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Nucleosides. 110. Synthesis and Antiherpes Virus Activity of Some 2'-Fluoro-2'-deoxyarabinofuranosylpyrimidine Nucleosides[1]

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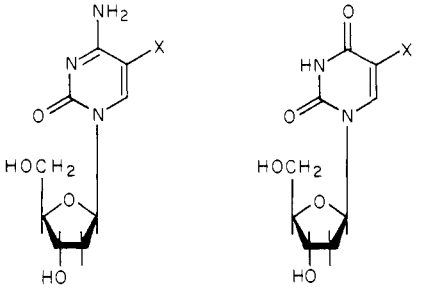
A series of 5-substituted 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)cytosines **7a–d** and their corresponding uracils **9a–d,f** were prepared by condensation of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinosyl bromide (**5**) with appropriately trimethylsilylated pyrimidines followed by saponification of the protected nucleosides **6** or **8**. 1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine (**7e**) was obtained by iodination of **7a**. Iodination of **8a** followed by removal of the protecting acyl-protecting groups afforded the 5-iodo nucleoside **9e**. Several of these 2'-fluoro-substituted nucleosides completely obviated replication of herpes simplex virus type 1 (HSV-1) in monolayers of Vero cells at concentrations of 10–100 μg/mL. The 5-iodocytosine analogue **7e** was the most effective, showing 99.5% suppression of viral replication even at concentrations of 0.1 μg/mL. The cytotoxicity of **7e** to L5178Y or P815 cells in culture was minimal. A comparison of the efficacy of **7e** against HSV-1 with other known nucleoside antiviral agents indicates that further in vitro and in vivo evaluation of **7e** is warranted.

Studies by Cooper[2] and Schildkraut et al.[3] showed that 5-bromo- and/or 5-iodo-2'-deoxycytidine (**1**, X = Br or I) inhibit the replication of herpes simplex virus (HSV) as effectively as their corresponding deoxyuridine analogues **2**. Their studies also showed that these deoxycytidine analogues are significantly less toxic to uninfected cells than are 5-iodo- (or 5-bromo-) 2'-deoxyuridine (**2**) apparently as a result of a virus-induced pyrimidine nucleoside kinase which converts the 5-halogenated deoxycytidines to their 5-halogenated deoxycytidylates and thence to the corresponding deoxyuridylates.



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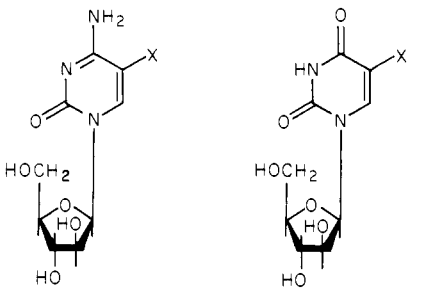

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series a, X = H; b, X = F; c, X = Cl; d, X = Br; e, X = I; f, X = CH_3

1-β-D-Arabinofuranosylcytosine (*ara*-C, **3a**), a potent anticancer drug,[4] also inhibits the multiplication of several DNA viruses in cell culture.[5] Therapeutic trials of *ara*-C in herpes infections in animal models were not encouraging because its therapeutic to toxic ratio approached unity.[6] Although 1-β-D-arabinofuranosyluracil (*ara*-U, **4a**) is devoid of antiviral or anticancer activity, the 5-halogeno analogues (**4**, X = Cl, Br, I) show antiviral activity in cell culture[7] and in vivo.[8] Gentry et al.[9] demonstrated that *ara*-T (**4f**) also is active against HSV types 1 and 2 as well as against equine herpes virus. More recently they[10] showed that 5-Me-*ara*-C (**3f**) is also active against herpes virus infected cells in which deoxycytidine deaminase is present, indicating that this nucleoside serves as an intracellular donor of *ara*-T that is phosphorylated to the nucleotide which then inhibits viral replication. (5-Me-*ara*-C is devoid of anticancer activity.[11]) The 5-halogeno-*ara*-C derivatives (**3**, X = F, Cl, Br, I) have also shown antiherpes virus activity in culture and were also active against experimental herpes keratitis in rabbits.[12]

