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Synthesis of 3′-Deoxynucleosides with 2-Oxabicyclo[3.1.0]hexane Sugar Moieties: Addition of Difluorocarbene to a 3′,4′-Unsaturated Uridine Derivative and 1,2-Dihydrofurans Derived from D- and L-Xylose[1]

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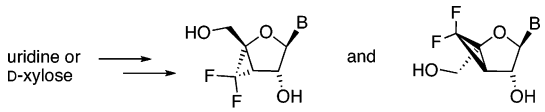
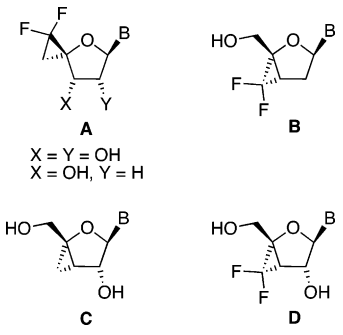


Syntheses of 3′-deoxy analogues of adenosine, cytidine, and uridine with a 2,2-difluorocyclopropane ring fused at C3′−C4′ are described. Treatment of a 2′,5′-protected-3′,4′-unsaturated derivative of uridine with difluorocarbene [generated from $(CF_3)_2Hg$ and NaI] gave a diastereomeric mixture of the 3′,4′-difluoromethylene compounds (α-L-arabino/β-D-ribo, ∼5:4). The limited stereoselectivity for addition at the β face results from competitive steric hindrance by an allylic 4-methoxybenzyloxy group at C2′ on the α face and a homoallylic nucleobase at C1′ on the β face. Protected uracil derivatives were converted into their cytosine counterparts via 4-(1,2,4-triazol-1-yl) intermediates. Treatment of 1,2-dihydrofurans derived from D- and L-xylose with difluorocarbene resulted in stereospecific addition at the β face (anti to the 1,2-*O*-isopropylidene group on the α face). Glycosylations with activated enantiomeric sugar derivatives with the fused difluorocyclopropane ring on the β face gave protected adenine nucleosides, whereas attempted glycosylation with an α-fused derivative gave multiple products. Removal of base- and sugar-protecting groups gave new difluoromethylene-bridged nucleoside analogues.

Introduction

Attachment of fluorine atoms on sugar moieties of nucleoside analogues can impart potent anticancer[2] and antiviral[3] activity. Deoxy- and deoxofluorination procedures, as well as nucleophilic substitution of leaving groups by fluoride, provide straightforward routes for generation of CF and CF_2 groups.[4] The small size and powerful electronegativity of fluorine can cause significant alterations of stereoelectronic effects, which restrict conformational equilibria of nucleosides[5] and stabilize glycosyl bonds.[6] We recently described syntheses of the difluoromethylene-bridged nucleoside analogues **A**[7] and **B**[8] by addition of difluorocarbene to enol ethers derived from adenosine and uridine. Difluorocarbene addition to the 5′-deoxy-4′,5′-unsaturated derivatives occurred readily to give the spirodifluorocyclopropyl compounds **A**. The fused-ring nucleosides **B**



(fluorinated 2′-deoxy analogues of **C**[9]) were obtained by addition of CF_2 to 2′,3′-dideoxy-3′,4′-unsaturated compounds. Effects of *gem*-difluoro substitution on the acidities of O2′ and O5′ or

(1) Nucleic Acid Related Compounds. 143. Paper 142: Nowak, I.; Robins, M. J. *J. Org. Chem.*, publisher online Mar. 3, 2007, http://dx.doi.org/10.1021/jo062544a.

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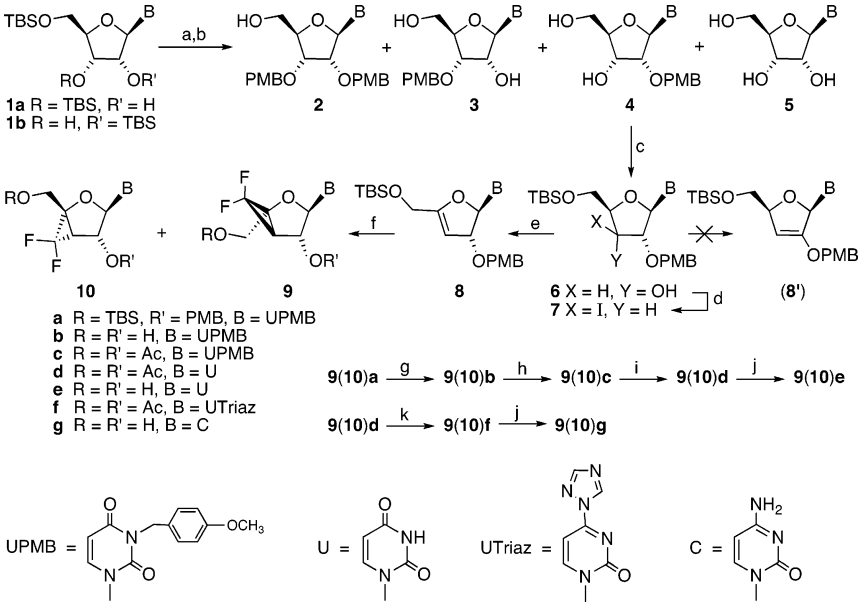
SCHEME 1[a]



[a] Reagents and conditions: (a) PMB-Cl/NaH/DMF/0 °C; (b) NH_4F/MeOH/65 °C; (c) TBS-Cl/pyridine; (d) I_2/Ph_3P/imidazole/toluene/75 °C; (e) DABCO/benzene/70 °C; (f) $(CH_3)_2Hg$/NaI/THF/75 °C; (g) CAN/MeCN/H_2O; (h) Ac_2O/pyridine; (i) CAN/MeCN/H_2O/70 °C; (j) NH_3/H_2O/1,4-dioxane; (k) 1,2,4-triazole/$POCl_3$/Et_3N/MeCN.

other properties of **D** relative to those of **C**[9] might result in altered biological responses that accrued from differences in phosphorylation, protein binding, etc. We now report addition of CF_2 [generated from NaI and $(CF_3)_2Hg$[10] (**Caution**)[11]] to a uridine-derived 2′-*O*-TBS-3′-deoxy-3′,4′-unsaturated nucleoside, which gave the uracil bicyclo[3.1.0]hexane analogue **D** and its 3′,4′-difluoromethylene-bridged diastereomer. Uracil to cytosine conversions via 4-(1,2,4-triazol-1-yl) intermediates[12] proceeded smoothly. Addition of CF_2 to the 2′-*O*-TBS enol ether derived from uridine was sluggish, and addition to a 2′-deoxy compound derived from adenosine was more difficult than that with a uridine-derived analogue.[8] Therefore, D- and L-xylose were converted into protected 1,2-dihydrofurans that were subjected to addition of CF_2. Activated derivatives of the enantiomeric adducts were coupled with adenine to provide purine bicyclo-[3.1.0]hexane analogues.

