Nucleosides. 139. Synthesis and Anticytomegalovirus and Antiherpes Simplex Virus Activity of 5'-Modified Analogues of 2'-Fluoroarabinosylpyrimidine Nucleosides

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In order to determine if modification of the 5'-position reduces or abolishes the antiviral activity of 2'-fluoro-5-iodo-*ara*-C (FIAC), 2'-fluoro-5-iodo-*ara*-U (FIAU), or 2'-fluoro-5-methyl-*ara*-U (FMAU) against human cytomegalovirus (HCMV) and herpes simplex virus (HSV), the 5'-deoxy, 5'-mercapto, and 5'-amino analogues of these nucleosides were prepared. 5'-Deoxy-FIAC and 5'-deoxy-FIAU were prepared by catalytic hydrogenation of 5'-iodo-FIAC and 5'-iodo-FIAU to 5'-deoxy-FAC and 5'-deoxy-FAU, respectively, followed by reiodination at C-5. Reduction of 5'-iodo-FMAU afforded 5'-deoxy-FMAU. These 5'-deoxy nucleosides were found to be inactive against HCMV, indicating that the conversion to 5'-phosphate by the cellular enzyme(s) is a requirement for antiviral activity against this virus. Other 5'-modified (NH₂ and SH) analogues were also prepared from 5'-*O*-tosyl-FIAC and 5'-*O*-tosyl-FMAU. Treatment of these tosylates with LiN₃ in DMF afforded the corresponding 5'-N₃ products. Catalytic hydrogenation of 5'-N₃-FMAU afforded 5'-NH₂-FMAU, whereas 5'-NH₂-FIAC was obtained by treatment of 5'-N₃-FIAC with Ph₃P in pyridine. 5'-Mercapto analogues were prepared by treatment of 5'-*O*-tosyl-3'-*O*-acetyl nucleosides with KSAc followed by deacetylation. 5'-NH₂-FMAU was the only compound that showed good activity against HSV-1 and HSV-2 in vitro. However, this compound was less potent and had a lower therapeutic index than FMAU.

Among many 2'-fluoro-β-D-arabinosylpyrimidines synthesized in our laboratory[1–4] as potential antitumor and/or antiviral agents, 2'-fluoro-5-iodo-*ara*-C (FIAC, 1a, Scheme I)[1,5,6] and 2'-fluoro-5-methyl-*ara*-U (FMAU, 1c)[2,6] have shown most potent and selective inhibitory activity against herpes simplex viruses types 1 and 2 (HSV-1 and -2)[1,2,5–9] and Varicella zoster virus (VZV).[5,6,8,9] These nucleosides are phosphorylated preferentially by a virus-specified thymidine kinase (TK),[5,6,10,11] which appears to account, in significant measure, for their selective antiherpetic activity.

Recently, these nucleosides were found to exhibit selective activity against human cytomegalovirus (HCMV),[12,13] a virus that does not specify an HCMV-TK for its replication.[14,15] It was suggested[12,13] therefore that the mechanism of action of these nucleosides against HCMV may be different qualitatively from that found for HSV.

In order to determine if phosphorylation to the 5'-nucleotide is a prerequisite for inhibition of HCMV by these nucleosides, we synthesized 5'-deoxy analogues of FIAC, FIAU, and FMAU (7a, 7b, and 7c, respectively). We also prepared several other 5'-modified analogues of FIAC and FMAU as potential antiviral agents on the basis of the rationale that certain 5'-amino-2',5'-dideoxypyrimidine nucleosides are phosphorylated selectively by virus-encoded TK[16,17] and exhibit antiherpesvirus activity.[18–20] They are also incorporated into the DNA of HSV-1.[21,22] The 5'-amino analogues 6 might also serve as substrates for the virus-coded TK and, on the basis of our previous studies,[1,6] the 2'-fluoro substituent may enhance the antiviral potency of 6. Should the 5'-amino-2'-fluoro nucleosides 6 be incorporated (with the phosphoramidate linkage) into viral DNA, they might provide a unique basis for antiviral activity. It would also be of interest to determine if the 5'-thiol of 9 acts by a similar mechanism.