It is apparent from the above-mentioned data that the nature of the substituent at C-5 of the pyrimidine nucleosides **1–4** is an important factor in the determination of biological activity. Moreover, since activity is noted for both 2'-deoxyribo- as well as 2'-deoxyarabinopyrimidine nucleosides, the C-2' substituent also plays a role in the determination of biological activity. This report describes the syntheses and preliminary evaluation of a series of 5-substituted 1-(2-deoxy-2-fluoroarabinofuranosyl)pyrimidines (**7** and **9**) as part of our program in the design and syntheses of nucleosides of potential value as anticancer and/or antiviral agents.

We had previously developed[13] a practical synthesis of 3-*O*-acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-D-arabinofuranosyl bromide (**5**), a key intermediate in the syntheses of the desired nucleosides. Thus, condensation of halogenose **5** with trimethylsilylated cytosines afforded the blocked nucleosides **6** which were deprotected by saponification to the 2'-F-*ara*-C type nucleosides **7a–d**. The 5-iodo analogue **7e** was obtained by iodination of **7a**. The uracil nucleoside analogues **9a–d,f** were obtained by condensation of **5** with the corresponding trimethyl-

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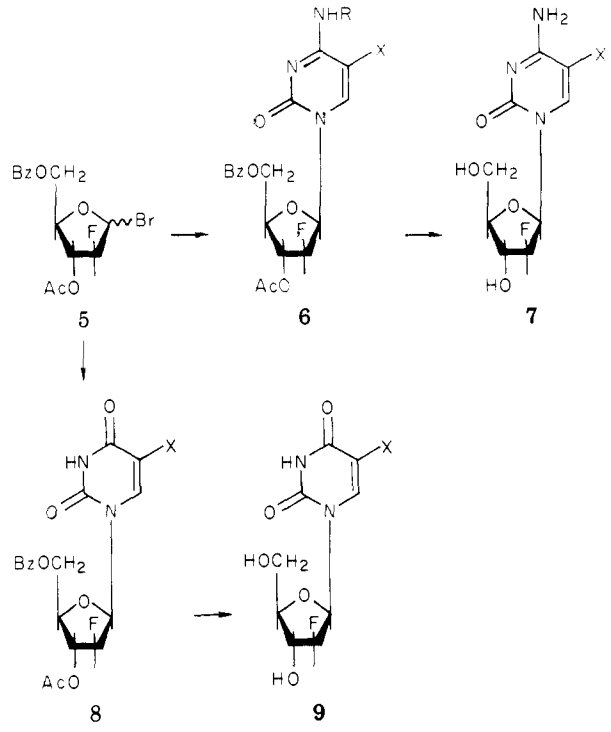
Table I. Capacity of 2′-Fluoro-2′-deoxyarabinosylcytosines and -uracils to Suppress HSV-1 Replication in Monolayers of Vero Cells

		antiviral act.[a] in μg/mL					cytotoxicity, ID_{50} in μg/mL[b]	
	X	0.01	0.1	1.0	10	100	L5178Y	P815
				Cytosine Nucleosides[c]				
7a[d]	H	−	+	+	+++	++++	0.05	0.05
7b	F	−	+	++	+++	ND[e]	0.5	0.4
7c	Cl	−	−	−	+++	ND	1.4	~1.0
7d	Br	−	+	++	+++++	ND	~10	>10
7e	I	+	++	++++	+++++	+++++	48	14
				Uracil Nucleosides				
9a	H	−	−	++	++	ND	>10	>10
9b	F	−	++	++++	+++++	ND	1.0	0.7
9c	Cl	−	−	−	++++	ND	1.4	3.4
9d	Br	−	−	++	++++	ND	0.9	1.6
9e	I	−	+	+++	++++	ND	0.9	0.8