Results and Discussion

A mixture of 2′,5′- and 3′,5′-di[*O*-(*tert*-butyldimethylsilyl)]-3-(4-methoxybenzyl)uridines[8] (**1a**/**1b**, 1:1) was alkylated [NaH/4-methoxybenzyl chloride (PMB-Cl)/DMF/0 °C]. Desilylation (NH_4F/MeOH[13]) gave 3-*N*,2′,3′-di-*O*-tri(PMB)uridine (**2**, 18%), 3-*N*,3′-*O*-di(PMB)uridine/3-*N*,2′-*O*-di(PMB)uridine (**3**/**4**, 1:2; 59%), and 3-*N*-(PMB)uridine (**5**, 16%). The apparent intermolecular transfer of TBS groups between secondary alcohol functions (resulting in the formation of **2** and **5**) was not observed in alkylations of **1a**/**1b** with methyl iodide or allyl bromide. Spontaneous crystallization of **2** allowed its separation by filtration of the desilylation reaction mixture; treatment of **2** with DAST gave the 5′-deoxy-5′-fluoro derivative (verified by ^{19}F NMR[14]), which confirmed the presence of the 5′-CH_2OH group. The 2′-*O*-PMB compound **4** eluted more rapidly than its 3′-*O*-PMB isomer **3**, which facilitated chromatographic purification of **4** (**3** could be purified by rechromatography of overlapping fractions).

Protection of **4** with TBS-Cl/pyridine gave the 5′-*O*-TBS-3-*N*,2′-*O*-di(PMB) derivative **6** (77%), which was treated with I_2/PPh_3/imidazole.[15] The stereochemically inverted iodide **7** (84%) was isolated exclusively—in contrast to the epimeric mixture obtained with a 2′-deoxy analogue.[8] Apparently, stereoelectronic effects and/or anchimeric assistance by the 2′-*O*-PMB group exerted greater control than "double S_N2 displacement" by iodide or participation by O2 of the nucleobase. Regioselective elimination of HI (**7** → **8**) proceeded smoothly with DABCO in hot benzene or toluene.[8] The ^1H NMR spectrum of enol ether **8** (96%) had no peaks corresponding to the 2′,3′-unsaturated structure **8′** (both 2′,3′- and 3′,4′-unsaturated isomers were produced with the 2′-deoxy analogue[8]). The allylic 2′-*O*-(PMB) group diminished the rate of addition of difluorocarbene to the double bond of **8** (~20-fold compared to that of the 2′-deoxy analogue). The α-L-arabino[16] diastereomer **9a** (46%) was the major product, which was separated from the β-D-ribo[16] isomer **10a** (37%) by chromatography. The β/α face selectivity (**9a**/

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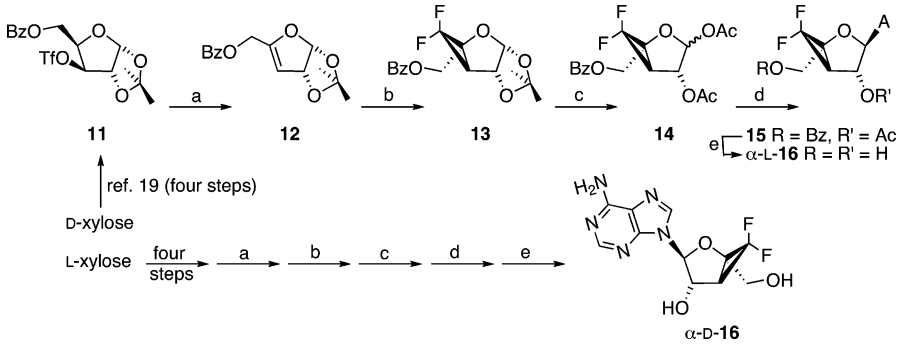
(16) For consistency with nucleoside nomenclature, the difluoromethylene bridge is considered to be a *C*-substituent on C3′ and C4′ (i.e., the orientation of the 5′-CH_2OH group is used to assign the D- or L-configuration). However, the $-CF_2-$ moiety on C4′ has a higher C-I-P priority than $-CH_2OH$. Therefore, configurations in the **9** "L-arabino" series are 3′*R*,4′*R* and those in the **10** "D-ribo" series are 3′*S*,4′*S*.

SCHEME 2[a]



[a] Reagents and conditions: (a) DBU/toluene/80 °C; (b) $(CF_3)_2Hg$/NaI/THF/70 °C; (c) $AcOH/Ac_2O/H_2SO_4$; (d) adenine/$SnCl_4$/CH_3CN/80 °C; (e) NH_3/H_2O/1,4-dioxane.

10a, 5:4) was low, presumably resulting from competing steric hindrance by the allylic (PMB-O) substituent at C2′ and the homoallylic [(3-*N*-(PMB)uracil] group at C1′. Treatment of **9a** (and **10a**) with CAN in aqueous acetonitrile at ambient temperature cleaved both of the 5′-*O*-TBS[17] and 2′-*O*-(PMB) ethers to give **9b** (and **10b**). Acetylation gave **9c** (72%, two steps) [and **10c** (59%, two steps)]. Treatment of **9c** (and **10c**) with CAN in aqueous acetonitrile at 70 °C[18] removed the 3-*N*-(PMB) group, and aqueous ammonia in 1,4-dioxane converted the diacetylated intermediates **9d** (and **10d**) into the target uracil nucleosides **9e** (48%, two steps) [and **10e** (67%, two steps)]. Treatment of **10d** with phosphoryl chloride/1,2,4-triazole/triethylamine[12] gave 4-(1,2,4-triazol-1-yl) derivative **10f** (90%) in high yield, whereas the analogous conversion of **9d** to **9f** (46%) produced several byproducts. Intermediates **9f** and **10f** were subjected to ammonolysis (NH_3/H_2O/1,4-dioxane) and chromatography (Dowex 1 × 2 [OH^-]) to give the cytosine nucleosides **9g** (77%) and **10g** (61%, isolated as the HBr salt).

We next focused on the synthesis of adenine analogues. The slow rate of addition of CF_2 to **8**, which gave nearly equal amounts of diastereomers **9a** and **10a**, and the large excess of $(CF_3)_2Hg$ needed to drive analogous additions with adenine nucleosides[7] prompted another approach. Coupling of adenine with a sugar derivative containing a preformed difluorocyclopropane ring circumvents addition of CF_2 to an adenosine-derived enol ether. Coupling also might be applicable with other base analogues, and enhanced stereoselectivity might be attained by addition of CF_2 to a suitably functionalized precursor.

Treatment of the known D-xylose triflate derivative **11**[19] (Scheme 2) with DBU in hot toluene gave 5-*O*-benzoyl-1,2-*O*-isopropylidene-α-D-*glycero*-pent-3-enofuranose (**12**). Diastereoselective addition of CF_2 to the β face of enol ether **12**, opposite to the α-oriented isopropylidene group, gave the tricyclic difluorocyclopropane **13** (86%). Treatment of **13** with $AcOH/Ac_2O/H_2SO_4$ gave an anomeric mixture of the 1,2-di-*O*-acetyl derivatives **14** (55%). We employed a benzoyl ester for protection of O5, rather than a benzyl ether,[9] because partial cleavage of a benzylic ether and acetylation occurred under the acidic acetolysis conditions. Adenine and **14** were coupled ($SnCl_4$ catalysis[20]) to give **15** in low yield (33%), and deprotection gave the adenine nucleoside α-L-**16** (Scheme 2). Because the enantiomers of 2′,3′-dideoxy-3′-thiacytidine (3TC) have significantly different anti-HIV and toxicity effects,[21] and D- and L-xylose are commercially available, we prepared the enantiomer α-D-**16** by the same sequence.

