), sh = shoulder. Microanalyses were performed by the Spectroscopic and Analytical Laboratory of Southern Research Institute. Where solvents were noted as part of the elemental analyses, they were seen in the ^{1}H NMR spectra in the proper amounts. Mass spectra were recorded on a Varian/MAT 311A double-focusing mass spectrometer in the fast atom bombardment (FAB) mode. HPLC analyses were carried out at a flow rate of 1 ml/min on a Hewlett-Packard 1100 series liquid chromatograph with a Phenomenex Sphereclone 5 μ ODS(1) column (4.6 × 250 mm) and UV monitoring (254 nm). Flash chromatographic separations were performed using 230–400 mesh silica gel from E. Merck. TLC was done on Analtech precoated (250 μm) silica gel (GF) plates. Compounds isolated as syrups were single spots on TLC or two spots for anomeric mixtures. No other impurities were seen in the NMR spectra of these compounds.

Methyl 3,5-Di-*O*-benzyl-2-fluoro-β-D-arabinofuranoside (5). To a solution of bromo sugar **2**[18] (5 g, 11.8 mmol) in dry MeOH (50 mL) at 0 °C was added a

0.5 M solution of $NaOCH_3$ in MeOH (23.64 mL) dropwise in a period of 30 min. Additional 0.5 M $NaOCH_3$ in MeOH (50 mL) was added, and the solution was stirred at room temperature for 2 h. The solution was rendered neutral with Dowex 50W- X8 (H^+) ion exchange resin, and the resin was filtered off with MeOH washing. The filtrates were combined and evaporated to dryness to afford crude **4**, which was a single spot on TLC (R_f 0.50, 9 : 1 $CHCl_3$/MeOH). This material was dissolved in dry THF (100 mL), and powdered KOH (2.64 g, 47 mmol) and benzyl chloride (3.45 mL; 30 mmol) were added to it. The suspension was refluxed overnight, then filtered. Collected solids were washed with THF, and the filtrate and washings were combined and evaporated to dryness. This residue was purified on a silica gel column using 91 : 9 cyclohexane/EtOAc as eluent to obtain pure 5 (3.2 g, 79%) as an oily wax: TLC 3 : 1 cyclohexane/EtOAc, R_f 0.55; MS m/z 347 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ7.25–7.35 (m, 10H, aromatic H′s), 4.96–5.15 (m, 1H, H-2), 4.95–4.97 (m, 1H, H-1), 4.56–4.72 (m, 4H, $PhCH_2$), 4.12–4.26 (m, 2H, H-3, H-4), 3.54–3.58 (m, 2H, H-5), 3.40 (s, 3H, CH_3).

Methyl 3-*O*-Benzyl-2-deoxy-2-fluoro-*β*-D-arabinofuranoside (6). To a solution of **5** (3.41 g, 9.86 mmol) in 1 : 1 MeOH/HOAc (33 mL) was added pyridine (34 μL) and 10% palladium on charcoal (463 mg). The mixture was hydrogenated at 50 psi for 22 h. The catalyst was removed by filtration and washed with several portions of MeOH. The combined filtrate and washes were evaporated to a residue, which was dissolved in EtOAc (65 mL), washed with saturated $NaHCO_3$ (20 mL) and water (2 × 20 mL), dried ($MgSO_4$), and evaporated to give **6** (1.76 g, 70%) as a syrup: TLC 1 : 1 hexane/EtOAc, R_f 0.60; MS m/z 257 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 7.26–7.36 (m, 5H, aromatic H's), 4.97–5.15 (m, 1H, H-2), 4.93–4.95 (m, 1H, H-1), 4.56–4.77 (m, 2H, $PhCH_2$), 4.37–4.47 (m, 1H, H-3), 4.11–4.15 (m, 1H, H-4), 3.61–3.80 (m, 2H, H-5), 3.50 (s, 3H, CH_3), 2.19. (dd, 1H, OH-5, J = 4.5 Hz and J = 7.8 Hz).

Methyl 3-*O*-Benzyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-D-arabinofuranoside (8). To a solution of 6 (3.08 g, 12.0 mmol) in anhydrous CH_2Cl_2 (72 mL) under argon was added 4Å molecular sieve powder (10.9 g). After being stirred at room temperature for 20 min, the mixture was treated in one portion with solid pyridinium chlorochromate (5.28 g, 24.0 mmol) at which time the reaction became very dark and thickened. After 3 h, the vigorously stirred mixture was filtered through a dry silica gel pad (59 g, 230–400 mesh), which was then washed with multiple portions of 3 : 1 EtOAc/hexane (500 mL total volume). The filtrate plus washes were evaporated to give crude **7** (2.75 g, 90% as a yellow oil): MS m/z 261 $(M+Li)^+$. This unstable aldehyde was dissolved in THF (30 mL), diluted with water (30 mL), and chilled to 0–5 °C. To this cloudy solution was added dropwise aqueous 37% formaldehyde (4.5 mL) followed by 2N NaOH (12 mL). The cooling bath was removed, and the reaction was stirred at room temperature 16 h, neutralized

