DMF (30 mL) was stirred at 70 °C under N_2 for 58 h before being diluted with H_2O and extracted with CH_2Cl_2. The extracts were washed with H_2O, dried (Na_2SO_4), and concentrated to leave an oil. Chromatography on silica gel (EtOAc/hexane/Et_3N 20:79:1 as eluent) gave **21** (1.27 g, 52%): mp 79.5–80.5 (CH_2Cl/hexane); ^1H NMR ($CDCl_3$) δ 1.24 (8 H, bs), 1.60 (2 H, quintet, J = 7 Hz, CH_2CN), 4.07 (2 H, t, J = 7 Hz, NCH_2), 6.95–7.60 (15 H, m); MS m/z 434 (MH^+). Anal. ($C_{30}H_{31}N_3 \cdot 0.5H_2O$) C, H, N.

5-[8-(3,4,5-Triphenyl-1*H*-pyrazol-1-yl)octyl]-2*H*-tetrazole (22). A mixture of **21** (1.25 g, 2.9 mmol) and (nBu)$_3$SnN$_3$ (1.15 g, 3.5 mmol) was stirred at 140 °C under N_2. After 2.5 h, the mixture was cooled, diluted with EtOAc, and washed with 0.5 N HCl (3×) and NaCl solutions. The solvent was evaporated, the residue dissolved in CH_2Cl_2, and a concentrated aqueous solution of KF added. The mixture was stirred for 24 h and extracted with CH_2Cl_2, and the residue recrystallized from hexane/CH_2Cl_2 (2:1) to give **22** (1.00 g, 73%): mp 158–160 °C; ^1H NMR ($CDCl_3$) δ 1.14 (8 H, m), 1.60 (2 H, t, J = 7 Hz), 1.79 (2 H, t, J = 7 Hz), 2.74 (2 H, t, J = 7 Hz, CH_2-tetrazole), 4.10 (2 H, t, J = 7 Hz, NCH_2), 6.90–7.50 (15 H, m); MS m/z 477 (MH^+). Anal. ($C_{30}H_{32}N_6$) C, H, N.

Blood Platelet Aggregometry. Platelet-rich plasma was prepared from human blood drawn into syringes containing $^1/_{10}$ volume of 3.8% sodium citrate. The blood was then subjected to centrifugation for 10 min at 140g and the platelet-rich plasma decanted. The test compound was dissolved in DMSO (5 μL) and added to PRP (0.9 mL) 3 min prior to the addition of ADP (5.86 μM). The aggregometer method of Born,[53] as modified by Mustard et al.,[54] was employed to measure platelet aggregation. Vehicle control trials were performed and compared with the extent of aggregation induced in PRP containing various concentrations of the test compounds. Dose–response curves were thus obtained and IC_{50} values determined. The data presented in Table I are the results of single determinations or the average of duplicates. Rabbit and rat PRP were prepared in a similar fashion,[55] and ADP in a final concentration of 29.3 μM was employed as the agonist.

Laser-Induced Thrombosis in Rabbits. This model, which has been described in detail[44,55] uses a ruby-laser flash to induce a small thrombus in the microcirculation of the ear of an English lop-ear rabbit. The mean thrombus area (μM^2) obtained for 10 trials in each rabbit served as a control value. The test compound was administered orally as a suspension in water and Tween 20, and the experiment repeated 2 h later. Drug efficacy was determined from a comparison of pre- and postdose mean thrombus areas. The results presented are an average of experiments conducted in five rabbits. BMY 42239 (**8d**) provided 55 ± 3% inhibition at a dose of 10 mg/kg po and octimibate (**5**) provided 39 ± 3% inhibition at a dose of 30 mg/kg po.

Radioligand Binding Studies. Radioligand binding assays were performed in 200-μL volumes containing 200 μg of platelet plasma membranes. The isolated membranes were added to a buffer composed of 10 mM $MgCl_2$, 1 mM EGTA, and 50 mM Tris/HCl (pH 7.4) with either 5 nM [^{3}H]iloprost or 5 nM [^{3}H]-PGD_2. The membranes were incubated at 0–4 °C for 90–120 min. After incubation, 5 mL of ice-cold 50 mM Tris/HCl (pH 7.4) was added, the tubes were vortexed, and the samples were rapidly filtered through presoaked Whatman GF/C filters. The filters were then washed four times with 5 mL of ice-cold 50 mM Tris/HCl (pH 7.4), blotted dry on absorbent paper, and counted in a scintillation counter. The specific binding was greater than 90% for [^{3}H]iloprost and 60% for [^{3}H]PGD_2 as determined using excess (10 μM iloprost and 100 μM PGD_2) cold ligand.

Acknowledgment. We thank Dr. Kim Colson for performing NMR experiments and Anna Bosza for help in preparing the manuscript.

