Synthesis and Biological Activity of Certain 4′-Thio-D-arabinofuranosylpurine Nucleosides

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A series of 4′-thio-D-arabinofuranosylpurine nucleosides was prepared and evaluated as potential anticancer agents. The details of a convenient and high-yielding synthesis of the carbohydrate precursor 1-*O*-acetyl-2,3,5-tri-*O*-benzyl-4-thio-D-arabinofuranose (**6**) are presented. Proof of structure and configuration at all chiral centers of the nucleosides was obtained through an X-ray crystal structure of **9**α as well as through NOE experiments on **9**β and **9**α. All six target compounds were evaluated in a series of human cancer cell lines in culture. Two target compounds, β anomers with diaminopurine (**12**) and guanine (**16**) as the bases, had significant cytotoxicity. One of these compounds (**12**) was selected for animal studies but was found to have no selectivity at the maximum tolerated dose in the murine colon 36 tumor model.

Interest in the synthesis and biological evaluation of purine nucleosides and their analogues has continued in recent years as new structures have been found to have clinical activity as both anticancer[1] and antiviral agents.[2] Fludarabine phosphate, which was developed in our laboratory,[3] has shown activity in a number of human cancers[4] and has been approved by the FDA for the treatment of refractory lymphocytic leukemia. The 2-bromo-, 2-chloro-, and 2-fluoro-2′-deoxyadenosines all have shown outstanding activity in murine leukemia models,[5] and the 2-chloro compound, known as cladribine,[6] has received FDA approval for the treatment of hairy cell leukemia. All of these 2-haloadenine nucleosides are resistant to deamination by adenosine deaminase[5] and are converted to the corresponding triphosphates. The 2-halo-2′-deoxyadenosines are readily cleaved by *Escherichia coli* purine nucleoside phosphorylase (PNP) to the 2-haloadenines, which have no selective cytotoxicity.[7] 2-Fluoroadenine has been detected as a metabolite of fludarabine phosphate in animals[8] and humans,[9] though the *arabino* nucleosides are considerably more stable to enzymatic and hydrolytic degradation than the 2′-deoxy compounds. Some years ago the resistance of 4′-thioinosine to cleavage by PNP was reported,[10] suggesting that this simple structural modification might impart resistance to phosphorolytic cleavage to nucleosides.

On the basis of these considerations, we have undertaken the synthesis and biological evaluation of a broad series of 4′-thionucleosides with modifications in both the nitrogen heterocyclic and the carbohydrate moieties.[11−16] A few 4′-thionucleosides were prepared some years ago, though researchers were hampered by laborious synthetic procedures.[17−24] Interest by many laboratories in the synthesis of various 4′-thionucleosides has heightened recently as it has become clear that this modification imparts desirable physical and biological properties to certain members of the class, as either the nucleoside or incorporated into oligonucleotide chains.[25] As a part of our research focused on the development of new anticancer agents, we decided to pursue the synthesis of certain 4′-thionucleosides with the *arabino* configuration in the carbohydrate. Some structures of this type were made over 20 years ago,[18,20,22] and in particular our interest was prompted by the significant cytotoxicity reported for 4′-thio-ara-C.[22] As noted above, a significant problem in obtaining these compounds is the laborious synthetic routes,[26] which have been a major deterrent to obtaining sufficient quantities to carry out both cell culture and animal investigations. Our work in the area of 4′-thioarabinofuranosyl nucleosides was initially disclosed several years ago.[15] Since then, another synthesis of 4′-thioarabinofuranosyl nucleosides has been reported, utilizing a very different and much longer synthetic approach to the key carbohydrate intermediate.[27]

We herein report the details of a convenient synthesis of a 4-thioarabinofuranose intermediate suitable for conversion to nucleosides and its conversion to a series of purine nucleoside analogues. These compounds have been examined in anticancer screens, and both in vitro and in vivo data are presented herein. To firmly establish the identity of the carbohydrate as well as the anomeric configuration of the nucleoside, the structure of one compound (**9**α) has been determined by X-ray crystallography, and that compound along with its anomer (**9**β) have been examined in detail using NMR spectroscopy.

Chemistry

We have developed a five-step sequence to the versatile carbohydrate precursor **6** using a strategy similar to that previously used in our laboratory[13] to prepare 2′-deoxy-4′-thionucleosides. The attractive features of intermediate **6** include its ready accessibility as well as

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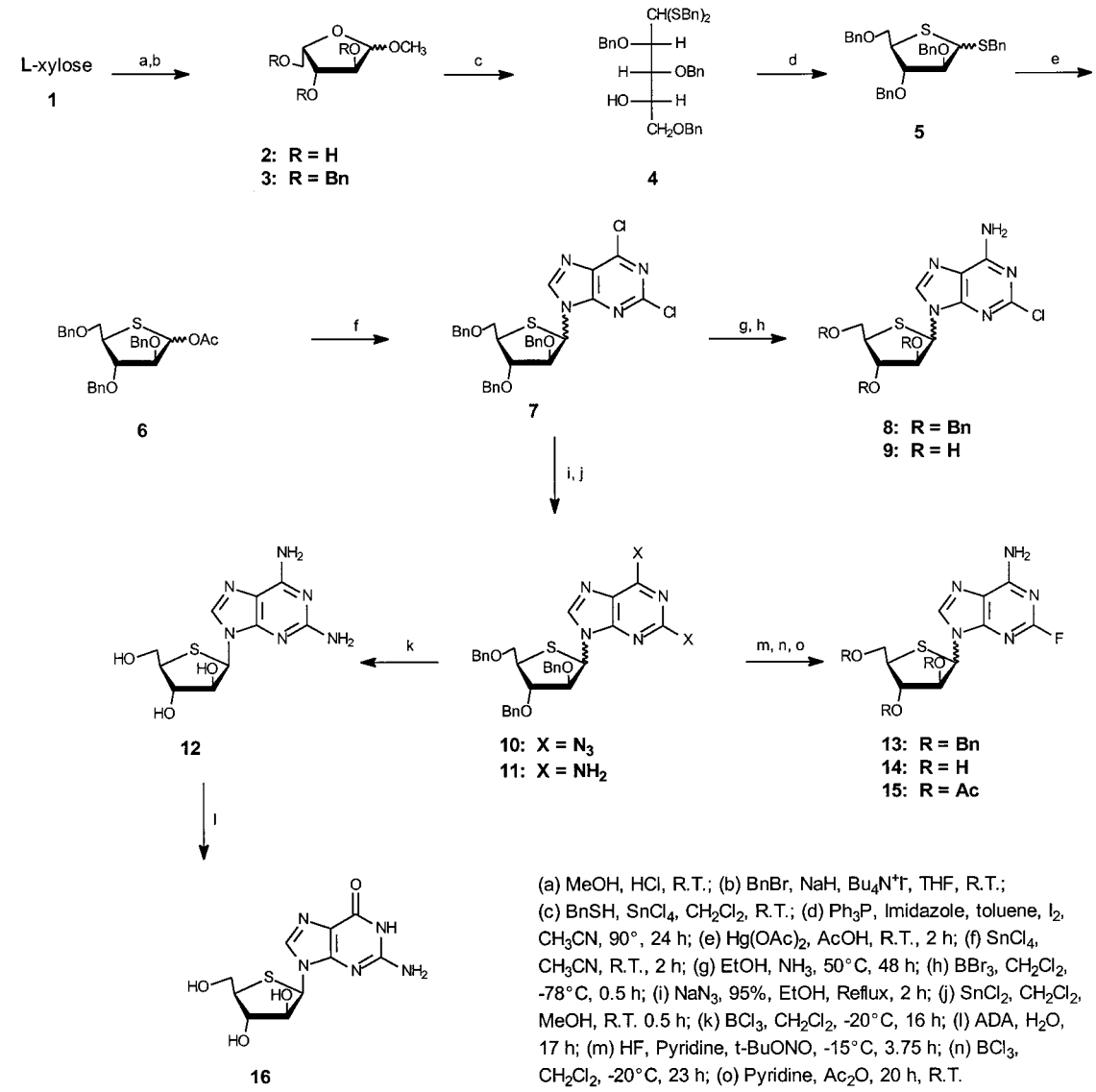
Scheme 1