We attempted to apply the coupling approach for synthesis of the β-D diastereomer. Gagneron et al.[9] reported a synthesis of compound **C** beginning with an unfluorinated analogue of the enantiomer of **13**. Their acid-catalyzed solvolysis of the isopropylidene group gave a product that was functionalized at O2 and subjected to S_N2 inversion at C2 (xylo to ribo). However, solvolysis of our difluoro analogue under acidic conditions gave mixtures of epimers and byproducts without a cyclopropane ring. The powerful electron-withdrawing effect of the CF_2 group affects the ease of formation and stability of oxocarbenium ions, and fluorine−carbon bonds in difluorocyclopropanes are susceptible to solvolysis because electron pairs on fluorine atoms stabilize α-carbocationic character. Products derived from allylic carbocation rearrangements are formed by ring opening of difluorocyclopropanes at the bond proximal to the CF_2 group when positive character is generated at positions α to the cyclopropane ring (whereas bond cleavage is distal to the CF_2 group with radical character at α positions).[22] Problems also were encountered with attempted S_N2 inversions at C2 of an isolated minor component. Stereoelectronic effects result in major differences in the reactivity and stability of such diastereomers.

Compounds **9e** and **9g** were obtained in crystalline forms suitable for X-ray analysis. The sugar moiety in **9e** (Figure 1) has a conformation in the $_1E$ ($P = 113.9°$) range and a maximum puckering amplitude (ν_{max}) of 29.6°. The rotational conformation about the glycosyl bond ($\chi = -115.0°$) is in the anti range. In contrast, the furanosyl ring in **9g** (Figure 2) is almost flat ($\nu_{max} = 6.2°$) with a weak preference for the $_2E$ ($P = 338.2°$) range, and the rotation about the glycosyl bond is shifted significantly ($\chi = -171.6°$). The nature of the base (uracil or cytosine) and/or crystal-packing forces seriously affected the pucker (and especially amplitude) of the furanosyl ring and base rotation in these conformationally restricted analogues.

In summary, we have synthesized new nucleoside analogues with 2-oxabicyclo[3.1.0]hexane sugar moieties that have a difluorocyclopropyl ring fused at C3′−C4′. Addition of difluo-

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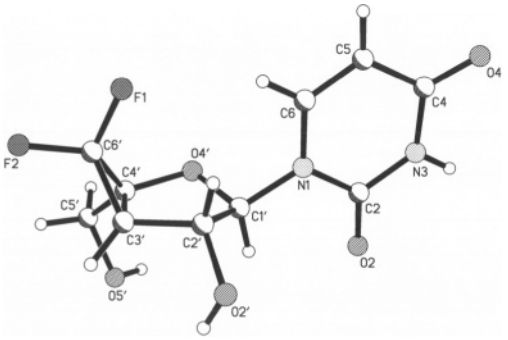

FIGURE 1. X-ray crystal structure of **9e**.

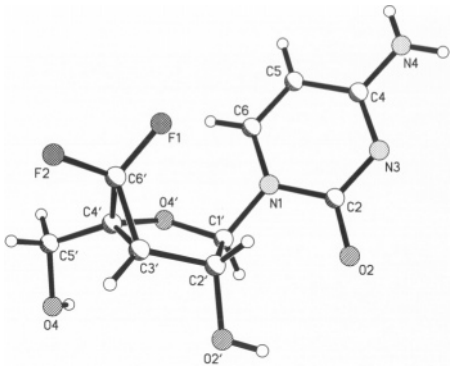

FIGURE 2. X-ray crystal structure of **9g**.

rocarbene to a 3′,4′ vinyl ether derived from uridine gave nearly equal amounts of the β-D-ribo[16] and α-L-arabino[16] diastereomers, which were converted into uracil and cytosine nucleoside analogues. Differences in ring puckering and base orientation were observed in X-ray crystal structures of a conformationally restricted uracil and cytosine β-D-ribofuranosyl pair. Addition of CF_2 to 3,4 enol ethers derived from the D and L enantiomers of 1,2-*O*-isopropylidene-α-xylofuranose gave adducts with the difluoromethylene bridge anti to the isopropylidene group. Acetolysis gave 1,2-di-*O*-acetyl derivatives, which underwent coupling with adenine to give the enantiomeric α-L-arabinofuranosyl nucleoside analogues. Acid-catalyzed methanolysis of the isopropylidene compounds gave mixtures containing epimerized and cyclopropane ring-opened byproducts, which thwarted attempts to obtain the adenine β-D-ribofuranosyl analogues.

Experimental Section[23]

3-*N*,2′-*O*-Di-(4-methoxybenzyl)uridine (4). NaH (3.2 g, 133 mmol) and PMB-Cl (10.1 mL, 11.6 g, 74.3 mmol) were added to an ice-cold solution of **1a**/**1b**[7] (1:1; 40.0 g, 67.6 mmol) in DMF (120 mL), and the suspension was stirred for 1.5 h at ~0 °C. Volatiles were evaporated in vacuo, and the residue was partitioned (H_2O, 200 mL/EtOAc, 200 mL). The aqueous phase was extracted (EtOAc, 2 × 200 mL), and the combined organic phase was dried ($MgSO_4$) and evaporated to give a yellow oil. NH_4F (6.0 g, 162 mmol) and MeOH (500 mL) were added, and the mixture was stirred at reflux for 20 h and then cooled to 0 °C. Crystalline material was filtered, washed with cold MeOH (50 mL), and dried to give 3-*N*,2′,3′-di-*O*-tri-(4-methoxybenzyl)uridine **2** (7.2 g, 18%): ^{1}H NMR ($CDCl_3$) δ 2.60 (br s, 1H), 3.68 (d, *J* = 12.2 Hz, 1H), 3.78, 3.79, 3.80 (3 × s, 3 × 3H), 3.94 (dd, *J* = 2.4, 12.2. Hz, 1H), 4.02 (d, *J* = 5.6 Hz, 1H), 4.18−4.22 (m, 2H), 4.34, 4.49 (2 × d, *J* = 11.2 Hz, 2H), 4.58, 4.71 (2 × d, *J* = 11.7 Hz, 2H), 4.96, 5.04 (2 × d, *J* = 13.7 Hz, 2H), 5.65 (d, *J* = 8.3 Hz, 1H), 5.72 (d, *J* = 3.4 Hz, 1H), 6.75, 6.85, 6.86, 7.21, 7.22, 7.47 (6 × m, 6 × 2H), 7.45 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.4, 55.18 (2C), 55.24, 61.2, 71.5, 71.9, 74.3, 77.6, 83.1, 91.7, 101.6, 113.6, 113.7, 113.8, 128.2, 129.2, 129.38, 129.45, 130.1, 130.8, 139.3, 150.6, 159.1, 159.36, 159.42, 162.6; FAB-MS *m*/*z* 627 ([M + Na^+], 100); HRMS ($C_{33}H_{36}N_2O_9Na$) calcd 627.2318, found 627.2319.