Registry No. **7a**, 134701-57-8; **7d**, 134701-69-2; **8a**, 134701-92-1; **8b**, 137743-29-4; **8c**, 134701-61-4; **8d**, 134701-70-5; **8e**, 134701-90-9; **8f**, 134701-68-1; **8g**, 137743-30-7; **8h**, 137743-31-8; **8i**, 137743-32-9; **8j**, 137743-33-0; **9**, 24567-08-6; **10c**, 134701-71-6; **11c**, 134701-72-7; **12a**, 137743-34-1; **12b**, 134701-95-4; **12c**, 134701-73-8; **12d**, 137743-35-2; **13a**, 137743-36-3; **13b**, 134701-96-5; **13c**, 134701-74-9; **13d**, 137743-37-4; **14**, 134701-98-7; **15**, 134701-58-9; **16**, 134701-59-0; **17**, 134701-75-0; **18a**, 134701-76-1; **18b**, 134701-80-7; **18c**, 134701-78-3; **19a**, 134702-05-9; **19b**, 137743-38-5; **19c**, 134702-06-0; **20**, 137743-39-6; **21**, 134702-03-7; **22**, 134702-04-8; 3,3,5-triphenyl-3*H*-pyrazole methyl 9-bromononanoate, 67878-15-3; *tert*-butyl bromoacetate, 5292-43-3.

Supplementary Material Available: A graph of the effect of **8d**, SQ 27986, and unlabeled PGD_2 on [^{3}H]PGD_2 binding to isolated platelet membranes (1 page). Ordering information is given on any current masthead page.

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Synthesis and Biologic Activity of 2′-Fluoro-2-halo Derivatives of 9-β-D-Arabinofuranosyladenine[1]

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The synthesis of 2-halo-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)adenines (**4b** and **4d**) by coupling the 2,6-dihalopurine with 3-acetyl-5-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide (**2**) followed by replacement of the 6-halogen with concomitant removal of the acyl blocking groups is described. 2-Fluoroadenine derivative **4g** had to be prepared by the diazotization–fluorination of 2-aminoadenine nucleoside **4e**. All three nucleosides provided good increases in life span of mice inoculated with P388 leukemia. The best results were obtained when the compounds were administered q3h×8 on days 1, 5, and 9 after implantation of the leukemia cells. The 2′,3′-dideoxynucleoside **5b**, prepared by deacetylation of **4f** and deoxygenation of the resultant **4h** followed by removal of the benzoyl group of **5a**, was slightly active against HIV in cell culture.

Fludarabine phosphate (9-β-D-arabinofuranosyl-2-fluoroadenine 5′-*O*-phosphate, F-*ara*-AMP, **1**) has shown activity in a number of human cancers in Phase I and II clinical trials.[3] It has group C status at the present time

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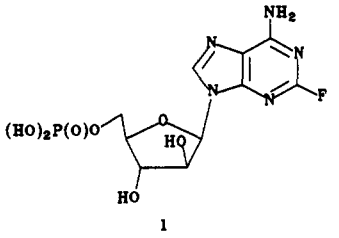

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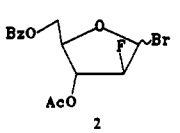

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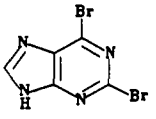

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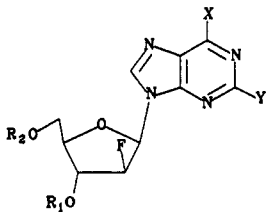

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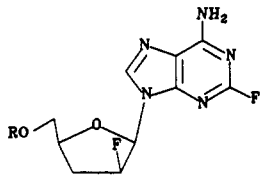

5

a) X=Y=Br, R_1=Ac, R_2=Bz
b) X=NH_2, Y=Br, R_1=R_2=H
c) X=Y=Cl, R_1=Ac, R_2=Bz
d) X=NH_2, Y=Cl, R_1=R_2=H
e) X=Y=NH_2, R_1=Ac, R_2=Bz
f) X=NH_2, Y=F, R_1=Ac, R_2=Bz
g) X=NH_2, Y=F, R_1=R_2=H
h) X=NH_2, Y=F, R_1=H, R_2=Bz

a) R=Bz
b) R=H

and has been approved by the FDA for the treatment of refractory lymphocytic leukemia. Despite this useful activity, fludarabine phosphate, like most cancer chemotherapeutic agents, has toxicity which is dose limiting.[3] This toxicity may be due, at least in part, to the cleavage of the F-*ara*-A, which results from rapid dephosphorylation of F-*ara*-AMP, to 2-fluoroadenine, a toxic purine with no anticancer activity.[4] Since extracts of *Escherichia coli*, but not mammalian cells, catalyze this conversion, it must occur in the intestine of mammals.[5]

The resistance of 9-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)hypoxanthine and the corresponding 2′-azido nucleoside to cleavage by mammalian purine nucleoside phosphorylase (PNP)[6] suggested that the corresponding adenine derivatives might be resistant to cleavage by *E. coli* PNP, even though this latter enzyme is notoriously less fastidious than the mammalian enzyme. This reasoning led us to propose studies of a number of 2-haloadenine arabinonucleosides substituted at the 2′-position. The 2′-chloro-, bromo-, and azidoarabinonucleosides were expediently prepared by displacement of the 2′-*O*-triflate from the 3′,5′-blocked siloxane ribonucleosides, and the 2′-amino compounds by reduction of the azido compounds. The 2-chloroadenine derivatives were not cytotoxic and had little activity against vaccinia virus. The 2-fluoroadenines were somewhat cytotoxic and the 2′-azido compound had modest but significant activity against vaccinia.[7] Since poor phosphorylation probably explains the low level of activity of these compounds, we turned our attention to the 2′-fluoroarabinonucleosides. The fluorine atom, being almost the same size as hydrogen, seemed less likely to interfere with phosphorylation, or with the activity of the resultant nucleotides, than the larger atoms or groups at *C*-2′.