(a) MeOH, HCl, R.T.; (b) BnBr, NaH, $Bu_4N^+I^-$, THF, R.T.; (c) BnSH, $SnCl_4$, CH_2Cl_2, R.T.; (d) Ph_3P, Imidazole, toluene, I_2, CH_3CN, 90°, 24 h; (e) $Hg(OAc)_2$, AcOH, R.T., 2 h; (f) $SnCl_4$, CH_3CN, R.T., 2 h; (g) EtOH, NH_3, 50°C, 48 h; (h) BBr_3, CH_2Cl_2, -78°C, 0.5 h; (i) NaN_3, 95%, EtOH, Reflux, 2 h; (j) $SnCl_2$, CH_2Cl_2, MeOH, R.T. 0.5 h; (k) BCl_3, CH_2Cl_2, -20°C, 16 h; (l) ADA, H_2O, 17 h; (m) HF, Pyridine, t-BuONO, -15°C, 3.75 h; (n) BCl_3, CH_2Cl_2, -20°C, 23 h; (o) Pyridine, Ac_2O, 20 h, R.T.

the availability of both α and *β* anomers for biological evaluation. Conversion of L-xylose to methyl 2,3,5-tri-*O*-benzyl-L-xylofuranoside (**3**) was accomplished in two steps by the usual method (Scheme 1). Conversion to dibenzyl dithioacetal **4** employing benzyl mercaptan and stannic chloride proceeded in 57% yield after chromatographic purification. Cyclization at C-4 involving a single inversion, thus converting the L-*xylo* to the D-*arabino* configuration, was accomplished with triphenylphosphine, iodine, and imidazole as previously described.[13] The final step, replacement of the benzylthio group at C-1 by an acetoxy group, involved treatment of **5** with mercuric acetate in acetic acid at room temperature. The overall yield of **6** from **1**, including four column purifications, was 30%, and afforded a ca. 1:1 mixture of α and *β* anomers. The other recently reported synthesis of **6** requires 13 steps with an overall yield of <10%.[27]

A series of purine nucleoside analogues were prepared through the coupling of **6** and 2,6-dichloropurine. A Lewis acid-catalyzed reaction utilizing $SnCl_4$ in acetonitrile was found to be an efficient method to achieve this coupling, and 40% and 35% yields of *β* and α anomers of **7** were obtained after chromatographic purification/separation. After treatment with ethanolic ammonia to produce the respective blocked 2-chloroadenine nucleosides **8***β* and **8**α, removal of the *O*-benzyl groups was accomplished with BBr_3 in CH_2Cl_2 at −78 °C to yield the final nucleoside targets **9***β* and **9**α. Treatment of **7***β* and **7**α with sodium azide in aqueous ethanol at reflux produced the corresponding 2,6-diazido intermediates **10**, which were subjected to reduction with $SnCl_2$ in CH_2Cl_2 to afford the blocked diaminopurine nucleosides **11***β* and **11**α in good yields. Deblocking **11***β* with BCl_3 in CH_2Cl_2 produced the target diamino nucleoside **12**. Conversion of **12** to the corresponding guanine nucleoside **16** was accomplished by treatment with adenosine deaminase. Though the deamination was slow, it went to completion at room temperature in 15−20 h. The 2-fluoroadenine nucleosides **14***β* and **14**α were also prepared starting from the separated diaminopurine nucleoside anomers **11***β* and **11**α. These compounds were treated with HF−pyridine and *tert*-butyl nitrite to produce the blocked 2-fluoroadenine nucleosides **13***β* and **13**α, which were deblocked with BCl_3 to the final target nucleosides. An acetylation/deacetylation sequence via **15**α was used to facilitate the purification of the intractable solid **13**α.

Table 1. NOE Data (Hz)[a]

compd	atom irradiated	H-8	H-1′	H-2′	H-3′	H-4′
9α	H-8		2.1	3.8		
	H-1′	2.0		2.0	1.2	
	H-2′	3.7	2.7		1.7	1.9
	H-3′		1.3	1.0		
	H-4′			1.9		
9β	H-8		1.0		7.3	
	H-1′	1.0		8.7		
	H-2′		9.7			3.8
	H-3′	7.8				1.5
	H-4′		5.4		1.7	

[a] See Experimental Section for details.

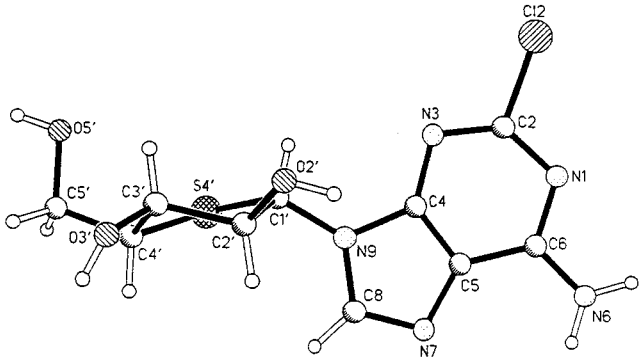


Figure 1. ORTEP drawing of **9**α.