to pH 6 with glacial acetic acid, and evaporated. The resulting residue was partitioned between CH_2Cl_2 and water. The aqueous layer was extracted twice with more CH_2Cl_2, and the combined organic layers were washed once with water, dried ($MgSO_4$), and evaporated to provide impure **8** (3.4 g). This material was purified by flash chromatography on silica gel (58 g) with 1 : 1 hexane/EtOAc as solvent to afford pure **8** (2.11 g, 61% from **6**) as a colorless syrup: TLC 1 : 1 hexane/EtOAc, R_f 0.25; MS *m/z* 293 $(M+Li)^+$; ^1H NMR ($CDCl_3$) δ7.30–7.40 (m, 5H, aromatic H's), 5.16 (ddd, 1H, H-2, $J_{1,2} = 4.7$ Hz, $J_{2,3} = 7.4$ Hz, $J_{2,F} = 53.4$ Hz), 4.97 (dd, 1H, H-1, $J_{1,F} = 1.3$ Hz, $J_{1,2} = 4.7$ Hz), 4.83 (dd, 1H, $PhCH_2$, $^5J_{H,F} = 1.3$ Hz, $J = 11.6$ Hz), 4.63 (d, 1H, $PhCH_2$, $J = 11.6$ Hz), 4.53 (dd, 1H, H-3, $J_{2,3} = 7.4$ Hz, $J_{3,F} = 18.0$ Hz), 3.70 (dd, 1H, H-6_b, $J_{6a,6b} = 12.2$ Hz, $J_{6b,OH} = 7.0$ Hz), 3.65 (dd, 1H-6_a, $J_{6a,6b} = 12.2$ Hz, $J_{6a,OH} = 7.4$ Hz), 3.57 (d, 2H, H-5, $J = 5.7$ Hz), 3.51 (s, 3H, CH_3), 2.38 (dd, 1H, OH-6, $J_{6a,OH} = 7.4$ Hz, $J_{6b,OH} = 7.0$ Hz), 2.28 (t, 1H, OH-5, $J_{5,OH} = 5.7$ Hz).

Methyl 2-Deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-D-arabinofuranoside (9). A solution of **8** (1.82 g, 6.36 mmol) in 1 : 1 MeOH/acetic acid (70 mL) containing 10% palladium on charcoal (352 mg) was hydrogenated at 50 psi for 22 h. More catalyst (160 mg) was added, and hydrogenation was resumed for 24 h. The catalyst was collected and washed with several portions of MeOH. The combined filtrates were evaporated, and the resulting oil was coevaporated with toluene to remove acetic acid. The residue was purified by flash chromatography on silica gel (30 g) with a gradient from 1 : 1 hexane/EtOAc to 100% EtOAc to yield essentially pure 9 (962 mg, 77%) as a syrup: TLC 3 : 1 EtOAc/hexane, R_f 0.20; MS *m/z* 197 $(M+H)^+$. This material was used directly below.

Methyl 3,5,6-Tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-D-arabinofuranoside (10). To an ice-cold solution of **9** (962 mg, 4.91 mmol) in anhydrous pyridine (25 mL) was added dropwise benzoyl chloride (2.9 mL, 24.5 mmol). The solution was allowed to warm to room temperature where it was kept for 24 h and then poured into a stirred ice/water mixture (300 mL). $CHCl_3$ (100 mL) was added, and after 15 min, the layers were separated. The aqueous layer was extracted with more $CHCl_3$ (3 × 100 mL). The combined organic layers were washed with water (100 mL), dried ($MgSO_4$), and evaporated to an oil, which was coevaporated twice with toluene. The residue was purified by flash chromatography on silica gel (75 g) with gradient elution from 5 : 1 to 3 : 1 hexane/EtOAc to provide **10** (2.37 g, 95%) as a colorless glass: TLC 3 : 1 hexane/EtOAc, R_f 0.50; MS *m/z* 509 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 7.90–8.05 (m, 6H, *o*-H of Ph), 7.34–7.54 (m, 9H, *m*- and *p*-H of Ph), 6.11 (dd, 1H, H-3, $J_{2,3} = 7.8$ Hz, $J_{3,F} = 17.5$ Hz), 5.39 (ddd, 1H, H-2, $J_{1,2} = 4.5$ Hz, $J_{2,3} = 7.7$ Hz, $J_{2,F} = 53.1$ Hz), 5.12 (dd, 1H, H-1, $J_{1,F} = 1.2$ Hz, $J_{1,2} = 4.5$ Hz), 4.75 (s, 2H, H-6), 4.59 (dd, 1H, H-5_a,

$J_{5a,5b} = 12.0$ Hz, $^5J_{H,F} = 0.6$ Hz), 4.51 (d, 1H, H-5$_b$, $J_{5a,5b} = 12.0$ Hz), 3.51 (s, 3H, CH_3).

3,5,6-Tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-D-arabinofuranoside (11). A solution of **10** (2.34 g, 4.61 mmol) in 9 : 1 trifluoroacetic acid/water (23 mL) was maintained at 55 °C for 44 h then cooled to room temperature and diluted with CH_2Cl_2 (25 mL). This solution was added slowly to a stirred mixture of ice and saturated $NaHCO_3$ (250 mL). More CH_2Cl_2, ice, and solid $NaHCO_3$ were added during the addition to control foaming and to keep the pH at ~7. The layers were separated, and the aqueous layer was extracted with more CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with water (2 × 150 mL), dried ($MgSO_4$), and evaporated to a white foam (2.19 g). This material was flash chromatographed on silica gel (50 g) with gradient elution from 3 : 1 to 2 : 1 hexane/EtOAc to give pure **11** (1.8 g, 79%, $\alpha:\beta$, 2 : 1) as a colorless glass: TLC 3 : 1 hexane/EtOAc, R_f 0.33; MS *m/z* 495 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.89–8.10 (m, 6H, *o*-H of Ph), 7.52–7.60 (m, 3H, *p*-H of Ph), 7.32–7.45 (m, 6H, *m*-H of Ph), 6.05 (dd, 1H, H-3β, $J_{2,3} = 6.0$ Hz, $J_{3,F} = 17.3$ Hz), 5.97 (d, 1H, H-3α, $J_{3,F} = 20.8$ Hz, $J_{2,3} = 0$ Hz), 5.71 (br d, 1H, H-1α, $J_{1,F} = 9.6$ Hz, $J_{1,2} = 0$ Hz), 5.63–5.68 (br m, 1H, H-1β), 5.30 (ddd, 1H, H-2β, $J_{1,2} = 4.0$ Hz, $J_{2,3} = 6.0$ Hz, $J_{2,F} = 52.5$ Hz), 5.20 (d, 1H, H-2α, $J_{1,2} = J_{2,3} = 0$ Hz, $J_{2,F} = 49.1$ Hz), 5.18 (d, 1H, H-5$_b\alpha$, $J_{5a,5b} = 11.9$ Hz), 5.00 (d, 1H, H-5$_b\beta$, $J_{5a,5b} = 11.9$ Hz), 4.43–4.75 (m, 6H, H-5$_a\alpha$, H-5$_a\beta$, H-6α and H-6β), 3.66–3.64 (br m, 1H, OH-1α and OH-1β).