Chemistry

Although application of the route used to prepare the arabinonucleosides mentioned above to the preparation of the desired 2′-fluoroarabinonucleosides was desirable, it seemed problematic since the fluoride ion is used to remove the siloxane blocking group. We did attempt it, with no success. Since other approaches beginning with a nucleoside also failed, these compounds had to be prepared by reaction of the appropriately blocked 2-fluoro sugar (**2**)[8] with 2,6-dichloropurine followed by modification of the purine, as reported for the preparation of 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)guanine.[9] This sequence was also applied to 2,6-dibromopurine (**3**) for the preparation of the 2-bromoadenine nucleoside. Sugar **2** was condensed with 2,6-dibromopurine (**3**)[10] in refluxing 1,2-dichloroethane in the presence of 4A molecular sieves. The anomeric configuration and position of substitution for **4a** were confirmed by ^{1}H NMR comparisons with **4c**. In both spectra, H-8 is a doublet with $J_{8,F'}$ = 3 Hz, as seen previously for β-isomers.[11] The anomeric configuration of **4a** was further confirmed by NOE difference spectroscopy. Irradiation of H-4′ resulted in a 3.3% NOE of the H-1′ signal, and irradiation of H-1′ resulted in a 2.2% NOE of the H-4′ signal, demonstrating that H-1′ and H-4′ are on the same side of the sugar ring, and hence that **4a** is the β-anomer.[12] Confirmation of the 9-substitution pattern of the purine ring was obtained from the hydrogen-coupled ^{13}C NMR spectrum of **4a**. That both C-8 ($^3J_{C\text{-}8,H\text{-}1'}$ = 4.4 Hz) and C-4 ($^3J_{C\text{-}4,H\text{-}1'}$ = 1.9 Hz) are coupled to H-1′ of the sugar was confirmed by selective decoupling of H-1′, and thus substitution at the 9-position is established. Amination and deprotection of **4a** or **4c** carried out in ethanolic ammonia yielded a mixture of the desired product and the 5′-*O*-benzoyl compound. This residual blocking group was removed by treating the mixture with

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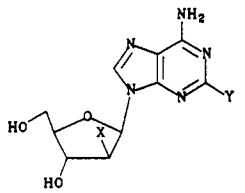
(12) Further details relating to the NMR data on compounds in this series will be presented in a separate paper.

Table I. Cytotoxicity of 2-Haloadenine Nucleosides[a]



compound[c] X	compound[c] Y	IC_{50},[b] μM HEp-2	L1210	CCRF-CEM	K562
OH	F[d]	9	3	0.4	0.15
H	F	0.2	0.9	0.2	ND[e]
F	F	0.34	0.38	0.14	0.3
OH	Cl	3	<3	10	ND
H	Cl	0.03	0.07	0.003	ND
F	Cl	0.012	0.23	0.05	0.003
OH	Br	4	~3	ND	ND
H	Br	0.02	0.9	0.02	ND
F	Br	0.22	0.26	0.02	0.05

[a] For details of the cytotoxicity determinations, see refs 4 and 7. [b] The concentration required to inhibit cell proliferation to 50% of untreated controls. [c] The arabino- and 2'-deoxyribonucleosides are described by Montgomery (Montgomery, J. A. *Med. Res. Rev.* **1982**, *2*, 271–308) and Bennett et al. (Bennett, L. L., Jr.; et al. *Nucleosides Nucleotides* **1985**, *4*, 107–116). [d] As the monophosphate. [e] No data.

LiOH in MeCN–H_2O to give **4b** or **4d**.

Nonaqueous diazotization of **4e**[9] with *tert*-butyl nitrite in 60% hydrogen fluoride/pyridine at −20 °C[13] produced 2-fluoro compound **4f**. Attempts to deprotect **4f** afforded unanticipated displacement of the 2-fluorine. Treatment of **4f** with ammonia in EtOH or NaOH in MeOH–H_2O gave an unacceptable amount of deblocked 2-NH_2 or 2-OCH_3 nucleoside. Deacylation of **4f** was accomplished with LiOH in MeCN–H_2O, which allowed a reasonable yield of **4g** free of any side products. The signal for H-8 in **4f** was also a doublet, confirming the β configuration.

In order to prepare the target dideoxy compound (**5b**), a closely related nucleoside with potential HIV activity, we first selectively removed the 3'-*O*-acetyl of **4f** with $NaHCO_3$ in MeOH.[14] The resulting product (**4h**) was then treated with (thiocarbonyl)diimidazole followed by reduction with tri-*n*-butyltin hydride to give **5a**.[15] The 5'-*O*-benzoyl group was removed with LiOH to produce compound **5b**.

Biological Results

In contrast to the previously reported 2'-substituted 9-β-D-arabinofuranosyl-2-haloadenines,[7] the 2'-fluoro compounds (**4b,d,g**) were quite cytotoxic to three human cell lines, HEp-2, CCRF-CEM, and K562, and the murine leukemia L1210. They, in fact, are significantly more cytotoxic than the corresponding 9-β-D-arabinofuranosyl-2-haloadenines, resembling more closely the 2'-deoxy-2-haloadenosines (see Table I). In view of the steric resemblance of fluorine to hydrogen, this result is not too surprising and may result largely from their more potent inhibition of nucleoside diphosphate reductase and DNA polymerase α,[16] since the rate of conversion to nucleotides is similar for the three 2-halo nucleosides (**4b**, **4d**, and **4g**).