To provide confirmatory evidence that the carbohydrate configuration and the anomeric configurations of our target compounds had been properly assigned, the NMR spectra of several compounds were examined by NOE difference spectroscopy (see Table 1). Specifically, NOE experiments were conducted on **9**α in Me_2SO-d_6 with 1 drop of D_2O, while those of **9**β were conducted in D_2O solution because of the severe overlap of the H-2′ and H-3′ resonances in Me_2SO-d_6. In both compounds, contacts between H-2′ and H-4′ demonstrated that the single inversion desired in converting **4** to **5** had indeed occurred. The NOE contacts between H-1′ and H-3′ confirm that **9**α is the α isomer, while irradiation of the H-8 signal of **9**β, causing enhancement of the H-3′ signal, confirms it as the β anomer. Both **9**β and **9**α appear to adopt predominantly the N conformation in solution. In **9**β, the large NOE between H-2′ and H-4′ and that between H-1′ and H-8 as well as the large $J_{2',3'}$ of 9.5 Hz support the N conformation. Similarly, the moderate NOE between H-2′ and H-4′, the NOE between H-1′ and H-3′, and the $J_{2',3'}$ of 7.7 Hz show that **9**α is also in the N conformation.

As a final structural proof for the series, and in order to corroborate the NMR assignments and to compare the carbohydrate conformation in solution and the solid state, the crystal structure of **9**α was determined by single-crystal X-ray diffraction analysis (Figure 1). The N conformation found for **9**α and shown in Figure 1 is consistent with the NMR data reported above. The X-ray analysis also confirms the α anomeric configuration. The arabinosyl group adopts a C2′-exo−C3′-endo pucker with a calculated pseudorotation of 8.22°.[28] The substitution of a sulfur for an oxygen in the sugar ring does not significantly affect the ring's geometry or conformation, as has been noted previously.[29] The endocyclic torsion angles starting with S4′ and proceeding around the S4′−C1′−C2′−C3′−C4′ ring are 7.6°, −33.3°, 49.9°, −42.7°, and 20.4°, respectively. The glycosidic torsion angle C8−N9−C1′−S4′ has a value of −57.71°. Crystallographic analysis show that the O5′-hydroxyl of **9**α is gauche−gauche with a torsion angle S4′−C4′−C5′−O5′ equal to −59.15°. The C1′ atom deviates from the mean plane through the purine base atoms by −0.14 Å, while the C3′ atom deviates by 0.64 Å from the mean plane through the four remaining sugar atoms and is in agreement with standard values.[28] Intermolecular hydrogen bonds stabilize the crystal packing of the compound. Hydrogen bonds form between O3′ and N1 atoms on two separate molecules (3.24 and 3.18 Å). The O5′ position hydrogen bonds to both N1 and O3′ (2.81 and 2.75 Å) and a final hydrogen bond joins O2′ and N7 (2.67 Å).

Table 2. Cytotoxicity Data: IC_{50} (μM)[a,b]

compd	CCRF-CEM (leukemia)	CAKI-1 (renal)	DLD-1 (colon)	NCI-H23 (lung)	SK-MEL-28 (melanoma)	SNB-7 (CNS)
12	0.34 (>134)[c]	20	>25	>25	0.34	1.0
14β	30	10	>90	>90	>90	>90
14α	>130	20	>100	>100	>100	>100
16	0.57	14	>20	>20	1.1	1.1

[a] Experimental details for the cell culture experiments on CCRF-CEM cells are in ref 32; experimental details for the other cell lines are in refs 33−35. [b] No cytotoxicity was seen for **9**β or **9**α at the highest concentration used: **9**β, 100 μM; **9**α, 200 μM. [c] In the presence of 2′-deoxycoformycin.

Biological Data

The cell culture cytotoxicity of all six target compounds was determined against six different human cancer cell lines, identified in Table 2. Neither of the two 2-chloroadenine-substituted nucleosides **9**β and **9**α was found to be cytotoxic in any of the cell lines at the highest concentrations utilized (see Table 2 footnote). Significant cytotoxicity was seen with both **12** and **16**, the diaminopurine and guanine analogues with the β configuration. Yoshimura et al. also reported significant cytotoxicity for these compounds in one cell line.[27] To determine whether **12** was cytotoxic as the diaminopurine nucleoside, or whether it required deamination in order to exert its cytotoxicity, it was incubated with CEM cells in the presence of 2′-deoxycoformycin, a potent inhibitor of adenosine deaminase. Under those conditions, no cytotoxicity was seen for **12**, leading to the conclusion that **16** is the cytotoxic agent. Modest cytotoxicity was seen for both **14**β and **14**α against the CAKI-1 renal line, and **14**β also had very modest activity against CEM cells. On the basis of these results, we prepared larger quantities of **12** for evaluation in an animal model. With nucleoside antimetabolites, we initiate animal evaluations using the murine colon 36 model in female CD2F1 mice, which has proven to be a good indicator of selectivity in compounds of this type. After subcutaneous tumor implantation, the drug was given by intraperitoneal injection three times a day at 4-h intervals for 9 days. The drug proved to be surprisingly toxic, and the maximum tolerated dose range was 0.004−0.016 mg/kg/dose. At these levels no selective inhibition of tumor growth was observed.

Experimental Section

Melting points were determined on a Mel-Temp apparatus and are uncorrected. ^1H NMR spectra were recorded on a Nicolet NT-300 NB spectrometer operating at 300.635 MHz (^1H). Chemical shifts are expressed in parts per million

downfield from tetramethylsilane. The NOE experiments were conducted on a degassed solution of DMSO-d_6. To minimize the effects of magnetic perturbations with the sample nonspinning, eight FIDs were acquired with the decoupler set to a desired frequency and eight FIDs were recorded with the decoupler off resonance. The process was repeated until 800 FIDs had been acquired. UV absorption spectra were determined on 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 ($\epsilon \times 10^{-3}$), 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. 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 HP1084B liquid chromatograph with a Waters Associates μBondapak C_{18} column (3.9 mm × 30 cm) and UV monitoring (254 nm). All chromatographic separations were carried out by flash chromatography using 230−400 mesh silica gel from E. Merck. TLC was carried out on Analtech precoated (250 μm) silica gel (GF) plates.

Crystallography. Crystals of **9**α suitable for X-ray diffraction studies were obtained by recrystallization from a 50% EtOH/H_2O solution. The crystal chosen for data collection was thin and platelike with approximate dimensions of 0.30 × 0.08 × 0.01 mm. The crystal belongs to the orthorhombic space group $P2_12_12_1$ with a = 5.1470(10) Å, b = 10.826(2) Å, c = 23.187(3) Å, V = 1292.0(4) Å^3, Z = 4, and D_{calc} = 1.634 g/cm^3. Intensities were measured on a Nicolet P3 single-crystal X-ray diffractometer using graphite monochromatized Cu Kα radiation (λ = 1.5418 Å) and $\omega-2\theta$ scans. Corrections were made for Lorentz and polarization effects but not for absorption (μ = 4.301 mm^{-1}). All crystallographic data collection was carried out using the Nicolet P3/V data collection system. A total of 1055 intensities were measured with $2\theta < 110.04°$. Of these reflections, 16 had a net intensity less than zero and were omitted from further calculations.