1-*O*-Acetyl-3,5,6-tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-α- and -β-D-arabinofuranoside (12). A solution of **11** (1.55 g, 3.14 mmol) in anhydrous pyridine (15 mL) at 0–5 °C was treated dropwise with acetic anhydride (0.90 mL, 9.54 mmol). After 10 min, the solution was allowed to warm to room temperature where it was held for 22 h. The solution was evaporated *in vacuo* to a stiff syrup, which was purified by flash chromatography on silica gel (50 g) with 3 : 1 hexane/EtOAc as solvent. Compound **12** (1.68 g, 100%, $\alpha:\beta$, 3 : 1) was isolated as a colorless glass: TLC 3 : 1 hexane/EtOAc, R_f α 0.43 and R_f β 0.48; MS *m/z* 554 $(M+NH_4)^+$, 477 $(M\text{-}OAc)^+$; ^{1}H NMR ($CDCl_3$) δ 7.89–8.10 (m, 6H, *o*-H of Ph), 7.50–7.60 (m, 3H, *p*-H of Ph), 7.34–7.45 (m, 6H, *m*-H of Ph), 6.54 (d, 1H, H-1β, $J_{1,F} = 0$, $J_{1,2} = 4.6$ Hz), 6.51 (d, 1H, H-1α, $J_{1,F} = 11.1$ Hz, $J_{1,2} = 0$), 6.11 (dd, 1H, H-3α, $J_{2,3} = 7.6$ Hz, $J_{3,F} = 17.6$ Hz), 6.03 (d, 1H, H-3β, $J_{3,F} = 19.0$ Hz), 5.54 (ddd, 1H, H-2β, $J_{1,2} = 4.6$ Hz, $J_{2,3} = 7.6$ Hz, $J_{2,F} = 52.9$ Hz), 5.27 (d, 1H, H-2α, $J_{2,F} = 49.0$ Hz), 4.56–4.85 (m, 8H, H-5α, H-5β, H-6α, and H-6β), 2.16 (s, 3H, CH_3-α), 2.09 (s, 3H, CH_3-β).

3,5,6-Tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-α and β-D-arabinofuranosyl bromide (13). To an ice-cold solution of **12** (1.68 g, 3.13 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise over 15 min 30% HBr in

acetic acid (16 mL). The clear yellow solution in a tightly sealed flask was allowed to warm to room temperature, stirred 15 h, and evaporated *in vacuo*. The resulting residue was partitioned between CH_2Cl_2 (50 mL) and ice-cold saturated $NaHCO_3$ (50 mL). The layers were separated, and the organic layer was washed with ice water (2 × 50 mL), dried ($MgSO_4$), and evaporated. This unstable **13** ($\alpha:\beta$, 6:1) was held under vacuum until used in the reaction below: TLC 3:1 hexane/EtOAc, R_f α 0.62 and R_f β 0.52; ^{1}H NMR ($CDCl_3$) δ 7.32–8.10 (m, 15H, Ph H's), 6.69 (d, 1H, H-1β, $J_{1,F} = 0$, $J_{1,2} = 4.8$ Hz), 6.62 (d, 1H, H-1α, $J_{1,F} = 13.4$ Hz, $J_{1,2} = 0$), 6.26 (d, 1H, H-3β, $J_{2,3} = 7.8$ Hz, $J_{3,F} =$ 15.7 Hz), 6.07 (d, 1H, H-3α, $J_{3,F} = 18.0$ Hz), 5.62 (d, 1H, H-2α, $J_{2,F} =$ 49.6 Hz), 5.48 (ddd, 1H, H-2β, $J_{1,2} = 4.8$ Hz, $J_{2,3} = 7.8$ Hz, $J_{2,F} = 54.6$ Hz), 4.58–4.95 (m, 8H, H-5α, H-5β, H-6α, and H-6β).

2,6-Dichloro-9-(3,5,6-tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-β- and -α-D-arabinofuranosyl)-9*H*-purine (14β and 14α). A suspension of 2,6-dichloropurine (650 mg, 3.44 mmol) in anhydrous MeCN (20 mL) under argon at room temperature was treated portionwise over 15 min with NaH (60% dispersion in mineral oil, 158 mg, 3.95 mmol). After an additional 20 min, a solution of **13** (1.74 g, 3.13 mmoles) in MeCN (8 mL) was added dropwise over 20 min, and the mixture was stirred at room temperature 18 h. Insoluble solids were collected and washed with CH_2Cl_2. The combined filtrate and washes were evaporated to an orange foam, which was flash chromatographed on silica gel (50 g). Elution with 3:1 hexane/isopropyl acetate afforded mixed products, **14**β and **14**α as white foams (1.70 g, 82%), which were used in subsequent reactions. Small samples of enriched fractions were further purified by preparative TLC (Analtech GF, 10 × 20 cm, 1,000 μ) with multiple development in 100:1 $CHCl_3$/MeOH to provide material for analysis.