We then compared the phosphorolytic cleavage, by *E. coli* purine nucleoside phosphorylase, of these compounds (Table I) and the arabinonucleosides previously prepared. The arabino- and 2'-deoxyribonucleosides are rapidly cleaved by this enzyme, whereas the arabinonucleosides substituted at 2' by Cl, N_3, or NH_2 are almost completely resistant. The 2'-fluoro compounds are less resistant to cleavage, being cleaved at roughly one-third the rate of the arabino- and 2'-deoxynucleosides.[17] This reduction in rate may be sufficient, since phosphorylation in mammalian cells is quite rapid. Studies on the metabolism of **4d** in mice have been initiated and will be reported later.[18]

Limited studies with the P388 leukemia in mice (Table II) using standard procedures[19] indicate that the most effective compound in this system is 2-chloro-2'-fluoronucleoside **4d**. That fact coupled with reduced cleavage in vivo and the lower toxicity of the cleavage product 2-chloroadenine, relative to 2-fluoroadenine, point to the selection of **4d** for more detailed studies designed to lead to a clinical trial.

Using standard assay conditions,[20,21] the 2',3'-dideoxynucleoside **5b** had an IC_{50} against HIV (strain IIIB) of 1.2 μg/mL in CEM cells and 9.4 μg/mL in MT2 cells in culture.

In addition to providing new drugs with apparent clinical potential, this study demonstrates, once again, that existing drugs can be modified to reduce undesirable catabolic metabolism without adversely affecting desired anabolic metabolism and that such modifications may provide metabolites that are more potent enzyme inhibitors and therefore potentially better drugs.[16] In this case, a detailed knowledge and understanding of purine metabolism is a necessary prerequisite for success. The modest activity of **5b** against HIV is in keeping with the finding that ddA must be deaminated to ddI to exhibit potent HIV activity, since the 2-fluoro group of **5b** prevents its deamination.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Nicolet NT 300NB spectrometer operating at 300.635 MHz

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Table II. Summary of the in Vivo Activity of the 9-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-2-haloadenines vs P388 Leukemia[a]

compound	optimal ip dosage[b]	schedule	median % ILS[c] (dying mice only)	log change[d]	tumor-free survivors
4d	100	qd, days 1–5	+38	−0.3	0/5
	200	qd, days 1–5	+59	−1.6	0/3
	20	q3h×8, days 1, 5, 9	+220	−6.6	1/6
	25	q3h×8, days 1, 5, 9	+118	−2.8	0/5
4g	100	qd, days 1–5	+63	−1.8	0/3
	25	q3h×8, days 1, 5, 9	+81	−0.1	0/6
4b	200	qd days 1–5	+33	+0.1	0/6
	30	q3h×8, days 1, 5, 9	+100	−1.0	0/6
	50	q3h×8, days 1, 5, 9	+41	+1.6	0/6

[a] CD2F1 mice were implanted ip with 10^6 P388 leukemia cells on day 0 (see ref 19 for details). [b] mg/kg per dose (≤LD_{10}). [c] Increase in life span. [d] log change in viable tumor cell population at the end of therapy compared to that at the start of therapy, based on the median day of death among the animals that died.

(^{1}H) or 75.6 MHz (^{13}C). Chemical shifts are expressed in parts per million downfield from tetramethylsilane. The hydrogen-decoupled ^{13}C NMR spectra were assigned by comparison of the $J_{C,H}$ values obtained from the hydrogen-coupled ^{13}C NMR spectra, and when necessary, selective hydrogen decoupling was performed in order to confirm the assignments. The NOE experiments were conducted on degassed solutions of $CDCl_3$. To minimize the effects of magnetic perturbations with the sample nonspinning, eight FID's were acquired with the decoupler set to a desired frequency and eight FID's were recorded with the decoupler off-resonance. The process was repeated until 800 FID's had been acquired. F refers to purine fluorine and F′ to sugar fluorine. Ultraviolet absorption spectra were determined on a Perkin-Elmer Lambda 9 spectrometer by dissolving each compound in ethanol and diluting 10-fold with 0.1 N HCl, pH 7 buffer, and 0.1 N NaOH. Numbers in parentheses are extinction coefficients ($\epsilon \times 10^{-3}$); sh = shoulder. Microanalyses were performed by Atlantic Microlab, Inc. (Atlanta, GA) or the Molecular Spectroscopy Section of Southern Research Institute. Analytical results indicated by elemental symbols were within ±0.4% of the theoretical values. Where solvents were noted as part of the elemental analysis, they were seen in the ^{1}H NMR spectrum 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 on a Hewlett-Packard HP 1084B liquid chromatograph with a Waters Associates μBondapak C_{18} column (3.9 mm × 30 cm) with UV monitoring (254 nm). All flash column chromatography used 230–400 mesh silica gel from E. Merck. TLC was done on Analtech precoated (250 μm) silica gel (GF) plates. The Bio-Beads SM-4 macroporous adsorbent (20–50 mesh) was obtained from Bio-Rad.

