A Completely Diastereoselective Electrophilic Fluorination of a Chiral, Noncarbohydrate Sugar Ring Precursor: Application to the Synthesis of Several Novel 2′-Fluoronucleosides

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A new and completely diastereoselective method for the introduction of fluorine into a noncarbohydrate sugar ring precursor has been developed. The use of *N*-fluorodibenzenesulfonimide (**5**) for the electrophilic fluorination of chiral lactone **4**, which is derived from L-glutamic acid, yields the key intermediate **6**. This is transformed into an anomeric acetate **8** and is used for the synthesis of a number of novel α-2′-fluoronucleosides. Since glutamic acid is used as the synthetic starting material, the L enantiomer may also be synthesized simply by using D-glutamic acid. The incorporation of fluorine into the 2′ position of the nucleoside provides several advantages including acid stability of the anomeric bond and general resistance to oxidative metabolism. Further, fluorine is a close mimic of hydroxyl groups in size and polarity and in its ability to act as a hydrogen bond acceptor. This may aid in the recognition of these nucleosides by the enzymes involved in nucleoside activation.

Introduction

The controlled introduction of fluorine into organic molecules, especially biomolecules and analogues of natural products, has received much attention from synthetic organic chemists in recent years. A number of excellent books and reviews on the synthetic aspects of selective C−F bond formation[1] and the biological effects of fluorine introduction into organic molecules[2] exist. Fluorine is a close steric replacement for hydrogen, and being the most electronegative element, it is capable of producing significant electronic changes in a molecule with minimal steric perturbation. In combination with the above factors, the higher strength of the C−F bond (116 kcal/mol vs C−H = 100 kcal/mol) can cause changes in substrate metabolism when fluorinated biomolecules are used as drugs.

Fluorine may also serve as an isopolar and isosteric mimic of a hydroxyl group since the C−F bond length (1.35 Å) is so similar to the C−O bond length (1.43 Å) and because fluorine is a hydrogen-bond acceptor. The ability of fluorine to mimic a hydroxyl group makes this atom uniquely suited to nucleoside analogues as a replacement of OH in the sugar portion of a nucleoside. In addition to our long standing interest in the synthesis of novel nucleoside analogues,[3] we were interested in incorporating an α-fluorine substituent at the 2′ position of the sugar ring for several reasons. First, the electronegativity of fluorine should stabilize the anomeric bond and suppress a significant pathway of in vivo decomposition,[4] thereby improving the acid stability of the nucleoside (Scheme 1).

Second, hydroxyl groups often serve as "handles" for the first step in oxidative degradation of biomolecules in vivo.[2c] By replacing OH with F, it is possible to create a ribo-like sugar that has a substituent at the 2′ position sterically and electronically similar to a hydroxyl group, but which cannot undergo oxidative catabolism. Thus, the in vivo half-life of the compound may be improved. Finally, few of the ribo or "down" 2′-fluoro nucleoside derivatives were known. Therefore, we endeavored to find a simple and efficient synthesis of these compounds in order to generate novel analogues for biological evaluation.

Herein we report the development of a completely diastereoselective reaction for effecting the introduction of fluorine into the sugar portion of novel nucleoside analogues. The key step in our synthetic route is the fluorination of a chiral, noncarbohydrate sugar ring precursor (4*S*)-5-(*tert*-butyldiphenylsiloxy)pentan-4-olide

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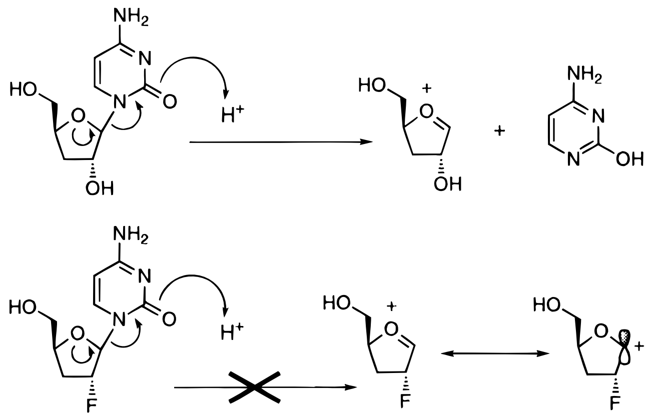
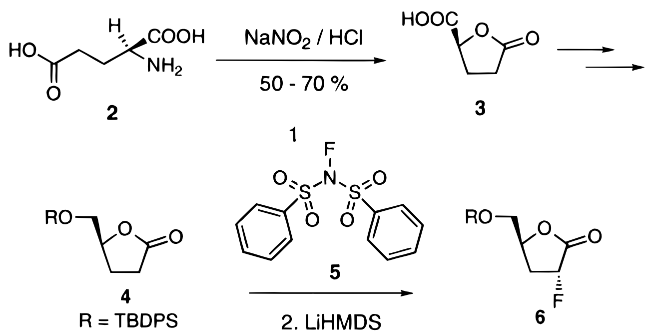
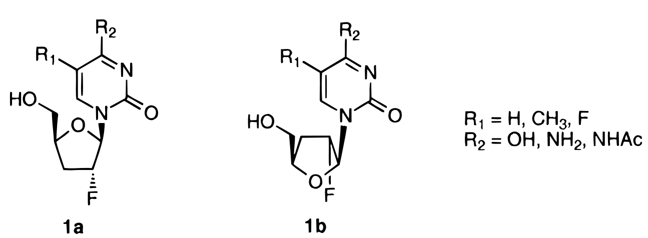
Scheme 1



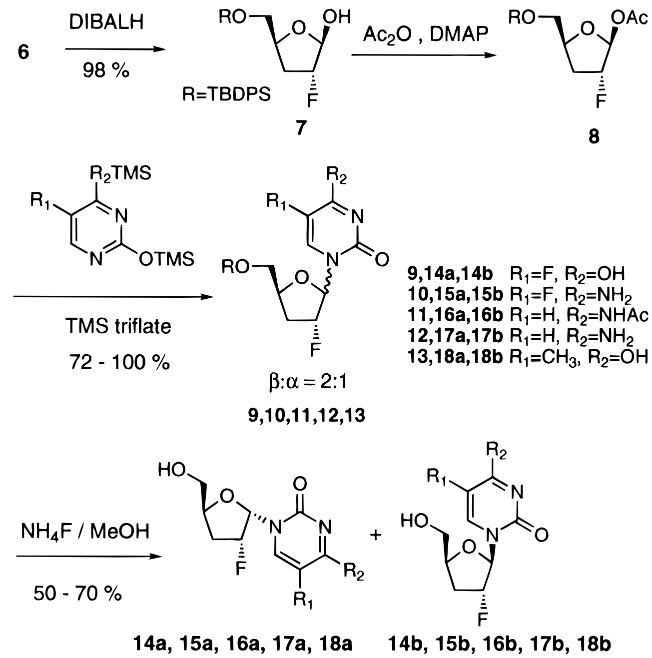
Scheme 2



(**4**) using the electrophilic fluorine source *N*-fluorodibenzenesulfonimide (**5**) (Scheme 2). This relatively new class of *N*-fluorosulfonimide reagents was originally developed by Barnette[5] in 1984 and since then has seen much refinement and use as a convenient and highly reactive source of electrophilic fluorine.[6] Most often, these reagents are used to deliver fluorine to nucleophiles such as enolates and metalated aromatics.[6a] Specifically, *N*-fluorodibenzenesulfonimide (NFSi) is an air stable, easily handled solid with sufficient steric bulk to stereoselectively fluorinate the enolate of silyl-protected lactone **4** in 100% de. In this paper, we describe the synthesis of fluorolactone **6** and its use as a common intermediate in the synthesis of a number of novel α-2′-fluoro nucleosides. A significant advantage of this methodology is the ability to access separately either the "natural" (**1a**) D or the "unnatural" (**1b**) L enantiomer of the nucleosides by appropriate choice of L- or D-glutamic acid starting material, respectively.