The filtrate was concentrated and chromatographed. Elution with EtOAc/hexanes (1:1) → EtOAc gave 3-*N*,3′-*O*-di-(4-methoxybenzyl)uridine (**3**) and 3-*N*,2′-*O*-di-(4-methoxybenzyl)uridine (**4**) (1:2; 19.2 g, 59%). Rechromatography of overlapping fractions allowed separation of **3** and **4**.

3: ^{1}H NMR ($CDCl_3$) δ 2.69 (br s, 2H), 3.77, 3.78 (2 × s, 2 × 3H), 3.77−3.82 (m, 1H), 3.98 (d, *J* = 12.2 Hz, 1H), 4.04−4.07 (m, 1H), 4.19−4.26 (m, 2H), 4.63, 4.67 (2 × d, *J* = 11.7 Hz, 2H), 4.98, 5.02 (2 × d, *J* = 13.7 Hz, 2H), 5.65 (d, *J* = 8.3 Hz, 1H), 5.71 (d, *J* = 3.9 Hz, 1H), 6.74, 6.84, 7.15, 7.46 (4 × m, 4 × 2H), 7.42 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.6, 55.17, 55.25, 61.8, 72.7, 72.8, 76.6, 83.0, 94.0, 102.1, 113.6, 114.0, 128.66, 128.70, 129.8, 130.8, 139.8, 151.0, 159.0, 159.7, 162.6; FAB-MS *m*/*z* 307 (100), 485 ([M + H^+], 32); HRMS ($C_{25}H_{29}N_2O_8$) calcd 485.1918, found 485.1917.

4: ^{1}H NMR ($CDCl_3$) δ 2.75 (br s, 2H), 3.64 (dd, *J* = 2.4, 12.2 Hz, 1H), 3.77, 3.82 (2 × s, 2 × 3H), 3.90 (dd, *J* = 2.0, 12.2 Hz, 1H), 4.11−4.12 (m, 1H), 4.24, 4.41 (2 × t, *J* = 5.1 Hz, 2 × 1H), 4.57, 4.60 (2 × d, *J* = 11.2 Hz, 2 × 2H), 4.99, 5.03 (2 × d, *J* = 13.7 Hz, 2H), 5.55 (d, *J* = 3.9 Hz, 1H), 5.74 (d, *J* = 8.3 Hz, 1H), 6.82, 6.90, 7.27, 7.43 (4 × m, 4 × 2H), 7.39 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 43.4, 55.1 (2C), 61.0, 68.4, 72.1, 79.6, 84.9, 90.0, 101.7, 113.6, 113.8, 128.67, 128.72, 129.9, 130.7, 138.9, 150.7, 159.0, 159.5, 162.6; FAB-MS *m*/*z* 485 ([M + H^+], 100); HRMS ($C_{25}H_{29}N_2O_8$) calcd 485.1918, found 485.1920.

Further elution of the original column (EtOAc/MeOH, 2:1) gave 3-*N*-(4-methoxybenzyl)uridine (**5**) (4.0 g, 16%): ^{1}H NMR (CD_3OD) δ 3.73 (dd, *J* = 2.9, 12.2 Hz, 1H), 3.75 (s, 3H), 3.84 (dd, *J* = 2.4, 12.2 Hz, 1H), 3.98−4.01 (m, 1H), 4.11−4.16 (m, 2H), 5.01 (s, 2H), 5.78 (d, *J* = 8.3 Hz, 1H), 5.92 (d, *J* = 3.9 Hz, 1H), 6.82, 7.32 (2 × m, 2 × 2H), 8.02 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (CD_3OD) δ 44.7, 55.8, 62.1, 71.1, 75.9, 86.2, 91.7, 102.2, 114.7, 130.3, 131.2, 140.9, 152.6, 160.6, 164.9; FAB-MS *m*/*z* 321 (100), 387 ([M + Na^+], 42); HRMS ($C_{17}H_{20}N_2O_7Na$) calcd 387.1168, found 387.1155.

5′-*O*-(*tert*-Butyldimethylsilyl)-3-*N*,2′-*O*-di(4-methoxybenzyl)-uridine (6). TBS-Cl (1.52 g, 10.1 mmol) was added to a stirred solution of **4** (4.15 g, 9.2 mmol) in pyridine (20 mL), and stirring was continued for 1 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:6 → 1:2) to give **6** (4.23 g, 77%) as a colorless oil: UV max 225, 266 nm (ε 23 900, 9900), min 213, 245 nm (ε 19 500, 4900); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 2.59 (d, *J* = 6.8 Hz, 1H), 3.77, 3.78 (2 × s, 2 × 3H), 3.78−3.84, 3.98−4.03 (2 × m, 2 × 2H), 4.11−4.17 (m, 1H), 4.70, 4.77 (2 × d, *J* = 13.7 Hz, 2 × 1H), 5.06 (s, 2 H), 5.63 (d, *J* = 7.8 Hz, 1H), 6.07 (d, *J* = 2.4 Hz, 1H), 6.75, 6.85, 7.18, 7.49 (4 × d, *J* = 8.8 Hz, 4 × 2H), 7.86 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.8, −5.7, 18.3, 25.8, 43.3, 55.0, 55.1, 61.4, 67.8, 71.5, 80.2, 84.5, 87.5, 101.4, 113.6, 113.8, 128.5, 129.0, 129.8, 130.6, 137.5, 150.7, 159.0, 159.5, 162.4; FAB-MS *m*/*z* 599 ([M + H^+], 100), 541, 461; HRMS ($C_{31}H_{43}N_2O_8Si$) calcd 599.2788, found 599.2795.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3-iodo-2-*O*-(4-methoxybenzyl)-β-D-xylofuranosyl]-3-(4-methoxybenzyl)uracil (7). A stirred solution of **6** (4.0 g, 6.8 mmol) in toluene (130 mL) was treated with PPh_3 (3.7 g, 14.1 mmol), imidazole (1.9 g, 28.3 mmol), and I_2 (3.6 g, 14.1 mmol) under N_2. The mixture was heated at 75 °C for 2.5 h, and cooled to ambient temperature. The clear supernatant was decanted and concentrated. Chromatography (EtOAc/hexanes, 1:9 → 1:3) gave **7** (4.0 g, 84%). An analytically

(23) Experimental details are in the Supporting Information.

