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Addition of Difluorocarbene to 4′,5′-Unsaturated Nucleosides: Synthesis and Deoxygenation Reactions of Difluorospirocyclopropane Nucleosides[1]

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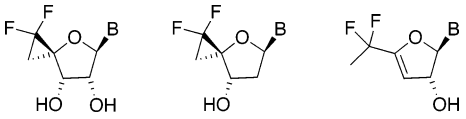

Synthetic routes to 4′-(2,2-difluorospirocyclopropane) analogues of adenosine, cytidine, and uridine are described. Treatment of 2′,3′-*O*-isopropylidene-4′,5′-unsaturated compounds derived from adenosine and uridine with difluorocarbene (generated from $PhHgCF_3$ and NaI) gave diastereomeric mixtures of the 2,2-difluorospirocyclopropane adducts. Stereoselectivity resulting from hindrance by the isopropylidene group favored addition at the β face. Removal of base and sugar protecting groups gave new difluorospirocyclopropane nucleoside analogues. The protected uridine analogue was converted into its cytidine counterpart via a 4-(1,2,4-triazol-1-yl) intermediate. Stannyl radical-mediated deoxygenation of the 3′-*O*-TBS-2′-thionocarbamate derivatives gave the 2′-deoxy products of direct hydrogen transfer. In contrast, identical treatment of the 2′-*O*-TBS-3′-thionocarbamate isomers resulted in opening of the vicinal difluorocyclopropane ring upon generation of a C3′ radical followed by homoallylic hydrogen transfer to give 4′-(1,1-difluoroethyl)-3′,4′-unsaturated nucleoside derivatives. Structural aspects and biological effect considerations are discussed.

Introduction

Relationships between structure and biological response activity are fundamental considerations in medicinal chemistry. Regioisomers, diastereomers, and enantiomers usually have increasingly subtle structural differences, but the contrasts in biological response effects can be striking. Conformational preferences are in an even more muted realm of structural effects. Small but meaningful binding energy differences can exist among molecular conformer ranges and targeted binding sites. Nucleic acid component analogues have been employed clinically for many decades, and major favorable drug versus side effects differences exist between nucleoside regioisomers,[2] diastereomers,[3] and enantiomers.[4]

Eyring, Robins, and co-workers systematically investigated nucleoside conformational effects with CD and ORD spectroscopy.[5] However, the pseudorotational mobility of furanosyl rings coupled with small energy differences among rotamers limited the analyses to tentative identification of rotational conformation populations about the glycosyl bond. Altona and Sundralingham defined pseudorotational parameters and correlated them with highly populated solid-state nucleoside/nucleotide conformations.[6] Altona,[7] Chattopadhyaya,[8] Marquez,[9] and others have refined and added additional parametrization to the fundamental

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Altona−Sundralingham[6] approach for analysis of predominant conformer populations of furanosyl derivatives.

Nucleoside analogues normally are prodrug forms of active pharmaceutical agents. They must undergo interactions with proteins in cellular and compartmental membranes (including active and/or facilitated transfer by transmembrane nucleoside transporters), nucleoside kinases, and mono- and/or dinucleotide kinases and then bind with target proteins (e.g., DNA polymerases, reverse transcriptases, and/or other nucleoside triphosphate metabolizing enzymes). It would be fortuitous if binding studies with a specific target protein (without consideration of the requisite multiple interactions with other proteins in the prior transport and activation pathways) gave strong positive correlations with biological response activities attributable to selective inhibition of the targeted protein. Therefore, continuing—and successful—searches for new nucleoside drug candidates necessarily involve intuitive design, synthesis, and empirical testing of novel candidate structures.

Marquez and co-workers have prepared and evaluated numerous "carbocyclic nucleosides" with a cyclopentane ring in place of the furanosyl moiety.[10] Bicyclo[3.1.0]hexane ring analogues of carbocyclic nucleosides have restricted cyclopentane (furanose surrogate) ring conformations. Selective interactions of such analogues with enzymes have been noted, although it is impossible to rigorously exclude binding effects that might result from the fused cyclopropane moiety that accompany conformational restriction of the cyclopentane ring.[11] A favorable pseudorotational bias can be amplified with (deoxy)oligonucleotide structures in which "locked-ring" conformations are produced in the monomers by generation of analogues with bicyclo[*x*,*y*,*z*] surrogates of the furanosyl moiety. Altered binding effects resulting from restricted conformations have been measured.[12]

Nucleoside analogues containing a difluorocyclopropane moiety deserve attention because simple nucleobase derivatives have shown biological activity.[13,14] Conformational constraints in fused or spiro modifications might contribute to increased potency. Fluorine substituents enhance hydrophobicity, and their potent electronegativity might contribute to long-range electronic effects such as increased anomeric bond stability. They also can function as precursors for strategically fluorinated ring-opened derivatives. Convenient methods for their preparation would be advantageous.