2,6-Dibromo-9-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purine (4a). A solution of 3-acetyl-5-benzoyl-2-deoxy-2-fluoroarabinofuranosyl bromide (2)[9,11] (~12 g, 33.2 mmol) in 400 mL of dry dichloroethane was stirred for 10 min with 4A molecular sieve (250 mL) before the addition of 2,6-dibromopurine (3) (9.3 g, 33.5 mmol).[10] The mixture was vigorously stirred with an overhead stirrer and placed in a preheated 100 °C oil bath. Heating was continued for 32 h until all the bromo sugar was consumed. (TLC, 2:1 cyclohexane–ethyl acetate, using 4-(4-nitrobenzyl)pyridine spray for detection.) After the mixture had cooled to room temperature, it was filtered through Celite. The solids were washed with dichloroethane, and the combined filtrates were evaporated to dryness in vacuo. The residue (16.5 g) was a mixture of three nucleosides that were separated by flash chromatography on 150 g of silica gel (230–400 mesh) using 2:1 cyclohexane–ethyl acetate as the eluting solvent. By combining pure fractions, the desired compound, which was the major nucleoside product, was obtained as a glass (3.64 g, 19.7%) that was chromatographically homogeneous but would not crystallize. A second column run on impure fractions gave 2.21 g (11.9%) more pure product for a total yield of 31.6%: MS *m/e* 557 $(M + 1)^+$; ^{1}H NMR ($CDCl_3$) δ 8.34 (d, 1, H-8, $^5J_{8,F'}$ = 3.0 Hz), 8.08 (m, 2, ortho phenyl hydrogens), 7.59 (m, 1, para phenyl hydrogen), 7.46 (m, 2, meta phenyl hydrogens), 6.54 (dd, 1, H-1′, $J_{1',2'}$ = 2.7 Hz, $J_{1',F'}$ = 22.0 Hz), 5.52 (dd, 1, H-3′, $J_{3',4'}$ = 2.5 Hz, $J_{3',F'}$ = 16.4 Hz), 5.22 (br dd, 1, H-2′, $J_{2',F'}$ = 49.9 Hz), 4.74 (m, 2, 5′-CH_2, $J_{4',5'}$ = 4.6 Hz), 4.45 (m, 1, H-4′), 2.22 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.25 (CO, acetyl), 166.06 (CO, benzoyl), 151.08 (C-4), 144.67 (d, C-8, $^4J_{8,F'}$ = 6.3 Hz), 143.80, 143.19 (C-2,6), 133.64 (C-5), 133.47 (para carbon), 129.70 (ortho carbons), 129.23 (ipso carbon), 128.56 (meta carbons), 92.35 (d, C-2′, $^1J_{2',F'}$ = 192.7 Hz), 83.80 (d, C-1′, $^2J_{1',F'}$ = 16.8 Hz), 81.78 (C-4′), 76.04 (d, C-3′, $^2J_{3',F'}$ = 30.3 Hz), 62.94 (C-5′), 20.64 (CH_3). Anal. ($C_{19}H_{15}Br_2FN_4O_5 \cdot 0.2C_6H_{12}$) C, H, N. The more abundant of the two other products was isolated and characterized as 2,6-dibromo-9-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-α-D-arabinofuranosyl)-9*H*-purine: ^{1}H NMR ($CDCl_3$) δ 8.26 (s, 1, H-8), 8.08 (m, 2, ortho phenyl hydrogens), 7.60 (m, 1, para phenyl hydrogens), 7.46 (m, 2, meta phenyl hydrogens), 6.51 (br dd, 1, H-1′, $J_{1',2'}$ = 1.4 Hz, $J_{1',F'}$ = 15.0 Hz), 5.78 (dt, 1, H-2′, $J_{2',F'}$ = 48.7 Hz, $J_{2',3'}$ = 1.6 Hz), 5.57 (dddd, 1, H-3′, $J_{3',F'}$ = 17.4 Hz, $J_{3',4'}$ = 3.1 Hz, $J_{1',3'}$ = 0.6 Hz), 4.85 (m, 1, H-4′), 4.64 (d, 2, H-5′, $J_{4',5'}$ = 5.1 Hz), 2.05 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.13 (CO, acetyl), 166.01 (CO, benzoyl), 150.73 (C-4), 143.98, 143.39 (C-2, C-6), 143.22 (C-8), 134.27 (C-5), 133.43 (para carbon), 129.76 (ortho carbons), 129.19 (ipso carbon), 128.49 (meta carbons), 96.74 (d, C-2′, $^1J_{C2',F'}$ = 190.5 Hz), 89.38 (d, C-1′, $^2J_{1',F'}$ = 36.9 Hz), 84.66 (C-4′), 76.24 (d, C-3′, $^2J_{3',F'}$ = 29.8 Hz), 63.08 (C-5′), 20.53 (CH_3). That this nucleoside is the α-anomer of **4a** was confirmed by NOE. Irradiation of H-4′ showed a 2.4% NOE of the H-8 signal and irradiation of H-8 resulted in a 2.5% NOE of the H-4′ signal, which demonstrates that the base and H-4′ are on the same side of the sugar ring. The coupling of both C-8 ($^3J_{C-6,H-1'}$ = 3.2 Hz) and C-4 ($^3J_{C-4,H-1'}$ = 2.1 Hz) with H-1′ of the sugar, confirmed by selective decoupling of H-1′, established the point of attachment at N-9.