pure sample was obtained by crystallization (MeOH) as colorless blocks: mp 96−98 °C; UV max 226, 265 nm (ϵ 25 700, 11 200), min 214, 245 nm (ϵ 22 600, 6800); ^{1}H NMR ($CDCl_3$) δ 0.10, 0.11 (2 × s, 2 × 3H), 0.90 (s, 9H), 3.76, 3.77 (2 × s, 2 × 3H), 3.78 (dd, J = 4.9, 10.7 Hz, 1H), 3.88 (q, J = 4.4 Hz, 1H), 3.98 (dd, J = 3.9, 10.7 Hz, 1H), 4.33−4.36 (m, 2H), 4.63 (d, J = 13.7 Hz, 1H), 4.71, 5.09 (2 × d, J = 13.7 Hz, 2 × 1H), 5.66 (d, J = 8.3 Hz, 1H), 5.92 (d, J = 3.9 Hz, 1H), 6.73 (d, J = 8.7 Hz, 2H), 6.83, 7.15, 7.48 (3 × d, J = 8.8 Hz, 3 × 2H), 7.62 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ −5.7, −5.4, 18.0, 25.1, 25.7, 43.2, 54.80, 54.85, 67.0, 72.0, 79.8, 86.4, 88.7, 101.3, 113.3, 113.5, 128.5, 128.7, 129.5, 130.5, 137.5, 150.5, 158.8, 159.3, 161.9; FAB-MS *m*/*z* 731 ([M + Na^+] 100%), 711, 605; HRMS ($C_{31}H_{41}IN_2O_7SiNa$) calcd 731.1625, found 731.1626.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-2-*O*-(4-methoxybenzyl)-*β*-D-*glycero*-pent-3-enofuranosyl]-3-(4-methoxybenzyl)uracil (8). A stirred solution of **7** (4.0 g, 5.6 mmol) and DABCO (2.0 g, 17.9 mmol) in benzene (50 mL) was refluxed for 20 h and concentrated. Chromatography (EtOAc/hexanes, 1:6 → 1:3) gave **8** (3.2 g, 96%) as a pale yellow oil: UV max 226, 265 nm (ϵ 27 700, 11 200), min 214, 245 nm (ϵ 24 500, 7300); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 3.76 (s, 3H), 3.79 (s, 3H), 4.23, 4.26 (2 × d, J = 13.7 Hz, 2 × 1H), 4.46 (s, 1H), 4.59, 4.72, 5.07, 5.09 (4 × d, J = 13.7 Hz, 4 × 1H), 5.17 (s, 1H), 5.71 (d, J = 8.3 Hz, 1H), 6.45 (s, 1H), 6.82, 6.85 (2 × d, J = 8.8 Hz, 2 × 2H), 7.10 (d, J = 8.3 Hz, 1H), 7.22, 7.48 (2 × d, J = 8.8 Hz, 2 × 2H); ^{13}C NMR ($CDCl_3$) δ −5.61, −5.57, 18.1, 25.6, 43.5, 55.0, 58.0, 70.4, 85.0, 90.8, 98.9, 102.2, 113.6, 113.7, 128.8, 129.3, 129.5, 129.6, 130.6, 136.5, 150.2, 159.0, 159.3, 162.2, 162.4; FAB-MS *m*/*z* 603 ([M + Na^+] 100%); HRMS ($C_{31}H_{40}N_2O_7SiNa$) calcd 603.2502, found 603.2509.

1-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3,4-*C*-(difluoromethylene)-2-*O*-(4-methoxybenzyl)-α-L-arabinofuranosyl]-3-(4-methoxybenzyl)uracil[16] **(9a) and 1-[5-*O*-(*tert*-Butyldimethylsilyl)-3-deoxy-3,4-*C*-(difluoromethylene)-2-*O*-(4-methoxybenzyl)-*β*-D-ribofuranosyl]-3-(4-methoxybenzyl)uracil**[16] **(10a).** Powdered NaI (30.0 g, 200 mmol) was stirred and heated (170 °C, oil bath) under vacuum for 1 h in a flask (500 mL) equipped with a Teflon valve, then allowed to cool to ambient temperature. $(CF_3)_2Hg$ (17.4 g, 50.8 mmol) in dried THF (50 mL) and **8** (15.0 g, 25.4 mmol) were injected through a septum (under N_2). The reaction mixture was heated at 70 °C for 24 h, and volatiles were evaporated. Chromatography (EtOAc/hexanes, 1:9 → 1:6) gave **9a** (7.4 g, 46%): ^{1}H NMR ($CDCl_3$) δ 0.09, 0.11 (2 × s, 2 × 3H), 0.93 (s, 9H), 2.27 (d, J = 15.6 Hz, 1H), 3.74, 3.76 (2 × s, 2 × 3H), 3.87 (d, J = 12.7 Hz, 1H), 4.04−4.08 (m, 2H), 4.40, 4.50 (2 × d, J = 12.2 Hz, 2H), 5.02, 5.07 (2 × d, J = 13.7 Hz, 2H), 5.68, 7.03 (2 × d, J = 8.3 Hz, 2 × 1H), 6.51 (d, J = 6.3 Hz, 1H), 6.68, 6.82, 7.06 7.49 (4 × m, 4 × 2H); ^{19}F NMR ($CDCl_3$) δ 129.5 (dd, J = 15.0, 168.7 Hz, 1F), 148.8 (d, J = 168.8 Hz, 1F); FAB-MS *m*/*z* 631 ([M + H^+] 40%), 121 (100%); HRMS ($C_{32}H_{41}F_2N_2O_7Si$) calcd 631.2645, found 631.2654.

Further elution of the column with EtOAc/hexanes (1:1) gave **10a** (6.0 g, 37%): ^{1}H NMR ($CDCl_3$) δ 0.05, 0.06 (2 × s, 2 × 3H), 0.88 (s, 9H), 2.27 (dd, J = 6.8, 14.6 Hz, 1H), 3.75−3.80 (m, 1H), 3.760, 3.764 (2 × s, 2 × 3H), 4.11 (dd, J = 3.4, 12.2 Hz, 1H), 4.44−4.54 (m, 3H), 5.03, 5.05 (2 × d, J = 13.7 Hz, 2H), 5.69 (d, J = 7.8 Hz, 1H), 5.97−6.00 (m, 1H), 6.74, 6.83, 7.11, 7.48 (4 × m, 4 × 2H), 7.29 (d, J = 7.8 Hz, 1H); ^{19}F NMR ($CDCl_3$) δ 133.3 (dd, J = 15.0, 170.9 Hz, 1F), 147.6 (d, J = 170.9 Hz, 1F); FAB-MS *m*/*z* 653 ([M + Na^+] 10%), 141 (100%); HRMS ($C_{32}H_{40}F_2N_2O_7$-SiNa) calcd 653.2465, found 653.2468.