Fluorocarbenes have singlet ground states and usually add stereospecifically to carbon−carbon double bonds without concomitant insertion into carbon−hydrogen bonds.[15] A number of methods have been reported for synthesis of *gem*-difluorocyclopropanes via carbene addition to C=C bonds of simple, volatile alkenes.[15−18] However, those alkenes were often used in large excess to trap the weakly electrophilic difluorocarbene, and harsh reaction conditions and/or carbene sources that are impractical from a preparative standpoint were employed. Seyferth's reagent [phenyl(trifluoromethyl)mercury] was chosen as our source of difluorocarbene[19] because it is a nonhygroscopic solid that permits mild reaction conditions and easy workup. However, its preparation is not trivial,[19b,20] and appropriate *CAUTION* should be exercised with organomercury compounds. Cech and co-workers had used bis(trifluoromethyl)-mercury in their studies on difluorocarbene insertion into the oxygen−silicon bond of 4-*O*-silylated nucleosides.[21]

Results and Discussion

Our strategy for synthesis of difluorocyclopropanated nucleosides involved the preparation of suitably protected vinyl ether precursors[22] followed by addition of difluorocarbene to the electron-rich double bond[23] and deprotection. Protecting groups would serve two roles: (1) replace mobile hydrogen atoms that are detrimental to the generation and lifetime of difluorocarbene and (2) exert a β-facial stereochemical bias for the carbene addition. Synthesis of the uridine and cytidine derivatives commenced with 1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil[24] (**1**) (Scheme 1). Attempted addition of difluorocarbene to **1** failed, presumably because of the presence of the acidic N3 proton. The 3-benzoyl derivative **2** underwent carbene addition smoothly to give the diastereomers **3a**/**3b** (5:1) in 91% yield. Elucidation of the structure of the major isomer **3a** by X-ray crystallography (Supporting Information) confirmed that the addition of difluorocarbene occurred predominantly at the less hindered β face of the furanose ring. The isopropylidene protecting group was removed, and the major adduct **4** was separated from the mixture. Mild basic hydrolysis gave the crystalline uracil nucleoside analogue **5** (63% overall). Aqueous ammonolysis of **3a** removed the benzoyl group to give **6** (99%), which was treated with 1,2,4-triazole/phosphoryl chloride/triethylamine in acetonitrile[25] to give the 4-(1,2,4-triazol-1-yl) derivative **7** (97%). Treatment of

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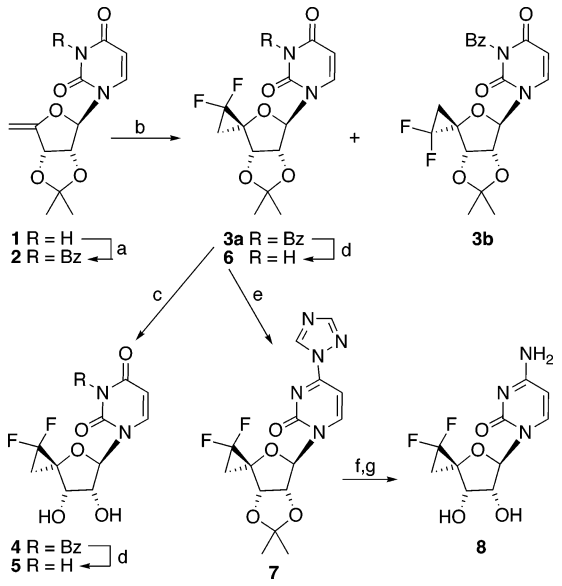
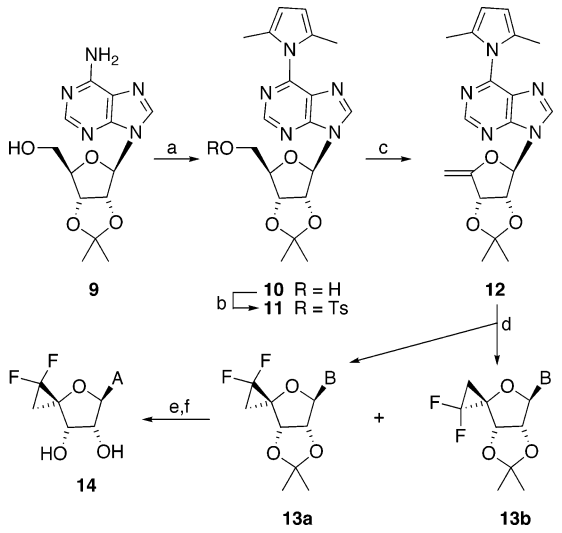
SCHEME 1[a]