Scheme 3



Results and Discussion

Lactone **4** was synthesized by the route shown in Scheme 2 from L-glutamic acid as described by Ravid et al.[7a] and Taniguchi et al.[7b] The enolate of lactone **4**, prepared at −78 °C with LiHMDS in THF, is known to be stable. Several syntheses using this enolate have been performed by our group and others,[8] including addition of electrophiles such as diphenyl diselenide, diphenyl disulfide, and alkyl halides in high yield. However, addition of a THF solution of **5** to the enolate of **4** gave poor yields of the desired monofluorinated product **6**. Numerous byproducts were formed including what we surmise to be a difluorinated lactone that is inseparable from other impurities. For this reason, the order of addition of the reagents was altered such that lactone **4** and NFSi **5** were dissolved together in THF and cooled to −78 °C. Slow addition of LiHMDS resulted in a reaction yielding **6** as the only product in addition to a small amount of unreacted starting material (Scheme 2).

Fluorolactone **6** could be obtained in 50−70% yield after silica gel column chromatography and crystallization. Remarkably, this reaction yielded a single diastereomer of **6**, presumably due to the interaction of the sterically bulky TBDPS group and the bulky fluorinating reagent **5**. Identification of fluorolactone **6** as the α or "down" fluoro isomer was accomplished by comparison to previously published NMR data[9] and by X-ray crystal structure determination of its enantiomer **20**.

Lactone **6** was transformed into the anomeric acetate **8** as shown in Scheme 3. It is of interest to note that lactol **7** exists exclusively as the *β* anomer and that

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Table 1. Anomeric Proton Chemical Shift (ppm)

compd	α	β
14a,b	6.11	5.89
15a,b	6.08	5.92
16a,b	6.09	5.90
17a,b	6.05	5.92
18a,b	6.11	5.93

acetate **8** shows no detectable α anomer by NMR, as reported by Niihata et al.[9]

Coupling of **8** with silylated pyrimidine bases was performed by standard Vorbruggen methodology[10] using TMS triflate as the Lewis acid. A number of bases were successfully coupled in high yields ranging from 72% to 100% after column chromatography.

Proton NMR indicated that the ratio of β to α nucleoside anomers was approximately 2:1 in all cases. The silyl-protected nucleosides could not be resolved by column chromatography into the separate anomers. However, after deprotection of the 5′-oxygen with NH_4F in methanol (Scheme 3), the α and β anomers could be readily separated.

The classification of the free nucleosides as α or β was based on the chemical shift of the anomeric proton (Table 1) and on the polarity of the nucleosides as observed by thin-layer chromatography. We observed a trend for all of the α/β pairs of free nucleosides such that the less polar compound of the two had an anomeric proton chemical shift that was notably upfield from that of the more polar compound.

The correlation between anomeric proton chemical shift and absolute structure was verified by comparison of **18a**[9] and **18b**[11] with previously published spectral data and through X-ray crystal structure determination of **14b** and **15b**. This finding is the opposite of the usual trend for nucleosides in which the α anomer is normally the less polar of the two. Presumably, in the "down" 2′-fluorinated nucleosides, the strong dipole of the C−F bond opposes the C−N anomeric bond dipole in the β isomer and reduces the overall molecular dipole. Conversely, the α anomer has a geometry that allows reinforcement of the molecular dipole through the addition of the C−F and C−N bond dipoles. Thus, the α anomer is more polar than the β anomer in the case of α-2′-fluoro nucleosides.

The α and β anomers **17a** and **17b** could not be separated by column chromatography because the free amino group caused the nucleosides to streak on silica gel. Therefore, it was necessary to use N^4-acetylcytosine to prepare **11** and then resolve **16a** and **16b**. The N^4-acetyl group was removed quantitatively with a saturated solution of ammonia in methanol in order to obtain separated **17a** and **17b**. It is interesting to note that when 5-fluorocytosine was used as the base (compound **10**), the anomers **15a** and **15b** were easily separated and no streaking on silica gel was observed. This is presumably due to the fact that the fluorine atom makes the neighboring amino group much less basic,[12] another example of the marked effects that fluorine can have on organic molecules.

Table 2. Antiviral Activity and Cytotoxicity

		toxicity IC_{50} (μM)		
compd	activity HIV−1 EC_{50} (μM)	vero cell	CEM cell	PBM cell
15b	53.0	40.5	>100	48.4
18b	41.0	>100	>100	7.2
AZT	0.004	29.0	14.0	>100

Of the 10 nucleosides listed in Table 1, only **17b**,[13] **18a**,[9] and **18b**[11] have been synthesized previously. They, like the numerous 2′-β or "up" fluoro nucleoside analogues[14] have been synthesized from natural precursors. Fluorine is usually introduced into these molecules through nucleophilic attack on an anhydro-nucleoside[15] or through replacement and inversion of a stereochemically fixed hydroxyl group with diethylaminosulfur trifluoride[16] (DAST). The advantage of our methodology is that no hydroxyl group is needed for fluorine introduction. Thus, we are not limited to natural nucleosides or sugars as starting materials, and it is easy to access the unnatural enantiomers of the 2′-fluoro nucleosides.

Accordingly, several unnatural nucleosides were synthesized using our synthetic route with D-glutamic acid (**19**) as the starting material (Scheme 4). The sugar ring precursor to **20** was fluorinated in the manner described above and coupled with various silylated bases.

Biological evaluation of several of the nucleosides was carried out in order to determine their activity against human immunodeficiency virus type 1 (HIV) and to screen them for toxicity. The results are summarized in Table 2, and 3′-azido-3′-deoxythymidine (AZT) is shown as a reference for comparison.

Unfortunately, only compounds **15b** and **18b** showed any antiviral activity against HIV but they exhibited toxicity as well, indicating that the compounds are nonselective inhibitors of HIV. However, the fact that these nucleosides are active and toxic may indicate that they might be phosphorylated. Compounds **14b**, **15a**, **16b**, **26a**, **26b**, **27a**, **27b**, **28a**, and **28b** were also tested but were inactive against HIV and nontoxic to all cells at >100 μM.