2-Bromo-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (4b). A solution of **4a** (5.84 g, 10.5 mmol) in 400 mL of ethanolic ammonia (saturated at 0 °C) was sealed in a glass-lined stainless steel bomb and left at room temperature for 3 days. The solution was evaporated to dryness and evaporated with ethanol to remove ammonia. The residue, containing the desired product and 5′-benzoyl compound, was dissolved in 440 mL of acetonitrile and 120 mL of water. Lithium hydroxide monohydrate (881 mg, 21 mmol) was added, and the solution was stirred for 16 h at room temperature. Thin-layer chromatography (5:1 $CHCl_3$–MeOH) indicated complete reaction. The chilled solution was carefully neutralized with glacial acetic acid and evaporated to dryness. The white solid residue was recrystallized from water. The product was dried in vacuo at room temperature at 100 °C for 2 h to yield 2.15 g (59.2%): mp 209–210 °C; TLC, 5:1 $CHCl_3$–MeOH, R_f 0.47; HPLC, 99.8%, 9:1 H_2O–MeCN; MS *m/e* 348 $(M + 1)^+$; UV λ_{max} pH 1, 264 (14.3); pH 7, 264 (14.9); pH 13, 264 (15.2); ^{1}H NMR (Me_2SO-d_6) δ 8.25 (d, 1, H-8, $^5J_{8,F'}$ = 2.0 Hz), 7.88 (br s, 2, NH_2), 6.31 (dd, 1, H-1′, $J_{1',2'}$ = 4.7 Hz, $J_{1',F'}$ = 13.9 Hz), 5.96 (d, 1, 3′-OH, $J_{3',3'\text{-OH}}$ = 5.1 Hz), 5.32 (dt, 1, H-2′, $J_{2',3'}$ = 4.0 Hz, $J_{2',F'}$ = 52.8 Hz), 5.07 (t, 1, 5′-OH, $J_{5',5'\text{-OH}}$ = 5.6 Hz), 4.43 (dq, 1, H-3′, $J_{3',4'}$ = 4.0 Hz, $J_{3',F'}$ = 21.1 Hz), 3.84 (m, 1, H-4′), 3.66 (m, 2,5′-CH_2, $J_{4',5'a}$ = $J_{4',5'b}$ = 6.0 Hz, $J_{5'a,5'b}$ = 13.0 Hz). Anal. ($C_{10}H_{11}BrFN_5O_3$) C, H, N.

2-Chloro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (4d). A solution of **4c**[9] (5.1 g, 10.9 mmol) in ethanol saturated (0 °C) with anhydrous ammonia (100 mL) was placed in a glass-lined stainless steel bomb and left at room temperature for 3 days. TLC (2:1 cyclohexane–ethyl acetate and 5:1 $CHCl_3$–MeOH) indicated the absence of starting material. However, two major products were present, the desired compound and its 5′-*O*-benzoyl analogue. The solution was evaporated to

dryness and coevaporated with acetonitrile. The residue was dissolved in acetonitrile (100 mL) and diluted with water (60 mL) before the addition of lithium hydroxide monohydrate (915 mg, 21.8 mmol). The solution was stirred at room temperature for 3 h, at which time TLC (5:1 $CHCl_3$–MeOH) indicated complete reaction. The solution was cooled, neutralized with acetic acid, and evaporated to dryness. Three recrystallizations from water gave the pure compound (1.4 g, 42.3%): mp 225–227 °C; TLC, 5:1 $CHCl_3$–MeOH, R_f 0.40; HPLC, 99%, 4:1 H_2O–MeCN; MS m/e 304 $(M + 1)^+$; UV λ_{max} pH 1, 263 (14.3); pH 7, 263 (15.3); pH 13, 263 (15.4); ^1H NMR (Me_2SO-d_6) δ 8.28 (d, 1, H-8, $^5J_{8,F'}$ = 2.5 Hz), 7.88 (br s, 2, NH_2), 6.33 (dd, 1, H-1′, $J_{1',2'}$ = 4.6 Hz, $J_{1',F'}$ = 13.9 Hz), 5.96 (d, 1, 3′-OH, $J_{3',3'\text{-OH}}$ = 5.1 Hz), 5.23 (dt, 1, H-2′, $J_{2',3'}$ = 3.9 Hz, $J_{2',F'}$ = 52.6 Hz), 5.08 (t, 1, 5′-OH, $J_{5',5'\text{-OH}}$ = 5.7 Hz), 4.43 (dq, 1, H-3′, $J_{3',F'}$ = 19.0 Hz), 3.86 (m, 1, H-4′, $J_{3',4'}$ = 4.4 Hz), 3.64 (m, 2, 5′-CH_2, $J_{4',5'a}$ = 4.8 Hz, $J_{4',5'b}$ = 5.8 Hz, $J_{5'a,5'b}$ = 11.8 Hz. Anal. ($C_{10}H_{11}ClFN_5O_3$) C, H, N.