Selective tosylation[23] of FIAC, FIAU, or FMAU at the 5'-position afforded the corresponding 5'-tosylates 2, which were converted into their respective 5'-iodides 4 by treatment with NaI in dimethylformamide (DMF). The same nucleosides 4 were also prepared in one step by direct

Scheme I

a, X = NH₂, R = I; **b**, X = OH, R = I; **c**, X = OH, R = Me; **d**, X = NH₂, R = H; **e**, X = OH, R = H
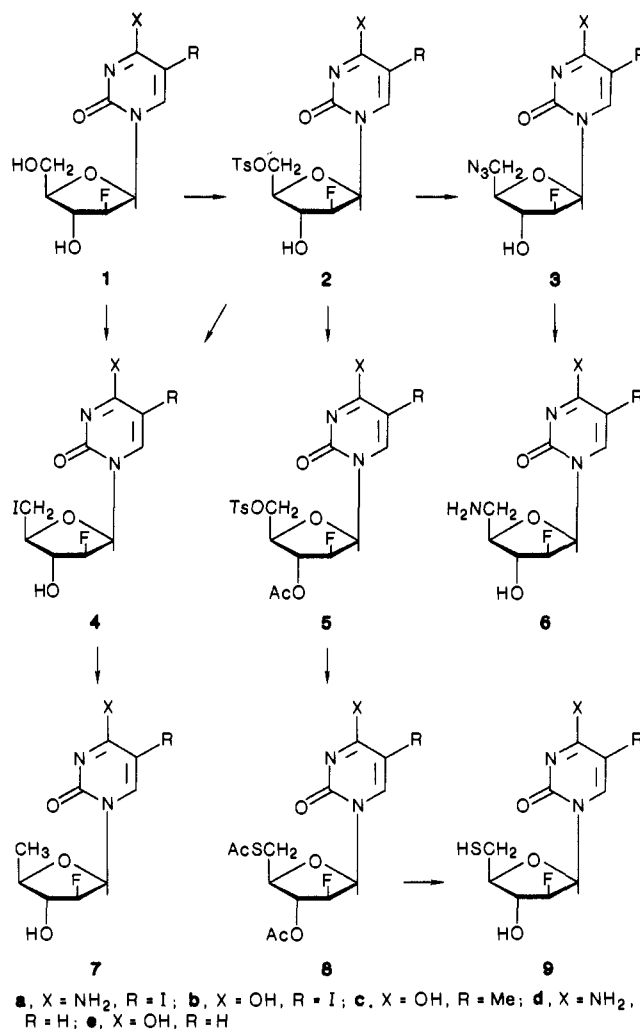
treatment of 1 with methyltriphenoxyphosphonium iodide in DMF.[24] Catalytic hydrogenolysis of 4c afforded 5'-

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Table I. Anti-HSV Activity of 5'-Modified 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)pyrimidine Nucleosides[a]

| compound | HSV-1 (strain F) | | HSV-2 (strain G) | | cytotoxicity |
	ED_{50}	ED_{90}	ED_{50}	ED_{90}	ID_{50}
6a (5'-NH$_2$-FIAC)	202	480	>400	>400	>400
6b (5'-NH$_2$-FIAU)	108	>200	>200	>200	>200
6c (5'-NH$_2$-FMAU)	0.78	3.0	5.6	14.0	6.7
7a (5'-deoxy-FIAC)	>400	>400	>400	>400	>400
7b (5'-deoxy-FIAU)	220	384	135	290	>400
7c (5'-deoxy-FMAU)	31.1	298	173	493	214
7d (5'-deoxy-FAC)	13.3	35.9	17.1	45.5	225
7e (5'-deoxy-FAU)	346	538	224	379	333
9a (5'-SH-FIAC)	216	444	>200	>200	337
9c (5'-SH-FMAU)	>200	>200	>200	>200	314
1a (FIAC)	0.023	0.048	0.03	0.08	21.7
1b (FIAU)	0.012	0.041	0.01	0.045	10.3
1c (FMAU)	0.018	0.047	0.023	0.09	2.8
5'-NH$_2$-IddUrd	1.86	26.6	>400	>400	>400
5'-NH$_2$-ddThd	7.7	153	>400	>400	>400