In conclusion, a short and efficient synthesis of a fluorinated noncarbohydrate sugar ring precursor for the preparation of nucleoside analogues has been developed. The key step in the synthesis involves the completely diastereoselective fluorination of chiral lactone **4** derived from inexpensive, readily available glutamic acid. This

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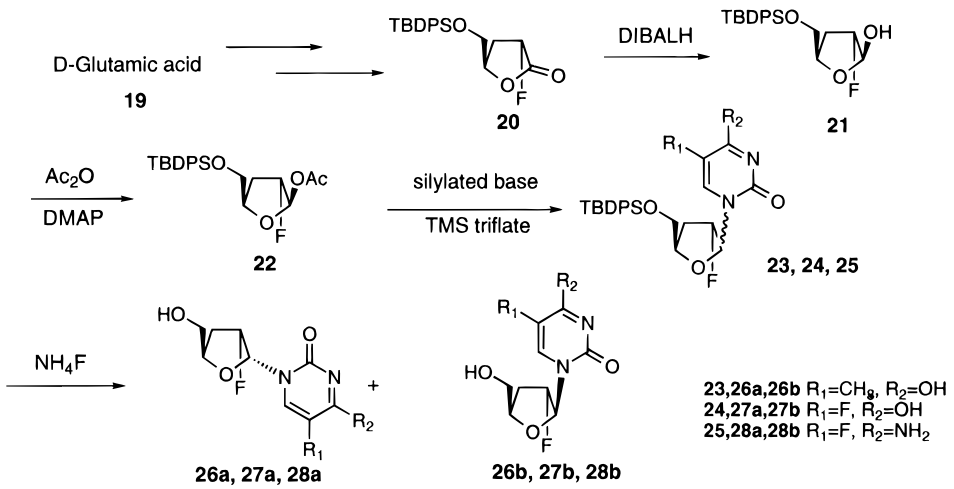
Scheme 4



route provides access to both natural and unnatural enantiomers of these nucleosides. Currently, these compounds are undergoing biological evaluation for activity against other viruses and as potential cancer chemotherapeutic agents. Investigations are underway to extend this methodology to the synthesis of purine nucleosides as well.

Experimental Section

General Procedures. *N*-Fluorodibenzenesulfonimide (**5**) was obtained from AlliedSignal, courtesy of Dr. Andrew J. Poss and Dr. George A. Shia, and was used without further purification. All other reagents were obtained from Aldrich Chemical Co. and were used without further purification. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Nicolet Impact 400 FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a NT-360 or Varian 400 MHz spectrometer. TLC plates were silica gel 60 F_{254} (0.25 mm thickness) purchased from EM Science. Flash chromatography was carried out with silica gel 60 (230−400 mesh ASTM) from EM Science. All reactions were performed in flame-dried glassware under an atmosphere of dry argon. Solvents were removed by rotary evaporation. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

(2*S*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2-fluoropentan-4-olide (20). To a flask was added (4*R*)-5-(*tert*-butyldiphenylsiloxy)-pentan-4-olide (20.0 g, 0.0564 mol, 1.0 equiv) and *N*-fluorodibenzenesulfonimide (NFSi, **5**) (17.80 g, 0.0564 mol, 1.0 equiv) in 250 mL of anhydrous THF. The solution was cooled to −78 °C and 68.0 mL (0.0680 mol, 1.2 equiv) of a 1.0 M solution of LiHMDS in THF was added dropwise over a period of 1 h. This was allowed to stir at −78 °C for an additional 2 h and was then warmed to room temperature to stir for 1 h. After completion, the reaction was quenched with 10 mL of a saturated NH_4Cl solution. The mixture was diluted with three volumes of diethyl ether and was poured onto an equal volume of saturated $NaHCO_3$. The organic layer was washed a second time with saturated $NaHCO_3$ and once with saturated NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated to a light yellow oil. The oil was purified by silica gel column chromatograpy using a 30% diethyl ether/70% hexanes solvent system. The resultant white solid was then crystallized from hot hexanes to yield 13.04 g (62% yield) of a transparent crystalline solid: R_f(30% diethyl ether/70% hexanes) = 0.26; mp 115−116 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.63−7.60 (m, 4H), 7.45−7.35 (m, 6H), 5.49 (dt, J = 52.9 and 7.9 Hz, 1H), 4.69 (d, J = 9.36 Hz, 1H), 3.91 (d, J = 11.5 Hz, 1H), 3.60 (d, J = 11.5 Hz, 1H), 2.72−2.40 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (d, J = 20.5 Hz), 135.5, 135.4, 132.3, 131.7, 130.1, 128.0, 127.9, 85.6 (d, J = 186.6 Hz), 77.3 (d, J = 5.3 Hz), 65.0, 31.8 (d, J = 20.5 Hz), 26.7, 19.1; IR (thin film) 2958, 1796, 1252, 1192, 1111, 1016 cm^{-1}; HRMS calcd for [M + Li] $C_{21}H_{25}O_3FSiLi$ 379.1717, found 379.1713. Anal. Calcd for $C_{21}H_{25}O_3FSi$: C, 67.71; H, 6.76. Found: C, 67.72; H, 6.78.

5-*O*-(*tert*-Butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-L-*erythro*-pentofuranose (21). To a flask were added lactone **20** (12.12 g, 0.0325 mol, 1.0 equiv) and 240 mL of anhydrous THF. The solution was cooled to − 78 °C, and 65 mL (0.065 mol, 2.0 equiv) of a 1.0 M solution of DIBALH in hexanes was added dropwise over a period of 30 min. This was allowed to stir at − 78 °C for 3 h, after which time the reaction was quenched by the slow addition of 2.93 mL (0.163 mol, 5.0 equiv) of water. The reaction was allowed to warm to room temperature and stir for 1 h, after which time a clear gelatinous solid formed throughout the entire flask. The reaction mixture was diluted with two volumes of diethyl ether and was poured onto an equal volume of saturated aqueous sodium potassium tartrate solution in an Erlenmeyer flask. This was stirred for 20 min until the emulsion had broken. The organic layer was separated, and the aqueous layer was extracted three times with 250 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to a light yellow oil. The product was purified by silica gel column chromatography using a 6:1 hexanes/ethyl acetate solvent system. The resulting clear oil was crystallized from boiling hexanes to give 11.98 g (98% yield) of a white crystalline solid: R_f(30% diethyl ether/70% hexanes) = 0.33; mp 66−67 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.68−7.66 (m, 4H), 7.55−7.38 (m, 6H), 5.39 (t, J = 7.6 Hz, 1H), 4.99 (dd, J = 52.2 and 4.3 Hz, 1H), 4.52 (m, 1H), 3.88 (dd, J = 10.8 and 2.5 Hz, 1H), 3.65 (d, J = 7.9 Hz, 1H), 3.49 (dd, J = 7.9 and 1.8 Hz, 1H), 2.44−2.07 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.5, 132.2, 132.1, 130.2, 130.0, 129.8, 127.9, 127.7, 99.8 (d, J = 31.1 Hz), 96.6 (d, J = 178.3 Hz), 79.4, 64.8, 29.9 (d, J = 21.2 Hz), 26.8, 19.2; IR (thin film) 3423, 2932, 1474, 1362, 1113 cm^{-1}; HRMS calcd for [M + Li] $C_{21}H_{27}O_3FSiLi$ 381.1874, found: 381.1877. Anal. Calcd for $C_{21}H_{27}O_3FSi$: C, 67.35; H, 7.27. Found: C, 67.42; H, 7.31.

1-*O*-Acetyl-5-*O*-(*tert*-butyldiphenylsilyl)-2,3-dideoxy-2-fluoro-L-*erythro*-pentofuranose (22). To a flask were added lactol **21** (8.50 g, 0.0227 mol, 1.0 equiv) and 170 mL of anhydrous CH_2Cl_2. Then, DMAP (0.277 g, 0.00227 mol, 0.1 equiv) and acetic anhydride (13.5 mL, 0.143 mol, 6.3 equiv) were added and the solution was stirred at room temperature overnight. Upon completion, the reaction was poured onto a saturated $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted three times with chloroform. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed to yield a light yellow oil. The oil was purified by silica gel column chroma-

tography using an 8:1 hexanes/ethyl acetate solvent system to give 9.85 g (99% yield) of a clear colorless oil: R_f(30% diethyl ether/70% hexanes) = 0.44; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.69−7.67 (m, 4H), 7.43−7.38 (m, 6H), 6.30 (d, J = 10.4 Hz, 1H), 5.06 (d, J = 54.9 Hz, 1H), 4.53 (m, 1H), 3.81 (dd, J = 10.8 and 4.3 Hz, 1H), 3.72 (dd, J = 10.8 and 4.3 Hz, 1H), 2.38−2.12 (m, 2H), 1.89 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 135.6, 135.5, 133.2, 133.1, 129.8, 129.7, 127.8, 127.7, 99.3 (d, J = 34.1 Hz), 95.5(d, J = 178.2 Hz), 81.4, 65.3, 31.6 (d, J = 20.5 Hz), 26.8, 21.1, 19.3; IR (thin film) 3074, 2860, 1750, 1589, 1229, 1113 cm^{-1}; HRMS calcd for [M − $OCOCH_3$] $C_{21}H_{26}O_2FSi$ 357.1686, found 357.1695. Anal. Calcd for $C_{23}H_{29}O_4FSi$: C, 66.32; H, 7.02. Found: C, 66.30; H, 7.04.