Compound **14**β: TLC 100:1 $CHCl_3$/MeOH, R_f 0.45; MS *m/z* 671 $(M+Li)^+$; ^{1}H NMR ($CDCl_3$) δ 8.44 (d, 1H, H-8, $J_{8,F} = 3.1$ Hz), 7.95–8.12 (m, 6H, *o*-H of Ph), 7.43–7.65 (m, 9H, *m*-H and *p*-H of Ph), 6.87 (dd, 1H, H-1′, $J_{1',2'} = 3.3$ Hz, $J_{1',F} = 19.8$ Hz), 6.27 (dd, 1H, H-3′, $J_{2',3'} = 1.5$ Hz, $J_{3',F} =$ 17.4 Hz), 5.45 (ddd, 1H, H-2′, $J_{2',3'} = 1.5$ Hz, $J_{1',2'} = 3.3$ Hz, $J_{2',F} = 50.5$ Hz), 5.02 (dd, 1H, H-5′$_b$, $^5J_{5',F} = 0.7$ Hz, $J_{5'a,5'b} = 12.0$ Hz), 4.93 (d, 1H, H-6′$_b$, $J_{6'a,6'b} = 11.9$ Hz), 4.75 (bd, 1H, H-5′$_a$, $J_{5'a,5'b} = 12.0$ Hz), 4.60 (d, 1H, H-6′$_a$, $J_{6'a,6'b} = 11.9$ Hz).

Compound **14**α: TLC 100:1 $CHCl_3$/MeOH, R_f 0.40; MS *m/z* 671 $(M+Li)^+$; ^{1}H NMR ($CDCl_3$) δ 8.44 (s, 1H, H-8); 7.84–8.12 (m, 6H, *o*-H of Ph), 7.36–7.61 (m, 9H, *m*-H and *p*-H of Ph), 6.54 (dd, 1H, H-1′, $J_{1',2'} = 3.6$ Hz, $J_{1',F} = 14.4$ Hz), 6.24 (dd, 1H, H-3′, $J_{2',3'} = 3.4$ Hz, $J_{3',F} =$ 23.6 Hz), 6.19 (ddd, 1H, H-2′, $J_{1',2'} = 3.6$ Hz, $J_{2',3'} = 3.4$ Hz, $J_{2',F} = 43.9$ Hz), 4.97 (dd, 1H, H-5′$_b$, $J_{5'a,5'b} = 12.0$ Hz, $^5J_{5',F} = 1.0$ Hz), 4.88 (d, 1H, H-6′$_b$, $J_{6'a,6'b} = 12.0$ Hz), 4.70 (d, 1H, H-5′$_a$, $J_{5'a,5'b} = 12.0$ Hz), 4.67 (bd, 1H, H-6′$_a$, $J_{6'a,6'b} = 12.0$ Hz).

2-Chloro-6-methoxy-9-(2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-D-arabinofuranosyl)-9*H*-purine (15*β*). A solution of **14** ($5\beta:1\alpha$) (172 mg, 0.26 mmol) in MeOH (10 mL) at room temperature was treated with 0.5 N $NaOCH_3$ in MeOH (0.52 mL) and stirred 4 h. Strong cation exchange resin (hydrogen form) was added to neutralize, and the mixture was stirred 10 min. The resin was collected and washed with several portions of MeOH. The combined filtrate and washes were evaporated, and the residue was purified by preparative TLC (Analtech GF, 20×20 cm, 2,000 μ) developed three times in 9:1 $CHCl_3$/MeOH. A MeOH extract of the product band gave after evaporation essentially pure **15***β* (56 mg, 75%) as a gummy solid: TLC 9:1 $CHCl_3$/MeOH, R_f 0.38; HPLC 98%, $t_R = 8.6$ min, 4:1 H_2O/MeCN; MS m/z 355 $(M+Li)^+$; ^1H NMR (DMSO-d_6) δ 8.61 (d, 1H, H-8, $J_{8,F} = 1.0$ Hz), 6.56 (dd, 1H, H-1′, $J_{1',F} = 5.6$ Hz, $J_{1',2'} = 6.3$ Hz), 6.03 (bs, 1H, OH), 5.55 (ddd, 1H, H-2′, $J_{1',2'} = 6.3$ Hz, $J_{2',3'} = 6.5$ Hz, $J_{2',F} = 56.7$ Hz), 5.22 (bs, 1H, OH), 5.04 (bs, 1H, OH), 4.65 (dd, 1H, H-3′, $J_{2',3'} = 6.5$ Hz, $J_{3',F} = 26.3$ Hz), 4.11 (s, 3H, CH_3), 3.64 (bd, 1H, H-5′$_b$, $J_{5'a,5'b} = 11.5$ Hz), 3.54 (bs, 2H, H-6′), 3.41 (dd, 1H, H-5′$_a$, $^5J_{5'a,F} = 1.6$ Hz, $J_{5'a,5'b} = 11.5$ Hz).

