Structure−Activity Relationships of 1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine Nucleosides as Anti-Hepatitis B Virus Agents

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Since 2′-fluoro-5-methyl-β-L-arabinofuranosyluracil (L-FMAU) has been shown to be a potent anti-HBV agent *in vitro*, it was of interest to study the structure−activity relationships of related nucleosides. Thus, a series of 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides have been synthesized and evaluated for antiviral activity against HBV in 2.2.15 cells. For this study, L-ribose was initially used as the starting material. Due to the commercial cost of L-ribose, we have developed an efficient procedure for the preparation of L-ribose derivative **6**. Starting from L-xylose, **6** was obtained in an excellent total yield (70%) through the pyridinium dichromate oxidation of the 3-OH group followed by stereoselective reduction with $NaBH_4$. It was further converted to the 1,3,5-tri-*O*-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (**10**), which was then condensed with various 5-substituted pyrimidine bases to give the nucleosides. Among the compounds synthesized, the lead compound, L-FMAU (**13**), exhibited the most potent anti-HBV activity (EC_{50} 0.1 μM). None of the other uracil derivatives showed significant anti-HBV activity up to 10 μM. Among the cytosine analogues, the cytosine (**27**) and 5-iodocytosine (**35**) derivatives showed moderately potent anti-HBV activity (EC_{50} 1.4 and 5 μM, respectively). The cytotoxicity of these nucleoside analogues has also been assessed in 2.2.15 cells as well as CEM cells. None of these compounds displayed any toxicity up to 200 μM in 2.2.15 cells. Thus, compound **13** (L-FMAU), **27**, and **35** showed a selectivity of over 2000, 140, and 40, respectively.

Introduction

Recently, a number of nucleosides with the unnatural L-configuration have been reported as potent chemotherapeutic agents against human immunodeficiency virus (HIV), hepatitis B virus (HBV), and certain forms of cancer. These include (−)-β-L-1-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]cytosine (3TC),[1−3] (−)-β-L-1-[2-(hydroxymethyl)-1,3-oxathiolan-4-yl]-5-fluorocytosine (FTC),[4,5] (−)- β-L-2′, 3′-dideoxypentofuranosyl-5-fluorocytosine (L-FddC),[6,7] and (−)-β-L-1-[2-(hydroxymethyl)-1,3-dioxolan-4-yl]cytosine [(−)-OddC].[8,9] It is interesting that these L-nucleosides have potent biological activity, while some of them show lower toxicity profiles than their D-counterparts. In view of this interesting discovery of L-nucleosides as biologically active compounds, we have recently synthesized 2′-fluoro-5-methyl-β-L-arabinofuranosyluracil (L-FMAU) and its derivative and evaluated these compounds as potential antiviral agents. From this effort we discovered L-FMAU as a potent antiviral agent against HBV as well as the Epstein−Barr virus.[10] In contrast to the D-enantiomers, L-FMAU did not exhibit any toxicities, including the interference of mitochondrial function,[11] resulting in lactic acidosis and hepatic failure as shown by β-D-2′-fluoro-5-iodoarabinofuranosyluracil (Fialuridine, D-FIAU).[12] No significant bone marrow toxicity was found for L-FMAU up to 100 μM.[10] Furthermore, in preliminary *in vivo* toxicity studies in mice for 30 days, L-FMAU did not show any apparent toxicities as well as significant abnormalities of clinical chemistry.[13] Additionally, L-FMAU exhibited *in vivo* antiviral activity against the duck hepatitis B virus in the Peking duck hepatitis model.[14] We also studied the biochemical mode of action of L-FMAU, in which it was discovered that L-FMAU is phosphorylated by the cellular thymidine kinase as well as by deoxycytidine kinase to the monophosphate and subsequently to the triphosphate by unknown kinases, which inhibits the HBV DNA polymerase.[15] However, we failed to detect any incorporation of a radiolabeled nucleoside to either the HBV DNA or the cellular DNA. Furthermore, the triphosphate did not inhibit cellular DNA polymerases.[15] As a result of these promising pharmacological and toxicological profiles, L-FMAU is currently considered as a clinical candidate for treatment of chronic HBV infection. In view of these promising results obtained for L-FMAU, it was of interest to study the structure−activity relationships (SAR) of the related class of nucleosides. Therefore, in this paper we report the synthesis and the SARs of 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-substituted-pyrimidine nucleosides as potential anti-HBV agents.

Results and Discussion

Synthesis. The synthesis of 2′-deoxy-2′-fluoro-β-L-arabinofuranosyl nucleosides reported in this paper was accomplished *via* the key intermediate **10**, which was initially prepared[10] from L-ribose according to a similar procedure used for the synthesis of D-FMAU.[16] However, due to the high commercial cost of L-ribose as a starting material, we developed a synthetic procedure for the L-ribose derivative **6**. Although several procedures have been reported for the synthesis of L-ribose,[17−20] on the basis of our experience, none of these methods seemed practical for large-scale preparation. Previously, it was reported that D-ribose was

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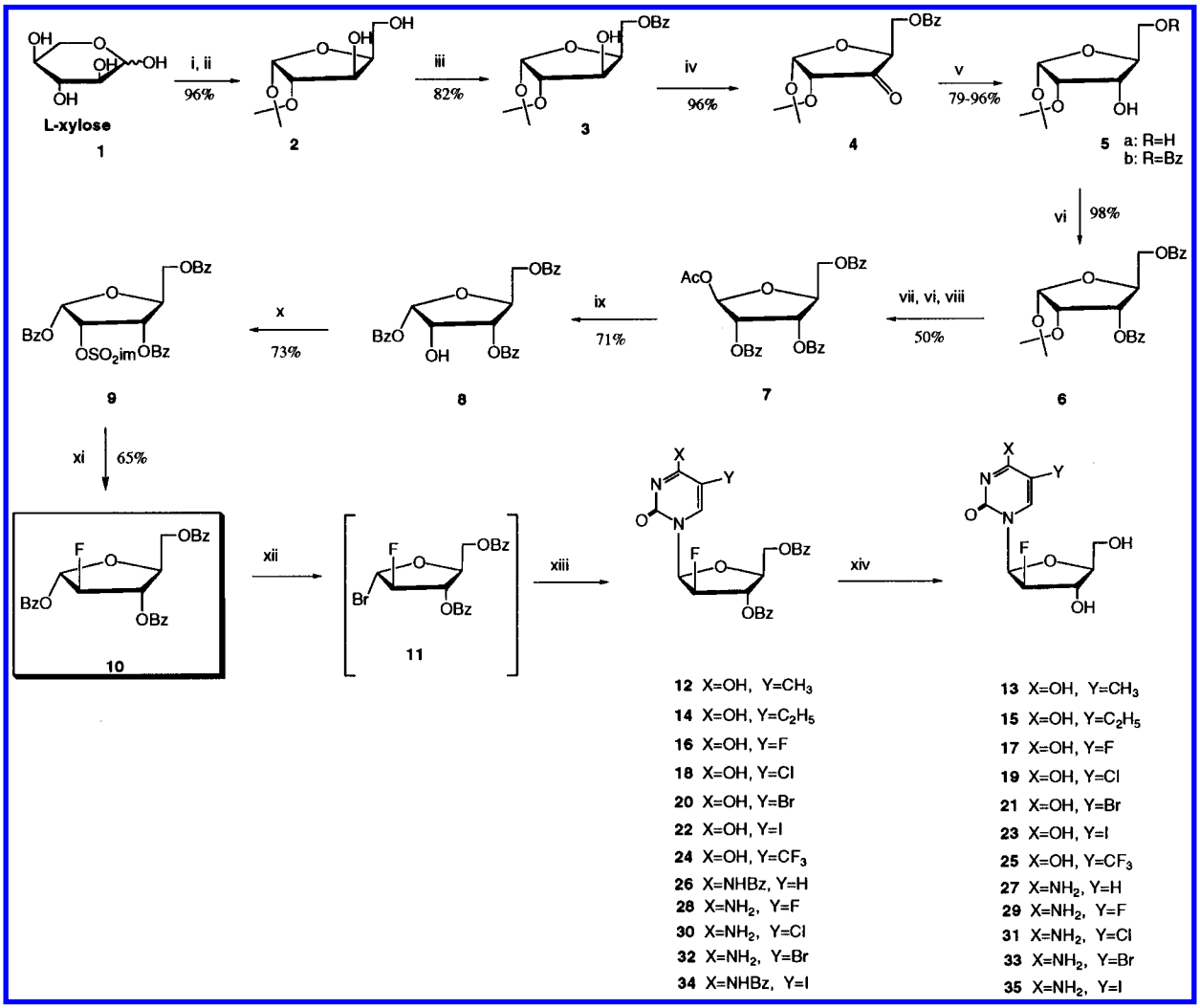
Scheme 1[a]