2-Fluoro-9-(3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (4f). Diamino compound **4e**[9] (700 mg, 1.63 mmol) was dissolved in 3:2 HF–pyridine (15 mL) at −25 °C and treated with *tert*-butyl nitrite (271 μL, 2.28 mmol).[13] After 1 h at −20 °C, the reaction was incomplete as indicated by TLC. More *tert*-butyl nitrite (70 μL, 0.59 mmol) was added, and the reaction was held at −20 °C for an additional 2 h. The cold reaction solution was added dropwise to saturated aqueous $NaHCO_3$ (1 L) containing ice. The foaming mixture was stirred vigorously for 20 min and then diluted with $CHCl_3$ (300 mL). The layers were separated, and the aqueous layer was extracted with more $CHCl_3$ (2 × 175 mL). The combined organic extracts were washed with water (3 × 175 mL), dried ($MgSO_4$), and evaporated to dryness. This residue in $CHCl_3$ was applied to a flash column containing 50 g of silica gel (230–400 mesh) with $CHCl_3$ as eluant. Fractions were combined to give essentially pure **4f** (500 mg, 70%). Crystallization of a small sample from EtOH gave pure **4f**: mp 208–209 °C; TLC, 95:5 $CHCl_3$–MeOH, R_f 0.45; HPLC, 99%; 1:1 H_2O–MeCN; MS m/e 434 $(M + 1)^+$; ^1H NMR (Me_2SO-d_6) δ 8.14 (d, H-8, $^5J_{8,F'}$ = 2.7 Hz), 8.00 (m, 2, ortho phenyl protons), 7.97 (br s, 2, NH_2), 7.68 (m, 1, para phenyl proton), 7.55 (m, 2, meta phenyl protons), 6.39 (dd, H-1′, $J_{1',2'}$ = 4.0 Hz, $J_{1',F'}$ = 18.0 Hz), 5.67 (m, 1, H-3′, $J_{3',4'}$ = 4.0 Hz, $J_{3',F'}$ = 18.9 Hz), 5.56 (ddd, 1, H-2′, $J_{2',3'}$ = 2.6 Hz, $J_{2',F'}$ = 50.6 Hz), 4.70 (A part of an ABX spin system, 1, H-5′a, $J_{5'a,5'b}$ = 12.0 Hz, $J_{4',5'a}$ = 3.8 Hz), 4.63 (B part of an ABX spin system, 1, H-5′b, $J_{4',5'b}$ = 5.7 Hz), 4.47 (dt, 1, H-4′), 2.15 (s, 3, CH_3). Anal. ($C_{19}H_{17}F_2N_5O_5$) C, H, N.

2-Fluoro-9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (4g). A suspension of **4f** (430 mg, 0.99 mmol) in 1:1 MeCN–H_2O (40 mL) was treated in one portion with solid lithium hydroxide monohydrate (125 mg, 2.97 mmol), a clear solution forming after stirring at room temperature for 20 min. A 3-h TLC aliquot showed the deblocking to be complete. Glacial acetic acid (57 μL) was added, and the solution was evaporated until a white solid deposited. After being chilled, the solid was collected, washed with cold water, and dried in vacuo at room temperature to give crude **4g** (252 mg). This solid was dissolved in 40 mL of water and applied to a water-equilibrated SM-4 Bio-Bead column (1.5 × 32 cm). After initial elution with water, the product was eluted with a stepwise gradient of 5% → 20% EtOH in water. The residue from the combined evaporated column fractions was crystallized from 25 mL of boiling water with charcoal treatment and dried in vacuo at 56 °C for 16 h to give pure **4g** (178 mg, 59%): mp 207–209 °C; TLC, 5:1 $CHCl_3$–MeOH, R_f 0.50; HPLC, 99%, 9:1 H_2O–MeCN; MS m/e 288 $(M + 1)^+$; UV λ_{max} pH 1, 261 (14.0), 268 (sh); pH 7, 260 (15.1), 268 (sh); pH 13, 261 (14.9), 268 (sh); ^1H NMR (Me_2SO-d_6) δ 8.24 (d, 1, H-8, $^5J_{8,F'}$ = 2.0 Hz), 7.90 (br s, 2, NH_2), 6.29 (dd, 1, H-1′, $J_{1',2'}$ = 4.6 Hz, $J_{1',F'}$ = 13.8 Hz), 5.97 (d, 1, 3′-OH, $J_{3',3'\text{-OH}}$ = 4.9 Hz), 5.22 (dt, 1, H-2′, $J_{2',3'}$ = 4.0 Hz, $J_{2',F'}$ = 52.7 Hz), 5.10 (t, 1, 5′-OH, $J_{5',5'\text{-OH}}$ = 5.6 Hz), 4.43 (dq, 1, H-3′, $J_{3',F'}$ = 18.9 Hz), 3.85 (m, 1, H-4′, $J_{3',4'}$ = 4.5 Hz), 3.66 (m, 2, 5′-CH_2, $J_{4',5'a}$ = 6.0 Hz, $J_{4',5'b}$ = 4.5 Hz, $J_{5'a,5'b}$ = 12.0 Hz). Anal. ($C_{10}H_{11}F_2N_5O_3 \cdot H_2O$) C, H, N.