2-Chloro-6-methoxy-9-(2-deoxy-2-fluoro-4-*C*-hydroxymethyl-α-D-arabinofuranosyl)-9*H*-purine (15*α*). Compound **14** ($7\alpha:1\beta$) (62 mg, 0.09 mmol) was reacted with 0.5 N $NaOCH_3$ (0.18 mL) as described above for preparing **15***β* to provide **15**α (23 mg, 82%) as a gum: TLC 9:1 $CHCl_3$/MeOH, R_f 0.44; HPLC 98%, $t_R = 9.5$ min, 4:1 H_2O/MeCN; MS m/z 355 $(M+Li)^+$; ^1H NMR (DMSO-d_6)δ 8.75 (s, 1H, H-8), 6.23 (dd, 1H, H-1′, $J_{1',2'} = 5.6$ Hz, $J_{1',F} = 13.9$ Hz), 5.70 (ddd, 1H, H-2′, $J_{1',2'} = 5.6$ Hz, $J_{2',3'} = 6.6$ Hz, $J_{2',F} = 55.5$ Hz), 5.15 (bs, 1H, OH), 4.61 (dd, 1H, H-3′, $J_{2',3'} = 6.6$ Hz, $J_{3',F} = 21.2$ Hz), 4.12 (s, 3H, CH_3), 3.68 (d, 1H, H-5′$_b$, $J_{5'a,5'b} = 11.8$ Hz), 3.44 (dd, 1H, H-5′$_a$, $^5J_{5'a,F} = 1.3$ Hz, $J_{5'a,5'b} = 11.8$ Hz), 3.43 (bs, 2H, H-6′).

2-Chloro-9-(2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-D-arabinofuranosyl)-9*H*-purin-6-amine (16*β*). A solution of **15***β* (62 mg, 0.18 mmol) in 60 mL of ethanolic ammonia (saturated at 5 °C) in a glass-lined stainless steel bomb was kept at 80 °C for 16 h and then evaporated. The residue was purified by preparative TLC (Analtech GF, 20×20 cm, 2,000 μ) with two developments in 5:1 $CHCl_3$/MeOH+1% concd NH_4OH. A warm MeOH extract of the product band provided after evaporation a residue that failed to crystallize. An acetone solution of this material was allowed to evaporate to a glass, which was scratched to a powder affording pure **16***β* (50 mg, 75%): TLC 5:1 $CHCl_3$/MeOH+1% concd NH_4OH, R_f 0.33; HPLC 97%, $t_R = 5.4$ min, 4:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 334 $(M+H)^+$; UV λ_{max} pH 1, 264 (14.1), pH 7, 263 (14.6), pH 13, 264 (14.9); ^1H NMR (DMSO-d_6)δ 8.32 (d, 1H, H-8, $^5J_{8,F} = 1.0$ Hz), 7.87 (bs, 2H, NH_2), 6.46 (dd, 1H, H-1′, $J_{1',2'} = 6.3$ Hz, $J_{1',F} = 5.9$ Hz), 5.92 (d, 1H, 3′-OH, $J_{3',3'\text{-OH}} = 5.4$ Hz), 5.50 (dt, 1H, H-2′, $J_{1',2'} = J_{2',3'} = 6.3$ Hz, $J_{2',F} = 56.7$ Hz), 5.13 (t, 1H, 6′-OH,

$J_{6',6'\text{-OH}} = 5.6$ Hz), 4.98 (dd, 1H, 5′-OH, $J_{5'b,5'\text{-OH}} = 5.7$ Hz, $J_{5'a,5'\text{-OH}} = 5.4$ Hz) 4.64 (ddd, 1H, H-3′, $J_{2',3'} = 6.3$ Hz, $J_{3',F} = 26.1$ Hz, $J_{3',3'\text{-OH}} = 5.4$ Hz), 3.63 (dd, 1H, H-5′$_b$, $J_{5'a,5'b} = 11.5$ Hz, $J_{5'b,5'\text{-OH}} = 5.7$ Hz), 3.52 (d, 2H, H-6′, $J_{6',6'\text{-OH}} = 5.6$ Hz), 3.39 (ddd, 1H, H-5′$_a$, $J_{5'a,5'b} = 11.5$ Hz, $^5J_{5'a,\ F} = 1.0$ Hz, $J_{5'a,5'\text{-OH}} = 5.6$ Hz). Anal. Calcd. for $C_{11}H_{13}ClFN_5O_4 \cdot 0.5$ acetone $\cdot$ 0.5 H_2O: C, 40.39; H, 4.61; N, 18.84. Found: C, 40.61; H, 4.45; N, 18.94.

2-Chloro-9-(2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*α*-D-arabinofuranosyl)-9*H*-purin-6-amine (16*α*). Compound **15**α (32 mg, 0.09 mmol) was reacted with ethanolic ammonia as described for preparing **16***β* to give **16**α (20 mg, 64%) as a white solid: TLC 5 : 1 $CHCl_3$/MeOH+1% concd NH_4OH, R_f 0.40; HPLC 100%, $t_R = 6.6$ min, 4 : 1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 334 $(M+H)^+$; UV λ_{max} pH 1, 264 (15.0), pH 7, 264 (15.2), pH 13 264 (15.2); ^{1}H NMR (DMSO-d_6)δ 8.48 (s, 1H, H-8), 7.92 (bs, 2H, NH_2), 6.12 (dd, 1H, H-1′, $J_{1',2'} = 5.8$ Hz, $J_{1',F} = 13.6$ Hz), 5.94 (d, 1H, 3′-OH, $J_{3',3'\text{-OH}} = 5.6$ Hz), 5.64 (ddd, 1H, H-2′, $J_{1',2'} = 5.8$ Hz, $J_{2',3'} = 6.5$ Hz, $J_{2',F} = 55.5$ Hz), 5.06 (dd, 1H, 5′-OH, $J_{5'b,5'\text{-OH}} = 5.6$ Hz, $J_{5'a,5'\text{-OH}} = 6.0$ Hz), 4.96 (t, 1H, 6′-OH, $J_{6',6'\text{-OH}} = 5.4$ Hz), 4.59 (ddd, 1H, H-3′, $J_{2',3'} = 6.5$ Hz, $J_{3',F} = 21.1$ Hz, $J_{3',3'\text{-OH}} = 5.6$ Hz), 3.67 (dd, 1H, H-5′b, $J_{5'b,5'\text{-OH}} = 5.6$ Hz, $J_{5'a,5'b} = 11.8$ Hz), 3.41–3.47 (m, 3H, H-5′a and H-6′). Anal. Calcd. for $C_{11}H_{13}ClFN_5O_4 \cdot 0.4$ H_2O: C, 38.76; H, 4.08; N, 20.54. Found: C, 38.79; H, 4.00; N, 20.34.