[a] Percent reduction of HSV-1 titer: >90% = +; >99% = ++; >99.9% = +++; >99.99% = ++++; complete obviation of HSV-1 replication = +++++. (−) = <90% reduction of HSV-1 titer. [b] Concentration required for 50% inhibition of growth of cells in vitro after 96 h of incubation at 37 °C. [c] All pyrimidine nucleosides listed in this table and others discussed elsewhere are of the 1-β-D configuration and are in the neutral form except for compounds **7a** and **7e** which are in the form of their hydrochloride salts. [d] J. A. Wright, D. P. Wilson, and J. J. Fox, *J. Med. Chem.*, **13**, 269 (1970). [e] ND = not done.

silylated uracils and subsequent removal of the blocking groups. Iodination of **6a** followed by saponification afforded the 5-iodo analogue **9e**.



series a, X = H; b, X = F; c, X = Cl; d, X = Br; e, X = I; f, X = CH_3; R = H or acetyl

The capacity of these 2′-fluoroarabinosyl nucleosides **7** and **9** to suppress replication of herpes simplex virus type 1 (HSV-1) in monolayers of Vero cells is shown in Table I. Five of these nucleosides (**7d,e** and **9b,d,e**) completely obviated replication of HSV-1 at concentrations of 100 μg/mL. At drug levels of 10 μg/mL, 2′-F-*ara*-5-IC (compound **7e**) was equally effective while the 5-bromo analogue **7d** was a close second. Even at levels of 0.1 μg/mL compound **7e** showed >99.5% suppression of viral replication in this system. By comparison, *ara*-A (9-β-D-arabinofuranosyladenine), an antiherpes drug with clinical efficacy,[14] has, in our hands, only approached these levels of viral suppression at doses 1000–10000-fold higher.

Of greater interest is the demonstration that the cytotoxicity of the cytosine nucleosides **7d,e** against L5178Y and P815 cells was minimal at best. This inverse relationship (high antiviral activity associated with minimal cytotoxicity) seems to be characteristic of the 2′-fluoroarabinosylcytosine nucleosides in Table I. This relationship does not hold for the corresponding uracil series (compounds **9**). Thus, though several of the 2′-fluoroarabinosyluracils (**9b,d,e**) exhibit significant inhibition of viral replication, they also show appreciable cytotoxicity against cells in culture.

The data in Table II attest to the importance of the 2′-fluoro substituent for the anti-HSV-1 activity exhibited by the 1-β-D-arabinofuranosyl nucleosides. Thus, 2′-fluoro-*ara*-5-iodocytosine (**7e**) is much more effective than 2′-deoxy-5-iodocytidine (IdC, **1e**) or arabinosyl-5-iodocytosine (**3e**) which indicates that the 2′-fluoro substituent confers better antiviral activity to these 5-iodocytosine nucleosides than does a 2′-hydroxyl or a 2′-hydrogen substituent. A similar conclusion may be reached from a comparison of the 5-iodouracil nucleosides **9e**, **2e**, and **4e**. Even in the thymine series, 2′-fluoroarabinosylthymine (**9f**) is clearly more effective against HSV-1 than is arabinosylthymine (**4f**).

Further in vitro and in vivo studies on HSV-1 and other herpes virus systems are underway in order to evaluate the possible clinical efficacy of 1-(2-fluoro-2-deoxy-β-D-arabinofuranosyl)-5-iodocytosine (**7e**).

Experimental Section

General. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were determined on a Thomas-Hoover capillary apparatus and were corrected. Melting points, crystallization solvents, and analytical data are listed in Table III.

1-(3-*O*-Acetyl-5-*O*-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorocytosine (6b). To a stirred solution of 5[13] (3.6 g, 0.01 mol) in CH_2Cl_2 (50 mL) was added crude 5-fluorotris(trimethylsilyl)cytosine (prepared from 3.78 g, 0.03 mol, of 5-fluorocytosine) in CH_2Cl_2 (25 mL), and the mixture was stirred for 5 days at room temperature. MeOH (7 mL) was added and the suspension was filtered through a Celite pad which was thoroughly washed with CH_2Cl_2. The combined filtrate and washings were evaporated to dryness in vacuo, and the residue was crystallized from EtOH to give 2.0 g of **6b**.