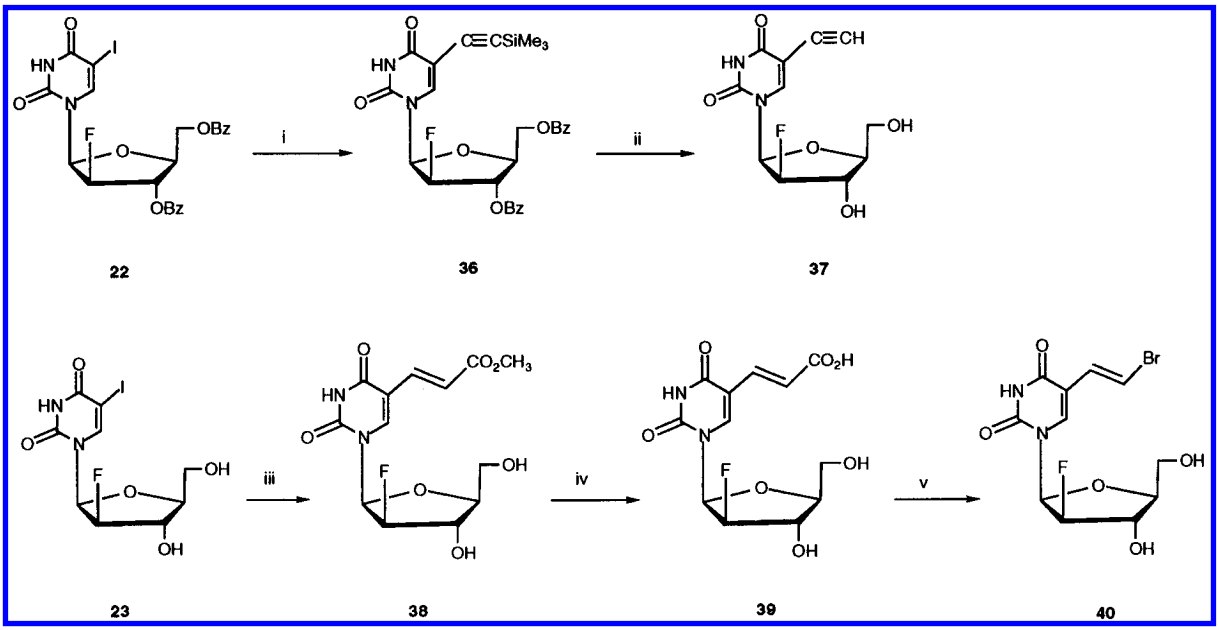


[a] Reagents: (i) $CuSO_4$, concentrated H_2SO_4, acetone; (ii) 0.2% HCl/H_2O; (iii) BzCl, py, CH_2Cl_2, 0 °C, 0.5−1 h; (iv) PDC, Ac_2O, CH_2Cl_2, reflux; (v) $NaBH_4$, 80% EtOH/H_2O or $NaBH_4$, EtOH, EtOAc; (vi) BzCl, py; (vii) 1% HCl/CH_3OH; (viii) Ac_2O, AcOH, concentrated H_2SO_4; (ix) (1) HCl(g), AcCl, CH_2Cl_2, 0 °C, (2) H_2O, CH_3CN; (x) SO_2Cl_2, DMF, CH_2Cl_2, −15 °C to room temperature, imidazole; (xi) KHF_2, 2,3-butanediol, 48% HF/H_2O, reflux; (xii) HBr/AcOH, CH_2Cl_2, room temperature; (xiii) silylated bases, 1,2-dichloroethane, reflux; (xiv) NH_3/CH_3OH.

synthesized from D-xylose *via* the oxidation−reduction procedure of the 3-OH group, albeit in a low yield.[21] We decided to adopt this strategy to synthesize the L-ribose derivative (Scheme 1). Thus, 1,2-*O*-isopropylidene-α-L-xylofuranose (**2**) was prepared from L-xylose,[22] which was then selectively protected at the 5-OH with BzCl in pyridine−CH_2Cl_2 at 0 °C to give **3** (79% yield from **1**). Although various oxidizing agents have been reported for the oxidation of the 3-OH of pentofuranose derivatives,[21,23,24] we found pyridinium dichromate (PDC) gave the best yield (96%). The resulting ketone **4** was stereoselectively reduced by $NaBH_4$ to the desired ribose derivative **5**. It should be mentioned that apparently due to the stereoelectronic effects of the 1,2-*O*-isopropylidene group, the hydride only attacked from the *β*-face, resulting in 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-L-ribofuranose (**5b**) as the exclusive product. When EtOH−H_2O (4:1) was used as the solvent, cleavage of the benzoyl group occurred, leading to a cumbersome workup and a lower yield (79%); however, using a mixture of EtOAc−EtOH (1:2) prevented the cleavage of the benzoyl group, resulting in a higher yield (96%). Compound **5a** or **5b** was benzoylated to give the dibenzoylated ribose derivative **6**,[25] which was treated successively without isolation with 1% HCl−MeOH, BzCl−pyridine, and then Ac_2O−AcOH−H_2SO_4 to give 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-L-ribofuranose (**7**) as a crystalline product in 50% yield. Treatment of **7** with saturated hydrogen chloride in CH_2Cl_2 at 0 °C followed by hydrolysis[26] gave **8** (71% yield), which was treated with SO_2Cl_2 and imidazole in DMF−CH_2Cl_2 to give the imidazolyl sulfonate **9** in 73% yield. The imidazole derivative **9** was fluorinated with KHF_2 and 48% HF−H_2O to give 1,3,5-tri-*O*-benzoyl-2-fluoro-α-L-arabinofuranose (**10**) in 65% yield.[16] It is noteworthy to mention that an improved fluorination reaction was recently reported.[27]

Bromination of the key intermediate **10** with HBr−AcOH gave a bromo derivative **11**, which was coupled with silylated thymine without catalyst in CH_3CN under refluxing conditions to give the protected nucleoside **12** as a mixture of anomers (*β*:α/3:1). Although the reaction finished within 3 h and the yield was high (94%), the separation of the anomers was difficult in both the protected as well as deprotected stages. Therefore, we searched for a more convenient procedure to improve the *β*/α ratio. From these efforts we found that using 1,2-dichloroethane (DCE) as the solvent for the conden-

Scheme 2[a]



[a] Reagents: (i) Et_3N, $(Ph_3P)_2PdCl_2$, CuI, (trimethylsilyl)acetylene, Ar, 50 °C; (ii) $NaOCH_3$, CH_3OH; (iii) methyl acrylate, $Pd(OAc)_2$, Ph_3P, 1,4-dioxane; (iv) (1) NaOH, (2) HCl; (v) DMF, $KHCO_3$, *N*-bromosuccinimide.

sation gave mainly the β-isomer **12** along with only trace amount of the α-anomer, which was easily removed by silica gel column chromatography or recrystallization, although the coupling reaction took a longer time with a lower yield (71%). We also found that using $CHCl_3$ as the solvent for the coupling reaction gave the best β/α ratio (20/1) which was consistent with the previously reported result.[28] The bromo sugar **11** was also condensed with other silylated 5-substituted uracil derivatives to give the protected nucleosides (**14**, **16**, **18**, **20**, **22**, and **24**), which were treated with NH_3−CH_3OH to give the final products (**15**, **17**, **19**, **21**, **23**, and **25**). The synthesis of cytosine derivatives was achieved by the condensation of the bromo sugar **11** with either the *N*-benzoylated (**26** and **34**) or unprotected bases (**28**, **30**, and **32**) in 1,2-dichloroethane. No significant differences in yields of the condensation was observed. The free nucleosides (**27**, **29**, **31**, **33**, and **35**) were obtained by the deprotection of **26**, **28**, **30**, **32**, and **34** with NH_3−CH_3OH.

The 5-ethynyluracil derivative **37** was obtained by treatment of the protected 5-iodo derivative **22** with (trimethylsilyl)acetylene in the presence of $(Ph_3P)_2PdCl_2$ and CuI, followed by deprotection with $NaOCH_3$−CH_3OH.[29] The synthesis of the (*E*)-5-bromovinyl derivative **40** was accomplished by using a similar procedure reported for the synthesis of 5-(bromovinyl)-2′-deoxyuridine (BVDU)[30] (Scheme 2). Thus, the free 5-iodouracil derivative **23** was treated with methyl acrylate in the presence of $Pd(OAc)_2$ and Ph_3P in dioxane. Saponification with NaOH followed by acidification with HCl gave **39**, which was decarboxylated in DMF in the presence of *N*-bromosuccinimide and K_2CO_3 to give **40**. The *E*-configuration was identified by the coupling constant (13.6 Hz) for the vinyl protons in the ^1H NMR spectrum.

The physical data for all the key intermediates and final products are summarized in Table 1. β-L-configuration of the synthesized nucleosides was confirmed by comparison of the ^1H NMR spectra (Table 2) with those of the corresponding D-isomers.[16,31−34] The C_1'−F coupling constants (16−18 Hz) in the ^{13}C NMR spectra were consistent with those reported for the β-D-configuration.[35] The structure of β-L-FMAU was also unambiguously confirmed by a single-crystal X-ray crystallography,[36] and the ORTEP drawing is shown in Figure 1.

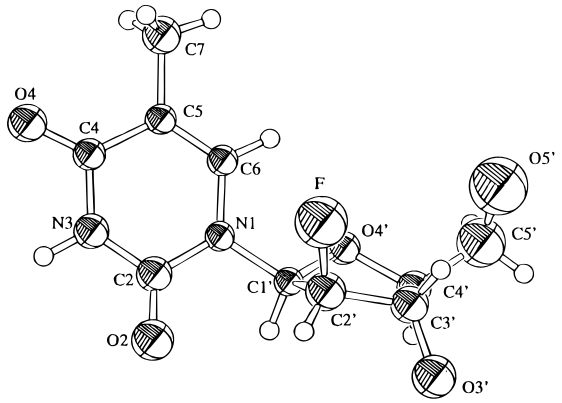


Figure 1. ORTEP drawing of L-FMAU.

Anti-Hepatitis B Virus Activity. The anti-hepatitis B virus activity (EC_{50}) and growth inhibition (IC_{50}) of the synthesized nucleosides were evaluated in 2.2.15 cells as previously described[10] and are shown in Table 3. Unlike the D-isomers such as FMAU, FEAU, and FIAU, neither 5-substitutions with halogen (F, Cl, Br, I) nor 5-substitutions with alkyl groups (ethyl, *E*-bromovinyl, or ethynyl) exhibited any significant anti-HBV activity up to 10 μM. The only active uracil derivative is the 5-methyl derivative, L-FMAU (**13**), which exhibited 20 times more potency than that of the D-counterpart (EC_{50} 0.1 μM vs 2.0 μM).[10] Change of the 5-methyl to a 5-trifluoromethyl group (**25**) also resulted in a decrease of the anti-HBV activity. Interestingly, the cytosine (**27**) and 5-iodocytosine (**35**) derivatives showed moderately potent anti-HBV activities (EC_{50} 1.4 and 5.0 μM, respectively), while other 5-substitutions such as F, Cl, and Br did not exhibit any significant antiviral activity.