2,6-Diazido-9-(3,5,6-tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-and-*α*-D-arabinofuranosyl)-9*H*-purine (17*β* and 17*α*). To a solution of **14** (9β : 1α) (1.27 g, 1.91 mmol) in warm EtOH (50 mL) was added dropwise with stirring a solution of NaN_3 (289 mg, 4.40 mmol) in H_2O (1.3 mL). The mixture was refluxed 0.5 h (TLC, 2 : 1 hexane/EtOAc), cooled to room temperature, and then chilled in ice for 2 h. The solid present was collected, washed with cold EtOH, and air dried before being dissolved in $CHCl_3$. This solution was washed once with H_2O, dried ($MgSO_4$), and evaporated to give **17***β* (902 mg, 77%) as a white solid of sufficient purity for the next step. The EtOH filtrate from the reaction mixture contained the alpha anomer and other minor impurities. The solvent was evaporated, and the residue was processed as described above to provide crude **17**α (456 mg). A small sample was purified for analysis by preparative TLC as reported for **14**α.

Compound **17***β*: TLC 100 : 1 $CHCl_3$/MeOH, R_f 0.45; MS m/z 679 $(M+H)^+$; ^{1}H NMR ($CDCl_3$) δ 8.19 (d, 1H, H-8, $^5J_{8,F} = 2.8$ Hz), 7.94–8.08 (m, 6H, *o*-H of Ph), 7.38–7.64 (m, 9H, *m*-H and *p*-H of Ph), 6.78 (dd, 1H, H-1′, $J_{1',2'} = 3.5$ Hz, $J_{1'\text{-}F} = 19.4$ Hz), 6.29 (dd, 1H, H-3′, $J_{2',3'} = 1.9$ Hz, $J_{3',F} = 17.1$ Hz), 5.43 (ddd, 1H, H-2′, $J_{2',3'} = 1.9$ Hz, $J_{1',2'} = 3.5$ Hz, $J_{2',F} = 50.8$ Hz), 4.98 (dd, 1H, H-5′b, $^5J_{5'b,F} = 0.6$ Hz, $J_{5'a,5'b} = 12.1$ Hz), 4.90 (d, 1H, H-6′b, $J_{6'a,6'b} = 12.0$ Hz), 4.74 (d, 1H, H-5′a, $J_{5'a,5'b} = 12.1$ Hz), 4.59 (d, 1H, H-6′a, $J_{6'a,6'b} = 12.0$ Hz).

Compound **17**α: TLC 100 : 1 $CHCL_3$/MeOH, R_f 0.40; MS m/z 679 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 8.18 (s, 1H, H-8), 7.86–8.11 (m, 6H, *o*-H of Ph), 7.34–7.60 (m, 9H, *m*-H and *p*-H of Ph), 6.46 (dd, 1H, H-1′, $J_{1',2'} = 4.0$ Hz, $J_{1',F} = 14.2$ Hz), 6.25 (ddd, 1H, H-2′, $J_{1',2'} = 4.0$ Hz, $J_{2',3'} = 3.7$ Hz, $J_{2',F} = 51.3$ Hz), 6.23 (dd, 1H, H-3′, $J_{2'-3'} = 3.7$ Hz, $J_{3',F} = 16.6$ Hz), 4.95 (dd, 1H, H-5′b, $^5J_{5'b,F} = 0.7$ Hz, $J_{5'a,5'b} = 11.8$ Hz), 4.85 (d, 1H, H-6′b, $J_{6'a,6'b} = 11.9$ Hz), 4.69 (d, 1H, H-6′a, $J_{6'a,6'b} = 11.9$ Hz), 4.68 (dd, 1H, H-5′a, $J_{5'a,5'b} = 11.8$ Hz).

9-(3,5,6-Tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (18β). A solution of **17**β (926 mg, 1.37 mmol) in 2 : 1 EtOH/N,N-dimethylacetamide (150 mL, warmed to dissolve) was treated with 5% palladium on carbon (120 mg) and hydrogenated for 16 h at room temperature and atmospheric pressure. The catalyst was removed by filtration and washed thoroughly with EtOH, then $CHCL_3$. The filtrate plus washes were evaporated *in vacuo* to a yellow glass. This material was purified by flash chromatography on silica gel (35 g) with 95 : 5 $CHCL_3$/MeOH as eluting solvent. The resulting foam solidified to a white powder upon sonication with ether to afford pure **18**β (696 mg, 81%): TLC 95 : 5 $CHCl_3$/MeOH+1% concd NH_4OH, R_f 0.48; MS m/z 627 $(M+H)^+$; ^1H NMR ($CDCl_3$) δ 7.95–8.05 (m, 6H, *o*-H of Ph), 7.79 (d, 1H, H-8, $^5J_{8,F} = 2.9$ Hz), 7.54–7.59 (m, 3H, *p*-H of Ph), 7.36–7.45 (m, 6H, *m*-H of Ph), 6.59 (dd, 1H, H-1′, $J_{1',2'} = 3.8$ Hz, $J_{1',F} = 18.7$ Hz), 6.44 (dd, 1H, H-3′, $J_{2',3'} = 2.4$ Hz, $J_{3',F} = 16.9$ Hz), 5.43 (ddd, 1H, H-2′, $J_{2',3'} = 2.4$ Hz, $J_{1',2'} = 3.8$ Hz, $J_{2',F} = 51.0$ Hz), 5.37 (bs, 2H, 6-NH_2), 4.93 (bd, 1H, H-5′b, $J_{5'a,5'b} = 11.6$ Hz), 4.89 (dd, 1H, H-6′b, $J_{6'a,6'b} = 11.8$ Hz), 4.86 (dd, 1H, H-5′a, $J_{5'a,5'b} = 11.6$ Hz, $J_{5'a,F} = 0.8$ Hz), 4.80 (bs, 2H, 2-NH_2), 4.64 (d, 1H, H-6′a, $J_{6'a,6'b} = 11.8$ Hz).