Representative Procedure for the Coupling of a Silylated Base with 22: L-5′-*O*-(*tert*-butyldiphenylsilyl)-2′,3′-dideoxy-2′-fluoro-5-fluorocytidine (25). To a flask equipped with a short-path distillation head were added 5-fluorocytosine (2.01 g, 15.6 mmol, 5.0 equiv), 35 mL of 1,1,1,3,3,3-hexamethyldisilazane, and a catalytic amount (∼1 mg) of $(NH_4)_2SO_4$. The white suspension was heated to boiling for 1 h until the base was silylated and reaction was a clear solution. The excess HMDS was distilled off and the oily residue that remained was placed under vacuum for 1 h to remove the last traces of HMDS. A white solid resulted which was dissolved, under argon, in 5 mL of anhydrous 1,2-dichloroethane. To this clear solution was added a solution of acetate **22** (1.30 g, 3.12 mmol, 1.0 equiv) in 5 mL of anhydrous 1,2-dichloroethane. To this was added, at room temperature, trimethylsilyl trifluoromethanesulfonate (3.32 mL, 17.2 mmol, 5.5 equiv). The reaction was monitored by TLC (10% methanol/90% CH_2Cl_2) and was observed to be complete in 4 h. The reaction mixture was poured onto saturated $NaHCO_3$. The organic layer was then separated, and the aqueous layer was extracted three times with chloroform. The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed to yield a white foam. The compound was purified by silica gel column chromatography using a gradient solvent system from 100% CH_2Cl_2 to 10% methanol in CH_2Cl_2. The compound was isolated as 1.51 g (99% yield) of a white foam: mixture of anomers R_f(100% EtOAc) = 0.36; mp 74−80 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (bs, 1H), 8.04 (d, J = 6.4 Hz, 0.67H), 7.67−7.63 (m, 4H), 7.51−7.39 (m, 6.33H), 6.11 (d, J = 20 Hz, 0.33H), 5.98 (d, J = 16.4 Hz, 0.67H), 5.88 (bs, 1H), 5.41 (d, J = 52.4 Hz, 0.33H), 5.23 (dd, J = 50.4 and 4 Hz, 0.67H), 4.56 (m, 0.33H), 4.45 (m, 0.67H), 4.23 (dd, J = 12.0 and 1.6 Hz, 0.67H), 3.89 (dd, J = 11.2 and 3.2 Hz, 0.33 H), 3.74−3.66 (m, 1H), 2.45−1.96 (m, 2H), 1.09 (s, 6H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6 (d, J = 14.4 Hz), 158.4 (d, J = 14.4 Hz), 153.9, 153.8, 136.6 (d, J = 240.5 Hz), 136.3 (d, J = 239.7 Hz), 135.6, 135.56, 135.5, 135.4, 133.1, 132.9, 132.5, 132.4, 130.1, 130.0, 129.9, 127.9, 127.8, 125.8 (d, J = 33.4 Hz), 124.6 (d, J = 32.6 Hz), 96.5 (d, J = 182.0 Hz), 91.7 (d, J = 185.1), 90.7 (d, J = 35.6 Hz), 87.7 (d, J = 15.2 Hz), 81.5, 79.5, 64.9, 63.0, 33.5 (d, J = 20.5 Hz), 30.6 (d, J = 20.4 Hz), 26.9, 26.8, 19.22, 19.18; IR (thin film) 3300, 2960, 1682, 1608, 1513, 1109 cm^{-1}; HRMS calcd for [M + Li] $C_{25}H_{29}N_3O_3SiF_2Li$; 492.2106, found 492.2085. Anal. Calcd for $C_{25}H_{29}N_3O_3SiF_2 \cdot {}^1/_2H_2O$: C, 60.71; H, 6.11; N, 8.50. Found: C, 60.67; H, 6.03; N, 8.44.

D-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-dideoxy-2′-fluoro-5-fluorouridine (9): yield = 87%, mixture of anomers R_f(1:1 hexanes/EtOAc) = 0.48; mp 65−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.0 (bm, 1H), 7.99 (d, J = 5.6 Hz, 0.63H), 7.65 (m, 4H), 7.42 (m, 6.37H), 6.12 (dd, J = 18.0 and 1.6 Hz, 0.37H), 6.00 (d, J = 16 Hz, 0.63H), 5.37 (dd, J = 54.6 and 2.4 Hz, 0.37H), 5.22 (dd, J = 50.4 and 4 Hz, 0.63H), 4.57 (m, 0.37H), 4.44 (m, 0.63H), 4.22 (dd, J = 12.2 and 2.0 Hz, 0.63H), 3.92 (dd, J = 11.2 and 3.2 Hz, 0.37 H), 3.70 (m, 1H), 2.22 (m, 2H), 1.09 (s, 5.67H), 1.074 (s, 3.33H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2 (d, J = 31.7 Hz), 157.1 (d, J = 25.8 Hz), 149.1, 148.8, 140.4 (d, J = 236.6 Hz), 140.1 (d, J = 235.2 Hz), 135.6, 135.5, 135.4, 132.9, 132.7, 132.4, 132.3, 130.1, 130.0, 129.9, 127.9, 127.8, 125.1 (d, J = 34.9 Hz), 123.6 (d, J = 34.1 Hz), 96.4 (d, J = 182.0 Hz), 92.0 (d, J = 185.9 Hz), 90.2 (d, J = 37.2 Hz), 87.0 (d, J = 15.2 Hz), 81.7, 79.8, 64.8, 63.0, 33.3 (d, J = 21.2 Hz), 31.0 (d, J = 21.2 Hz), 26.9, 26.8, 19.2; IR (thin film) 3185, 1722, 1117 cm^{-1}; HRMS calcd for [M + 1] $C_{25}H_{29}N_2O_4SiF_2$ 487.1866, found 487.1853. Anal. Calcd for $C_{25}H_{28}N_2O_4SiF_2$: C, 61.71; H, 5.80; N, 5.76. Found: C, 61.72; H, 5.86; N, 5.72.