Compounds **6a,c,d** (see Table III) were also obtained in a similar manner using the trimethylsilyl derivatives prepared from N^4-

Table II. Comparison of Antiherpes Virus Activity of Certain 2'-Fluoro Nucleosides with Their Corresponding Nonfluorinated Arabino and/or 2'-Deoxyribo Analogues

nucleoside	antiviral act.[a] in μg/mL					cytotoxicity, ID_{50} in μg/mL[b]	
	0.01	0.1	1.0	10	100	L5178Y	P815
ara-C	−	−	+	++++	++++	0.02	0.02
2'-F-*ara*-C (**7a**)	−	+	+	+++	++++	0.05	0.05
ara-IC (**3e**)	−	−	+	++++	ND	0.2	0.08
IdC (1e)	−	−	+	+++	ND	>100	>100
2'-F-*ara*-IC (**7e**)	+	++	++++	+++++	+++++	48	14
ara-IU (**4e**)	−	−	−	+	++++	30	16
IdU (**2e**)	−	−	−	+	+++++	4.2	0.9
2'-F-*ara*-IU (**9e**)	−	+	+++	++++	ND	0.9	0.8
ara-T (**4f**)	−	−	+	+++++	+++++	>100	13
2'-F-*ara*-T (**9f**)	−	+	+++	+++++	ND	1.6	1.9

[a,b] See corresponding footnotes in Table I.

Table III[a]

compd	mp, °C	crystn solvent	formula
6a	198-201	EtOH	$C_{20}H_{20}FN_3O_7$
6b	237-239 dec	EtOH	$C_{18}H_{17}F_2N_3O_6$
6c	233	EtOH	$C_{18}H_{17}ClFN_3O_6$
6d	206	EtOH	$C_{18}H_{17}BrFN_3O_6$
8a	179-180	EtOH	$C_{18}H_{17}FN_2O_7$
8b	177-179	EtOH	$C_{18}H_{16}F_2N_2O_7$
8f	169-170	EtOH	$C_{17}H_{17}FN_2O_6$[b]
7a	240-242	EtOH	$C_9H_{12}FN_3O_4$
7b	188-189 dec	EtOH	$C_9H_{11}F_2N_3O_4$[c]
7c	205-206	EtOH	$C_9H_{11}ClFN_3O_4$
7d	201-102	EtOH	$C_9H_{11}BrFN_3O_4$
7e	177-181 dec	MeOH	$C_9H_{11}FIN_3O_4 \cdot HCl$
9a	162	*i*-PrOH-Et_2O	$C_9H_{11}FN_2O_5$
9b	167-168	EtOH	$C_9H_{10}F_2N_2O_5$
9c	195-196	H_2O	$C_9H_{10}ClFN_2O_5$
9d	214-216	H_2O	$C_9H_{10}BrFN_2O_5$
9e	216-217	EtOH	$C_9H_{10}FIN_2O_5$
9f	185-185.5	H_2O	$C_{10}H_{13}FN_2O_5$

[a] All compounds in Table III gave satisfactory C, H, F, and N analyses. [b] Deacetylation occurred during work-up; confirmed by NMR. [c] The HCl salt of **7b** was also obtained: mp 203-206 °C dec.

acetylcytosine, 5-chlorocytosine, and 5-bromocytosine, respectively.

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorocytosine (7b). Compound **6b** (1.1 g) was dissolved in saturated NH_3–MeOH (30 mL). After 16 h, the solvent was removed in vacuo and the residue was triturated with acetone. Crystalline **7b** (460 mg) was filtered. The filtrate was evaporated in vacuo and the residue was triturated with ~7 mL of HCl–MeOH. The HCl salt of **7b** (100 mg) was obtained as colorless crystals.

Similarly, treatment of **6a,c,d** with NH_3–MeOH afforded the corresponding free nucleosides **7a,c,d** (see Table III).

1-(3-O-Acetyl-5-O-benzoyl-2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracil (8a). A mixture of **5** ((11.5 g) and crude 2,4-bis[(trimethylsilyl)oxy]pyrimidine (prepared from 5 g of uracil) in 150 mL of CH_2Cl_2 was stirred for 5 days at room temperature. MeOH (5 mL) was added to the mixture and the suspension was filtered through a Celite pad. The filtrate was evaporated in vacuo and the residue was triturated with Et_2O to give crude **8a** (5.8 g) which was recrystallized from EtOH. Pure **8a** (4.2 g) was obtained as colorless leaflets.