9-(3,5,6-Tri-*O*-benzoyl-2-deoxy-2-fluoro-4-*C*-hydroxymethyl-α-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (18α). Compound 17α (388 mg, 0.57 mmol) was hydrogenolyzed with 5% Pd/C (50 mg) as described for preparing **18**β to provide **18**α (305 mg, 85%) as a foam: TLC 95 : 5 $CHCL_3$/MeOH+1% concd NH_4OH, R_f 0.52; MS m/z 627 $(M+H)^+$; ^1H NMR ($CDCL_3$ δ 7.83–8.10 (m, 6H, *o*-H of Ph), 7.72 (s, 1H, H-8), 7.30–7.59 (m, 9H, *m*-H and *p*-H of Ph), 6.45 (dt, 1H, H-2′, $J_{1',2'} = J_{2',3'} = 4.5$ Hz, $J_{2',F} = 51.6$ Hz), 6.25 (dd, 1H, H-1′, $J_{1',2'} = 4.5$ Hz, $J_{1',F} = 10.0$ Hz), 6.19 (dd, 1H, H-3′, $J_{2',3'} = 4.5$ Hz, $J_{3',F} = 12.8$ Hz), 5.41 (bs, 2H, 6-NH_2), 5.10 (d, 1H, H-6′b, $J_{6'a,6'b} = 12.0$ Hz), 4.91 (d, 1H, H-5′b, $J_{5'a,5'b} = 12.0$ Hz), 4.80 (bs, 2H, 2-NH_2), 4.77 (d, 1H, H-6′a, $J_{6'a,6'b} = 12.0$ Hz), 4.75 (d, 1H, H-5′a, $J_{5'a,5'b} = 12.0$ Hz).

9-(2-Deoxy-2-fluoro-4-*C*-hydroxymethyl-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (19β). A suspension of **18**β (691 mg, 1.10 mmol) in MeOH (50 mL) at room temperature was treated in one portion with 0.5 N $NaOCH_3$ in

MeOH (1.10 mL). A clear solution was observed after 5 min, and the reaction was stirred an additional 2 h. After being neutralized with glacial acetic acid, the reaction was evaporated. The resulting residue was purified by preparative TLC (Analtech GF, 20×20 cm, 2,000 μ) with two developments in 30 : 10 : 1 $CHCl_3$/MeOH/NH_4OH. A hot MeOH extract of the product band was evaporated to dryness. From this material, pure **19***β* (327 mg, 86%) was obtained as a gelatinous white solid from EtOH: mp 142 °C; TLC 30 : 10 : 1 $CHCL_3$/MeOH/NH_4OH, R_f 0.35; HPLC 100%, $t_R = 5.9$ min, 3 : 1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)MeOH; MS m/z 321 $(M+Li)^+$; UV λ_{max} pH 1, 252 (12.2), 290 (10.6), pH 7, 255 (10.1), 279 (10.7), pH 13, 255 (9.9), 279 (10.7); ^{1}H NMR (DMSO-d_6) δ 7.86 (d, 1H, H-8, $^5J_{8,F} = 1.3$ Hz), 6.75 (bs, 2H, 6-NH_2), 6.37 (dd, 1H, H-1′, $J_{1',2'} = 6.2$ Hz, $J_{1',F} = 7.6$ Hz), 5.86 (d, 1H, 3′-OH, $J_{3'\text{-}3'\text{-OH}} = 5.3$ Hz), 5.81 (bs, 2H, 2-NH_2), 5.37 (ddd, 1H, H-2′, $J_{2',3'} = 5.9$ Hz, $J_{1',2'} = 6.2$ Hz, $J_{2',F} = 56.8$ Hz), 5.23 (bt, 1H, 6′-OH, $J_{6',6'\text{-OH}} = 5.0$ Hz), 4.93 (dd, 1H, 5′-OH, $J_{5'a,5'\text{-OH}} = 5.3$ Hz, $J_{5'b,5'\text{-OH}} = 5.6$ Hz), 4.60 (ddd, 1H, H-3′, $J_{3',3'\text{-OH}} = 5.3$ Hz, $J_{2',3'} = 5.9$ Hz, $J_{3',F} = 25.4$ Hz), 3.62 (dd, 1H, H-5′b, $J_{5'b,5'\text{-OH}} = 5.6$ Hz, $J_{5'a,5'b} = 11.5$ Hz), 3.47 (d, 2H, H-6′, $J_{6',6'\text{-OH}} = 5.0$ Hz), 3.35 (dd, 1H, H-5′a, $J_{5'a,F} = 0.8$ Hz, $J_{5'a,5'\text{-OH}} = 5.3$ Hz, $J_{5'a,5'b} = 11.5$ Hz). Anal. Calcd. for $C_{11}H_{15}FN_6O_4 \cdot 0.75\ H_2O \cdot 0.25\ CH_3CO_2H$: C, 40.29; H, 5.15; N, 24.52. Found: C, 40.20; H, 4.98; N, 24.52.