[a] Tested in Vero cells by a plaque reduction assay. ED_{50} and ED_{90} are effective concentrations (μM) required to inhibit replication of HSV by 50% and 90%, respectively. ID_{50} is concentration necessary for 50% inhibition of growth of rapidly dividing Vero cells.

deoxy-FMAU (**7c**) in high yield. Reduction of **4a** and **4b**, however, gave the corresponding completely deiodinated products (**7d** and **7e**, respectively), which were reiodinated to give 5'-deoxy-FIAC (**7a**) and 5'-deoxy-FIAU (**7b**).

The 5'-tosylate of FIAC and FMAU (**2a** and **2c**) were converted into the 5'-azido nucleosides (**3a** and **3c**) by treatment with LiN$_3$ in DMF. Catalytic reduction of **3c** afforded 5'-amino-5'-deoxy-FMAU (**6c**). 5'-Amino-5'-deoxy-FIAC (**6a**) was obtained from **3a** by treatment with triphenylphosphine in pyridine.[25] Treatment of **2a** or **2c** directly with KSAc in various solvents led to formation of intractable mixtures. However, after acetylation of **2** to **5**, the latter was found to undergo smooth conversion to the corresponding 5'-SAc derivatives **8**, which were deacetylated to FIAC-5'-thiol (**9a**) and FMAU-5'-thiol (**9c**).

The 5'-deoxynucleosides **7a-c** were inactive against HCMV in vitro at the highest concentration tested (1 mM). They are about 1000 times less active than the corresponding parent antivirals **1** against HSV-1 and HSV-2 (Table I). These results establish the importance of phosphorylation at the C-5' hydroxyl group for FIAC and FMAU to exert anti-HCMV activity. They are also consistent with a more recent report by Colacino and Lopez,[26] which indicated that the HCMV viral DNA polymerase may use available FIAC triphosphate (product of cellular kinases) more efficiently as an alternative substrate for incorporation into DNA and may be more susceptible to analogue inhibition than the cellular enzyme.

It is also interesting to note that 5'-amino-5'-deoxy-FMAU (**6c**) showed activity against HSV-1 and -2 and was also quite cytotoxic, although the FIAC and FIAU analogues (**6a** and **6b**) were practically inactive. This antiviral characteristic of **6c** is interesting since 5'-amino-IddUrd and 5'-amino-ddThd are noncytotoxic at 400 μM concentration, and the thymine nucleoside is less active than 5'-amino-IddUdR against HSV-1 (Table I). Replacement of the 5'-hydroxy function of FIAC and FMAU by a hydrogen or SH group reduced or eliminated the antiviral activity.
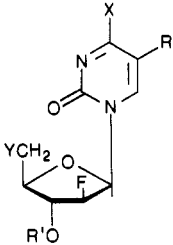
Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Column chromatography was performed on silica gel G60 (70–230 mesh, ASTM, Merck). Elementary analyses were performed by M-H-W Laboratories, Phoenix, AZ, and Spang Microanalytical Laboratory, Eagle Harbor, MI, and all the new compounds were analyzed correctly (Table II). ^{1}H NMR spectra are recorded on a JEOL PFT-100 or JEOL FX90Q spectrometer with Me$_4$Si as the internal standard (Table III). 5'-Amino-2',5'-dideoxy-5-iodouridine (5'-NH$_2$-IddUrd)