Compound **8f** was also obtained in a similar manner (see Table III).

Conversion of 6a to 8a. A solution of **6a** (200 mg) in 80% AcOH (20 mL) was heated under reflux for 1.5 h. The mixture was evaporated in vacuo and the residue was dissolved in a small amount of EtOH. To the solution was added Et_2O, and the precipitate was filtered and recrystallized from EtOH to afford 80 mg of compound identical with **8a** obtained previously by an alternate route.

Conversion of 6b to 8b. A mixture of **6b** (650 mg) in 80% AcOH (50 mL) was heated under reflux for 48 h. After removal of the solvent in vacuo the residue was chromatographed over a column of silica gel G 60 (22 × 2 cm) using $CHCl_3$–MeOH (30:1 v/v) as the eluant. The crystalline product (300 mg) obtained was identical with **8b** obtained by condensation of **5** and 2,4-bis[(trimethylsilyl)oxy]-5-fluoropyrimidine (see below).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-fluorouracil (9b). Method A. Compound **8b** (170 mg) was dissolved in saturated NH_3–MeOH (10 mL) and the mixture left standing for 16 h. The solvent was removed by evaporation in vacuo, and the residue crystallized from EtOH to give 66 mg of **9b**.

Similarly, compounds **9a,f** were obtained from **8a,f**, respectively (see Table III).

Method B. To a solution of **5**[13] (3.5 g, 0.01 mol) in CH_2Cl_2 (10 mL) was added 2,4-bis[(trimethylsilyl)oxy]-5-fluoropyrimidine (prepared from 2.6 g, 0.02 mol, of 5-fluorouracil) in CH_2Cl_2 (50 mL), and the mixture was stirred for 5 days at room temperature. MeOH (3 mL) was added and the suspension was filtered through a Celite pad which was thoroughly washed with CH_2Cl_2. TLC (10:1 v/v $CHCl_3$–MeOH) showed that the filtrate contained one major component contaminated with some partially deacylated products. The major component (**8b**) was isolated by chromatography on a silica gel G 60 (22 × 2.5 cm) column with 50:1 (v/v) $CHCl_3$–MeOH as the solvent. Appropriate fractions (checked by TLC) were collected and evaporated in vacuo to a syrup which was dissolved in saturated NH_3–MeOH (50 mL). After 2 days at room temperature, the solvent was removed by evaporation and the residue triturated with $CHCl_3$. The insoluble material was crystallized from EtOH to give 265 mg of **9b** which was identical with an authentic sample prepared by hydrolytic deamination of **6b** to **8b** followed by deacylation.

In a similar manner, **9c** and **9d** were prepared by condensation of **5** with the corresponding silylated 5-halogenouracils (see Table III).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodocytosine Hydrochloride (7e). A mixture of **7a** (HCl salt, 610 mg), AcOH (2.2 mL), HIO_3 (196 mg), I_2 (327 mg), CCl_4 (1.5 mL), and H_2O (0.75 mL) was stirred at 40–50 °C for 2.5 h and then at room temperature overnight. H_2O (6 mL) was added and the yellow precipitate (650 mg; mp 115–125 °C dec) filtered. Anal. Calcd for $C_9H_{11}FIN_3O_4 \cdot HCl \cdot 0.5HI \cdot 0.5H_2O$: C, 22.45; H, 2.80; F, 3.95; I, 39.60; N, 8.73 (C, H, F, I, N).

The above product (610 mg) was dissolved in H_2O (100 mL) and the red-brown solution passed through a column of Amberlite IR-45 (OH^-, 20 mL). The column was washed with H_2O (200 mL). The combined eluates and washings were evaporated in vacuo, and the colorless residue was dissolved in HCl–MeOH (10 mL). Compound **7e** (HCl salt, 190 mg) deposited as colorless crystals (see Table III).