9-(2-Deoxy-2-fluoro-4-*C*-hydroxymethyl-*α*-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (19*α*). Compound **18***β* (305 mg, 0.49 mmol) was treated as described for the preparation of **19***β* from **18***β*. Pure **19**α (115 mg, 75%) crystallized from EtOH: mp 205–206 °C; TLC 30 : 10 : 1 $CHCl_3$/MeOH/NH_4OH, R_f 0.48; HPLC 100%, $t_R = 7.7$ min, 3 : 1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 315 $(M+H)^+$; UV λ_{max} pH 1, 252 (12.1), 290 (10.3), pH 7, 255 (9.9), 280 (10.3), pH 13, 256 (10.2), 279 (10.8); ^{1}H NMR (DMSO-d_6) δ 8.02 (s, 1H, H-8), 6.83 (bs, 2H, 6-NH_2), 6.00 (dd, 1H, H-1′, $J_{1',2'} = 6.2$ Hz, $J_{1',F} = 13.8$ Hz), 5.93 (d, 1H, 3′-OH, $J = 5.7$ Hz), 5.82 (bs, 2H, 2-NH_2), 5.58 (ddd, 1H, H-2′, $J_{1',2'} = 6.2$ Hz, $J_{2',3'} = 6.6$ Hz, $J_{2'\text{-F}} = 55.8$ Hz), 5.21 (dd, 1H, 5′-OH, $J_{5'a,5'\text{-OH}} = 4.9$ Hz, $J_{5'b,5'\text{-OH}} = 6.3$ Hz), 5.05 (t, 1H, 6′-OH, $J_{6'a,6'\text{-OH}} = 5.7$ Hz), 4.55 (ddd, 1H, H-3′, $J_{3',3'\text{-OH}} = 5.7$ Hz, $J_{2',3'} = 6.6$ Hz, $J_{3',F} = 21.1$ Hz), 3.64 (dd, 1H, H-5′b, $J_{5'b,5'\text{-OH}} = 6.3$ Hz, $J_{5'a,5'b} = 11.8$ Hz), 3.44 (dd, 1H, H-5′a, $^5J_{5'a,F} = 1.2$ Hz, $J_{5'a,5'\text{-OH}} = 4.9$ Hz, $J_{5'a,5'b} = 11.8$ Hz), 3.37–3.43 (m, 2H, H-6′). Anal. Calcd. for $C_{11}H_{15}FN_6O_4$: C, 42.04; H, 4.81; N, 26.74. Found: C, 41.96; H, 4.76; N, 26.65.

2-Amino-9-(2-deoxy-2-fluoro-4-*C*-hydroxymethyl-*β*-D-arabinofuranosyl)-1,9-dihydro-6*H*-purin-6-one (20*β*). A solution of **19***β* (56 mg, 0.16 mmol) in H_2O (5 mL) at room temperature was treated with adenosine deaminase (7.9 mg, ~12 units, Type II: crude powder, Sigma). After 94 h, the reaction mixture was diluted with H_2O (5 mL), and this solution was

applied to a strong cation exchange column (1×12 cm) hydrogen form (AG 50W-X4, 100–200 mesh, Bio-Rad) equilibrated with H_2O. Gradient elution from 0–100% 0.25 N NH_4OH with UV monitoring at 254 nm provided product containing fractions that were combined and evaporated. The resulting residue was coevaporated with EtOH and then triturated with acetone to give **20**β (45 mg, 84%) as a white solid: mp 262–264 °C; TLC 9:2 MeCN/1N NH_4OH, R_f 0.40; HPLC 99%, $t_R = 3.8$ min, 3:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)/MeOH; MS m/z 316 $(M+H)^+$; UV λ_{max} pH 1, 256 (12.2), 282 (sh), pH 7, 252 (13.3), 275 (sh), pH 13, 263 (11.1); ^{1}H NMR (DMSO-d_6) δ 10.25 (bs, 1H, 1-NH), 7.87 (d, 1H, H-8, $^5J_{8,F} = 1.3$ Hz), 6.52 (bs, 2H, NH_2), 6.31 (dd, 1H, H-1′, $J_{1',2'} = 6.0$ Hz, $J_{1',F} = 7.2$ Hz), 5.88 (bs, 1H, 3′-OH), 5.37 (ddd, 1H, H-2′, $J_{1',2'} = 6.0$ Hz, $J_{2',3'} = 6.3$ Hz, $J_{2',F} = 56.8$ Hz), 5.14 (bs, 1H, 6′-OH), 4.94 (bs,1H, 5′-OH), 4.55 (dd, 1H, H-3′, $J_{2',3'} = 6.3$ Hz, $J_{3',F} = 25.6$ Hz), 3.61 (bd, 1H, H-5′b, $J_{5'a,5'b} = 11.5$ Hz), 3.47 (bs, 2H, H-6′), 3.34 (bdd, 1H, H-5′a, $J_{5'a,F} = 1.3$ Hz, $J_{5'a,5'b} = 11.5$ Hz). Anal. Calcd. for $C_{11}H_{14}FN_5O_5 \cdot 0.10$ EtOH $\cdot$ 0.50 H_2O: C, 40.90; H, 4.78; N, 21.29. Found: C, 41.01; H, 4.75; N, 21.08.

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