D-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-dideoxy-2-fluoro-5-fluorocytidine (10): yield = 99%, mixture of anomers R_f(100% EtOAc) = 0.36; mp 75−81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (bm, 1H), 8.05 (d, J = 6.0 Hz, 0.67H), 7.67−7.63 (m, 4H), 7.51−7.39 (m, 6.33H), 6.10 (d, J = 20 Hz, 0.33H), 5.98 (d, J = 16.4 Hz, 0.67H), 5.62 (bm, 1H), 5.41 (d, J = 52.4 Hz, 0.33H), 5.23 (dd, J = 51.6 and 4 Hz, 0.67H), 4.57 (m, 0.33H), 4.48 (m, 0.67H), 4.24 (dd, J = 12.4 and 2.0 Hz, 0.67H), 3.89 (dd, J = 11.2 and 3.2 Hz, 0.33 H), 3.74−3.66 (m, 1H), 2.39−1.95 (m, 2H), 1.09 (s, 6H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (d, J = 14.4 Hz), 158.3 (d, J = 15.2 Hz), 153.8, 153.7, 136.5 (d, J = 240.5 Hz), 136.2 (d, J = 241.8 Hz), 135.59, 135.56, 135.4, 133.0, 132.9, 132.5, 132.4, 130.1, 130.0, 129.9, 127.9, 127.8, 124.8 (d, J = 31.9 Hz), 96.5 (d, J = 181.3 Hz), 91.8 (d, J = 175.2 Hz), 90.7 (d, J = 24.9 Hz), 87.8 (d, J = 21.2 Hz), 81.6, 79.6, 64.9, 63.0, 33.5 (d, J = 19.7 Hz), 30.6 (d, J = 21.3 Hz), 26.9, 26.8, 19.2, 14.2; IR (thin film) 3304, 2959, 1680, 1621, 1508, 1105 cm^{-1}; HRMS calcd for [M + Li] $C_{25}H_{29}N_3O_3SiF_2Li$ 492.2106, found 492.2110. Anal. Calcd for $C_{25}H_{29}N_3O_3SiF_2$: C, 61.84; H, 6.02; N, 8.65. Found: C, 61.86; H, 6.09; N, 8.55.

D-N^4-Acetyl-5′-*O*-(*tert*-butyldiphenylsilyl)-2′,3′-dideoxy-2′-fluorocytidine (11): yield = 91%, mixture of anomers R_f(15% EtOH, 85% EtOAc) = 0.75; mp 81−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.58 (bs, 1H), 8.40 (d, J = 7.2 Hz, 0.61H), 7.86 (d, J = 7.6 Hz, 0.38H), 7.67−7.65 (m, 4H), 7.51−7.41 (m, 6H), 7.27 (d, J = 8.4 Hz, 1H), 6.12 (t, J = 15.8 Hz, 1H), 5.51 (d, J = 52.6 Hz, 0.38H), 5.21 (dd, J = 50.8 and 2.9 Hz, 0.61H), 4.62 (m, 0.38H), 4.54 (m, 0.61H), 4.28 (d, J = 11.5 Hz, 0.61H), 3.95 (dd, J = 11.9 and 3.2 Hz, 0.38H), 3.79−3.70 (m, 1H), 2.46−2.04 (m, 5H), 1.12 (s, 5.49H), 1.07 (s, 3.42H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 171.3, 163.4, 154.9, 144.9, 144.1, 135.5, 135.4, 133.0, 132.8, 132.5, 132.2, 130.2, 130.1, 129.9, 128.0, 127.8, 96.8 (d, J = 91.1 Hz), 96.2 (d, J = 147.9 Hz), 92.3, 91.2 (d, J = 35.7 Hz), 90.5, 88.5 (d, J = 15.9 Hz), 81.9, 80.1, 64.7, 62.9, 33.5 (d, J = 20.5 Hz), 30.5 (d, J = 20.5 Hz), 26.9, 26.8, 24.9, 24.8, 19.3, 19.2; IR (thin film) 3237, 2932, 1722, 1671, 1559, 1493, 1107 cm^{-1}; HRMS calcd for [M + Li] $C_{27}H_{32}N_3O_4FSiLi$ 516.2306, found 516.2310. Anal. Calcd for $C_{27}H_{32}N_3O_4FSi$: C, 63.63; H, 6.33; N, 8.24. Found: C, 63.45; H, 6.42; N, 8.09.

D-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-dideoxy-2′-fluorocytidine (12): yield = 72%, mixture of anomers R_f(15% EtOH, 85% EtOAc) = 0.50; mp 98−104 °C; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.97 (d, J = 7.2 Hz, 0.64H, H-6), 7.65 (m, 4H), 7.47−7.38 (m, 6.36H), 6.15 (d, J = 20.5 Hz, 0.36H), 6.05 (d, J = 16.6 Hz, 0.64H), 5.83 (d, J = 7.9 Hz, 0.36H), 5.46 (d, J = 7.2 Hz, 0.64H), 5.30−5.10 (m, 1H), 4.55 (m, 0.36H), 4.44 (m, 0.64H), 4.22 (d, J = 9.7 Hz, 0.64H), 3.88−3.63 (m, 1.36H), 2.38−1.95 (m, 2H), 1.09 (s, 5.76H), 1.06 (s, 3.24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 155.8, 141.5, 140.5, 135.6, 135.4, 133.1, 132.9, 132.8, 132.4, 130.1, 130.0, 129.8, 128.0, 127.9, 127.8, 96.7 (d, J = 181.3 Hz), 93.4 (d, J = 140.3 Hz), 94.5, 90.8 (d, J = 35.6 Hz), 90.8, 87.8 (d, J = 15.9 Hz), 81.2, 79.4, 65.0, 63.2, 33.7 (d, J = 21.2 Hz), 30.8 (d, J = 20.4 Hz), 26.9, 26.8, 19.3, 19.2; IR (thin film) 3470, 3339, 1644, 1487, 1113 cm^{-1}; HRMS calcd for [M + Li] $C_{25}H_{30}N_3O_3FSiLi$ 474.2201, found 474.2198. Anal. Calcd for $C_{25}H_{30}N_3O_3FSi$: C, 64.21; H, 6.47; N, 8.99. Found: C, 64.04; H, 6.58; N, 8.76.

L-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-dideoxy-2′-fluorothymidine (23): yield = 87%, mixture of anomers R_f(10% MeOH/90% CH_2Cl_2) = 0.56; mp 61−65 °C; ^{1}H NMR (360, MHz, $CDCl_3$) δ 9.48 (bs, 1H), 7.67 (m, 4H), 7.45−7.37 (m, 7H), 6.15 (dd, J = 20.2 and 3.2 Hz, 0.36H), 5.99 (d, J = 18.4 Hz, 0.64H), 5.34 (d, J = 51.8 Hz, 0.36H), 5.24 (dd, J = 52.2 and 4.3 Hz, 0.64H), 4.59 (m, 0.36H), 4.45 (m, 0.64H), 4.17 (dd, J = 12.2 and 2.5 Hz, 0.64H), 3.91 (dd, J = 11.9 and 2.9 Hz, 0.36H), 3.81 (dd, J = 11.5 and 2.9 Hz, 0.64H), 3.68 (dd, J = 10.8 and 3.6 Hz, 0.36H), 2.40−2.12 (m, 2H), 1.94 (s, 1.08H), 1.61 (s, 1.92H), 1.10 (s, 5.76H), 1.07 (s, 3.24H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 164.0, 150.4, 150.2, 136.4, 135.6, 135.5, 135.4,

135.3, 135.2, 133.0, 132.8, 132.6, 130.1, 130.0, 129.9, 127.94, 127.90, 127.8, 110.8, 109.8, 96.4 (d, J = 181.3 Hz), 92.1 (d, J = 185.8 Hz), 90.7 (d, J = 36.4 Hz), 86.6 (d, J = 15.2 Hz), 80.9, 79.4, 64.9, 63.6, 33.4 (d, J = 20.5 Hz), 32.0 (d, J = 21.2 Hz), 27.0, 26.8, 19.4, 19.2, 12.6, 12.2; IR (thin film) 3183, 3050, 1696, 1506, 1188 cm $^{-1}$; HRMS calcd for [M + Li] $C_{26}H_{31}N_2O_4SiF$ 489.2197, found 489.2175. Anal. Calcd for $C_{26}H_{31}N_2O_4SiF$: C, 64.71; H, 6.47; N, 5.80. Found: C, 64.88; H, 6.56; N, 5.76.