The structure was determined by direct methods using the computer program SHELXS-86[30] and refined using the computer program SHELXL-93.[31] All computations were performed using a Digital Equipment Corp. Alpha computer station. All non-hydrogen atoms were located from an *E*-map and their positions partially refined. All hydrogen atom positions were located using difference Fourier maps. The structure was refined using full-matrix least-squares analysis on F^2 in which all non-hydrogen atoms were given anisotropic thermal parameters. Hydrogen atoms were constrained to have idealized geometry with tetrahedral angles. The hydrogen atom coordinates were reidealized before each cycle and were tethered to the atoms to which they were attached. The final R factor for 1039 independent reflections and 181 variables was 0.0704, and the goodness-of-fit was 1.102. Figure 1 shows a computer-generated model of **9**α. Positional parameters and thermal parameters have been deposited as Supporting Information.

2,3,5-Tri-*O*-benzyl-L-xylose Dibenzyl Dithioacetal (4). L-Xylose (**1**; 25 g, 167 mmol) was stirred for 5 h in 0.5% HCl in MeOH (675 mL) at room temperature and then neutralized with Amberlite IRA-400 OH anion-exchange resin. The filtrate and washings were combined and evaporated to dryness, and the crude product was purified by silica gel chromatography ($CHCl_3$/MeOH, 92:8) to afford 26.2 g of methyl L-xylofuranoside (**2**; 95% yield) as an α and β (1:1) mixture: MS 164 $(M)^+$, 165 $(M + H)^+$, 133 $(M - OCH_3)^+$.

To an ice-cold solution of **2** (10 g, 60.9 mmol) in dry THF (350 mL) was added sodium hydride (60% dispersion in mineral oil, 14.8 g, 370 mmol), and the reaction mixture was stirred for 15 min under N_2. To this reaction mixture was added solid tetrabutylammonium iodide (0.36 g, 0.96 mmol) followed by a dropwise addition of benzyl bromide (36.6 g, 214 mmol). The reaction mixture was stirred for 3 days at room temperature. After the addition of CH_3OH (25 mL) the solution was evaporated under reduced pressure, and the crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 9:1) to afford pure methyl 2,3,5-tri-*O*-benzyl-L-xylofuranoside (**3**; 23 g, 87% yield): MS 435 $(M + H)^+$, 433 $(M - H)^+$, 403 $(M - OCH_3)^+$; ^{1}H NMR ($CDCl_3$) δ 7.38−7.25 (m, 30H, aromatic *H*'s), 4.94 (d, 1H, H-1α, $J_{1,2}$ = 4.3 Hz), 4.87 (d, 1H, H-1β, $J_{1,2}$ = 0.9 Hz), 4.64−4.45 (m, 10H, PhCH_2's), 4.37 (m, 1H, H-4α), 4.27 (dt, 1H, H-4β, $J_{4,5a}$ = 3.7 Hz, $J_{4,5b}$ = 6.5 Hz, $J_{3,4}$ = 6.2 Hz), 4.17 (t, 1H, H-3α, $J_{3,4}$ = 6.9 Hz, $J_{2,3}$ = 5.6 Hz), 4.07 (dd, 1H, H-3β, $J_{3,4}$ = 6.2 Hz, $J_{2,3}$ = 2.5 Hz), 4.00 (dd, 1H, H-2α, $J_{2,3}$ = 5.6 Hz), 3.95 (t, 1H, H-2β, $J_{2,3}$ =2.5 Hz), 3.70 (dd, 1H, H-5aα, $J_{4,5a}$ = 4.5 Hz, $J_{5a,5b}$ = 10.4 Hz), 3.66 (dd, 1H, H-5aβ, $J_{4,5a}$ = 3.7 Hz, $J_{5a,5b}$ =10.7 Hz), 3.54 (dd, 1H, H-5bα, $J_{4,5b}$ = 7.5 Hz), 3.49 (dd, 1H, H-5bβ, $J_{4,5b}$ = 6.5 Hz).

To a solution of **3** (42 g, 97 mmol) in CH_2Cl_2 (1000 mL) were added benzyl mercaptan (49.6 g, 400 mmol) and $SnCl_4$ (4.93 g, 18.9 mmol), and the reaction mixture was stirred at room temperature overnight. After neutralization with 5% aqueous $NaHCO_3$ (750 mL), the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (500 mL). The combined organic layers were evaporated, and crude **4** was purified by silica gel chromatography (cyclohexane/EtOAc, 99:1) to afford **4** (8.53 g, 57%) of sufficient purity to carry forward: MS 657 $(M + Li)^+$; ^{1}H NMR ($CDCl_3$) δ 7.35−7.29 (m, 19H, aromatic *H*'s), 7.19−7.13 (m, 4H, aromatic *H*'s), 7.01−6.96 (m, 2H aromatic *H*'s), 4.86 (d, 1H, PhCH*H*, J = 11.1 Hz), 4.70 (two overlapping d's, 2H, PhC*H*H, PhCH*H*, J = 11.1 Hz, J = 11.2 Hz), 4.43 (d, 1H, PhC*H*H, 11.2 Hz), 4.40 (d, 1H, PhCH*H*, J = 11.9 Hz), 4.36 (d, 1H, PhC*H*H, J = 11.9 Hz), 4.07 (dd, 1H, H-2, $J_{1,2}$ = 3.0 Hz, $J_{2,3}$ = 7.5 Hz), 3.75−3.67 (m, 4H, two PhCH_2's), 3.68 (d, 1H, H-1, $J_{1,2}$ = 3.0 Hz), 3.36−3.25 (m, 2H, H-4, H-5a), 3.15−3.12 (m, 1H, H-5b), 2.22 (d, 1H, 4-OH, J = 6.2 Hz).

2,3,5-Tri-*O*-benzyl-1-*O*-acetyl-4-thio-D-arabinofuranose (6). To a solution of **4** (13.0 g, 20 mmol) in dry 2:1 toluene/acetonitrile (200 mL) were added triphenylphosphine (15.7 g, 60 mmol), iodine (12.7 g, 50 mmol), and imidazole (5.44 g, 80 mmol). The reaction mixture was stirred at 90 °C for 24 h after which time the solution was evaporated to dryness. The crude product was purified by silica gel chromatography (cyclohexane/EtOAc, 4:1) to afford benzyl 2,3,5-tri-*O*-benzyl-1,4-dithio-D-arabinofuranoside as a syrup (**5**; 9.0 g, 83%): MS 543 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.40−7.20 (m, 20H, aromatic *H*'s), 4.69−4.42 (m, 6H, three PhCH_2O's), 4.37 (m, 1H, H-1), 4.20 (m, 2H, H-2, H-3), 3.87 (s, 2H, PhCH_2S-), 3.80 (dd, 1H, H-5a, $J_{4,5a}$ = 7.4 Hz, $J_{5a,5b}$ = 9.3 Hz), 3.55 (dd, 1H, H-5b, $J_{4,5b}$ = 7.1 Hz), 3.47 (m, 1H, H-4). Anal. ($C_{33}H_{34}O_3S_2$·0.25H_2O) C, H.