2-Fluoro-9-(5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (4h). A suspension of **4f** (312 mg, 0.72 mmol) in MeOH (25 mL) at 10 °C was treated with solid $NaHCO_3$ (181 mg, 2.16 mmol).[14] After being stirred at room temperature for 2.5 h, the reaction was quenched by the addition of glacial acetic acid (170 μL) and evaporated to dryness. This residue in hot EtOH was applied to two silica gel thick plates (Analtech, GF, 2000 μm) that were developed in 9:1 $CHCl_3$–MeOH. The product was extracted with hot EtOH and evaporated to dryness to give essentially pure **4h** (208 mg, 74%): MS m/e 392 $(M + 1)^+$. This material was used directly in the next step.

2-Fluoro-9-(5-*O*-benzoyl-2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (5a). Compound **4h** (191 mg, 0.49 mmol) was dissolved in dry acetonitrile (20 mL) at 45 °C and then treated with 1,1′-(thiocarbonyl)diimidazole (339 mg, 1.7 mmol).[15] The resulting cloudy yellow solution was stirred under N_2 at 45 °C for 24 h at which time TLC analysis (EtOAc) showed one major product. The reaction was evaporated to dryness, and the residue was dissolved in dry toluene (15 mL). Addition of AIBN (13.7 mg, 0.08 mmol) and tri-*n*-butyltin hydride (1.3 mL, 4.7 mmol) produced a yellow mixture that was placed directly in a 120 °C bath. A clear solution was observed after a 5-min reflux, and after 1 h the reaction was complete as indicated by TLC. The solvent was removed in vacuo, and the resulting syrup was coevaporated once with EtOH. Trituration of this residue with petroleum ether (50 mL) produced a white solid that was collected and washed with fresh solvent to give 214 mg of crude **5a**. This material in hot EtOH was applied to two Analtech silica gel plates (GF, 2000 μm). After three developments in 9:1 $CHCl_3$–MeOH, the product band was extracted with boiling EtOH. The residue from evaporation of the combined extracts was crystallized from boiling EtOH to yield sufficiently pure **5a** (160 mg, 87%): mp 215–217 °C; MS m/e 376 $(M + 1)^+$. Without any further purification, this material was used in the deprotection step below.

2-Fluoro-9-(2,3-dideoxy-2-fluoro-β-D-arabinofuranosyl)-9*H*-purin-6-amine (5b). A suspension of **5a** (135 mg, 0.36 mmol) in 3:1 MeCN–H_2O was treated in one portion at room temperature with solid $LiOH \cdot H_2O$ (38 mg, 0.9 mmol). The stirred mixture became a clear solution after 0.5 h. At 7 h an aliquot examined by TLC (5:1 $CHCl_3$–MeOH) showed the absence of **5a**. Glacial acetic acid (35 μL) was added, and the reaction was evaporated to dryness. This residue in hot acetonitrile was applied to one silica gel thick plate (Analtech, GF, 2000 μm). After the plate was developed three times in 5:1 $CHCl_3$–MeOH, the product band was extracted with boiling MeCN. Evaporation of this extract gave slightly impure material that was chromatographed as above on three prep plates (Analtech, GF, 1000 μm). The resulting residue was crystallized from boiling H_2O (25 mL) containing EtOH (0.5 mL). The white solid was collected, washed with cold H_2O, and dried in vacuo at 56 °C for 16 h to give pure **5b** (71 mg 73%): mp 249–250 °C; TLC, 5:1 $CHCl_3$–MeOH, R_f 0.60; HPLC, 100%, 85:15 H_2O–MeCN; MS m/e 272 $(M + 1)^+$; UV λ_{max} pH 1, 261 (13.6), 268 (sh); pH 7 and pH 13, 260 (15.0), 268 (sh); ^1H NMR (Me_2SO-d_6) δ 8.25 (d, 1, H-8, $J_{8,F'}$ = 2.3 Hz), 7.89 (br s, 2, NH_2), 6.20 (dd, 1, H-1′, $J_{1',2'}$ = 3.9 Hz, $J_{1',F'}$ = 15.7 Hz), 5.43 (dm, 1, H-2′, $J_{2',3'a}$ = 3.7 Hz, $J_{2',3'b}$ = 6.0 Hz, $J_{2',F'}$ = 54.4 Hz), 4.17 (m, 1, H-4′), 3.62 (B part of an ABX spin system, 1, H-5′b, $J_{4',5'b}$ = 4.3 Hz, $J_{5'a,5'b}$ = 12.0 Hz), 3.59 (A part of an ABX spin system, 1, $J_{4',5'a}$ = 5.3 Hz), 2.55 (dddd, 1, H-3′b, $J_{3'b,4'}$ = 7.6 Hz, $J_{3'a,3'b}$ = 14.2 Hz, $J_{F',3'b}$ = 28.1 Hz), 2.24 (dddd, 1, H-3′a, $J_{3'a,4'}$ = 6.3 Hz, $J_{F',3'a}$ = 27.1 Hz). Anal. ($C_{10}H_{11}F_2N_5O_2$) C, H, N.

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Registry No. **2**, 56632-81-6; **3**, 1196-41-4; **4a**, 134217-12-2; **4a**(α-anomer), 137648-19-2; **4b**, 134217-13-3; **4c**, 103884-99-7; **4d**, 123318-82-1; **4e**, 103885-02-5; **4f**, 134217-14-4; **4g**, 134217-15-5; **4h**, 137648-18-1; **5a**, 137648-17-0; **5b**, 137648-20-5.