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Table II. New Compounds

compd	X	Y	R	R'	formula	analyses
2a	NH_2	OTs	I	H	$C_{16}H_{17}FIN_3O_6S$	C, H, N, I
2b	OH	OTs	I	H	$C_{16}H_{16}FIN_2O_7S$	C, H, N, I
2c	OH	OTs	Me	H	$C_{17}H_{19}FN_2O_7S$	C, H, N, S
3a	NH_2	N_3	I	H	$C_9H_{10}FIN_6O_3$	C, H, N, I
3b	OH	N_3	I	H	$C_9H_9FIN_5O_4$	C, H, N, I
3c	OH	N_3	Me	H	$C_{10}H_{12}FN_5O_4$	C, H, N
4a	NH_2	I	I	H	$C_9H_{10}FI_2N_3O_3$	C, H, N
4b	OH	I	I	H	$C_9H_9FI_2N_2O_4$	C, H, N
4c	OH	I	Me	H	$C_{10}H_{12}FIN_2O_4$	C, H, N
5a	NH_2	OTs	I	Ac	$C_{18}H_{19}FIN_3O_7S$	C, H, N
5c	OH	OTs	Me	Ac	$C_{19}H_{21}FN_2O_8S$	C, H, N
6a	NH_2	NH_2	I	H	$C_9H_{12}FIN_4O_3$	C, H, N, I
6b	OH	NH_2	I	H	$C_9H_{11}FIN_3O_4$	C, H, N, I
6c	OH	NH_2	Me	H	$C_{10}H_{14}FN_3O_4$	C, H, N
7a	NH_2	H	I	H	$C_9H_{11}FIN_3O_3$	C, H, N
7b	OH	H	I	H	$C_9H_{10}FIN_2O_4$	C, H, N, I
7c	OH	H	Me	H	$C_{10}H_{13}FN_2O_4$	C, H, N
7d	NH_2	H	H	H	$C_9H_{12}FN_3O_3$	C, H, N
7e	OH	H	H	H	$C_9H_{11}FN_2O_4$	C, H, N
8a	NH_2	SAc	I	Ac	$C_{13}H_{15}FIN_3O_5S$	C, H, N, I
8c	OH	SAc	Me	Ac	$C_{14}H_{16}FN_2O_6S$	C, H, N
9a	NH_2	SH	I	H	$C_9H_{11}FIN_3O_3S$	C, H, N, S
9c	OH	SH	Me	H	$C_{10}H_{13}FN_2O_4S$	C, H, N, S

Table III. ¹H NMR Parameters of 5'-Modified 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)pyrimidines[a]

	chemical shifts, δ							coupling constants, Hz					
no.	H-1'	H-2'	H-3'	H-4'	H-5'	H-6	others	$J_{1',2'}$	$J_{1',F}$	$J_{2',3'}$	$J_{2',F}$	$J_{3',4'}$	$J_{3',F}$
2a	6.09dd	4.99ddd	4.01–4.15m		4.29d	7.79s	2.43s (MePh)	3.67	18.9	3.67	57.3		
2b	6.09dd	5.01ddd	385–444m			7.82d	2.42s(MePh)	4.11	17.3	2.47	52.6		
2c	6.16dd	5.08ddd	3.82–4.17m		4.32d	7.33s	1.79s(5-Me), 2.42s(MePh)	4.27	16.5	4.27	49.1		
3a	6.10dd	5.01ddd	4.16m	4.06m	3.65m	7.83s		3.66	18.6	3.66	54.6		20.0
3b	6.11dd	5.05ddd	4.45–3.97m		3.68m	7.90d		3.84	17.2	2.47	52.4		
3c	6.17d	5.06ddd	4.20dm	3.95m	3.65m	7.39s	1.80s(5-Me)	4.12	17.9	4.12	52.5		20.1
4a	6.16dd	5.06dd	4.13dd	3.87dd	3.58m	7.96s		3.66	19.1	0	52.2	2.0	15.0
4b	6.14dd	5.07ddd	4.13dm	3.83m	3.53m	7.97d		3.98	18.0	2.47	52.9		19.5
4c	6.19dd	5.08ddd	4.16dd	3.33–3.97m		7.47s	1.82s(5-Me)	4.12	17.8	4.12	55.5	4.8	20.0
5a	6.09dd	5.24dd	5.19dd	4.37m	4.21d	7.79s	2.09s(OAc), 2,43s(MePh)	3.82	18.8	0	50.8	4.0	18.5
5c	6.15dd	5.33m	5.21dm	4.39m	4.24d	7.36s	1.78s(5-Me), 2.78s(OAc), 2.41s(MePh)	3.82	17.2	3.82	51.8	4.0	26.4
6a	6.03dd	4.96ddd	4.18dd	3.73m	2.79d	7.99s		3.51	18.5	3.51	52.5	5.0	19.4
6b	6.05dd	5.01ddd	4.22dd	3.72m	2.81m	8.18d		4.12	15.9	3.02	52.7	4.9	19.8
6c	6.07dd	5.00ddd	4.10dd	3.69m	2.81d	7.55s	1.86s(5-Me)	4.13	17.3	4.13	53.1	5.0	21.3
7a	6.01dd	4.44dd	3.97dd	3.90m	1.34d	7.75s		3.35	19.5	0	50.3	2.0	15.0
7b	6.02dd	4.97ddd	4.19–3.70m		1.35d	7.82d		3.66	18.3	3.66	52.6	2.0	
7c	6.07dd	4.95ddd	3.98dd	3.83m	1.32d	7.36s	1.80s(5-Me)	4.28	17.4	4.0	53.0	4.0	18.0
7d	6.06dd	4.93dd	4.03dd	3.87m	1.36d	7.53d	5.79d(H-5, $J_{5,6}$ = 7.3 Hz)	3.50	19.0	0	49.2	2.4	14.0
7e	5.92dd	4.99ddd	3.95–3.49m		1.18d	7.39dd	5.49d(H-5, $J_{5,6}$ = 8.2 Hz)	4.27	17.4	4.27	52.9	2.75	
8a	6.07dd	5.26dd	5.18dd	4.20m	3.35d	7.80s	2.11s(SAc), 2.40s(OAc)	3.51	19.7	0	50.8	4.0	18.5
8c	6.12dd	5.30dm	5.17dm	4.10m	3.35d	7.44s	1.82s(5-Me), 2.12s(SAc), 2.38s(OAc)	4.0	18.9	4.0	49.4	4.0	17.7
9a	6.07dd	5.00ddd	4.21dm	3.87m	2.52d	7.98s		3.56	19.2	3.56	52.1		18.9
9c	6.13dd	5.03ddd	4.24dm	3.87m	2.84d	7.46s	1.81s(5-Me)	4.10	17.2	4.10	52.0	4.0	19.9