To a suspension of mercuric acetate (7.29 g, 22.9 mmol) in AcOH (96 g) was added **5** (5.42 g, 10 mmol), and the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and washed successively with water, saturated aqueous $NaHCO_3$, and 5% aqueous KCN solution. The organic layer was dried over Na_2SO_4 and concentrated. Chromatography of the crude product using cyclohexane/EtOAc (98:2) as eluent gave a mixture of α and β (1:1) anomers of **6** (3.73 g, 78%) as a colorless syrup: MS 479 $(M + H)^+$; ^{1} H NMR ($CDCl_3$) δ 7.35−7.23 (m, 15H, aromatic *H*'s), 6.07 (d, 0.25H, H-1β, $J_{1,2}$ = 4.0 Hz), 5.98 (d, 0.75H, H-1α, $J_{1,2}$ = 2.8 Hz), 4.83−4.45 (m, 6H, PhCH_2's), 4.26 (dd, 0.75H, H-2α, $J_{2,3}$ = 5.4 Hz), 4.17−4.11 (m, 0.5H, H-2β, H-3β), 4.03 (t, 0.75H, H-3α, $J_{3,4}$ = 6 Hz), 3.80−3.67 (m, 1.25H, H-4α, H-5aα, H-5aβ), 3.53−3.39 (m, 1.75H, H-5bα, H-4β, H-5bβ), 2.06 (s, 3H, CH3-α and CH3-β). Anal. ($C_{28}H_{30}O_5S$·0.75H_2O) C, H.

9-(2,3,5-Tri-*O*-benzyl-4-thio-β- and -α-D-arabinofuranosyl)-2,6-dichloropurine (7β and 7α). To a stirred mixture of **6** (0.956 g, 2 mmol) and 2,6-dichloropurine (0.568 g, 3 mmol) in acetonitrile (50 mL) at room temperature was added a solution of $SnCl_4$ in CH_2Cl_2 (3 mL of 1.0 M) over 1 min, and stirring was continued for 2 h. The reaction was quenched by pouring it into a mixture of 50 mL of CH_2Cl_2 and 25 mL of saturated $NaHCO_3$. The organic phase was dried ($MgSO_4$) and

concentrated. The residue was purified by silica gel chromatography (cyclohexane/EtOAc, 9:1) to afford **7**β (485 mg, 40%) eluting first followed by **7**α (425 mg, 35%).

Compound 7β: MS 608 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 1H, H-8), 7.36−7.17 (m, 13H, aromatic *H*'s), 6.94 (m, 2H, aromatic *H*'s), 6.22 (d, 1H, H-1′, $J_{1',2'} = 4.9$ Hz), 4.68 (d, 1H, PhC*H*H, $J = 11.6$ Hz), 4.54 (s, 2H, PhCH_2-), 4.52 (s, 2H, PhCH_2-), 4.50 (d, 1H, PhCH*H*-, $J = 11.6$ Hz), 4.35−4.26 (m, 2H, H-2′, H-3′), 3.68 (dd, 1H, H-5′a, $J_{4',5'a} = 4.6$ Hz, $J_{5'a,5'b} = 10.0$ Hz), 3.65 (dd, 1H, H-5′b, $J_{4',5'b} = 4.8$ Hz), 3.54 (m, 1H, H-4′, $J_{3',4'} = 5.0$ Hz); ^{13}C NMR ($CDCl_3$) δ 153.3 (C-2), 152.5 (C-4), 151.3 (C-6), 146.8 (C-8), 137.4, 137.2, 136.1 (ipso C's), 130.7 (C-5), 128.6, 128.5, 128.3, 128.21, 127.9, 127.6 (aromatic C's), 84.6 (C-3′), 80.7 (C-2′), 73.4, 73.3, 73.2 (three Ph*C*H_2-'s), 68.3 (C-5′), 57.4 (C-1′, $J = 162.0$ Hz), 47.0 (C-4′).

Compound 7α: MS 608 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H, H-8), 7.36−7.21 (m, 13H, aromatic *H*'s), 7.01 (m, 2H, aromatic *H*'s), 6.09 (d, 1H, H-1′, $J_{1',2'} = 2.1$ Hz), 4.69 (s, 2H, PhCH_2-), 4.57 (d, 1H, PhC*H*H-, $J = 12.0$ Hz), 4.51 (d, 1H, PhC*H*H-, $J = 12.0$ Hz), 4.48 (d, 1H, PhCH*H*-, $J = 11.9$ Hz), 4.33 (d, 1H, PhCH*H*-, $J = 11.9$ Hz), 4.26 (t, 1H, H-2′, $J_{1',2'} = 2.1$ Hz, $J_{2',3'} = 2.5$ Hz), 4.23 (t, 1H, H-3′, $J_{3',4'} = 2.5$ Hz), 4.07 (m, 1H, H-4′), 3.80 (dd, 1H, H-5′a, $J_{4',5'a} = 8.2$ Hz, $J_{5'a,5'b} = 9.5$ Hz), 3.56 (dd, 1H, H-5′b, $J_{4',5'b} = 6.7$ Hz); ^{13}C NMR ($CDCl_3$) δ 152.5 (C-2), 152.4 (C-4), 151.3 (C-6), 146.2 (C-8), 137.7, 136.7 136.5 (ipso C's), 131.2 (C-5), 128.4, 128.1, 127.9, 127.8, 127.7, 127.6 (aromatic C's), 88.3 (C-3′), 85.2 (C-2′), 73.2, 72.7, 72.4 (three PhCH_2-'s), 71.5 (C-5′), 64.5 (C-1′, $J = 160.0$ Hz), 53.7 (C-4′).