L-5′-*O*-(*tert*-Butyldiphenylsilyl)-2′,3′-dideoxy-2′-fluoro-5-fluorouridine (24): yield = 85%, mixture of anomers R_f(1:1 hexanes/EtOAc) = 0.48; mp 65−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (bs, 0.4H), 9.00 (bs, 0.6H) 8.01 (d, J = 5.4 Hz, 0.6H), 7.65 (m, 4H), 7.42 (m, 6.4H), 6.10 (dd, J = 20.2 and 1.4 Hz, 0.4H), 6.00 (d, J = 16.0 Hz, 0.6H), 5.35 (dd, J = 52.4 and 1.6 Hz, 0.4H), (5.22, dd, J = 51.2 and 4 Hz, 0.6H), 4.57 (m, 0.4H), 4.44 (m, 0.6H), 4.22 (dd, J = 12.4 and 2.0 Hz, 0.6H), 3.91 (dd, J = 11.2 and 2.9 Hz, 0.4H), 3.70 (m, 1H), 2.45−2.00 (m, 2H), 1.09 (s, 5.4H), 1.07 (s, 3.6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (d, J = 26.5 Hz), 148.8, 148.6, 140.3 (d, J = 236.7 Hz), 140.1 (d, J = 235.1 Hz), 135.6, 135.5, 135.4, 132.9, 132.7, 132.4, 132.3, 130.2, 130.1, 129.9, 127.9, 127.8, 125.1 (d, J = 34.9 Hz), 123.6 (d, J = 34.2 Hz), 96.4 (d, J = 182.9 Hz), 92.0 (d, J = 186.6 Hz), 90.2 (d, J = 36.0 Hz), 86.9 (d, J = 15.1 Hz), 81.7, 79.8, 64.8, 63.0, 33.2 (d, J = 20.5 Hz), 30.9 (d, J = 20.4 Hz), 26.9, 26.8, 19.2; IR (thin film) 3191, 1719, 1113 cm $^{-1}$; HRMS calcd for [M + Li] $C_{25}H_{28}N_2O_4SiF_2Li$ 493.1946, found 493.1952. Anal. Calcd for $C_{25}H_{28}N_2O_4SiF_2$: C, 61.71; H, 5.80; N, 5.76. Found: C, 61.73; H, 5.83; N, 5.77.

Representative Procedure for the Deprotection of Silyl-Protected Nucleosides: α- and β-L-2′,3′- dideoxy-2′-fluoro-5-fluorocytidine (28a and 28b). Nucleoside **25** (1.098 g, 2.26 mmol, 1.0 equiv) was dissolved in 15 mL of methanol to which was added ammonium fluoride (0.838 g, 22.6 mmol, 10.0 equiv). This was stirred vigorously for 24 h, after which time TLC (15% ethanol/85% ethyl acetate) revealed that the reaction was complete. The reaction mixture was diluted with three volumes of ethyl acetate and was filtered through a small (1 cm) silica gel plug. The plug was rinsed with 200 mL of 15% ethanol/85% ethyl acetate solution, and the solvent was removed to yield a white foam. The compound was purified by silica gel column chromatography using a 15% ethanol/85% ethyl acetate solvent system which also effected the separation of the α and β anomers. The yield of α as a white foam was 0.190 g (0.768 mmol, 34% yield), and the yield of β as a white foam was 0.290 g (1.17 mmol, 52% yield). **28a**: R_f(15% EtOH, 85% EtOAc) = 0.22; mp 199−203 °C (dec); ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 6.8 Hz, 1H), 6.07 (d, J = 19.2 Hz, 1H), 5.37 (d, J = 54.0 Hz, 1H), 4.60 (m, 1H), 3.80 (dd, J = 12.0 and 3.2 Hz, 1H), 3.56 (dd, J = 12.4 and 4.4 Hz, 1H), 2.40−2.00 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7 (d, J = 13.6 Hz), 153.2, 135.9 (d, J = 239.0 Hz), 126.2 (d, J = 31.1 Hz), 92.4 (d, J = 183.6 Hz), 86.7 (d, J = 15.2 Hz), 79.6, 62.7, 33.3 (d, J = 20.5 Hz); IR (KBr) 3343, 3100, 1683, 1517, 1104 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{11}N_3O_3F_2Li$ 254.0929, found 254.0919. Anal. Calcd for $C_9H_{11}N_3O_3F_2 \cdot {}^1/_2H_2O$: C, 42.19; H, 4.72; N, 16.40. Found: C, 42.44; H, 4.56; N, 16.56. **28b**: R_f(15% EtOH, 85% EtOAc) = 0.37; mp 182−186 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.32 (d, J = 7.6 Hz, 1H), 7.79 (bs, 1H), 7.53 (bs, 1H), 5.81 (d, J = 16.8 Hz, 1H), 5.37 (t, J = 4.8 Hz), 5.18 (dd, J = 51.6 and 3.2 Hz, 1H), 4.32 (m, 1H), 3.88 (dd, J = 12.0 and 2.8 Hz, 1H), 3.59 (dd, J = 12.4 and 2.4 Hz, 1H), 2.20−1.99 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 157.7 (d, J = 13.7 Hz), 153.2, 136.1 (d, J = 237.4 Hz), 125.3 (d, J = 33.4 Hz), 97.3 (d, J = 176.8 Hz), 89.9 (d, J = 35.7 Hz), 81.6, 60.2, 30.3 (d, J = 19.7 Hz); IR (KBr) 3487, 2948, 1678, 1509, 1122 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{11}N_3O_3F_2Li$ 254.0929, found: 254.0935. Anal. Calcd for $C_9H_{11}N_3O_3F_2$: C, 43.73; H, 4.49; N, 17.00. Found: C, 43.69; H, 4.53; N, 16.92.

α-D-2′,3′-Dideoxy-2′-fluoro-5-fluorouridine (14a): yield = 19%; R_f(100% EtOAc) = 0.38; mp 153−155 °C; ^{1}H NMR (360 MHz, CD_3OD) δ 7.80 (d, J = 6.8 Hz, 1H), 6.11 (d, J = 18.7 Hz, 1H), 5.35 (d, J = 52.9, 1H), 4.59 (m, 1H), 3.81 (d, J = 11.9 Hz, 1H), 3.57 (dd, J = 12.6 and 3.6 Hz, 1H), 2.36−2.15 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6 (d, J = 25.8 Hz), 150.7, 141.5 (d, J = 230.6 Hz), 127.0 (d, J = 34.9 Hz), 93.9 (d, J = 185.1 Hz), 88.5 (d, J = 15.1 Hz), 81.8, 64.3, 34.3 (d, J = 20.5 Hz); IR (KBr) 3421, 3081, 1685, 1478, 1111 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{10}N_2O_4F_2Li$ 255.0769, found 255.0778. Anal. Calcd for $C_9H_{10}N_2O_4F_2$: C, 43.56; H, 4.06; N, 11.29. Found: C, 43.59; H, 4.11; N, 11.17.