1-[2,5-Di-*O*-acetyl-3-deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl]-3-(4-methoxybenzyl)uracil (9c). A solution of CAN (15.4 g, 28.1 mmol) in H_2O (20 mL) was added to a stirred solution of **9a** (6.0 g, 9.4 mmol) in CH_3CN (200 mL). Stirring was continued at ambient temperature for 2.5 h, H_2O was added, and the solution was extracted (EtOAc, 3 × 100 mL). The combined organic phase was concentrated in vacuo, and chromatography (EtOAc/hexanes, 1:4 → EtOAc) gave **9b** (3.6 g, 97%). This material was dissolved in pyridine (10 mL) and Ac_2O (5 mL), and the solution was stirred for 17 h at ambient temperature. Volatiles were evaporated in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:2 → EtOAc) to give **9c** as a yellow oil (3.12 g, 72%): UV max 223, 259 nm (ϵ 13 300, 8800), min 216, 240 nm (ϵ 12 800, 5800); ^{1}H NMR ($CDCl_3$) δ 2.02, 2.08 (2 × s, 2 × 3H), 2.39 (d, J = 15.1 Hz, 1H), 3.69 (s, 3H), 4.37−4.45 (m, 2H), 4.86, 4.99 (2 × d, J = 13.7 Hz, 2 × 1H), 5.20 (d, J = 6.3 Hz, 1H), 5.78 (d, J = 8.3 Hz, 1H), 6.47 (d, J = 6.3 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 7.19 (d, J = 8.3 Hz, 1H), 7.30 (d, J = 8.8 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ 129.3 (dd, J = 15.0, 170.9 Hz, 1F), 149.7 (d, J = 170.9 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.6, 33.3 (t, J = 12.1 Hz), 43.8, 55.1, 59.4, 68.0 (t, J = 11.9 Hz), 74.7, 95.5 (d, J = 3.7 Hz), 103.6, 110.4 (t, J = 297.7 Hz), 113.6, 128.5, 130.3, 136.0 (d, J = 7.3 Hz), 150.7, 159.0, 161.8, 169.4, 170.3; FAB-MS *m*/*z* 503 ([M + Na^+] 100%); HRMS ($C_{22}H_{22}F_2N_2O_8Na$) calcd 503.1245, found 503.1242.

1-[2,5-Di-*O*-acetyl-3-deoxy-3,4-*C*-(difluoromethylene)-*β*-D-ribofuranosyl]-3-(4-methoxybenzyl)uracil (10c). Treatment of **10a** (7.4 g, 11.6 mmol) according to the procedure described for **9a** → **9b** → **9c** gave **10c** as a yellow oil (3.28 g; 59%, two steps). UV max 223, 258 nm (ϵ 13 600, 8 800), min 217, 240 nm (ϵ 13 100, 5 800); ^{1}H NMR ($CDCl_3$) δ 2.03, 2.05 (2 × s, 2 × 3H), 2.69 (dd, J = 14.6, 7.0 Hz, 1H), 3.70 (s, 3H), 4.37 (dd, J = 13.2, 1.8 Hz, 1H), 4.51 (d, J = 13.2 Hz, 1H), 4.92, 4.96 (2 × d, J = 13.6 Hz, 2 × 1H), 5.50 (d, J = 3.7 Hz, 1H), 5.71 (d, J = 8.0 Hz, 1H), 5.74 (m, 1H), 6.75 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ 133.6 (dd, J = 14.9, 170.9 Hz, 1F), 148.7 (d, J = 170.9 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 20.57, 20.63, 33.1 (t, J = 12.6 Hz), 43.6, 55.2, 59.7, 71.6 (t, J = 11.5 Hz), 77.4, 96.7, 102.8, 111.5 (dd, J = 294.5, 306.7 Hz), 113.7, 128.4, 130.6, 139.6, 150.4, 159.1, 162.0, 170.2, 170.5; FAB-MS *m*/*z* 481 ([M + H^+] 100%); HRMS ($C_{22}H_{23}F_2N_2O_8$) calcd 481.1422, found 481.1418.

1-[3-Deoxy-3,4-*C*-(difluoromethylene)-*β*-D-ribofuranosyl]uracil (10e). A solution of CAN (12.3 g, 22.5 mmol) in H_2O (15 mL) was added to a stirred solution of **10c** (2.7 g, 5.63 mmol) in CH_3CN (150 mL), and stirring was continued at 70 °C for 1.5 h. H_2O was added, the mixture was extracted (EtOAc, 3 × 100 mL), and volatiles were evaporated in vacuo from the combined organic phase. The residue was chromatographed (EtOAc/hexanes, 1:3 → EtOAc) to give crude 1-[2,5-di-*O*-acetyl-3-deoxy-3,4-*C*-(difluoromethylene)-*β*-D-ribofuranosyl]uracil (**10d**, 1.5 g). This material was added to a stirred solution of 1,4-dioxane (18 mL) and 30% NH_3/H_2O (5 mL), and stirring was continued overnight. Volatiles were evaporated, and the residue was dissolved (H_2O, 20 mL) and applied to a column of Dowex 1 × 2 (OH^-) resin (in H_2O). Elution [H_2O → MeOH → AcOH/MeOH (1:10)] and evaporation of volatiles from UV-absorbing fractions gave **10e** (740 mg; 48%, 2 steps) as a yellow syrup. An analytically pure sample was obtained after several recrystallizations (EtOH): mp 180−182 °C; UV max 259 nm (ϵ 9600), min 229 nm (ϵ 2800); ^{1}H NMR (CD_3OD) δ 2.43 (d, J = 16.6 Hz, 1H), 3.89 (d, J = 13.2 Hz, 1H), 3.98 (dd, J = 13.2, 2.9 Hz, 1H), 4.52 (d, J = 6.3 Hz, 1H), 5.79 (d, J = 7.8 Hz, 1H), 6.33 (d, J = 6.3 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H); ^{19}F NMR (CD_3OD) δ 129.7 (dd, J = 16.0, 168.7 Hz, 1F), 148.9 (d, J = 168.7 Hz, 1F); ^{13}C NMR (CD_3OD) δ 36.2 (t, J = 11.4 Hz), 59.1, 72.2 (t, J = 11.8 Hz), 76.1, 98.6 (d, J = 4.6 Hz), 104.0, 113.6 (t, J = 296.0 Hz), 141.3 (d, J = 6.9 Hz), 152.4, 165.8; EI-MS *m*/*z* 276 ([M^+] 2%); HRMS ($C_{10}H_{10}F_2N_2O_5$) calcd 276.0557, found 276.0563. Anal. Calcd for $C_{10}H_{10}F_2N_2O_5$: C, 43.49; H, 3.65; N 10.14. Found: C, 43.31; H, 3.86; N 9.96.

1-[3-Deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl]-uracil (9e). Treatment of **9c** (3.1 g, 6.46 mmol) with CAN followed by ammonolysis (as described for **10c** → **10e**) gave **9e** (1.19 g; 67%, 2 steps) as a colorless oil. Purification by PTLC (EtOAc/MeOH, 7:1) gave **9e**: UV max 259 nm (ϵ 9600), min 229 nm (ϵ 3000); ^{1}H NMR (Me_2CO-d_6) δ 2.65 (dd, J = 6.8, 16.2 Hz, 1H),

3.84 (d, J = 13.2 Hz, 1H), 4.01 (dd, J = 13.2, 3.4 Hz, 1H), 5.10−5.13 (m, 1H), 5.70 (d, J = 8.3 Hz, 1H), 5.84 (dd, J = 2.4, 4.9 Hz, 1H), 7.74 (d, J = 8.3 Hz, 1H); ^{19}F NMR (Me_2CO-d_6) δ 132.8 (dd, J = 168.7, 17.1 Hz, 1F), 146.4 (d, J = 168.7 Hz, 1F); ^{13}C NMR (Me_2CO-d_6) δ 32.6 (t, J = 11.7 Hz), 58.2, 73.9 (t, J = 11.2 Hz), 76.8, 94.5 (d, J = 5.5 Hz), 103.5, 114.8 (dd, J = 292.2, 306.9 Hz), 142.6, 151.5, 164.2; FAB-MS m/z 277 ([M + H$^+$] 60%), 140 (100%); HRMS ($C_{10}H_{11}F_2N_2O_5$) calcd 277.0636, found 277.0651.