[a] The spectra were recorded in Me_2SO-d_6 solutions. Signals are quoted as s (singlet), d (doublet), dd (double doublet), ddd (double double-doublet), m (multiplet), dm (double multiplet), and coupling constants reported are first order.

and 5'-amino-5'-deoxythymidine (5'-NH_2-ddThd) were prepared by the method of Lin et al.[18,19]

1-(2-Deoxy-2-fluoro-5-*O*-tosyl-β-D-arabinofuranosyl)thymine (2c). To an ice-cooled solution of FMAU (1.04 g, 4 mmol) in pyridine (20 mL) was added TsCl (0.92 g, 4.8 mmol). After stirring at 4 °C for 24 h, the mixture was poured onto an ice–water mixture (20 mL) and then extracted with $CHCl_3$ (20 mL × 2). The combined extracts were washed with aqueous $NaHCO_3$ (20 mL × 3) and water (20 mL × 3), dried ($MgSO_4$), and concentrated in vacuo. Recrystallization of the residue from 95% EtOH af-

forded 2c (1.06 g, 64%), mp 206–207 °C. The ¹H NMR spectral data are reported in Table III.

In a similar manner, FIAC and FIAU were converted into the corresponding 5'-*O*-tosylates 2a, mp 199 °C dec, and 2b, mp 220–221 °C. The ¹H NMR characteristics of these nucleosides are listed in Table III.

1-(2,5-Dideoxy-2-fluoro-5-iodo-β-D-arabinofuranosyl)-5-iodocytosine (4a). A mixture of FIAC (1.30 g, 3.5 mmol) and methyltriphenoxyphosphonium iodide (1.82 g, 4.0 mmol) in DMF (12 mL) was stirred for 30 min at room temperature and then

diluted with MeOH (6 mL). The mixture was concentrated in vacuo and the solid residue was dissolved in $CHCl_3$. The solution was washed with 5% $Na_2S_2O_3$ and water, dried (Na_2SO_4), and then concentrated in vacuo. The residue was recrystallized from MeOH to give **4a** (1.10 g, 60%), mp 225–227 °C.