β-D-2′,3′-Dideoxy-2′-fluoro-5-fluorouridine (14b): yield = 48%; R_f(100% EtOAc) = 0.54; mp 152−154 °C; ^{1}H NMR (360 MHz, CD_3OD) δ 8.41 (d, J = 7.2 Hz, 1H), 5.89 (d, J = 16.6 Hz, 1H), 5.21 (dd, J = 51.5 and 3.6 Hz, 1H), 4.41 (m, 1H), 4.00 (d, J = 12.6 Hz, 1H), 3.67 (d, J = 12.2 Hz, 1H), 2.25−2.09 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.7 (d, J = 25.8 Hz), 150.7, 141.8 (d, J = 229.8 Hz), 126.3 (d, J = 36.4 Hz), 98.3 (d, J = 179 Hz), 91.9 (d, J = 37.1 Hz), 83.6, 61.9, 31.9 (d, J = 20.5 Hz); IR (KBr) 3417, 3056, 1684, 1474, 1105 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{10}N_2O_4F_2Li$ 255.0769, found 255.0764. Anal. Calcd for $C_9H_{10}N_2O_4F_2$: C, 43.56; H, 4.06; N, 11.29. Found: C, 43.37; H, 3.98; N, 11.22.

α-D-2′,3′-Dideoxy-2′-fluoro-5-fluorocytidine (15a): yield = 27%; R_f(15% EtOH/85% EtOAc) = 0.22; mp 198−202 °C (dec); ^{1}H NMR (400 MHz, CD_3OD) δ 7.78 (d, J = 6.8 Hz, 1H), 6.07 (d, J = 18.8 Hz, 1H), 5.37 (d, J = 54.0 Hz, 1H), 4.59 (m, 1H), 3.80 (dd, J = 12.0 and 3.2 Hz, 1H), 3.57 (dd, J = 12.4 and 4.4 Hz, 1H), 2.38−2.14 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.9 (d, J = 13.6 Hz), 156.5, 138.3 (d, J = 240.4 Hz), 127.5 (d, J = 33.4 Hz), 93.6 (d, J = 184.3 Hz), 89.5 (d, J = 15.9 Hz), 81.8, 64.4, 34.5 (d, J = 20.5 Hz); IR (KBr) 3486, 3098, 1681, 1519, 1108 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{11}N_3O_3F_2Li$ 254.0929, found 254.0929. Anal. Calcd for $C_9H_{11}N_3O_3F_2Li \cdot {}^1/_2H_2O$: C, 42.19; H, 4.72; N, 16.40. Found: C, 41.86; H, 4.75; N, 16.36.

β-D-2′,3′-Dideoxy-2′-fluoro-5-fluorocytidine (15b): yield = 51%; R_f(15% EtOH/85% EtOAc) = 0.37; mp 181−183 °C (dec); ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, J = 7.2 Hz, 1H), 5.92 (dd, J = 16.2 and 1.2 Hz, 1H), 5.18 (dd, J = 50.8 and 4.0 Hz, 1H), 4.46 (m, 1H), 4.05 (dd, J = 12.4 and 2.4 Hz, 1H), 3.72 (dd, J = 12.8 and 2.4 Hz, 1H), 2.27−2.05 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.9 (d, J = 13.6 Hz), 156.5, 138.5 (d, J = 240.5 Hz), 126.9 (d, J = 33.4 Hz), 98.4 (d, J = 179.0 Hz), 92.5 (d, J = 36.4 Hz), 83.6, 61.9, 31.6 (d, J = 20.5 Hz); IR (KBr) 3494, 2944, 1689, 1522, 1106 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{11}N_3O_3F_2Li$ 254.0929, found 254.0936. Anal. Calcd for $C_9H_{11}N_3O_3F_2$: C, 43.73; H, 4.49; N, 17.00. Found: C, 43.84; H, 4.47; N, 17.05.

α-D-N^4-Acetyl-2′,3′-dideoxy-2′-fluorocytidine (16a): yield = 17%; R_f(15% EtOH/85% EtOAc) = 0.40; mp 208−212 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ (10.91, bs, 1H), 8.05 (d, J = 7.2 Hz, 1H), 7.25 (d, J = 7.2 Hz, 1H), 6.08 (dd, J = 19.1 and 2.9 Hz, 1H), 5.42 (d, J = 52.2 Hz, 1H), 4.97 (bs, 1H), 4.54 (m, 1H), 3.63 (d, J = 13.0 Hz, 1H), 3.47 (d, J = 13.3 Hz, 1H), 2.35−2.15 (m, 2H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 162.6, 154.3, 145.7, 94.9, 92.0 (d, J = 183.6 Hz), 87.5 (d, J = 15.9 Hz), 80.2, 62.6, 33.3 (d, J = 19.7 Hz), 24.4; IR (KBr) 3436, 3227, 1702, 1661, 1442, 1102 cm^{-1}; HRMS calcd for [M + Li] $C_{11}H_{14}N_3O_4FLi$ 278.1128, found 278.1136. Anal. Calcd for $C_{11}H_{14}N_3O_4F$: C, 48.71; H, 5.20; N, 15.49. Found: C, 48.73; H, 5.23; N, 15.52.

β-D-N^4-Acetyl-2′,3′-dideoxy-2′-fluorocytidine (16b): yield = 31%; R_f(15% EtOH/85% EtOAc) = 0.50; mp 174−178 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ (10.90, bs, 1H), 8.46 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.2 Hz, 1H), 5.90 (d, J = 16.9 Hz, 1H), 5.27 (d, J = 52.9 Hz, 1H), 5.27 (bs, 1H), 4.39 (m, 1H), 3.88 (d, J = 13.0 Hz, 1H), 3.61 (d, J = 13.0 Hz, 1H), 2.09 (s, 3H), 2.20−1.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 162.6, 154.4, 144.7, 97.0 (d, J = 177.5 Hz), 95.0, 90.7 (d, J = 36.6 Hz), 82.2, 60.3, 30.3 (d, J = 19.7 Hz), 24.3; IR (KBr) 3447, 3245, 1703, 1656, 1497, 1122 cm^{-1}; HRMS calcd for [M + Li] $C_{11}H_{14}N_3O_4FLi$ 278.1128, found: 278.1133. Anal. Calcd for $C_{11}H_{14}N_3O_4F$: C, 48.71; H, 5.20; N, 15.49. Found: C, 48.65; H, 5.22; N, 15.46.

α-L-2′,3′-Dideoxy-2′-fluorothymidine (26a): yield = 24%; R_f(100% EtOAc) = 0.25; mp 147−149 °C; ^{1}H NMR (360 MHz, CD_3OD) δ 7.45 (s, 1H), 6.11 (dd, J = 19.4 and 2.9 Hz, 1H), 5.30 (d, J = 53.6 Hz, 1H), 4.58 (m, 1H), 3.79 (dd, J = 12.2 and 2.2 Hz, 1H), 3.55 (dd, J = 12.2 and 3.6 Hz, 1H), 2.40−2.15 (m, 2H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.6, 152.3,

138.6, 110.5, 93.9 (d, J = 185.1 Hz), 88.3 (d, J = 15.1 Hz), 81.7, 64.4, 34.5 (d, J = 20.5 Hz), 12.6; IR (KBr) 3436, 3166, 1727, 1667, 1362, 1186 cm^{-1}; HRMS calcd for [M + Li] $C_{10}H_{13}N_2O_4FLi$ 251.1019, found: 251.1014. Anal. Calcd for $C_{10}H_{13}N_2O_4F$: C, 49.18; H, 5.37; N, 11.47. Found: C, 49.32; H, 5.40; N, 11.29.