1-[3-Deoxy-3,4-*C*-(difluoromethylene)-*β*-D-ribofuranosyl]cytosine Hydrobromide (10g·HBr). Et_3N (6.17 mL, 4.49 g, 44.5 mmol) was added dropwise to a cooled (∼0 °C) stirred mixture of 1,2,4-triazole (3.22 g, 46.7 mmol), $POCl_3$ (0.94 mL, 1.50 g, 9.8 mmol), and MeCN (28 mL). A solution of **10d** (1.6 g, 4.4 mmol) in MeCN (18 mL) was added, and stirring was continued for 2 h at ambient temperature. Et_3N (4.29 mL, 3.13 g, 30.9 mmol) and H_2O (1.7 mL) were added, and stirring was continued for 10 min. Volatiles were evaporated at ambient temperature, and the residue was partitioned [ice-cold, saturated $NaHCO_3/H_2O$ (100 mL)//CH_2Cl_2 (100 mL)]. The aqueous phase was extracted (CH_2Cl_2, 100 mL), and the combined organic phase was washed (brine, 50 mL) and dried ($MgSO_4$). Volatiles were evaporated to give 1-[2,5-di-*O*-acetyl-3-deoxy-3,4-*C*-(difluoromethylene)-*β*-D-ribofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2-one (**10f**) (1.64 g, 90%) as a yellow syrup: FAB-MS m/z 434 ([M + Na$^+$] 100%); HRMS ($C_{16}H_{15}F_2N_5O_6$Na) calcd 434.0879, found 434.0880.

NH_3/H_2O (30%, 6 mL) was added to a stirred solution of this material in 1,4-dioxane (18 mL), and stirring was continued for 12 h at ambient temperature. Volatiles were evaporated, and the residue was dissolved (H_2O, 20 mL) and applied to a column of Dowex 1 × 2 (OH$^-$) resin (in H_2O). Elution [H_2O, MeOH] and evaporation of volatiles from UV-absorbing fractions gave **10g** (870 mg) as a yellow syrup. A solution of this material in MeOH was treated with 5% HBr/H_2O and volatiles were evaporated. The red residue was chromatographed on silica gel (EtOAc → EtOAc/MeOH, 2:1), and crystallized (EtOH) to give **10g**·HBr (870 mg, 61%) as a white powder: mp 218−220 °C; UV max 278 nm (ϵ 10 000), min 245 nm (ϵ 4200); ^{1}H NMR (CD_3OD) δ 2.61 (d, J = 15.1, 7.3 Hz, 1H), 3.88 (d, J = 13.2 Hz, 1H), 3.98 (dd, J = 13.2, 3.4 Hz, 1H), 4.97−5.00 (m, 1H), 5.82 (dd, J = 2.4, 4.4 Hz, 1H), 6.18, 8.13 (2 × d, J = 7.8 Hz, 2 × 1H); ^{19}F NMR (CD_3OD) δ 133.1 (dd, J = 15.0, 170.9 Hz, 1F), 147.2 (d, J = 170.9 Hz, 1F); ^{13}C NMR (CD_3OD) δ 33.3 (t, J = 11.8 Hz), 58.6, 75.2 (t, J = 11.4 Hz), 77.9, 95.8, 96.1 (d, J = 4.8 Hz), 114.7 (dd, J = 291.4, 305.9 Hz), 147.3, 148.5, 161.5; EI-MS m/z 276 ([M + H$^+$] 60%); HRMS ($C_{10}H_{12}F_2N_3O_4$) calcd 276.0796, found 276.0800. Anal. Calcd for $C_{10}H_{12}BrF_2N_3O_4$: C, 33.73; H, 3.40; N, 11.80. Found: C, 33.77; H, 3.55; N, 11.86.

1-[3-Deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl]cytosine (9g). Et_3N (6.95 mL, 5.05 g, 50.1 mmol) was added dropwise to a cooled (∼0 °C) stirred mixture of 1,2,4-triazole (3.62 g, 52.5 mmol), $POCl_3$ (1.06 mL, 1.69 g, 11.0 mmol), and MeCN (31 mL). A solution of 1-[2,5-di-*O*-acetyl-3-deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl]uracil **9d** (1.8 g, 5.0 mmol) in MeCN (20 mL) was added, and stirring was continued for 2 h at ambient temperature. Et_3N (4.83 mL, 3.52 g, 34.8 mmol) and H_2O (1.94 mL) were added, and stirring was continued for 10 min. Volatiles were evaporated at ambient temperature, and the residue was partitioned [ice-cold saturated $NaHCO_3/H_2O$ (100 mL)//CH_2Cl_2 (100 mL)]. The aqueous phase was extracted (CH_2Cl_2, 100 mL), and the combined organic phase was washed (brine, 50 mL) and dried ($MgSO_4$). Volatiles were evaporated to give a yellow oil (1.7 g). Chromatography (EtOAc/hexanes, 1:2 → 2:1) gave a mixture of unidentified products (mainly two, 330 mg) and 1-[2,5-di-*O*-acetyl-3-deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2-one (**9f**) (940 mg, 46%) as a colorless syrup: FAB-MS m/z 434 ([M + Na$^+$] 13%), 321, 239 (100%); HRMS ($C_{16}H_{15}F_2N_5O_6$Na) calcd 434.0879, found 434.0880.

NH_3/H_2O (30%, 6 mL) was added to a stirred solution of this material in 1,4-dioxane (18 mL), and stirring was continued for 12 h at ambient temperature. Volatiles were evaporated, and the residue was dissolved (H_2O, 20 mL) and applied to a column of Dowex 1 × 2 (OH$^-$) resin (in H_2O). Elution [H_2O, MeOH (1 L)] and evaporation of volatiles from UV-absorbing fractions gave a residue that was chromatographed (EtOAc → EtOAc/MeOH, 10:1) to give **9g** (490 mg, 77%) as colorless crystals: mp >250 °C dec; UV max 242, 269 nm (ϵ 8500, 8300), min 225, 257 nm (ϵ 7100, 8000); ^{1}H NMR (CD_3OD) δ 2.40 (d, J = 16.6 Hz, 1H), 3.89 (d, J = 13.7 Hz, 1H), 3.96 (dd, J = 13.7, 3.4 Hz, 1H), 4.56 (d, J = 5.9 Hz, 1H), 5.93 (d, J = 7.3 Hz, 1H), 6.36 (d, J = 5.9 Hz, 1H), 7.54 (d, J = 7.3 Hz, 1H); ^{19}F NMR (CD_3OD) δ 130.0 (dd, J = 17.1, 168.7 Hz, 1F), 148.9 (d, J = 168.7 Hz, 1F); ^{13}C NMR (CD_3OD) δ 36.5 (t, J = 11.8 Hz), 59.2, 72.8 (t, J = 11.3 Hz), 77.2, 97.0, 100.1 (d, J = 5.3 Hz), 113.7 (t, J = 296.0 Hz), 141.7 (d, J = 6.1 Hz), 158.6, 167.7; EI-MS m/z 298 ([M + Na$^+$] 60%), 242 (100%); HRMS ($C_{10}H_{11}F_2N_3O_4$Na) calcd 298.0615, found 298.0632. Anal. Calcd for $C_{10}H_{11}F_2N_3O_4$: C, 43.64; H, 4.03; N, 15.27. Found: C, 43.57; H, 4.16; N, 15.33.