2-Chloro-9-(4-thio-β-D-arabinofuranosyl)adenine (9β). A mixture of compound **7**β (608 mg, 1 mmol) and saturated ethanolic ammonia (100 mL) was heated at 50 °C in a glass-lined stainless steel pressure vessel for 48 h. The reaction mixture was evaporated to dryness to afford a solid (**8**β) that was dissolved in CH_2Cl_2 (50 mL) and was treated at −78 °C under argon with a solution of 1 M BBr_3 in CH_2Cl_2 (12 mL). After the mixture stirred for 0.5 h at −78 °C, CH_3OH (10 mL) was added, followed by pyridine (10 mL), and the solution was evaporated to dryness. The brown-colored crude product was purified by silica gel chromatography ($CHCl_3$/MeOH, 7:1) to afford compound **9**β as a white powder that was crystallized from EtOH (257 mg, 81%): mp 207−209 °C; MS 318 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 8.39 (s, 1H, H-8), 7.78 (br s, 2H, NH_2), 5.90 (d, 1H, H-1′, $J_{1',2'} = 5.2$ Hz), 5.74 (d, 1H, 2′-OH, $J = 4.3$ Hz), 5.51 (d, 1H, 3′-OH, $J = 4.6$ Hz), 5.18 (t, 1H, 5′-OH, $J = 5.1$ Hz), 4.12−4.08 (m, 2H, H-3′, H-2′), 3.80 (dd, 1H, H-5′a, $J_{4',5'a} = 4.3$ Hz, $J_{5'a,5'b} = 11.2$ Hz), 3.77 (dd, 1H, H-5′b, $J_{4',5'b} = 6.5$ Hz), 3.22 (mm, 1H, H-4′, $J_{3',4'} = 6.4$ Hz). Anal. ($C_{10}H_{12}ClN_5O_3S$) C, H, N.

2-Chloro-9-(4-thio-α-D-arabinofuranosyl)adenine (9α). This compound was prepared from **7**α by the same procedure as reported for **9**β in 56% yield after two crystallizations from EtOH: mp 237 °C dec; TLC 3:1:0.1 $CHCl_3$−MeOH−NH_4OH, R_f 0.55; MS 318 $(M + H)^+$; UV λ_{max} pH 1, 266 (14.7), pH 7, 265 (15.6), pH 13, 266 (15.3); ^{1}H NMR (DMSO-d_6) δ 8.47 (s, 1H, H-8), 7.82 (br s, 2H, NH_2), 5.83 (d, 1H, 2′-OH, $J = 5.5$ Hz), 5.66 (d, 1H, 3′-OH, $J = 5.0$ Hz), 5.65 (d, 1H, H-1′, $J_{1',2'} = 7.1$ Hz), 4.98 (dd, 1H, 5′-OH, $J_{5'a,OH} = 4.6$ Hz, $J_{5'b,OH} = 6.0$ Hz), 4.48 (m, 1H, H-2′, $J_{2',3'} = 7.7$ Hz), 3.90 (m, 1H, H-5′a, $J_{4',5'a} = 3.8$ Hz, $J_{5'a,5'b} = 10.9$ Hz), 3.75 (m, 1H, H-3′, $J_{3',4'} = 8.2$ Hz), 3.64 (m, 1H, H-4′), 3.44 (m, 1H, H-5′b, $J_{4',5'b} = 8.3$ Hz). Anal. ($C_{10}H_{12}ClN_5O_3S$) C, H, N.

9-(2,3,5-Tri-*O*-benzyl-4-thio-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (11β). A solution of **7**β (303 mg, 0.5 mmol) and sodium azide (162.5 mg, 2.5 mmol) in 20 mL of 95% EtOH was heated at reflux for 2 h. The solvent was removed in vacuo, and the residue was partitioned between CH_2Cl_2 and H_2O. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to yield 290 mg of a yellowish solid (**10**β) [TLC $CHCl_3$/MeOH, 97:3; R_f 0.45; MS *m*/*z* 621 $(M + H)^+$], which was redissolved in 20 mL of CH_2Cl_2 and 2 mL of CH_3OH. This solution was treated with $SnCl_2$ (190 mg, 1 mmol), and the resulting suspension was stirred for 30 min. After evaporation of solvent, purification was accomplished by silica gel chromatography ($CHCl_3$/MeOH, 97:3) to afford **11**β (225 mg, 79%), which was suitable for deblocking: MS 569 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H, H-8), 7.37−7.20 (m, 13H, aromatic *H*'s), 7.01 (m, 2H, aromatic *H*'s), 6.15 (d, 1H, H-1′, $J_{1',2'} = 5.3$ Hz), 5.36 (bs, 2H, NH_2), 4.68 (d, 1H, PhCH*H*, $J = 11.7$ Hz), 4.67 (bs, 2H, NH_2), 4.58−4.50 (m, 4H, two PhCH_2's), 4.32 (dd, 1H, H-3′, $J_{3',4'} = 6.3$ Hz), 4.22 (dd, 1H, H-2′, $J_{2',3'} = 7.0$ Hz), 3.72−3.62 (m, 2H, H-5′a, H-5′b), 3.53 (m, 1H, H-4′).

9-(2,3,5-Tri-*O*-benzyl-4-thio-α-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (11α). This compound was prepared in 75% yield by the same procedure as reported above for **11**β but starting from **7**α, affording material suitable for deblocking: MS 569 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 7.89 (s, 1H, H-8), 7.35−7.24 (m, 13H, aromatic CH's), 7.13−7.18 (m, 2H, aromatic CH's), 6.00 (d, 1H, H-1′, $J_{1',2'} = 4.0$ Hz), 5.44 (bs, 2H, NH_2), 4.74 (bs, 1H, NH_2), 4.64 (d, 1H, PhC*H*H-, $J = 12.1$ Hz), 4.58 (d, 1H, PhCH*H*-, $J = 12.1$ Hz), 4.52−4.49 (m, 4H, $PhCH_2$'s), 4.41 (t, 1H, H-2′, $J_{2',3'} = 3.2$ Hz), 4.19 (t, 1H, H-3′, $J_{3',4'} = 4.0$ Hz), 4.01 (ddd, 1H, H-4′), 3.76 (dd, 1H, H-5′b, $J_{4',5'b} = 7.4$ Hz, $J_{5'a,5'b} = 9.6$ Hz), 3.54 (dd, 1H, H-5′a, $J_{4',5'a} = 6.7$ Hz).