Table 1. Physical and Optical Data

no.	mp, °C (solv)[a]	$[\alpha]^{25}_D$	formula	anal.
3	82−83 (A)	−12.14 (*c* 0.37, $CHCl_3$)	$C_{15}H_{18}O_6$	C,H
4	91−93 (B)	−132.00 (*c* 1.0, $CHCl_3$)	$C_{15}H_{16}O_6$	C, H
5a	86−87 (B)	−31.50 (*c* 0.62, $CHCl_3$)	$C_8H_{14}O_5$	C, H
5b	131−132 (B)	+46.22 (0.11, CH_3OH)	$C_{15}H_{18}O_6$	C,H
6	83−85 (A)	−122.38 (*c* 0.9, $CHCl_3$)	$C_{22}H_{22}O_7$	C, H
8	137−138 (A)	−81.96 (*c* 0.55, $CHCl_3$)	$C_{26}H_{22}O_8 \cdot 0.3H_2O$	C, H
9	124−125 (B)	−68.98 (*c* 0.37, $CHCl_3$)	$C_{29}H_{24}N_2O_{10}S$	C, H, N, S
10	77−78 (D)	−4.82 (*c* 0.51, $CHCl_3$)	$C_{26}H_{21}FO_7 \cdot 0.5C_2H_5OH$	C, H, F
12	118−120 (E)	+22.40 (*c* 0.31, $CHCl_3$)	$C_{24}H_{21}FN_2O_7 \cdot 0.5CH_3OH$	C, H, F, N
13	184−185 (E)	−111.77 (*c* 0.23, CH_3OH)	$C_{10}H_{13}FN_2O_5 \cdot 0.2H_2O$	C, H, F, N
14	148−149 (E)	+23.62 (*c* 0.21, $CHCl_3$)	$C_{25}H_{23}FN_2O_7$	C, H, F, N
15	158−161 (E)	−96.30 (*c* 0.47, CH_3OH)	$C_{11}H_{15}FN_2O_5$	C, H, F, N
16	190−193 dec (E)	+10.76 (*c* 0.29, $CHCl_3$)	$C_{23}H_{18}F_2N_2O_7 \cdot 0.5H_2O$	C, H, N
17	167−168 (E)	−93.42 (*c* 0.29, CH_3OH)	$C_9H_{10}F_2N_2O_5 \cdot 0.2H_2O$	C, H, N
18	189−191 (E)	+30.45 (*c* 0.35, $CHCl_3$)	$C_{23}H_{18}ClFN_2O_7$	C, H, N
19	195−196 (F)	−107.23 (*c* 0.18, CH_3OH)	$C_9H_{10}ClFN_2O_5 \cdot 0.33C_2H_5OH$	C, H, N
20	193−195 (E)	+37.65 (*c* 0.28, $CHCl_3$)	$C_{23}H_{18}BrFN_2O_7 \cdot 0.5CHCl_3$	C, H, N
21	214−215 (F)	−109.61 (*c* 0.15, CH_3OH)	$C_9H_{10}BrFN_2O_5 \cdot 0.5C_2H_5OH$	C, H, N
22	194−195 (G)	+44.02 (*c* 0.21, $CHCl_3$)	$C_{23}H_{18}FIN_2O_7$	C, H, F, I, N
23	218−220 (E)	−57.82 (*c* 0.33, CH_3OH)	$C_9H_{10}FIN_2O_5$	C, H, F, I, N
24	186−187 (E)	+5.19 (*c* 0.21, $CHCl_3$)	$C_{24}H_{18}F_4N_2O_7$	C, H, N
25	202−203 (G)	−87.47 (*c* 0.33, CH_3OH)	$C_{10}H_{10}F_4N_2O_5$	C, H, N
26	foam	−4.33 (*c* 0.21, $CHCl_3$)	$C_{30}H_{24}FN_3O_7$	C, H, N
27	240−242 (E)	−114.17 (*c* 0.21, CH_3OH)	$C_9H_{12}FN_3O_4 \cdot 0.7H_2O \cdot 0.2CH_3OH$	C, H, N
28	foam	−6.70 (*c* 0.35, $CHCl_3$)	$C_{23}H_{19}F_2N_3O_6 \cdot 0.5H_2O$	C, H, N
29	188−189 dec (F)	−108.36 (*c* 0.16, CH_3OH)	$C_9H_{11}F_2N_3O_4$	C, H, N
30	foam	+23.15 (*c* 0.19, $CHCl_3$)	$C_{23}H_{19}ClFN_3O_6 \cdot 0.6H_2O$	C, H, N
31	205−206 (F)	−99.54 (*c* 0.26, CH_3OH)	$C_9H_{11}ClFN_3O_4 \cdot 0.5C_2H_5OH$	C, H, N
32	foam	+24.09 (*c* 0.27, $CHCl_3$)	$C_{23}H_{19}BrFN_3O_6$	C, H, N
33	201−202 (F)	−82.86 (*c* 0.18, CH_3OH)	$C_9H_{11}BrFN_3O_4 \cdot 0.2C_2H_5OH$	C, H, N
34	226−228 (E)	+41.29 (*c* 0.19, $CHCl_3$)	$C_{30}H_{23}FIN_3O_7$	C, H, F, I, N
35	211−212 dec (E)	−65.40 (*c* 0.34, CH_3OH)	$C_9H_{11}FIN_3O_4$	C, H, F, I, N
36	212−214 (E)	+80.63 (*c* 0.19, $CHCl_3$)	$C_{28}H_{27}FN_2O_7Si \cdot 0.5H_2O$	C, H, N
37	206−208 dec (H)	−89.52 (*c* 0.27, CH_3OH)	$C_{11}H_{11}FN_2O_5 \cdot 0.2H_2O$	C, H, N
40	190−192 dec (E)	−59.40 (*c* 0.17, CH_3OH)	$C_{11}H_{12}BrFN_2O_5$	C, H, N

[a] Solvent for either recrystallization or chromatography: A, Et_2O; B, hexanes/EtOAc; C, CH_3OH; D, 95% EtOH/H_2O; E, $CH_3OH/CHCl_3$; F, EtOH; G, 2-propanol; H, EtOH/hexanes.

The toxicities of these nucleosides have also been assessed in 2.2.15 cells as well as CEM cells. No significant toxicities were found for any of these analogues with concentrations up to 200 μM, which indicated a high selectivity (over 2000, 140, and 40 for compound **13**, **27**, and **35**, respectively).

The results obtained above are consistent with the general observation that L-nucleosides often showed lower toxicity than their D-isomers and most of the active L-nucleosides against HIV and/or HBV are cytosine derivatives.[1−8] Therefore, L-FMAU may be unique in a sense that this is the only thymine derivative of an L-nucleoside discovered so far with potent anti-HBV activity. Furthermore, L-FMAU is the only 2′-deoxy nucleoside with a 3′-OH group, while all the other identified anti-HBV L-nucleosides lack that OH group. It is well-known that HBV replicates by a multistep mechanism that involves the reverse transcription of a pregenomic RNA;[37] therefore, most of the active L-nucleosides such as 3TC, FTC, and L-FddC are 2′,3′-dideoxycytidine analogues, which may act as chain terminators.[38] The structural uniqueness of L-FMAU may implicate that the mode of action of L-FMAU is different from that of other cytosine derivatives, and therefore, potential cross-resistance problems may be avoided after a prolonged use of these compounds in patients. Although presently the precise mechanism of action of L-FMAU is not clear, preliminary biochemical study suggested that inhibition of viral DNA polymerase may account for its anti-HBV activity.[15]

In summary, we have developed an efficient procedure for the preparation of the L-ribose derivative **6** from L-xylose, which was further used for the synthesis of L-FMAU (**13**) as well as other 1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)pyrimidine nucleosides. From the study of comprehensive structure−activity relationships, we discovered that L-FMAU exhibited the most potent anti-HBV activity among these pyrimidine nucleoside analogues with a high selectivity index (>2000). The cytosine (**27**) and 5-iodocytosine (**35**) derivatives also showed moderately potent anti-HBV activity with selectivities of 140 and 40, respectively. The anti-EBV activity study of these new analogues is still ongoing in laboratories. Although further biochemical studies are needed to elucidate the antiviral mechanism of these L-nucleosides, synthesis of additional nucleoside analogues is warranted.

Experimental Section

Melting points were determined on a Mel-temp II and are uncorrected. ^{1}H NMR spectra were recorded on a JEOL FX 90Q Fourier-transform spectrometer for 90 MHz or on a Bruker 250 AM for 250 MHz, 300 AC for 300 MHz, or 400 AMX spectrometer for 400 MHz, with Me_4Si as internal standard. Chemical shifts (δ) are reported in parts per million (ppm), and signals are reported as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), or br s (broad singlet). IR spectra were measured on a Nicolet 510P FT-IR spectrometer. Optical rotations were performed on a JASCO DIP-370 digital polarimeter. TLC were performed on Uniplates (silica gel) purchased from Analtech Co. Column chromatography was performed using either silica gel 60 (220−440 mesh) for flash chromatography or silica gel G (TLC grade >440 mesh) for vacuum flash column chromatography. UV spectra were obtained on a Beckman DU-7 or on a Beckman DU 650 spectrophotometer. Elemental analyses were performed by

Table 2. ^{1}H NMR Data of Synthesized Nucleosides and Some $C_{1'}$−F Coupling Constants of ^{13}C NMR