***β*-L-2′,3′-Dideoxy-2′-fluorothymidine (26b)**: yield = 61%, R_f (100% EtOAc) = 0.38; mp 186−188 °C; ^{1}H NMR (360 MHz, CD_3OD) δ 7.94 (s, 1H), 5.93 (d, J = 17.6 Hz, 1H), 5.20 (d, J = 51.8 Hz, 1H), 4.40 (m, 1H), 3.98 (d, J = 11.9 Hz, 1H), 3.68 (d, J = 13.0 Hz, 1H), 2.37−2.10 (m, 2H), 1.83 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 166.7, 152.3, 138.2, 111.0, 98.4 (d, J = 178.3 Hz), 92.1 (d, J = 36.4 Hz), 83.1, 62.4, 32.5 (d, J = 20.5 Hz), 12.6; IR (KBr) 3478, 3052, 1684, 1363, 1192, 1005 cm^{-1}. Anal. Calcd for $C_{10}H_{13}N_2O_4F$: C, 49.18; H, 5.37; N, 11.47. Found: C, 49.29; H, 5.44; N, 11.36.

α-L-2′,3′-Dideoxy-2′-fluoro-5-fluorouridine (27a): yield = 35%, R_f (100% EtOAc) = 0.38; mp 155−157 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.80 (d, J = 6.8 Hz, 1H), 6.13 (d, J = 20.0 Hz, 1H), 5.35 (d, J = 54.4 Hz, 1H), 4.63 (m, 1H), 3.81 (dd, J = 11.9 and 3.2 Hz, 1H), 3.58 (dd, J = 12.4 and 2.0 Hz, 1H), 2.41−2.15 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.6 (d, J = 25.8 Hz), 150.7, 141.5 (d, J = 230.6 Hz), 127.0 (d, J = 34.9 Hz), 93.9 (d, J = 184.3 Hz), 88.5 (d, J = 15.1 Hz), 81.9, 64.3, 34.3 (d, J = 20.5 Hz); IR (KBr) 3401, 3098, 1661, 1458, 1018 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{10}N_2O_4F_2Li$ 255.0769, found 255.0771. Anal. Calcd for $C_9H_{10}N_2O_4F_2$: C, 43.56; H, 4.06; N, 11.29. Found: C, 43.70; H, 4.17; N, 11.15.

***β*-L-2′,3′-Dideoxy-2′-fluoro-5-fluorouridine (27b)**: yield = 51%, R_f (100% EtOAc) = 0.54; mp 153−156 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.46 (d, J = 6.8 Hz, 1H), 5.94 (d, J = 16.4 Hz, 1H), 5.25 (dd, J = 51.6 and 4.0 Hz, 1H), 4.41 (m, 1H), 4.05 (dd, J = 12.8 and 2.4 Hz, 1H), 3.72 (dd, J = 12.4 and 2.4 Hz, 1H), 2.34−2.09 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 159.7 (d, J = 25.8 Hz), 150.7, 141.8 (d, J = 230.6 Hz), 126.3 (d, J = 35.7 Hz), 98.3 (d, J = 184.6 Hz), 91.9 (d, J = 36.4 Hz), 83.6, 61.9, 31.9 (d, J = 20.5 Hz); IR (KBr) 3482, 3037, 1702, 1654, 1402, 1103 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{10}N_2O_4F_2Li$ 255.0769, found: 255.0764. Anal. Calcd for $C_9H_{10}N_2O_4F_2$: C, 43.56; H, 4.06; N, 11.29. Found: C, 43.59; H, 4.06; N, 11.17.

***β*-D-2′,3′-Dideoxy-2′-fluorocytidine (17b).** Nucleoside **16** (0.160 g, 0.59 mmol) was dissolved in 10 mL of saturated methanolic ammonia. After the solution was stirred for 5 min, the reaction was complete. The methanolic ammonia was removed, and the resultant white solid was placed under vacuum and heated gently in a 60 °C water bath for 2 h to remove the acetamide byproduct through sublimation. The white solid was crystallized from 5% methanol/95% methylene chloride to give a quantitative yield of a white crystalline solid: R_f (15% EtOH/85% EtOAc) = 0.18; mp 191−195 °C (dec); ^{1}H NMR (360 MHz, CD_3OD) δ 8.10 (d, J = 7.2 Hz, 1H), 5.92 (d, J = 17.3 Hz, 1H), 5.82 (d, J = 7.6 Hz, 1H), 5.13 (d, J = 50.0 Hz, 1H), 4.39 (m, 1H), 3.97 (d, J = 12.2 Hz, 1H), 3.68 (dd, J = 13.0 and 2.5 Hz, 1H), 2.21−2.00 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD) δ 165.9, 155.0, 140.8, 97.3 (d, J = 176.8 Hz), 93.6, 90.3 (d, J = 35.6 Hz), 81.3, 60.7, 31.0 (d, J = 20.5 Hz); IR (KBr) 3397, 3112, 1680, 1400, 1178, 1070 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{12}N_3O_3FLi$ 236.1024, found: 236.1028. Anal. Calcd for $C_9H_{12}N_3O_3F$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.01; H, 5.21; N, 18.29.

α-D-2′,3′-Dideoxy-2′-fluorocytidine (17a): yield = quantitative, R_f (15% EtOH/85% EtOAc) = 0.08; mp 234−237 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.52 (d, J = 7.6 Hz, 1H), 7.21 (bm, 2H), 6.05 (dd, J = 20.4 and 3.2 Hz, 1H), 5.73 (d, J = 7.2 Hz, 1H), 5.28 (d, J = 52.4 Hz, 1H), 4.93 (t, J = 5.6 Hz, 1H), 4.45 (m, 1H), 3.58 (m, 1H), 3.43 (m, 1H), 2.26−2.13 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.8, 155.0, 141.6, 93.3, 92.2 (d, J = 182.8 Hz), 86.6 (d, J = 15.1 Hz), 79.4, 62.8, 33.3 (d, J = 19.7 Hz); IR (KBr) 3366, 3199, 1659, 1399, 1122 cm^{-1}; HRMS calcd for [M + Li] $C_9H_{12}N_3O_3FLi$ 236.1023, found 236.1014. Anal. Calcd for $C_9H_{12}N_3O_3F$: C, 47.16; H, 5.28; N, 18.33. Found: C, 47.40; H, 5.34; N, 18.51.

Antiviral and Cytotoxicity Assays. Anti-HIV-1 activity of the compounds was determined in human peripheral blood mononuclear (PBM) cells as described previously.[17] Stock solutions (20−40 mM) of the compounds were prepared in sterile DMSO and then diluted to the desired concentration in complete medium. 3′-Azido-3′-deoxythymidine (AZT) stock solutions were made in water. Cells were infected with the prototype HIV-1_{LAI} at a multiplicity of infection of 0.01. Virus obtained from the cell supernatant was quantitated on day 6 after infection by a reverse transcriptase assay using poly-$(rA)_n$·oligo$(dT)_{12-18}$ as template-primer. The DMSO present in the diluted solution (<0.1%) had no effect on the virus yield. The toxicity of the compounds was assessed in human PBM, CEM, and Vero cells, as described previously.[17] The antiviral EC_{50} and cytotoxicity IC_{50} was obtained from the concentration−response curve using the median effective method described by Chou and Talalay.[18]

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Supporting Information Available: X-ray crystal structures of **6**, **18a**, and **18b**; ^{1}H and ^{13}C NMR data with subjective peak assignments (39 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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