5'-Deoxy-5'-iodo-FIAU (**4b**), mp 245 °C dec, and 5'-deoxy-5'-iodo-FMAU (**4c**), mp 231–232 °C, were also prepared in a similar manner with FIAU or FMAU as the starting material. See Table III for the ¹H NMR parameters of **4a–c**.

1-(2,5-Dideoxy-2-fluoro-β-D-arabinofuranosyl)thymine (5'-Deoxy-FMAU, 7c). A solution of **4c** (200 mg, 0.55 mmol) in a mixture of water (10 mL) and EtOH (20 mL) was adjusted to pH 10 with concentrated NH_4OH. The solution was hydrogenated at room temperature, at atmospheric pressure in the presence of 5% $Pd/BaSO_4$ (800 mg) for 4 h. The catalyst was removed by filtration through a Celite pad and the filtrate was concentrated in vacuo. Recrystallization of the residue from $EtOH-Et_2O$ gave **7c** (105 mg, 83%), mp 200–202 °C.

Reduction of **4a** and **4b** in a similar manner afforded 1-(2,5-dideoxy-2-fluoro-β-D-arabinofuranosyl)cytosine (5'-deoxy-FAC, **7d**), mp 117–119 °C, and 1-(2,5-dideoxy-2-fluoro-β-D-arabinofuranosyl)uracil (5'-deoxy-FAU, **7e**), mp 218–219 °C, respectively. The ¹H NMR parameters of these 5'-deoxynucleosides **7c–e** are reported in Table III.

1-(2,5-Dideoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (5'-Deoxy-FIAC, 7a). A mixture of **7d** (110 mg, 0.5 mmol), HIO_3 (45 mg, 0.25 mmol), I_2 (75 mg, 0.30 mmol), water (0.2 mL), HOAc (0.4 mL), and CCl_4 (0.1 mL) was stirred at 45–55 °C for 2 h. After cooling to room temperature, the reaction mixture was passed through a column of Amberlite IR-45 (OH⁻) resin, and the resin was washed with water and EtOH. The combined filtrate and washings were concentrated in vacuo, and the residue was recrystallized from EtOH–water to give **7a** (143 mg, 81%), mp 220–225 °C dec. The ¹H NMR spectral data for **7a** are given in Table III.

1-(2,5-Dideoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (5'-Deoxy-FIAU, 7b). To a mixture of **7e** (172 mg, 0.75 mmol) and I_2 (95 mg, 0.38 mmol) in HOAc (5.0 mL) was added fuming HNO_3 gradually until the color of I_2 disappeared (~2 h). Water (50 mL) was added and the mixture was concentrated in vacuo. Recrystallization of the residue from MeOH–water afforded **7b** (240 mg, 90%) as colorless needles, mp 230 °C. See Table III for the ¹H NMR parameters of **7b**.

1-(5-Azido-2,5-dideoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (3a). A mixture of **2a** (1.00 g, 1.90 mmol) and LiN_3 (1.86 g, 3.80 mmol) in DMF (15 mL) was heated at 70–75 °C for 3 h and then concentrated in vacuo. The residue was triturated with a small amount of cold water and then recrystallized from EtOH to give **3a** (603 mg, 80%) as colorless crystals, mp 229 °C dec.

In a similar manner, **2c** (628 mg, 1.5 mmol) was converted into 1-(5-azido-2,5-dideoxy-2-fluoro-β-D-arabinofuranosyl)thymine (**3c**) (348 mg, 80%), mp 192–193 °C.

The ¹H NMR spectral characteristics of **3a–c** are reported in Table III.

1-(5-Amino-2,5-dideoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (5'-Amino-5'-deoxy-FIAC, 6a). Mixture of **3a** (396 mg, 1.0 mmol) and Ph_3P (420 mg, 1.6 mmol) in pyridine (10 mL) was stirred at room temperature for 4 h. After dilution with concentrated NH_4OH (1 mL), the mixture was stirred for an additional 3 h and then concentrated in vacuo. The residue was triturated with Et_2O to give a crystalline mass, which was collected by filtration and recrystallized from EtOH–water to afford **6a** (301 mg, 83%), mp 205–213 °C dec. Table III lists the ¹H NMR parameters of **6a**.