5-*O*-Benzoyl-3-deoxy-1,2-*O*-isopropylidene-3,4-*C*-(difluoromethylene)-*β*-L-arabinofuranose (13). A solution of 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-*O*-triflyl-α-D-xylofuranose[19] (**11**) (28.0 g, 62.2 mmol) and DBU (14.2 g, 13.9 mL, 93.3 mmol) in toluene (100 mL) was stirred for 1 h at 80 °C. Volatiles were evaporated in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:6) to give 5-*O*-benzoyl-1,2-*O*-isopropylidene-3-deoxy-α-D-*glycero*-pent-3-enofuranose (**12**) (15.0 g, 87%) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.46, 1.49 (2 × s, 2 × 3H), 4.83−4.90 (m, 2H), 5.29−5.34 (m, 2H), 6.12 (d, J = 5.4 Hz, 1H), 7.43−8.06 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.5, 27.7, 58.8, 83.1, 100.5, 106.2, 112.0, 128.1, 129.2, 129.4, 133.0, 156.2, 165.3; FAB-MS m/z 277 ([M + H$^+$] 15%), 105 (100%); HRMS ($C_{15}H_{17}O_5$) calcd 277.1076, found 277.1059.

A solution of NaI (39.1 g, 260.9 mmol) and $(CF_3)_2Hg$ (22.1 g, 65.2 mmol) in THF (60 mL) was added to this material (15.0 g, 54.3 mmol), and the mixture was stirred and heated for 2 h at 70 °C in a sealed flask. The resulting brown solution was concentrated, then chromatographed (EtOAc/hexanes, 1:6 → 1:2) to give **13** (17.5 g, 99%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.35, 1.49 (2 × s, 2 × 3H), 2.58 (d, J = 16.1 Hz, 1H), 4.73 (dd, J = 2.9, 13.2 Hz, 1H), 4.83 (d, J = 13.2 Hz, 1H), 4.88 (d, J = 3.9 Hz, 1H), 5.76 (t, J = 3.9 Hz, 1H), 7.41−7.46 (m, 2H), 7.54−7.59 (m, 1H), 8.06−8.10 (m, 2H); ^{19}F NMR ($CDCl_3$) δ 136.6 (dd, J = 17.1, 173.0 Hz, 1F), 150.8 (d, J = 173.0 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 27.3, 28.1, 32.6 (t, J = 11.1 Hz), 60.0, 69.5 (t, J = 11.1 Hz), 81.2, 108.4 (d, J = 7.6 Hz), 110.7 (dd, J = 296.8, 302.1 Hz), 115.4, 128.3, 129.3, 129.8, 133.2, 156.1; FAB-MS m/z 349 ([M + Na$^+$] 80%), 269 (100%); HRMS ($C_{16}H_{16}F_2O_5$Na) calcd 349.0864, found 349.0864.

1-[3-Deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl]adenine (α-L-16). A mixture of **13** (15 g, 46 mmol), AcOH (138 mL), Ac_2O (28 mL), and concentrated H_2SO_4 (4.5 mL) was stirred for 8 h at ambient temperature. The solution was partitioned [EtOAc (300 mL)/H_2O (500 mL)], and the aqueous phase was extracted (EtOAc, 2 × 200 mL). The combined organic phase was dried ($MgSO_4$), concentrated, and chromatographed (EtOAc/hexanes, 1:6 → 1:1) to give 1,2-di-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3,4-*C*-(difluoromethylene)-L-arabinofuranose (**14**) (9.4 g, 55%). $SnCl_4$ (17.3 mL, 39.8 g, 152.4 mmol) was added to a cold (−20 °C) stirred mixture of this material and adenine (6.86 g, 50.8 mmol) in dried CH_3CN (160 mL). The resulting clear, dark solution was stirred and heated for 30 min at 80 °C, cooled to ambient temperature, and washed with saturated $NaHCO_3/H_2O$. Volatiles were evaporated from the organic layer, and the residue was chromatographed (EtOAc → EtOAc/MeOH, 10:1) to give 9-(2-*O*-acetyl-5-*O*-benzoyl-3-deoxy-3,4-*C*-(difluoromethylene)-α-L-arabinofuranosyl)adenine (**15**) (3.71 g, 33%). A solution of this material (1.5 g, 3.37 mmol) in 1,4-dioxane (20 mL) and NH_3/H_2O (30%, 5 mL) was stirred overnight at ambient temperature. Volatiles were evaporated, and the residue was chromatographed (Dowex 1 × 2 [OH$^-$]; (MeOH → AcOH/MeOH, 1:4)). UV-absorbing fractions were concentrated

and chromatographed on silica gel (EtOAc → EtOAc/MeOH, 10:1) to give α-L-**16** (740 mg, 73%): $[\alpha]^{24}_D$ −36.8° (*c* 0.57, MeOH); UV max 259 nm (ϵ 14 000), min 227 nm (ϵ 2500); ^{1}H NMR (CD_3OD) δ 2.53 (d, J = 16.1 Hz, 1H), 3.90 (d, J = 13.2 Hz, 1H), 4.03 (dd, J = 3.4, 13.2 Hz, 1H), 5.03 (s, J = 6.3 Hz, 1H), 6.39 (d, J = 6.3 Hz, 1H), 8.215, 8.223 (2 × s, 2 × 1H); ^{19}F NMR (CD_3OD) δ 130.4 (dd, J = 17.1, 166.6 Hz, 1F), 150.0 (d, J = 166.6 Hz, 1F). ^{13}C NMR (DMSO-d_6) δ 34.9 (t, J = 10.7 Hz), 57.4, 70.5 (t, J = 11.4 Hz), 73.8, 95.3 (d, J = 6.1 Hz), 112.4 (dd, J = 293.7, 299.1 Hz), 118.5, 138.6, 149.8, 153.1, 156.1; EI-MS *m*/*z* 299 ([M^+] 7%), 242, 177, 148 (100%); HRMS ($C_{11}H_{11}F_2N_5O_3$) calcd 299.0830, found 299.0826.

1-[3-Deoxy-3,4-*C*-(difluoromethylene)-α-D-arabinofuranosyl]-adenine (α-D-16). L-Xylose was subjected to the identical sequence used for conversion of D-xylose to α-L-**16**. NMR and mass spectra of the enantiomers of compounds **11**−**16** were identical with those described; α-D-**16**: $[\alpha]^{24}_D$ 34.2° (*c* 0.38, MeOH).

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Supporting Information Available: General experimental details, NMR spectra, X-ray CIF data for **9e** (code XL555) and **9g** (code XL567). This material is available free of charge via the Internet at http://pubs.acs.org.

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