1-(2-Deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (9e). To a mixture of **8a** (400 mg) and I_2 (130 mg) in AcOH (5 mL) was added fuming HNO_3 (sp gr 1.5) dropwise with stirring until the color of I_2 disappeared. After evaporation in vacuo, the residue was triturated with H_2O and the insoluble product (515 mg) was collected by filtration.

The crude product (200 mg) was dissolved in saturated NH_3–MeOH (50 mL). After 2 days, the solvent was removed by

evaporation and the residue dissolved in a small amount of EtOH. To the solution was added Et_2O and the product was collected by filtration and recrystallized from EtOH to give 86 mg of **9e** (see Table III).

5-Iodo-2′-deoxycytidine (IdC) and 5-iodo-2′-deoxyuridine (IdU) were commercial samples obtained from Sigma Chemical Co., St. Louis, Mo. *ara*-IC was synthesized according to Honjo et al.[15] *ara*-IU (4e) was prepared according to Hunter.[16]

Antiviral Assay. Vero cell monolayers were infected with approximately 1 plaque-forming unit (PFU) per cell of herpes simplex virus type 1 (HSV-1) strain 2931 and incubated for 2 h. Maintenance media containing the various concentrations of drugs were used to overlay the monolayers. Supernatant fluids were collected 24 h later and titered on Vero cell monolayers as described previously.[17] Percent inhibition over controls was calculated.

Cell Culture Studies (by Dr. J. H. Burchenal). The technique of Fischer[18] was employed with modifications.[19] Mouse cell lines L5178Y and P815 were incubated in McCoy's medium with 15% fetal calf serum. The initial inoculum was 40 000–60 000 leukemic cells/mL. For growth inhibition studies, 0.1 mL of a 50-fold concentration of the nucleoside in question was added to 5 mL of the cell-containing media. The tubes were set up in triplicate, loosely capped, and allowed to incubate in 5% CO_2 at 37 °C for 96 h. Growth to $\sim 10^6$ cells/mL occurred in the control tubes. The contents of each tube was counted on a Coulter counter and the percentage of inhibition of growth was calculated.

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Preparation of the Enantiomeric Forms of 9-(5-Deoxy-α-*threo*-pent-4-enofuranosyl)adenine and 9-(3,5-Dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine and in Vitro Antileukemic Screening

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The preparation and use of 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-xylofuranose and 5-deoxy-5-iodo-1,2-*O*-isopropylidene-α-D-arabinofuranose in the synthesis of the L and D forms of 9-(5-deoxy-α-*threo*-pent-4-enofuranosyl)adenine, respectively, are described. The preparation of 9-(3,5-dideoxy-β-D-*glycero*-pent-4-enofuranosyl)adenine (**19**) was accomplished from either 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-α-D-*erythro*-pentofuranose or 3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose. In each case, acetolysis was performed to obtain the acetates which were condensed with 6-(benzamidochloromercuri)purine by the titanium tetrachloride method. Treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene and removal of the blocking groups produced the desired nucleosides. Only **19** showed inhibitory activity toward leukemia L1210 in vitro.

The nucleoside antibiotic decoyinine (angustmycin A) was reported to have antibacterial and antitumor activity.[1] The structure of decoyinine was shown to be 9-(6-deoxy-β-D-*erythro*-hex-5-enulofuranosyl)adenine.[2] The closely related compound which lacked the anomeric hydroxymethyl group, 9-(5-deoxy-β-D-*erythro*-pent-4-enofuranosyl)adenine, was shown to inhibit *Streptococcus faecalis* with the same potency as decoyinine.[3] In order to further explore the biological effects of 4′,5′ unsaturation in nucleosides and to possibly improve upon the range and extent of biological activity, this laboratory set out to prepare a number of compounds in this series.

Previous reports from this laboratory have described the synthesis of several 4′,5′-unsaturated nucleosides.[4,5] Originally the synthesis of such unsaturated nucleosides was undertaken starting from a preformed nucleoside.[4,6] It became evident in time that synthesis by this route created a number of problems, among which were cyclonucleoside

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