no.	H-1′	H-2′	H-3′	H-4′	H-5′,5″	$J_{C1'-F}$	others	solvent
12	6.35 (dd, J_{F-H} = 22.4)	5.32 (dd, J_{F-H} = 50.2)	5.64 (dd, J_{F-H} = 20.4)	4.50 (m)	4.82 (m)		8.55 (s, NH), 7.37, 8.12 (m, Ar), 1.76, (s, CH_3)	$CDCl_3$
13	6.10 (dd, J_{F-H} = 15.4)	5.04 (dt, J_{F-H} = 52.8)	4.22 (dq, J_{F-H} = 18.4)	3.76 (m)	3.63 (m)	16.59	11.45 (s, NH), 7.59 (s, H-6), 5.88 (d, 3′-OH), 5.13 (t, 5′-OH), 1.78 (s, CH_3)	DMSO-d_6
14	6.35 (dd, J_{F-H} = 22.1)	5.32 (dd, J_{F-H} = 50.3)	5.65 (dd, J_{F-H} = 17.8)	4.50 (m)	4.83 (m)		8.16 (s, NH), 7.32, 8.11 (m, Ar), 2.21, (q, **CH_2**CH_3), 0.97 (t, CH_2**CH_3**)	$CDCl_3$
15	6.14 (dd, J_{F-H} = 14.1)	5.08 (dt, J_{F-H} = 53.2)	4.24 (dq, J_{F-H} = 20.3)	3.78 (m)	3.64 (m)	17.02	11.43 (s, NH), 7.57 (s, H-6), 5.88 (d, 3′-OH), 5.17 (t, 5′-OH), 2.21 (q, **CH_2**CH_3), , 1.02 (t, CH_2**CH_3**)	DMSO-d_6
16	6.30 (dd, J_{F-H} = 21.2)	5.33 (dd, J_{F-H} = 50.1)	5.62 (dd, J_{F-H} = 17.0)	4.76 (m)	4.85 (m)		8.23 (s, NH), 7.44, 8.10 (m, Ar)	$CDCl_3$
17	6.07 (dd, J_{F-H} = 14.0)	5.06 (dt, J_{F-H} = 52.8)	4.22 (dt, J_{F-H} = 20.4)	3.76 (m)	3.62 (m)		11.95 (s, NH), 8.10 (d, H-6, J = 6.89), 5.90 (d, 3′-OH), 5.22 (t, 5′-OH)	DMSO-d_6
18	6.30 (dd, J_{F-H} = 21.1)	5.32 (dd, J_{F-H} = 50.1)	5.64 (dd, J_{F-H} = 17.3)	4.54 (m)	4.82 (m)	16.58	8.19 (s, NH), 7.44, 8.10 (m, Ar)	$CDCl_3$
19	6.10 (dd, J_{F-H} = 14.3)	5.08 (dt, J_{F-H} = 52.8)	4.24 (dt, J_{F-H} = 19.9)	3.82 (m)	3.66 (m)		11.70 (s, NH), 8.13 (s, H-6), 5.87 (d, 3′-OH), 5.20 (t, 5′-OH)	DMSO-d_6
20	6.30 (dd, J_{F-H} = 21.1)	5.32 (dd, J_{F-H} = 50.2)	5.64 (dd, J_{F-H} = 17.4)	4.54 (m)	4.82 (m)		8.14 (s, NH), 7.45, 8.11 (m, Ar)	$CDCl_3$
21	5.94 (dd, J_{F-H} = 14.0)	4.92 (dt, J_{F-H} = 52.8)	4.09 (dt, J_{F-H} = 21.0)	3.65 (m)	3.48 (m)		11.63 (s, NH), 8.12 (s, H-6), 5.70 (d, 3′-OH), 5.06 (t, 5′-OH)	DMSO-d_6
22	6.29 (dd, J_{F-H} = 19.4)	5.53 (dd, J_{F-H} = 50.6)	5.68 (dd, J_{F-H} = 23.6)	4.60 (m)	4.73 (m)		11.95 (s, NH), 7.50, 8.06 (m, Ar)	$CDCl_3$
23	6.08 (dd, J_{F-H} = 13.7)	5.07 (dt, J_{F-H} = 53.0)	4.24 (br d, J_{F-H} = 21.0)	3.81 (m)	3.55 (m)	17.03	11.82 (s, NH), 8.24 (s, H-6), 5.95 (d, 3′-OH), 5.30 (t, 5′-OH)	DMSO-d_6
24	6.31 (dd, J_{F-H} = 20.7)	5.37 (dd, J_{F-H} = 49.9)	5.64 (dd, J_{F-H} = 14.5)	4.58 (m)	4.85 (m)		7.43, 8.12 (m, Ar, NH)	$CDCl_3$
25	6.14 (dd, J_{F-H} = 11.0)	5.16 (dt, J_{F-H} = 52.8)	4.20 (dq, J_{F-H} = 20.1)	3.81 (m)	3.59 (m)		12.05 (br s, NH), 8.51 (s, H-6), 5.94 (d, 3′-OH), 5.34 (t, 5′-OH)	DMSO-d_6
26	6.42 (dd, J_{F-H} = 21.0)	5.57 (dd, J_{F-H} = 49.7)	5.65 (dd, J_{F-H} = 16.5)	4.60 (m)	4.83 (m)		7.44, 8.11 (m, Ar, NH)	$CDCl_3$
27	6.08 (dd, J_{F-H} = 18.4)	4.92 (dt, J_{F-H} = 52.2)	4.16 (dt, J_{F-H} = 18.6)	3.79 (m)	3.53 (m)		7.61 (d, H-6, J = 7.4), 7.21 (br d, NH_2), 5.72 (d, H-5, J = 7.5)	DMSO-d_6
28	6.36 (dd, J_{F-H} = 21.7)	5.43 (dd, J_{F-H} = 49.8)	5.60 (dd, J_{F-H} = 16.8)	4.52 (m)	4.80 (m)		7.44, 8.10 (m, Ar, NH_2)	$CDCl_3$
29	6.03 (dd, J_{F-H} = 16.6)	4.97 (dt, J_{F-H} = 49.7)	4.18 (dt, J_{F-H} = 19.4)	3.78 (m)	3.58 (m)		7.90 (d, H-6, J = 8), 7.61, 7.86 (2S, NH_2) 5.82 (d, 3′-OH), 5.11 (t, 5′-OH)	DMSO-d_6
30	6.38 (dd, J_{F-H} = 21.4)	5.44 (dd, J_{F-H} = 49.7)	5.62 (dd, J_{F-H} = 16.8)	4.53 (m)	4.81 (m)		7.44, 8.11 (m, Ar, NH_2)	$CDCl_3$
31	6.04 (dd, J_{F-H} = 16.6)	4.98 (dt, J_{F-H} = 52.4)	4.18 (dt, J_{F-H} = 17.0)	3.78 (m)	3.58 (m)	16.69	7.96 (s, H-6), 7.33, 7.96 (2s, NH_2), 5.84 (d, 3′-OH), 5.14 (t, 5′-OH)	DMSO-d_6
32	6.38 (dd, J_{F-H} = 21.4)	5.42 (dd, J_{F-H} = 49.8)	5.62 (dd, J_{F-H} = 16.8)	4.52 (m)	4.82 (m)		7.44, 8.11 (m, Ar, NH_2)	$CDCl_3$
33	6.04 (dd, J_{F-H} = 16.6)	4.98 (dt, J_{F-H} = 52.5)	4.18 (dt, J_{F-H} = 20.1)	3.78 (m)	3.60 (m)		8.02 (s, H-6), 7.12, 7.97 (2s, NH_2), 5.82 (d, 3′-OH), 5.16 (t, 5′-OH)	DMSO-d_6
34	6.41 (dd, J_{F-H} = 20.0)	5.48 (dd, J_{F-H} = 50.0)	5.65 (dd, J_{F-H} = 17.5)	4.58 (m)	4.85 (m)		10.93 (br s, NH), 7.45, 8.20 (m, Ar)	$CDCl_3$
35	6.05 (dd, J_{F-H} = 16.80)	4.98 (dt, J_{F-H} = 52.5)	4.18 (m)	3.78 (m)	3.60 (m)		8.04 (s, H-6), 6.74, 7.94 (2s, NH_2), 5.84 (d, 3′-OH), 5.17 (t, 5′-OH)	DMSO-d_6
36	6.28 (dd, J_{F-H} = 21.1)	5.32 (dd, J_{F-H} = 50.1)	5.62 (dd, J_{F-H} = 17.1)	4.55 (m)	4.80 (m)		8.19 (s, NH), 7.44, 8.10 (m, Ar), 0.23 (s, $SiMe_3$)	$CDCl_3$
37	5.90 (dd, J_{F-H} = 14.6)	4.86 (dt, J_{F-H} = 52.7)	4.04 (dt, J_{F-H} = 20.8)	3.62 (m)	3.43 (m)		11.58 (s, NH), 7.90 (s, H-6), 5.68 (d, 3′-OH), 4.99 (t, 5′-OH), 3.91 (s, CC**H**)	DMSO-d_6
38	6.14 (dd, J_{F-H} = 14.2)	5.10 (dt, J_{F-H} = 52.6)	4.26 (dt, J_{F-H} = 19.8)	3.84 (m)	3.69 (m)		11.79 (s, NH), 8.35 (s, H-6), 7.41 (d, H_a, J = 15.9), 6.90 (d, H_b, J = 15.8), 5.81 (d, 3′-OH), 5.25 (t, 5′-OH), 3.69 (s, COO**CH_3**)	DMSO-d_6
39	6.12 (dd, J_{F-H} = 14.0)	5.08 (dt, J_{F-H} = 52.7)	4.27 (dt, J_{F-H} = 19.6)	3.81 (m)	3.65 (m)		11.80 (s, NH), 8.28 (s, H-6), 7.31 (d, H_a, J = 15.8), 6.79 (d, H_b, J = 15.9), 5.90 (d, 3′-OH), 5.23 (t, 5′-OH)	DMSO-d_6
40	6.10 (dd, J_{F-H} = 14.7)	5.04 (dt, J_{F-H} = 52.6)	4.23 (dt, J_{F-H} = 19.9)	3.80 (m)	3.63 (m)		11.70 (s, NH), 7.97 (s, H-6), 7.26 (d, H_a, J = 13.6), 6.88 (d, H_b, J = 13.6), 5.86 (d, 3′-OH), 5.12 (t, 5′-OH)	DMSO-d_6

Atlantic Microlab, Inc., Norcross, GA, or Galbraith Laboratories, Inc., Knoxville, TN. Dry 1,2-dichloroethane (DCE) and acetonitrile were obtained by distillation from CaH.

1,2-*O*-Isopropylidene-α-L-xylofuranose (2). Compound **2** was prepared from L-xylose in 96% yield by the method reported for the synthesis of the D-isomer:[22] ^{1}H NMR ($CDCl_3$) δ 5.98 (d, J = 3.8 Hz, 1H, H-1), 4.52 (d, J = 3.6 Hz, 1H, H-2), 4.31 (br d, 1H, H-3), 4.08 (m, 3H, H-4 and H-5), 1.32 and 1.25 (2s, 6H, 2 CH_3).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-xylofuranose (3). To a stirred solution of **2** (91.5 g, 482 mmol) in pyridine (80 mL) and CH_2Cl_2 (400 mL) at 0 °C was added dropwise BzCl (56 mL, 482 mmol). The mixture was stirred at 0 °C for 1 h and washed successively with dilute HCl and saturated $NaHCO_3$ and dried ($MgSO_4$). Evaporation of solvent and recrystallization from Et_2O gave **3** as a white solid (116 g, 82%): ^{1}H NMR ($CDCl_3$) δ 7.43, 8.07 (m, 5H, Ar-H), 5.97 (d, 1H, J = 3.6 Hz, H-1), 4.80 (q, 1H, H-4), 4.60 (d, 1H, J = 3.6 Hz, H-2), 4.40, 4.20 (m, 3H, H-5, H-5′, H-3), 3.50 (br s, 1H, D_2O exchangeable, 3-OH), 1.51 and 1.32 (2s, 6H, 2 CH_3).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-*erythro*-pentofuranos-3-ulose (4). To a stirred solution of **3** (40.0 g, 136 mmol) in CH_2Cl_2 (450 mL) were added pyridinium dichromate (PDC, 30.7 g, 81.6 mmol) and Ac_2O (42.3 mL, 449 mmol), and the mixture was refluxed for 1.5 h. The solvent was evaporated, and EtOAc (50 mL) was added. The mixture was applied to a silica gel pad (10 cm × 5 cm) and eluted with EtOAc. The combined eluant was concentrated and coevaporated with toluene (2 × 50 mL). The residue was recrystallized from hexanes−EtOAc to give **4** as a white solid (38.0 g, 96%): IR (KBr) 1773, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.97, 7.42 (m, 5H, Ar-H), 6.14 (d, 1H, J = 4.4 Hz, H-1), 4.74, 4.68 (m, 2H, H-4, H-2), 4.50, 4.44 (m, 2H, H-5, H-5′), 1.52 and 1.44 (2s, 6H, 2 CH_3).