[a] Reagents and conditions: (a) $BzCl/Et_3N/CH_2Cl_2$; (b) $PhHgCF_3/NaI/DME/90$ °C; (c) $HCl/H_2O/THF$; (d) $NH_3/H_2O/MeOH$; (e) 1,2,4-triazole/$POCl_3/Et_3N/CH_3CN$; (f) NH_3/H_2O/1,4-dioxane; (g) TFA/H_2O (9:1).

SCHEME 2[a]



[a] Reagents and conditions: (a) 2,5-hexanedione/150 °C; (b) TsCl/pyridine/−20 → 15 °C; (c) KO^{t}Bu/THF/0 °C; (d) $PhHgCF_3$/NaI/DME/90 °C; (e) TFA/H_2O (9:1); (f) $NaHCO_3/H_2O$.

7 with aqueous ammonia followed by removal of the isopropylidene group with TFA/H_2O (9:1), neutralization of the TFA salt, and extraction gave the cytosine nucleoside analogue **8**. The hydrochloride−hemihydrate salt of **8** (79%, overall for three steps) was obtained by acidification with 5% HCl/H_2O.

Synthesis of the adenosine analogue **14** (Scheme 2) became our next focus. A procedure reported[26] for *N*,*O*-peracylation of 2′,3′-*O*-isopropylideneadenosine (**9**) followed by selective deprotection of O5′ was not readily reproducible, and other methods for transient protection−deprotection were not pursued because of the sensitivity of the second *N*-acyl group. Prolonged heating of **9** in 2,5-hexanedione gave the 2,5-dimethylpyrrole derivative

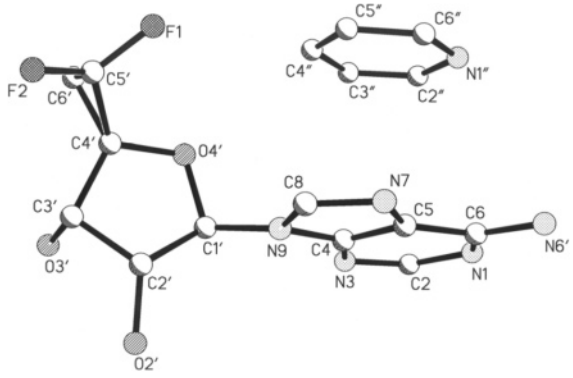


FIGURE 1. X-ray crystal structure of the monomeric **14**·pyridine unit.

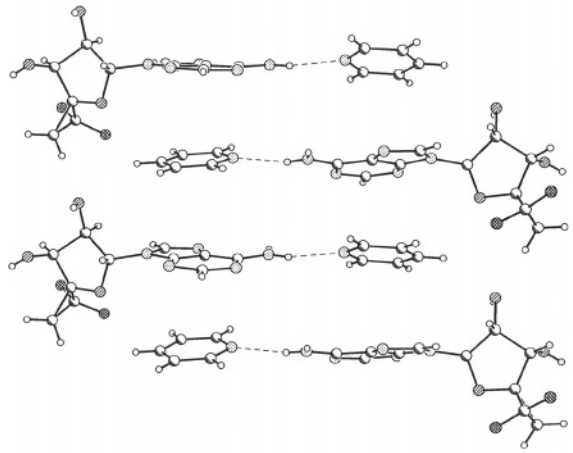


FIGURE 2. X-ray crystal structure of the supramolecular **14**·pyridine complex.