9-(4-Thio-β-D-arabinofuranosyl)-9*H*-purine-2,6-diamine (12). An ice-cold solution of **11**β (654 mg, 1.15 mmol) in CH_2Cl_2 (2.6 mL) was added dropwise to a solution of 1 M BCl_3 in CH_2Cl_2 (100 mL) at −50 °C. Solid precipitated from the solution near the end of addition. The reaction in a tightly sealed flask was stored at −20 °C for 16 h. The resulting clear solution was evaporated to dryness at −20 °C to give a dark residue. A solution of this material in ice-cold CH_2Cl_2 (25 mL) was evaporated to dryness four times to provide a foam. Ice-cold saturated aqueous $NaHCO_3$ (20 mL) was added to the foam, and the mixture was stirred vigorously until the pH remained stable (pH 7−8). Water (150 mL) was added to form a clear solution that was extracted with two portions of CH_2Cl_2 (50 mL, 25 mL) to remove color and impurities. The colorless aqueous layer was held briefly under vacuum to remove residual CH_2Cl_2 before being applied to a column (13 × 190 mm) of Bio Beads SM-4 (100−200 mesh; Bio-Rad Laboratories) equilibrated in water. Water elution with fractions monitored at 254 nm provided pure **12** that was crystallized from hot H_2O (233 mg, 68%). More **12** was obtained from the column with a MeOH wash (33 mg, 10%): mp 285 °C dec (lit.[27] mp 292−295 °C); TLC 3:1:0.1 $CHCl_3$−MeOH−NH_4OH, R_f 0.30; HPLC 100%, 3:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)−MeOH; MS 299 $(M + H)^+$; UV λ_{max} pH 1, 255 (11.1), 291 (10.9), pH 7, 257 (9.72), 280 (11.6), pH 13, 258 (9.67), 280 (11.8); ^{1}H NMR and microanalytical data have been previously reported.[27]

2-Fluoro-9-(2,3,5-tri-*O*-benzyl-4-thio-β-D-arabinofuranosyl)adenine (13β). Diamino compound **11**β (91 mg, 0.16 mmol) was dissolved in 1:1 HF−pyridine at 0−5 °C by vigorous stirring and sonication. To this cloudy solution at −20 °C was added *tert*-butyl nitrite (30 μL, 0.24 mmol). After 2.75 h, more *tert*-butyl nitrite (8 μL, 0.065 mmol) was added, and the reaction was held at −15 °C for an additional 1 h. The cold reaction solution was added dropwise over 0.5 h to a vigorously stirred mixture of saturated aqueous $NaHCO_3$ and ice (400 mL). The mixture was stirred until most of the ice had melted. Small portions of solid $NaHCO_3$ were added to stabilize the pH at 7−8 (monitor with pH paper). $CHCl_3$ (50 mL) was added, the layers were separated, and the aqueous layer was extracted with more $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ layers were washed with H_2O (2 × 50 mL), dried ($MgSO_4$), and evaporated to dryness. The resulting residue was taken up in $CHCl_3$ and applied to two Analtech GF plates (20 × 20 cm, 1000 μm) that were developed in 95:5 $CHCl_3$/MeOH. Extraction of the desired band with 1:1 $CHCl_3$/MeOH yielded upon evaporation essentially pure **13**β (70 mg, 76%). This residue was used directly in the deprotection step described below. Crystallization of a small sample from MeOH gave pure **13**β: mp 196−197 °C; TLC 98:2 $CHCl_3$−MeOH, R_f 0.50; HPLC 100%, 9:1 MeCN/H_2O; MS 572 $(M + H)^+$; UV (EtOH) λ_{max} 263 (16.8), 271 (sh); ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H, H-8), 7.36−7.18 (m, 13H, aromatic CH's), 6.99 (m, 2H, aromatic

CH's), 6.16 (d, 1H, H-1′, $J_{1',2'}$ = 5.3 Hz), 5.76 (bs, 2H, NH_2), 4.69 (d, 1H, PhC*H*H-, *J* = 11.7 Hz), 4.55 (dd, 1H, PhC*H*H, *J* = 11.3 Hz), 4.53 (s, 2H, PhC*H*H), 4.47 (d, 1H, PhC*H*H, *J* = 11.7 Hz), 4.44 (d, 1H, PhC*H*H, *J* = 11.3 Hz), 4.33 (dd, 1H, H-3′, $J_{3',4'}$ = 6.3 Hz), 4.20 (dd, 1H, H-2′, $J_{2',3'}$ = 7.4 Hz), 3.70 (m, 1H, H-5′b, $J_{4',5'b}$ = 4.7 Hz), 3.68 (m, 1H, H-5′a, $J_{4',5'a}$ = 4.6 Hz), 3.53 (m, 1H, H-4′). Anal. ($C_{31}H_{30}FN_5O_3S\cdot0.25H_2O$) C, H, N.

2-Fluoro-9-(2,3,5-tri-*O*-benzyl-4-thio-2-D-arabinofuranosyl)adenine (13α). Conversion of **11**α to **13**α was accomplished in 62% yield by the procedure reported above for **13***β*: mp 135−136 °C; TLC 98:2 $CHCl_3$−MeOH, R_f 0.40; HPLC 100%, 9:1 MeCN−H_2O; MS 572 $(M + H)^+$; UV (EtOH) λ_{max} 263 (16.7), 270 (sh); ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H, H-8), 7.34−7.19 (m, 13H, aromatic CH's), 7.06−7.09 (m, 2H, aromatic CH's), 6.04 (d, 1H, H-1′, $J_{1',2'}$ = 2.5 Hz), 5.95 (bd, 1H, NH_2), 4.70 (d, 1H, PhCH*H*, *J* = 12.3 Hz), 4.64 (d, 1H, PhC*H*H, *J* = 12.3 Hz), 4.55 (d, 1H, PhCH*H*, *J* = 12.0 Hz), 4.50 (d, 1H, PhC*H*H, *J* = 12.0 Hz), 4.47 (d, 1H, PhC*H*H, *J* = 12.1 Hz), 4.40 (d, 1H, PhCH*H*, *J* = 12.1 Hz), 4.33 (t, 1H, H-2′, $J_{2',3'}$ = 2.9 Hz), 4.22 (t, H, H-3′, $J_{3',4'}$ = 3.1 Hz), 4.05 (ddd, 1H, H-4′), 3.78 (dd, 1H, H-5′b, $J_{4',5'b}$ = 8.0 Hz, $J_{4',5'b}$ = 9.6 Hz), 3.56 (dd, 1H, H-5′a, $J_{4',5'a}$ = 6.7 Hz). Anal. ($C_{31}H_{30}FN_5O_3S$) C, H, N.