1,2-*O*-Isopropylidene-α-L-ribofuranose (5a). To a stirred mixture of **4** (37.0 g, 127 mmol) in EtOH−H_2O (400:100 mL) at 0 °C was added $NaBH_4$ (23.3 g, 612 mmol) portionwise, and the suspension was stirred at room temperature for 4 h. It was filtered, and the filtrate was evaporated to dryness and coevaporated with methanol. After silica gel column chroma-

Table 3. Median Effective (EC_{50}) and Inhibitory (IC_{50}) Concentration of 2′-Fluoro-β-L-arabinofuranosyl Pyrimidine Nucleosides in 2.2.15 Cells and Cytotoxicity in CEM Cells

no.	base	EC_{50} (μM) anti-HBV activity in 2.2.15 cells	IC_{50} (μM) 2.2.15	IC_{50} (μM) CEM	selectivity 2.2.15-HBV
13	5-methyluracil (T)	0.1	>200	>200	>2000
15	5-ethyluracil	>10	>200	ND[a]	
17	5-fluorouracil	>10	>200	ND	
19	5-chlorouracil	>10	>200	ND	
21	5-bromouracil	>10	>200	ND	
23	5-iodouracil	>10	>200	ND	
25	5-(trifluoromethyl)uracil	>10	>200	ND	
27	cytosine	1.4	>200	>100	>140
29	5-fluorocytosine	>10	>200	ND	
31	5-chlorocytosine	>10	>200	ND	
33	5-bromocytosine	>10	>200	ND	
35	5-iodocytosine	5	>200	ND	>40
37	5-ethynyluracil	>10	>200	ND	
40	5(*E*)-(bromovinyl)uracil	>10	>200	>100	

[a] ND: not determined.

tography (0−15% $CH_3OH-CH_2Cl_2$) and recrystallization from EtOAc−hexanes, **5a** was obtained as white needles (19.0 g, 79%): IR (KBr) 3356 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.83 (d, 1H, J = 4.0 Hz, H-1), 4.60 (t, 1H, H-2), 4.06, 3.72 (m, 4H, H-3, H-4, H-5, H-5′), 2.38 (d, 1H, D_2O exchangeable, 3-OH), 1.83 (t, 1H, D_2O exchangeable, 5-OH), 1.58 and 1.38 (2s, 6H, 2 CH_3).

5-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-ribofuranose (5b). To a stirred solution of **4** (14.0 g, 48 mmol) in anhydrous EtOH (60 mL) and EtOAc (30 mL) at 0 °C was added portionwise $NaBH_4$ (2.2 g, 57 mmol). The mixture was stirred at 0 °C for 1 h and then neutralized with dilute AcOH. Solvent was evaporated, and the residue was redissolved with CH_2Cl_2, washed with water, and dried ($MgSO_4$). Removal of solvent and recrystalliztion from EtOAc−hexanes gave **5b** as a white solid (13.8 g, 96.5%): ^1H NMR ($CDCl_3$) δ 7.40, 8.04 (m, 5H, Ar), 5.86 (d, 1H, J = 5.0 Hz, H-1), 4.72 (m, 3H, H-4, H-5), 4.10 (m, 1H, H-2), 4.40 (br s, 1H, D_2O exchangeable, 3-OH), 3.95 (dd, J = 4.1, 8.3 Hz, 1H, H-3), 1.60 and 1.38 (2s, 6H, 2 CH_3).

3,5-Di-*O*-Benzoyl-1,2-*O*-isopropylidene-α-L-ribofuranose (6). To a stirred solution of **5a** (19.0 g, 100 mmol) in pyridine (300 mL) at 0 °C was added dropwise BzCl (40 mL, 348 mmol), and the mixture was stirred at room temperature for 3 h. The solvent was evaporated and the residue was extracted with EtOAc, washed with saturated $NaHCO_3$, and dried (Na_2SO_4). Removal of solvent and recrystallization of the residue from ether gave **7** as a white solid (39.0 g, 98%): ^1H NMR ($CDCl_3$) δ 8.07, 7.36 (m, 10H, Ar-H), 5.94 (d, 1H, J = 3.6 Hz, H-1), 5.05, 5.00 (m, 1H, H-2), 4.73, 4.63 (m, 3H, H-4, H-5, H-5′), 1.58 and 1.35 (2s, 6H, 2 CH_3).

1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-L-ribofuranose (7). Method A. Compound **7** was prepared from L-ribose in 54% total yield according to a procedure for the synthesis of the D-isomer.[39]

Method B. A suspension of **6** (38.0 g, 95 mmol) in 1% HCl/CH_3OH (300 mL) was stirred at room temperature until a clear solution was obtained (30 h). Pyridine (20 mL) was added and then evaporated to dryness. The residue was coevaporated with pyridine (2 × 30 mL) and then redissolved in 100 mL of anhydrous pyridine at 0 °C. To this solution was added dropwise BzCl (17.0 mL, 146 mmol), and the mixture was stirred at room temperature for 3 h. It was evaporated to dryness and then extracted with EtOAc. The combined extracts were washed successively with dilute HCl solution and saturated $NaHCO_3$ and dried (Na_2SO_4). Removal of the solvent gave a syrup that was stirred in a mixture of glacial acetic acid (400 mL) and Ac_2O (100 mL) at 0 °C. To this solution was added dropwise concentrated H_2SO_4 (10 mL), and then the mixture was stirred at room temperature overnight. The mixture was poured into ice−water and extracted with $CHCl_3$ (4 × 100 mL). The combined extract was washed with saturated $NaHCO_3$ and dried (Na_2SO_4). Removal of solvent and recrystallization of the residue from methanol gave **7** as a white solid (23.9 g, 49.6%): mp 124−125 °C (lit.[18] mp 129−130 °C); $[\alpha]_D$ −45.6 (*c* 1.0, $CHCl_3$) [lit.[18] $[\alpha]_D$ −43.6 (*c* 1.0, $CHCl_3$)]; ^1H NMR ($CDCl_3$) δ 7.32, 8.13 (m, 15H, Ar-H), 6.44 (s, 1H, H-1), 5.84 (m, 2H, H-2 and H-3), 4.65 (m, 3H, H-4 and H-5), 2.00 (s, 3H, C*H*$_3$COO).

1,3,5-Tri-*O*-benzoyl-α-L-ribofuranose (8). HCl(g) was bubbled through a solution of **7** (23.9 g, 47.4 mmol) in anhydrous CH_2Cl_2 (220 mL) and AcCl (3.6 mL) at 0 °C for 1.5 h. The resulting solution was kept in a refrigerator for 12 h and then evaporated *in vacuo*, and the residue was coevaporated with toluene (3 × 70 mL) and redissolved in CH_3CN (50 mL). To this stirred solution was added dropwise water (6 mL). The white precipitate obtained was dissolved in $CHCl_3$, washed with saturated $NaHCO_3$, and dried ($MgSO_4$). Removal of solvent and coevaporation with Et_2O gave a white solid (15.5 g, 71.0%): ^1H NMR ($CDCl_3$) δ 7.31, 8.19 (m, 15H, Ar-H), 6.69 (d, J = 4.6 Hz, H-1), 5.59 (dd, J = 6.7, 1.8 Hz, 1H, H-3), 4.64, 4.80 (m, 4H, H-2, H-4 and H-5), 2.30 (br s, D_2O exchangeable, OH).

1,3,5-Tri-*O*-benzoyl-2-*O*-(imidazolylsulfonyl)-α-L-ribofuranose (9). To a stirred solution of **8** (15.0 g, 32.4 mmol) in anhydrous CH_2Cl_2 (150 mL) and DMF (40 mL) at −40 °C was added sulfuryl chloride (10.6 mL, 91.0 mmol) through a syringe. The resulting solution was stirred at −40 °C for 30 min and then gradually warmed up to room temperature. After 3 h, imidazole (32.0 g, 469 mmol) was added at 0 °C, and the mixture was stirred at room temperature for 15 h. The hazy solution was diluted with CH_2Cl_2 (300 mL) and washed with ice−water (400 mL), and the aqueous layer was extracted again with CH_2Cl_2 (3 × 75 mL). The combined organic layer was dried ($MgSO_4$). Removal of solvent and purification by silica gel column chromatography (5:1−1:1 hexanes−EtOAc) gave **9** as a white solid (14.0 g, 73.0%): ^1H NMR ($CDCl_3$) δ 7.00, 8.10 (m, 18H, Ar-H), 6.72 (d, J = 4.4 Hz, 1H, H-1), 5.60 (dd, J = 6.5, 2.9 Hz, 1H, H-3), 5.26 (dd, J = 4.5, 6.2 Hz, 1H, H-2), 4.58, 4.80 (m, 3H, H-4 and H-5).