1-(3-O-Acetyl-2-deoxy-2-fluoro-5-O-tosyl-β-D-arabinofuranosyl)-5-iodocytosine (5a). A mixture of **2a** (5.30 g, 10.0 mmol) and Ac_2O (4.0 mL) in dry pyridine (100 mL) was stirred at room temperature for 3 h and then the reaction was quenched by addition of EtOH (10 mL). After concentration of the mixture

in vacuo, the residue was crystallized from EtOH to afford **5a** (4.85 g, 85%), mp 157–159 °C.

In a similar manner **2c** (2.0 g, 4.83 mmol) was acetylated to give 1.78 g (82%) of **1-(3-O-acetyl-2-deoxy-2-fluoro-5-O-tosyl-β-D-arabinofuranosyl)thymine (5c)**, mp 120–125 °C dec. The ¹H NMR parameters of **5a** and **5c** are listed in Table III.

1-(3-O-Acetyl-5-S-acetyl-2,5-dideoxy-2-fluoro-5-thio-β-D-arabinofuranosyl)thymine (8c). A suspension of **5c** (640 mg, 1.42 mmol) and KSAc (640 mg, 5.60 mmol) in Me_2CO (15 mL) was stirred at room temperature for 16 h. The mixture was cooled to 0 °C and filtered. The filtered cake was washed with Me_2CO (10 mL). The combined filtrate and washings were concentrated in vacuo, and the residue was chromatographed on a silica gel column using $CHCl_3-MeOH$ (10:1, v/v) as the eluent. The major fraction containing the nucleosides was evaporated in vacuo, and the residue was crystallized from EtOH to afford **8c** (396 mg, 78%) as colorless crystals, mp 114–116 °C.

1-(3-O-Acetyl-5-S-acetyl-2,5-dideoxy-2-fluoro-5-thio-β-D-arabinofuranosyl)-5-iodocytosine (8a), mp 118–125 °C dec, was obtained from **5a** in a similar manner. The ¹H NMR data for **5a** and **5c** are reported in Table III.

1-(2,5-Dideoxy-2-fluoro-5-thio-β-D-arabinofuranosyl)thymine (9c). A mixture of **8c** (718 mg, 2.0 mmol) in 1 M HCl/MeOH (20 mL) was heated at 45 °C for 3 h under N_2. A small amount of insoluble materials was removed by filtration, and the filtrate was concentrated in vacuo. Recrystallization of the residue from $CHCl_3$–petroleum ether afforded **9c** (398 mg, 72%), mp 202–204 °C.

By following the same procedure but using **8a**, **1-(2,5-dideoxy-2-fluoro-5-thio-β-D-arabinofuranosyl)-5-iodocytosine (9a)**, mp 223–225 °C dec, was obtained. The ¹H NMR spectral data for **9a** and **9c** are listed in Table III.

Anti-HCMV Evaluation. Nucleosides were assessed for anti-HCMV activity by using a previously described microtiter assay[27] in which antiviral efficacy was determined by inhibition of the development and spread of cytopathology induced by HCMV (strain AD169) in human foreskin fibroblasts. Each drug was evaluated at 10-fold dilutions ranging from 10^{-3} to 10^{-9} M at both a high and low virus inoculum. Medium with fresh drug was replenished every 2–3 days, and plates were read at days 8–12 after viral inoculation. Drug-induced cytopathology was screened morphologically by evaluation of the thinning or loss of the cell monolayers in uninfected control wells. With each of the nucleosides, no appreciable viral inhibition was detected at 10^{-4} M concentration, while direct cell cytotoxicity was present at 10^{-3} M.

Anti-HSV Evaluation. The newly synthesized nucleosides **6**, **7**, and **9** were screened for activity against HSV-1 (strain F) and HSV-2 (strain G) by a plaque reduction assay in Vero cells, using the methodologies previously described.[28] Cytotoxicity assays were conducted in rapidly dividing Vero cells, as previously described.[28]

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