10[27] in reasonable yield (56%). The 2,5-dimethylpyrrole substituent at C6 is stable in the presence of basic and organomercury reagents, but it is easily cleaved with release of the 6-amino group in TFA/H_2O.[27] Tosylation of **10** in pyridine at low temperature followed by immediate subjection of the sensitive tosylate **11** to base-promoted elimination gave **12**. Addition of difluorocarbene to the enol ether **12** proceeded less readily (∼60%) but with higher diastereoselectivity (**13a**/**13b**, ∼15:1, ^{19}F NMR) than had the analogous reaction with **2**. Starting **12** that remained in the product mixture (∼20%) could be converted into **13** by addition of fresh $PhHgCF_3$, but this was not advantageous because product loss (presumably resulting from complexation with mercury species) occurred during each treatment. Target compound **14** was obtained by hydrolysis (TFA/H_2O) of the crude **13a**/**13b** mixture followed by neutralization and chromatography. Crystallization of **14** did not occur with the usual solvents, but yellow-green blades (**14**·pyridine) were obtained from a pyridine-containing solution. X-ray analysis identified the structure (Figures 1 and 2), which includes hydrogen bonding between the amino group of **14** and the pyridine nitrogen atom (N−N distance: 3.6 Å, Figure 2) and π-stacking interactions between pyridine and the imidazole ring of the nucleobase. The resulting supramolecular "ladder" has parallel strands of alternating rings—a structural feature reminiscent of DNA. The crystalline complex retained pyridine, even upon prolonged heating at 90 °C in vacuo, and melting/decomposition in a capillary tube began at ∼160 °C. Analogous

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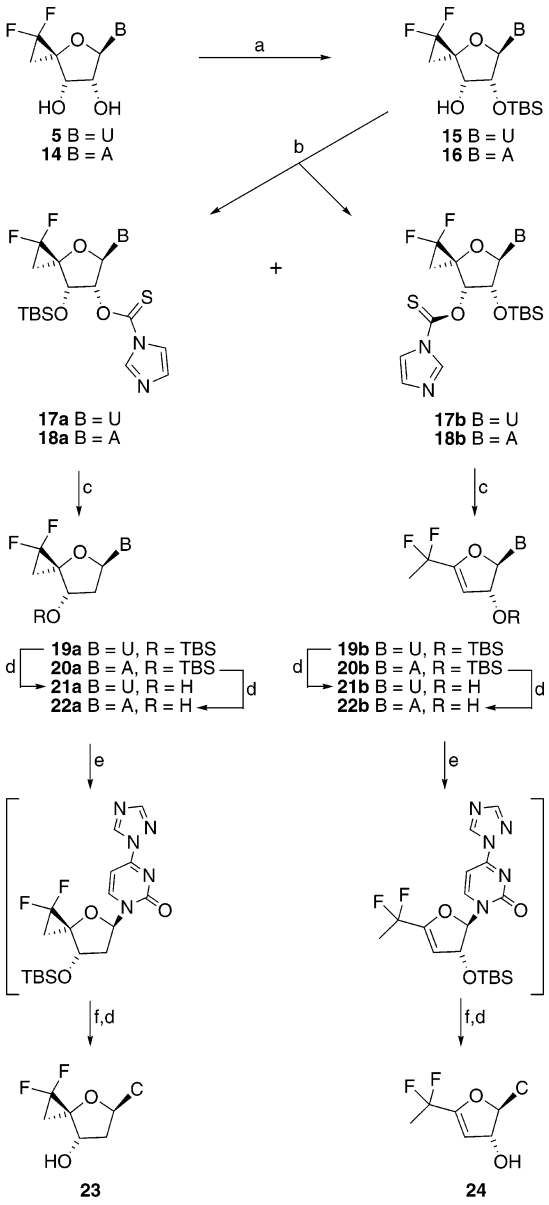
SCHEME 3[a]



[a] Reagents and conditions: (a) TBS-Cl/pyridine; (b) Im_2CS/toluene/70 °C; (c) Bu_3SnH/AIBN/toluene/90 °C; (d) Bu_4NF/THF; (e) 1,2,4-triazole/$POCl_3$/Et_3N/acetonitrile; (f) NH_3/H_2O/1,4-dioxane.

treatment of the cytosine compound **8** did not result in formation of such a pyridine complex.