1,3,5-Tri-*O*-benzoyl-2-deoxy-2-fluoro-α-L-arabinofuranose (10). A suspension of **9** (14.0 g, 23.6 mmol) and KHF_2 (7.4 g, 94.4 mmol) in 2,3-butanediol (120 mL) was stirred under N_2 at 160 °C. To this was added HF−H_2O (48%, 3.4 mL, 94.4 mmol), and the mixture was stirred at 160 °C for 1 h. It was quenched by brine−ice and then extracted with CH_2Cl_2 (4 × 50 mL). The combined extract was washed successively with brine, water, and saturated $NaHCO_3$ and dried ($MgSO_4$ and activated charcoal). It was applied on a silica gel pad (5 cm × 5 cm), eluted with CH_2Cl_2 to give a syrup which was recrystallized from 95% EtOH to give **10** (7.1 g, 65%): ^1H NMR ($CDCl_3$) δ 7.38, 8.11 (m, 15H, Ar-H), 6.76 (d, J = 9.2 Hz, 1H, H-1), 5.39 (d, J_{F-H} = 48.3 Hz, 1H, H-2), 5.63 (dd, J = 2.9, 16.6 Hz, 1H, H-3), 4.65, 4.81 (m, 3H, H-4 and H-5).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)thymine (12). General Procedure for Coupling. To a solution of **10** (2.78 g, 6.0 mmol) in anhydrous CH_2Cl_2 (20 mL) was added HBr−AcOH (45% v/v, 4.6 mL, 25 mmol), and the solution was stirred at room temperature for 20 h. The mixture was evaporated to dryness, dissolved in CH_2Cl_2 (50 mL), and washed with saturated $NaHCO_3$ (3 × 30 mL). Removal of solvent gave **11** as a syrup (2.55 g, 100%) that was

used without further purification. At the same time, thymine (1.9 g, 15 mmol) and $(NH_4)_2SO_4$ (0.1 g) were stirred in refluxing HMDS (30 mL) under nitrogen for 17 h, and the homogeneous solution obtained was evaporated under vacuum to give the silylated thymine.

A solution of **11** in dichloroethane (DCE, 25 mL) was added to the silylated thymine, and the mixture was refluxed under N_2 for 15 h. It was quenched with ice−water, extracted with CH_2Cl_2 (3 × 45 mL), washed with saturated $NaHCO_3$ (3 × 50 mL) and brine, and dried ($MgSO_4$). Removal of solvent gave a white solid which was purified on silica gel column (1% MeOH−$CHCl_3$) to give **12** (2.0 g, 71%): UV (MeOH) λ_{max} 264.0 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)thymine (13, L-FMAU). A solution of **12** (1.70 g, 3.60 mmol) in saturated NH_3−CH_3OH (30 mL) was stirred at room temperature for 15 h and then evaporated to dryness. The residue was purified by silica gel column chromatography (15:1 $CHCl_3$−CH_3OH) to give **13** (0.75 g, 80%): UV(H_2O) λ_{max} 265.0 (ϵ 9695) (pH 2), 265.5 (ϵ 9647) (pH 7), 265.5 nm (ϵ 7153) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-ethyluracil (14). A mixture of **11** (prepared from **10**, 0.50 g, 1.1 mmol) and silylated 5-ethyluracil (0.75 g, 5.4 mmol) in DCE (10 mL) was refluxed for 20 h under N_2. After workup and silica gel column chromatography (0−1% CH_3OH−$CHCl_3$), **14** was obtained as a white solid (0.557g, 100%): UV(CH_3OH) λ_{max} 263.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-ethyluracil (15). Compound **14** (0.50 g, 1.0 mmol) was treated with saturated NH_3−CH_3OH (50 mL) as described for **12**. After silica gel column chromatography (0−5% CH_3OH−$CHCl_3$), **15** was obtained as a white solid (0.240 g, 84%): UV(H_2O) λ_{max} 265.0 (ϵ 8350) (pH 2), 265.5 (ϵ 8600) (pH 7), 265.5nm (ϵ 10 100) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-fluorouracil (16). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-fluorouracil (0.330 g, 5.4 mmol) in DCE (15 mL) was refluxed for 48 h under N_2. After workup and silica gel column chromatography (50:1 $CHCl_3$−CH_3OH), **16** was obtained as a white solid (0.400 g, 85%): UV(EtOH) λ_{max} 266.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-fluorouracil (17). Compound **16** (0.330 g, 0.7 mmol) was treated with saturated NH_3−CH_3OH (50 mL) as described for **12**. After silica gel column chromatography (15:1−10:1 $CHCl_3$−CH_3OH), **17** was obtained as a white solid (0.130 g, 71%): UV(H_2O) λ_{max} 266.5 (ϵ 10 497) (pH 2), 267.5 (ϵ 9874) (pH 7), 266.5 nm (ϵ 8702) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-chlorouracil (18). A mixture of **11** (prepared from **10**, 0.370 g, 0.8 mmol) and silylated 5-chlorouracil (0.293 g, 2.0 mmol) in DCE (15 mL) was refluxed for 24 h under N_2. After workup and silica gel column chromatography (50:1 $CHCl_3$−CH_3OH), **18** was obtained as a white solid (0.200 g, 51%): UV(MeOH) λ_{max} 273.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-chlorouracil (19). Compound **18** (0.100 g, 0.2 mmol) was treated with saturated NH_3−CH_3OH as described for **12**. After purification by preparative TLC (9:1 $CHCl_3$−CH_3OH) and recrystallization in EtOH, **19** was obtained as a white solid (0.046 g, 80%): UV(H_2O) λ_{max} 274.0 (ϵ 9544) (pH 2), 275.5 (ϵ 9620) (pH 7), 274.0 nm (ϵ 7690) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-bromouracil (20). A mixture of **11** (prepared from **10**, 0.370 g, 0.8 mmol) and silylated 5-bromouracil (0.380 g, 2.0 mmol) in DCE (15 mL) was refluxed for 48 h under N_2. After workup and recrystallization from $CHCl_3$−CH_3OH, **20** was obtained as a white crystal (0.220 g, 52%): UV(MeOH) λ_{max} 274.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-bromouracil (21). Compound **20** (0.187 g, 0.35 mmol) was treated with saturated NH_3−CH_3OH as described for **12**. After purification by preparative TLC (10:1 $CHCl_3$−CH_3OH), **21** was obtained as a white solid (0.087 g, 76%): UV (H_2O) λ_{max} 277.5 (ϵ 6549) (pH 2), 277.0 (ϵ 5826) (pH 7), 275.5 nm (ϵ 4880) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-iodouracil (22). A mixture of **11** (prepared from **10**, 0.390 g, 0.85 mmol) and silylated 5-iodouracil (0.400 g, 1.7 mmol) in DCE (10 mL) was refluxed for 36 h under N_2. After workup, a yellow solid (0.350 g, 71%) was obtained which was recrystallized from 2-propanol to give **22** as a white solid (0.270 g, 55%): UV (methanol) λ_{max} 276.0 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-iodouracil (23). Compound **22** (0.210 g, 0.36 mmol) was treated with saturated NH_3−MeOH as described for **12**. After purification by preparative TLC (15:1 $CHCl_3$−MeOH), **23** was obtained as a white solid (0.120 g, 89%): UV(H_2O) λ_{max} 285.5 (ϵ 7643) (pH 2), 291.5 (ϵ 8261) (pH 7), 277.0 nm (ϵ 5512) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-(trifluoromethyl)uracil (24). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-(trifluoromethyl)uracil (0.360 g, 2.0 mmol) in DCE (15 mL) was refluxed for 20 h under N_2. After workup and silica gel column chromatography (50:1 $CHCl_3$−CH_3OH), **24** was obtained as a white solid (0.254 g, 49%): UV (EtOH) 255.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-(trifluoromethyl)uracil (25). Compound **24** (0.210 g, 0.4 mmol) was treated with saturated NH_3−CH_3OH as described for **12**. After purification by preparative TLC (15:1 $CHCl_3$−CH_3OH), **25** was obtained as a white powder (0.083 g, 66%): UV(H_2O) λ_{max} 260.0 (ϵ 11 630) (pH 2), 260.0 (ϵ 10 244) (pH 7), 258.5 nm (ϵ 7953) (pH 11).

***N*⁴-Benzoyl-1-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)cytosine (26).** A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated N^4-benzoylcytosine (0.540 g, 2.5 mmol) in CH_3CN (10 mL) was refluxed for 12 h under N_2. After workup and purification by preparative TLC (100:1 $CHCl_3$−CH_3OH), **26** was obtained (0.160 g, 29%): UV (EtOH) λ_{max} 261.5, 302.0 nm.

1-(2-deoxy-2-fluoro-β-L-arabinofuranosyl)cytosine (27). Compound **26** (0.150 g, 0.27 mmol) was treated with saturated NH_3/MeOH as described for **12**. After purification by preparative TLC (9:1 $CHCl_3$−CH_3OH), **27** was obtained as a white powder (0.060 g, 91%): UV(H_2O) λ_{max} 277.0 (ϵ 12 338) (pH 2), 269.5 (ϵ 7900) (pH 7), 270.0 nm (ϵ 9185) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-fluorocytosine (28). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-fluorocytosine (0.320 g, 2.5 mmol) in DCE (20 mL) was refluxed for 24 h under N_2. After silica gel column chromatography (20:1 $CHCl_3$−CH_3OH), **28** was obtained as a white foam (0.180 g, 38.5%): UV(EtOH) λ_{max} 277.0 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-fluorocytosine (29). Compound **28** (0.140 g, 0.3 mmol) was treated with saturated NH_3−CH_3OH as described for **12**. After trituration in acetone followed by recrystallization from EtOH, **29** was obtained as a white solid (0.078 g, 100%): UV(H_2O) λ_{max} 284.0 (ϵ 11 145) (pH 2), 279.5 (ϵ 8138) (pH 7), 279.0 nm (ϵ 9000) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-chlorocytosine (30). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-chlorocytosine (0.440 g, 3.0 mmol) in DCE (30 mL) was refluxed for 24 h under N_2. After silica gel column chromatography (20:1 $CHCl_3$−CH_3OH), **30** was obtained as a white foam (0.385 g, 80%): UV (EtOH) λ_{max} 282.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-chlorocytosine (31). Compound **30** (0.315 g, 0.65 mmol) was treated with saturated NH_3−CH_3OH as described for **12**. After trituration in acetone followed by recrystallization from EtOH, **31** was obtained as a white powder (0.106 g, 59%): UV(H_2O) λ_{max} 291.0 (ϵ 11 226) (pH 2), λ_{max} 285.0 (ϵ 8813) (pH 7), 284.5 nm (ϵ 9859) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-bromocytosine (32). A mixture of **11** (prepared from **10**, 0.460 g, 1.0 mmol) and silylated 5-bromocytosine (0.475 g, 2.5 mmol) in DCE (30 mL) was refluxed for 24 h under N_2. After silica gel column chromatography (20:1 $CHCl_3$−CH_3OH), **32** was obtained as a white foam (0.350 g, 66%): UV (EtOH) λ_{max} 285.0 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-bromocytosine (33). Compound **32** (0.290 g, 0.55 mmol) was treated with saturated NH_3−CH_3OH as described for **12**. After trituration in acetone followed by recrystallization from EtOH, **33** was obtained as a white solid (0.088 g, 50%): UV(H_2O) λ_{max} 294.0 (ϵ 9284) (pH 2), 286.5 (ϵ 6757) (pH 7), 286.5 nm (ϵ 7721) (pH 11).