2-Fluoro-9-(4-thio-*β*-D-arabinofuranosyl)adenine (14*β*). An ice-cold solution of **13***β* (69 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise under argon to 5 mL of 1.0 M BCl_3 in CH_2Cl_2 chilled to −40 °C. The mixture, which contained a small amount of undissolved solid, was stirred at −30 °C for 30 min and then allowed to stand at −20 °C for 23 h. The resulting clear solution was evaporated to dryness beginning at −20 °C. The residue was coevaporated with cold CH_2Cl_2 (4 × 3 mL) producing a solid that was suspended in cold aqueous saturated $NaHCO_3$ (5 mL). After addition of EtOH (5 mL) the mixture was heated to boiling, treated with charcoal, filtered (Celite), and concentrated to provide crude **14***β*. This material was purified by preparative TLC (Analtech GF taper plates, 20 × 20 cm, 1000 μm) with development in 3:1:0.1 $CHCl_3$/MeOH/NH_4OH. The isolated material was crystallized from EtOH to give pure **14***β* (19 mg, 53%): mp 235 °C; TLC 3:1:0.1 $CHCl_3$−MeOH−NH_4OH, R_f 0.60; HPLC 99%, 7:3 $NH_4H_2PO_4$ (0.01 M, pH 5.1)−MeOH; MS 302 $(M + H)^+$; UV λ_{max} pH 1, 263 (15.4), 270 (sh), pH 7, 262 (16.5), 270 (sh), pH 13, 263 (16.8), 270 (sh); ^{1}H NMR (DMSO-d_6) δ 8.35 (s, 1H, H-8), 7.77 (bs, 2H, NH_2), 5.87 (d, 1H, H-1′, $J_{1',2'}$ = 5.0 Hz), 5.72, (bd, 1H, 2′-OH, *J* = 4.1 Hz), 5.49 (d, 1H, 3′-OH, *J* = 4.8 Hz), 5.17 (bt, 1H, 5′-OH, *J* = 4.8 Hz), 4.12−4.05 (m, 2H, H-2′, H-3′), 3.82 (m, 1H, H-5′a, $J_{4',5'a}$ = 4.2 Hz, $J_{5'a,5'b}$ = 11.2 Hz), 3.76 (m, 1H, H-5′b, $J_{4',5'b}$ = 6.9 Hz), 3.22 (m, 1H, H-4′). Anal. ($C_{10}H_{12}FN_5O_3S\cdot0.3C_2H_5OH\cdot0.6H_2O$) C, H, N.

2-Fluoro-9-(4-thio-α-D-arabinofuranosyl)adenine (14α). Treatment of **13**α (357 mg, 0.62 mmol) with BCl_3 as reported above for **13***β* provided crude **14**α (222 mg) as an intractable solid containing 10% of an unknown impurity. This material was dissolved in pyridine (10 mL) at 5 °C and treated with acetic anhydride (0.63 mL, 6.5 mmol). This solution was stirred at room temperature for 20 h and then poured into ice water (300 mL). $CHCl_3$ (50 mL) was added, the layers were separated, and the aqueous layer was extracted with additional $CHCl_3$ (2 × 50 mL). The combined $CHCl_3$ layers were washed with H_2O (2 × 25 mL), dried ($MgSO_4$), and evaporated to give 196 mg of crude acetylated nucleoside **15**α. Purification of **15**α was accomplished by preparative TLC (Analtech GF, 20 × 20 cm, 2000 μm) developed twice in 4:1 EtOAc/cyclohexane. The EtOAc extract of the plate bands was evaporated and then crystallized from hot 2-propanol to yield a white solid (116 mg): mp 175−176 °C; TLC 4:1 EtOAc/cyclohexane, R_f 0.50; MS 428 $(M + H)^+$; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H, H-8), 6.07 (d, 1H, H-1′, $J_{1',2'}$ = 4.1 Hz), 6.02 (bs, 2H, NH_2), 5.73 (t, 1H, H-2′, $J_{2',3'}$ = 5.2 Hz), 5.48 (t, 1H, H-3′, $J_{3',4'}$ = 4.8 Hz), 4.39 (dd, 1H, H-5′a, $J_{4',5'a}$ = 7.0 Hz, $J_{5'a,5'b}$ = 11.2 Hz), 4.21 (m, 1H, H-5′b, $J_{4',5'b}$ = 6.5 Hz), 4.13 (m, 1H, H-4′), 2.12 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.07 (s, 3H, CH_3).

Acetylated nucleoside **15**α (109 mg, 0.25 mmol) was treated with 25 mL of EtOH saturated with NH_3 at 5 °C. The reaction mixture was refrigerated for 5 days and then evaporated. The white solid residue was crystallized from boiling EtOH (10 mL) to give pure **14**α (72 mg, 38% from **13**α): mp 290 °C dec; TLC 3:1:0.1 $CHCl_3$−MeOH−NH_4OH, R_f 0.60; HPLC 99%, 7:3 $NH_4H_2PO_4$ (0.01 M, pH 5.1)−MeOH; MS 302 $(M + H)^+$; UV λ_{max} pH 1, 262 (14.8), 270 (sh), pH 7, 262 (15.6), 270 (sh), pH 13, 262 (15.7), 270 (sh); ^{1}H NMR (DMSO-d_6) δ 8.39 (s, 1H, H-8), 7.83 (bs, 2H, NH_2), 5.81 (d, 1H, 2′-OH, *J* = 6.0 Hz), 5.63 (d, 1H, 3′-OH, *J* = 5.0 Hz), 5.61 (d, 1H, H-1′, $J_{1',2'}$ = 7.1 Hz), 4.96 (t, 1H, 5′-OH, *J* = 4.7, 6.0 Hz), 4.48 (dd, 1H, H-2′, $J_{2',3'}$ = 7.7 Hz), 3.89 (dd, 1H, H-5′b, $J_{4',5'b}$ = 3.7 Hz, $J_{5'a,5'b}$ = 10.8 Hz), 3.73 (t, 1H, H-3′, $J_{3',4'}$ = 7.1 Hz), 3.64 (dt, 1H, H-4′), 3.42 (dd, 1H, H-5′a, $J_{4',5'a}$ = 8.1 Hz). Anal. ($C_{10}H_{12}FN_5O_3S\cdot0.15C_2H_5OH$) C, H, N.

9-(4-Thio-*β*-D-arabinofuranosyl)guanine (16). To a solution of **12** (51 mg, 0.17 mmol) in 20 mL of water was added 100 units of calf intestine adenosine deaminase type VIII (40 μL; Boehringer Mannheim GmbH). The reaction was stirred for 17 h, the solution was boiled for 3 min to deactivate the enzyme, and the suspension was treated with charcoal and filtered through Celite. The filtrate was concentrated to give gelatinous **16** which was dissolved in hot H_2O (4 mL) and filtered through a 0.45-μm filter (25 mm; Gelman Acrodisc GHP-GF). The clear filtrate was lyophilized to provide **16** as a fluffy white solid (44 mg, 73%): mp >250 °C dec (lit.[27] mp 260−264 °C); TLC 4:1 MeCN/1 N NH_4OH, R_f 0.40; HPLC 99.6%, 9:1 $NH_4H_2PO_4$ (0.01 M, pH 5.1)−MeOH; MS 300 $(M + H)^+$; UV λ_{max} pH 1, 257 (12.5), 282 (sh), pH 7, 255 (14.8), 273 (sh), pH 13, 257 (sh), 268 (12.3); ^{1}H NMR and microanalytical data have been reported.[27]

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Supporting Information Available: Listings of atomic coordinates, bond lengths, bond angles, anisotropic displacement parameters, hydrogen coordinates, and isotropic displacement parameters (6 pages). Ordering information is given on any current masthead page.

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