Transformations into deoxygenated derivatives were then investigated. Diols **5** and **14** were treated with TBS chloride in pyridine, and the 2′-*O*-TBS ethers **15** (98%) and **16** (72%) were isolated (Scheme 3). Treatment of **15** and **16** with 1,1′-thiocarbonyldiimidazole in hot toluene gave the O2′ and O3′ thiocarbamates **17a**/**18a** and **17b**/**18b** (∼1:2 ratios), respectively. The imidazole byproduct apparently catalyzed O2′/O3′ equilibration of the TBS groups prior to thiocarbamate formation. Barton deoxygenation of **17a** and **18a** gave the 2′-deoxy products **19a** and **20a**, respectively (direct hydrogen transfer to the C2′ radical). In contrast, the 3′-thiocarbamate derivatives **17b** and **18b** underwent deoxygenative radical generation at C3′ followed by an expected[28] difluorocyclopropylcarbinyl to allylcarbinyl radical rearrangement and hydrogen transfer to the homoallylic center to give alkenes **19b** and **20b**, respectively.

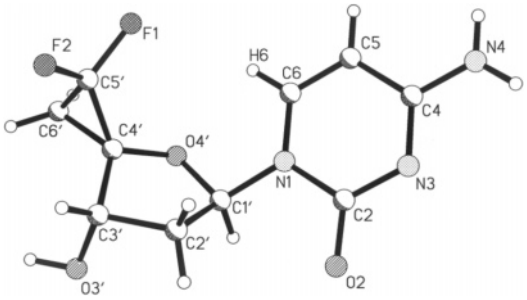


FIGURE 3. X-ray crystal structure of **23**.

Dolbier had shown that ring opening of such difluorocyclopropylcarbinyl radicals is very rapid and that the C−C bond distal to the CF_2 group is cleaved.[28,29]

The TBS ethers **19a**, **19b**, **20a**, and **20b** were deprotected (Bu_4NF/THF) and purified [chromatography on Dowex 1 × 2 (OH^-)] to give the respective uracil, **21a** and **21b**, and adenine, **22a** and **22b**, analogues (Scheme 3). Treatment of **19a** and **19b** with 1,2,4-triazole/$POCl_3$/Et_3N/acetonitrile[25] and ammonolysis of the 4-(1,2,4-triazoyl) intermediates gave the protected 4-amino compounds, which were deprotected (Bu_4NF/THF) and purified [Dowex 1 × 2 (OH^-) chromatography] to give the cytosine nucleoside analogues **23** and **24**. The C6 signal in ^{13}C NMR spectra of the uracil **21a** and cytosine **23** compounds is split into a doublet ($J = \sim 2$ Hz), which presumably results from through space (ts) coupling with one of the fluorine atoms (F1) on the cyclopropane ring. Such coupling indicates spatial proximity between F1 and H6. It has been well documented that $^{19}F-^{13}C$ ts couplings can be transmitted via overlap of fluorine lone-pair and C−H bond orbitals,[30−34] and weak hydrogen bonding attractions have been suggested.[33] The 2.53 Å distance between H6 and F1 in our X-ray crystal structure of **23** (Figure 3) is slightly less than the sum of the van der Waals radii, 1.20 Å for hydrogen and 1.35 Å for fluorine,[35] in harmony with the observed ts couplings. It is noteworthy that ∼2 Hz ts coupling is not present in our NMR spectra of **5** and **8**, which contain the same respective nucleobases—but have hydroxyl groups at both C2′ and C3′. The most highly populated solution conformation ranges must be different for the ribose-like (**5** and **8**) and 2′-deoxy (**21a** and **23**) compounds.

Conformational analysis of **14**·pyridine indicates that the furanosyl ring adopts a C3′-exo ($_3$E) pucker with a pseudorotational phase angle of $P = 185.4°$ and a maximum puckering amplitude of $\nu_{max} = 33.8°$.[9,36] Comparison of the X-ray crystal structures of **14**·pyridine and 2′,3′-dideoxyadenosine[37] (ddA)

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TABLE 1. Comparison of Solid-State Conformational Parameters for 14·Pyridine and ddA

compd	P^a	$\nu_{max}{}^a$	χ^a
14	185.4	33.8	−99.7
ddA	190.4	35.7	−95.9

[a] Values in degrees.

(Table 1) reveals striking similarities in their pseudorotational parameters. Both are located in the southern hemisphere (*S*) of the pseudorotation cycle, they have almost equal ring puckering, and the base rotations about the glycosyl bond (characterized by χ) are nearly equivalent. It is amazing that this level of conformational similarity exists for two nucleoside analogues with such dissimilar sugar moieties, especially with respect to the cis-vicinal OH groups present in **14** and absent in ddA. Alternative substrate activity and enzyme inactivation have been observed upon incubation of 5′-deoxy-4′,5′-unsaturated adenosine analogues with *S*-adenosylhomocysteine hydrolase,[38] and studies with this enzyme are in progress.