***N*⁴-Benzoyl-1-(3,5-di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-iodocytosine (34).** A mixture of **11** (prepared from **10**, 0.150 g, 0.32 mmol) and silylated N^4-benzoyl-5-iodocytosine (0.550 g, 1.6 mmol) in DCE (10 mL) was refluxed for 24 h under N_2. After workup and silica gel column chromatography (0−1% CH_3OH−$CHCl_3$), **34** was obtained as a white solid (0.100 g, 45%): UV (CH_3OH) λ_{max} 345.0, 316.0 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-iodocytosine (35). Compound **34** (0.100g, 0.27 mmol) was treated with saturated NH_3−MeOH as described for **12**. After silica gel column chromatography (0−10% CH_3OH−$CHCl_3$), **35** was obtained as a white solid (0.035 g, 71%): UV(H_2O) λ_{max} 306.0 (ϵ 8300) (pH 2), 292.0 (ϵ 5710) (pH 7), 292.0 nm (ϵ 5400) (pH 11).

1-(3,5-Di-*O*-benzoyl-2-deoxy-2-fluoro-β-L-arabinofuranosyl)-5-[2-(trimethylsilyl)acetylenyl]uracil (36). Argon was purged through Et_3N (60 mL) for 0.5 h. To this was added **22** (0.580 g, 1.0 mmol), followed by (trimethylsilyl)acetylene (0.283 mL, 2.0 mmol), CuI (30 mg), and $(Ph_3P)_2PdCl_2$ (30 mg). The mixture was stirred at 50−60 °C for 4.5 h and then evaporated to dryness. The residue was dissolved in $CHCl_3$ (100 mL), washed with 5% EDTA solution (3 × 50 mL) and saturated $NaHCO_3$, and dried ($MgSO_4$). Afetr removal of the solvent, followed by purification on a silica gel column (50:1 $CHCl_3$−CH_3OH) and recrystallization from $CHCl_3$−CH_3OH, **36** was obtained as a white powder (0.400 g, 73%): UV (EtOH) λ_{max} 241.0, 284.5 nm.

1-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-ethynyluracil (37). Compound **36** (0.350 g, 0.64 mmol) was stirred in 0.2 N $NaOCH_3$−CH_3OH (15 mL) at room temperature for 4 h. It was neutralized with Dowex 50W×8 (H^+) resin, then filtered, and washed with methanol. The combined filtrate was evaporated to dryness. Column separation (9:1 $CHCl_3$−CH_3OH) and recrystallization from EtOH−hexanes gave **37** as a white solid (0.140 g, 82%): UV(H_2O) λ_{max} 284.5 (ϵ 8932) (pH 2), 284.5 (ϵ 10 383) (pH 7), 281.5 nm (ϵ 9556) (pH 11).

(*E*)-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-[2-(methoxycarbonyl)vinyl]uracil (38). A mixture of Ph_3P (0.040 g, 0.15 mmol), $Pd(OAc)_2$ (0.020 g, 0.08 mmol), and Et_3N (0.4 mL, 2.8 mmol) in 1,4-dioxane (15 mL) was refluxed to form a dark-red solution and then cooled to just below reflux. To this was added methyl acrylate (0.36 mL, 4.0 mmol), followed by **23** (0.300 g, 0.8 mmol) with dioxane (10 mL) and Et_3N (0.15 mL). The mixture was refluxed for 0.5 h, filtered through a Celite pad, and washed with dioxane. The combined filtrate was evaporated to dryness and purified on a silica gel column (9:1 $CHCl_3$−CH_3OH) to give **38** as a white foam (0.145 g, 54%): UV(MeOH) λ_{max} 299.0 nm; ^{1}H NMR (DMSO-d_6) δ 11.79 (s, 1H, D_2O exchangeable, CONH), 8.35 (s, 1H, H-6), 7.41 (d, 1H, J = 15.9 Hz, Ha), 6.90 (d, 1H, J = 15.8 Hz, Hb), 6.14 (dd, J_{F-H} = 14.2 Hz, H-1′), 5.81 (d, 1H, D_2O exchange 3′-OH), 5.25 (t, 1H, D_2O exchangeable, 5′-OH), 5.10 (dt, J_{F-H} = 52.6 Hz, 1H, H-2′), 4.26 (dt, J_{F-H} = 19.8 Hz, 1H, H-3′), 3.84 (m, 1H, H-4′), 3.69 (dm, 2H, H-5′a,b). Anal. ($C_{12}H_{15}F\ N_2O_7 \cdot 0.8H_2O$) C, H, N.

(*E*)-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-(2-carboxyvinyl)uracil (39). A solution of **38** (0.135 g, 0.41mmol) in a 2 N NaOH solution (5 mL) was stirred at room temperature for 1.5 h and then cooled in an ice bath. It was carefully adjusted to *ca*. pH 1 with 12 N HCl and stirred for 10 min. The white precipitate was collected by filtration and washed with water and acetone to give **39** as a white powder (0.096 g, 74%): mp 284 °C dec; UV(MeOH) λ_{max} 298.0, 268.0 nm (shoulder); ^{1}H NMR (DMSO-d_6) δ 11.80 (s, 1H, D_2O exchangeable, CONH), 8.28 (s, 1H, H-6), 7.31 (d, 1H, J = 15.8 Hz, Ha), 6.79 (d, 1H, J = 15.9 Hz, Hb), 6.12 (dd, J_{F-H} = 14.0 Hz, H-1′), 5.90 (d, 1H, D_2O exchangeable 3′-OH), 5.23 (t, 1H, D_2O exchangeable, 5′-OH), 5.08 (dt, J_{F-H} = 52.7 Hz, 1H, H-2′), 4.27 (dt, J_{F-H} = 19.6Hz, 1H, H-3′), 3.81 (m, 1H, H-4′), 3.65 (dm, 2H, H-5′a,b). Anal. ($C_{12}H_{13}FN_2O_7 \cdot 1.6H_2O$) C, H, N.

(*E*)-(2-Deoxy-2-fluoro-β-L-arabinofuranosyl)-5-(2-bromovinyl)uracil (40). A suspension of **39** (0.080 g, 0.25 mmol) and $KHCO_3$ (0.100 g, 1.0 mmol) in DMF (1.5 mL) was stirred at room temperature for 20 min. To this was added *N*-bromosuccinimide (0.053 g, 0.3 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature for 1.5 h, filtered, and washed with methanol. The filtrate was evaporated to dryness and purified on PTLC (6:1 $CHCl_3$−CH_3OH). After coevaporation with ether, **40** was obtained as a white foam (0.047 g, 53%): UV(H_2O) λ_{max} 250.0 (ϵ 15 844) (pH 2), 250.0 (ϵ 14 622) (pH 7), 254.0 nm (ϵ 15 912) (pH 11).

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Supporting Information Available: X-ray data for L-FMAU (35 pages). Ordering information is given on any current masthead page.

References

(1) Belleau, B.; Dixit, D.; Nguyen-Ga, N.; Kraus, J.-L. *International Conference on AIDS*. Montreal, Canada, June 4−9, 1990, paper no. T.C.O.1.

(2) Soudeyns, H.; Yao, Q.; Belleau, B.; Kraus, J.-L.; Nguyen-Ga, N.; Spira, B.; Wainberg, M. A. Anti-human immunodeficiency virus type 1 activity and *in vitro* toxicity of 2′-deoxy-3′-thiacytidine (BCH-189), a novel heterocyclic nucleoside analog. *Antimicrob. Agents Chemother.* **1991**, *35*, 1386−1390.

(3) Doong, S.-L.; Tsai, C. H.; Schinazi, R. F.; Liotta, D. C.; Cheng, Y.-C. Inhibition of the replication of hepatitis B virus in vitro by 2′,3′-dideoxy-3′-thiacytidine and related analogues. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8495−8499.

(4) Schinazi, R. F.; McMillan, A.; Cannon, D.; Mathis, R.; Lloyd, R. M.; Peck, A.; Sommadossi, J.-P.; St Clair, M.; Wilson, J.; Furman, P. A.; Painter, G.; Choi, W.-B.; Liotta, D. C. Selective inhibition of human immunodeficiency viruses by racemates and enatiomers of *cis*-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-cytosine. *Antimicrob. Agents Chemother.* **1992**, *36*, 2423−2431.

(5) Furman, P. A.; Davis, M.; Liotta, D. C.; Paff, M.; Frick, L. W.; Nelson, D. J.; Dornsife, R. E.; Wurster, J. A.; Wilson, L. J.; Fyfe, J. A.; Tuttle, J. V.; Miller, W. H.; Condreay; L.; Averette, D. R.; Schinazi, R. F.; Painter, G. R. The anti-hepatitis B virus activities, cytotoxicities, and anabolic profiles of the (−) and (+) enantiomers of *cis*-5-fluoro-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl] cytosine. *Antimicrob. Agents Chemother.* **1992**, *36*, 2686−2692.

(6) Gosselin, G.; Schinazi, R. F.; Sommadossi, J.-P.; Mathe, C.; Bergogne, M.-C.; Aubertin, A.-M.; Kirn, A.; Imbach, J.-L. Anti-human immunodeficiency virus activities of the β-L-enantiomer of 2′,3′-dideoxycytidine and its 5-fluoro derivative in vitro. *Antimicrob. Agents Chemother.* **1994**, *38*, 1292−1297.

(7) Lin, T. S.; Luo, M. Z.; Pai, S. B.; Dutschuman, G. E.; Cheng, Y.-C. Synthesis and biological evaluation of 2′,3′-dideoxy-L-pyrimidine nucleosides as potential antiviral agents against human immunodeficiency virus (HIV) and hepatitis B virus (HBV). *J. Med. Chem.* **1994**, *37*, 798−803.

(8) Kim, H. O.; Shanmuganathan, K.; Alves, A. J.; Jeong, L. S.; Beach, J. W.; Schinazi, R. F.; Chang, C.-N.; Cheng, Y.-C. and Chu, C. K. Potent anti-HIV and anti-HBV activities of (−)-L-β-dioxolane-C and (+)-L-β-dioxolane-T and their asymmetric synthesis. *Tetrahedron Lett.* **1992**, *33*, 6899−6902.

(9) Grove, K. L.; Guo, X.; Liu, S.-H.; Gao, Z.; Chu, C. K.; Cheng, Y.-C. Anticancer activity of β-L-dioxolane-cytidine, a novel nucleoside analogue with the unnatural L configuration. *Cancer Res.* **1995**, *55*, 3008−3011.

(10) Chu, C. K.; Ma, T. W.; Shanmuganathan, K.; Wang, C. G.; Xiang, Y. J.; Pai, S. B.; Yao, G. Q.; Sommadossi, J.-P.; Cheng, Y.-C. Use of 2′-fluoro-5-methyl-β-L-arabinofuranosyluracil as a novel antiviral agent for hepatitis B virus and Epstein-Barr virus. *Antimicrob. Agents Chemother.* **1995**, *39*, 979−981.

(11) Parker, W. B. and Cheng, Y.-C. Mitochondrial toxicity of antiviral nucleoside analogues. *J. NIH Res.* **1994**, *6*, 57−61.

(12) McKenzie, R.; Fried, M. W.; Sallie, R.; ConJee Varam, H.; Di Bisceglie, A. M.; Park, Y.; Savarese, B.; Kleiner, D.; Tsokos, M.; Luciano, C.; Pruett, T.; Stotka, J. L.; Straus, S. E.; Hoofnagle, J.-H. Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational analogue for chronic hepatitis B. *N. Engl. J. Med.* **1995**, *333*, 1099−1105.

(13) Cheng, Y.-C. Unpublished results.

(14) Zoulim, F.; Trepo, C.; Cheng, Y.-C. unpublished results.

(15) Pai, S. B.; Liu, S.-H.; Zhu, Y.-L.; Chu, C. K.; Cheng, Y.-C. Inhibition of hepatitis B virus by a novel L-nucleoside, 2′-fluoro-5-methyl-β-L-arabinofuranosyluracil. *Antimicrob. Agents Chemother.* **1996**, *40*, 380−386.
(16) Tann, C. H.; Brodfuehrer, P. R.; Brundidge, S. P.; Sapino, C., Jr.; Howell, H. G. Fluorocarbohydrates in synthesis. An efficient synthesis of 1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-5-iodouracil (β-FIAU) and 1-(2-deoxy-2-fluoro-β-d-arabinofuranosyl) thymine (β-FMAU). *J. Org. Chem.* **1985**, *50*, 3644−3646
(17) Walker, T. E.; Hagenkamp, H. P. C. A new synthesis of L-ribofuranose derivatives. *Carbohydr. Res.* **1974**, *32*, 413−417.
(18) Kenneth, J. R.; Edward, M. A. 9-β-L-ribofuranosyladenine (L-adenosine), configurational inversion within a furanoid ring. In *Synthetic Procedures in Nucleic Acids Chemistry, V. 1*; Zorbach, W. W., Tipson, R. S., Eds.; Wiley: New York, 1968; pp 163−167.
(19) Abe, Y.; Takizawa, T.; Kunieda, T. Epimerization of aldoses catalyzed by dioxobis (2,4-pentanedionato-o,o′)-molybdenum (VI). An improved procedure for C-2 epimer preparation. *Chem. Pharm. Bull.* **1980**, *28* (4), 1324−1326.
(20) Batch, A.; Czernecki, S. New synthesis of L-ribofuranose derivatives. *J. Carbohydr. Chem.* **1994**, *13* (6), 935−940.
(21) Oka, K.; Wada, H. Synthesis of *D*-ribose from D-xylose. *Yakugaku Zasshi.* **1963**, *83*, 890−891; *Chem. Abstr.* **1964**, *60*, 1825d.
(22) Gosselin, G.; Bergogne, M.-C.; Imbach, J.-L. 1,2-Di-*O*-acetyl-3,5-di-*O*-benzoyl-D-xylofuranose, a versatile precursor for the synthesis of various β-D-pentofuranosyl nucleosides and related analogs. In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques, Part 4*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1991; pp 41−45.
(23) Aspinall, G. O.; King, R. R. Base-catalyzed degradations of carbohydrates. IV. Formation of 2,3-anhydro-2-methyl-α-D-allopyranose derivatives from 3-deoxy-D-erythro-hex-2-enopyranoses. *Can. J. Chem.* **1973**, *51*, 394−401.
(24) Gosselin, G.; Puech, F.; Genu-Dellac, C.; Imbach, J. L. 1,2-Di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3-fluoro-D-xylofuranose, a versatile precursor for the synthesis of 3-deoxy-3-fluoro-β-D-xylofuranosyl nucleosides as potential antiviral agents. *Carbohydr. Res.* **1993**, 249, 1−17.
(25) After we completed the research work for this paper, a similar methodology for the synthesis of compound **6** was recently reported in the literature. Chelain, E.; Floch, O.; Czernecki, S. New synthesis of L-ribofuranose derivatives from L-xylose. *J. Carbohydr. Chem.* **1995**, *14*, 1251−1256.
(26) Chavis, C.; Dumont, F.; Wightman, R.; Ziegler, J.-C.; Imbach, J.-L. 2′-*O*-methyl nucleosides, stereospecific synthesis via a readily available 2′-*O*-methylated ribofuranose derivative. In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques, Part 3*; Townsend, L. B., Tipson, R. S., Eds.; Wiley: New York, 1986; pp 76−80.
(27) Chou, T. S.; Becke, L. M.; O'Toole, J. C.; Carr, M. A.; Parker, B. E. Triethylamine poly(hydrogen fluorides) in the synthesis of a fluorinated nucleoside glycon. *Tetrahedron. Lett.* **1996**, *37*, 17−20.
(28) Howell, H. G.; Brodfuehreu, P. R.; Brundidge, S. P.; Benigni, D. A.; Sapino, C., Jr. Antiviral Nucleosides. A stereospecific, total synthesis of 2′-fluoro-2′-deoxy-β-D-arabinofuranosyl nucleosides. *J. Org. Chem.* **1988**, *53*, 85−88 and references cited therein.
(29) Robins, M. J.; Barr, P. J. Nucleic acid related compounds. 39. Efficient conversion of 5-iodo to 5-alkynyl and derived 5-substituted uracil bases and nucleosides. *J. Org. Chem.* **1983**, *48*, 1854−1862.
(30) Jones, A. S.; Rahim, S. G.; Verhelst, G.; Walker, R. T. E- and Z-5-(2-bromovinyl)-2′-deoxyuridine, a potent anti-herpes virus agent (E-isomer) and its diastereoisomer (Z-isomer). In *Nucleic Acid Chemistry, Improved and New Synthetic Procedures, Methods and Techniques, Part 3*; Townsend, L. B., Tipson, R. S., Eds.; John Wiley & Sons, Inc.: New York, 1986; pp 61−64.
(31) Watanabe, K. A.; Reichman, U.; Hirota, K.; Lopez, C.; Fox, J. J. Nucleosides. 110. Synthesis and antiherpes virus activity of some 2′-fluoro-2′-deoxy-arabinofuranosylpyrimidine nucleosides. *J. Med. Chem.* **1979**, *22*, 21−24.
(32) Watanabe, K. A.; Su, T.-L.; Reichman, U.; Greenberg, N.; Lopez, C.; Fox, J. J. Nucleosides. 129. Synthesis of antiviral nucleosides, 5-alkenyl-1-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)uracils. *J. Med. Chem.* **1984**, *27*, 91−94.
(33) Watanabe, K. A.; Su, T.-L.; Klein, R. S.; Chu, C. K.; Matsuda, A.; Chun, M. W.; Lopez, C.; Fox, J. J. Nucleosides. 123. Synthesis of antiviral nucleosides, 5-substituted 1-(2-deoxy-2-halogeno-β-D-arabinofuranosyl) cytosines and uracils, some structure-activity relationships. *J. Med. Chem.* **1983**, *26*, 152−156.
(34) Smee, D. F.; Chernow, M.; Kraft, M.; Okamoto, P. M.; Prisbe, E. J. Synthesis and anti- herpetic activity of a 2′-fluoroarabinosyl analog of trifluridine. *Nucleosides Nucleotides.* **1988**, *7*, 155−165.
(35) Mansuri, M. M.; Krishnan, B.; Martin, J. C. A potentially simple ^{13}C NMR method to assign regio- and stereochemistry of 2′-deoxy-2′-fluoroarabinofuranosyl nucleosides. *Tetrahedron Lett.* **1991**, 1287−1290.
(36) X-ray data for L-FMAU: crystal dimensions, 0.30 × 0.20 × 0.10 mm; crystal color and habit, colorless prisms; empirical formula, $C_{10}H_{13}FN_2O_5$; formula weight, 260.22; crystal system, monoclinic; lattice parameters, $a = 10.433(1)$, $b = 10.855(2)$, $c = 10.557(1)$ Å, $\beta = 108.871(8)°$; space group, $P2_1$ (No. 4), $Z = 4$. There are two molecules in the asymmetric unit.
(37) Miller, R. H.; Kaneko, S.; Chung, C. T.; Girones, R.; Purcell, R. H. Compact organization of the hepatitis B virus genome. *Hepatology* **1989**, *9*, 322−327.
(38) Severini, A.; Liu, X.-Y.; Wilson, J. S.; Tyrrell, D. L. J. Mechanism of inhibition of duck hepatitis B virus polymerase by (−)-β-L-2′,3′-dideoxy-3′-thiacytidine. *Antimicrob. Agents Chemother.* **1995**, *39*, 1430−1435.
(39) Ness, R. K.; Diehl, H. W.; Fletcher, H. G., Jr. New benzoyl derivatives of D-ribofuranose and *aldehydo*-D-ribose. The preparation of crystalline 2,3,5-tri-*O*-benzoyl-β-D-ribose from D-ribose. *J. Am. Chem. Soc.* **1954**, *76*, 763−767.

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