In conlusion, we have developed synthetic routes to new difluoro-substituted spirocyclopropane derivatives of uracil **5**, cytosine **8**, and adenine **14** nucleosides as well as their 2′-deoxy and ring-opened 3′-deoxy analogues. Development of suitable protecting group strategies was crucial for the successful and steroselective addition of difluorocarbene to unsaturated sugar nucleosides. The heteroatom array in compounds **2** and **12** is more extensive than in any alkenes shown to undergo difluorocyclopropanation previously. We employed the base-stable 6-(2,5-dimethylpyrrol-1-yl) substituent on a nucleoside purine ring for the first time, and mild acid treatment released the masked 6-amino group of adenine. Barton deoxygenation at C2′, and with concomitant cyclopropylcarbinyl radical ring-opening at C3′, provided access to the structurally unique deoxynucleosides **21**−**24**. An X-ray crystal analysis of our supramolecular **14**·pyridine complex revealed similarities with DNA secondary structures. Intriguing through-space F···H−C interactions were detected by ^{13}C NMR and supported by X-ray crystal distances in **21a** and **23**. Studies of new analogues derived from a 2-oxabicyclo[3.1.0]hexane template and biological response properties will be reported separately.

Experimental Section[39]

3-Benzoyl-1-[(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]uracil (3a). Et_3N (4.7 mL, 3.4 g, 34.1 mmol) and BzCl (2.6 mL, 2.9 g, 22.7 mmol) were added to a stirred solution of **1**[24] (3.00 g, 11.4 mmol) in dried CH_2Cl_2 (30 mL) under N_2, and stirring was continued for 4 h. The mixture was concentrated and chromatographed (EtOAc/hexanes, 1:4 → 1:1) to give 3-benzoyl-1-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)uracil (**2**) (2.87 g, 68%) as a yellow syrup: UV_{max} 253 nm (ϵ 20 800), min 225 nm (ϵ 5600); ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 3H), 1.51 (s, 3H), 4.38 (d, *J* = 1.8 Hz, 1H), 4.60 (d, *J* = 1.8 Hz, 1H), 5.06 (d, *J* = 6.1 Hz, 1H), 5.24 (d, *J* = 6.1 Hz, 1H), 5.68 (s, 1H), 5.85 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.49−7.53 (m, 2H), 7.65−7.69 (m, 1H), 7.91−7.94 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 25.1, 26.4, 79.2, 82.6, 87.2, 96.5, 102.2, 113.6, 129.1, 130.3, 130.8, 135.2, 142.5, 148.9, 161.7, 162.3, 168.1; MS *m*/*z* 370 ([M^+], 7), 355, 295, 265, 105 ([$PhCO^+$], 100), 77; HRMS ($C_{19}H_{18}N_2O_6$) calcd 370.1164, found 370.1155.

Powdered NaI (1.50 g, 10.0 mmol) was stirred and heated (170 °C, oil bath) under vacuum for 1 h in a flask (250 mL) equipped with a Teflon valve. The bath was allowed to cool to 110 °C, and a solution of **2** (0.86 g, 2.34 mmol) in dried CH_2Cl_2 (2 mL) was injected through a septum (under N_2). Volatiles were evaporated in vacuo, and heating at 110 °C was continued for 1 h. The bath was allowed to cool to ambient temperature, and solid $PhHgCF_3$ (1.22 g, 3.51 mmol) was added (under N_2). The flask was evacuated and cooled to −78 °C. Dried DME (∼10 mL) was transferred under vacuum from a blue solution containing sodium and benzophenone. The reaction mixture was heated at 90 °C overnight, and volatiles were evaporated. The concentrated mixture was deposited on silica gel and chromatographed (EtOAc/hexanes, 1:4 → 1:1) to give **3a**/**3b** (∼5:1; 0.89 g, 91%) as a yellow oil that was recrystallized (MeOH) to give an analytical sample of **3a**: UV max 253 nm (ϵ 18 800), min 225 nm (ϵ 5800); ^{1}H NMR ($CDCl_3$) δ 1.36 (s, 3H), 1.53 (s, 3H), 1.65−1.80 (m, 2H), 5.00 (d, *J* = 6.1 Hz, 1H), 5.38 (d, *J* = 6.1 Hz, 1H), 5.51 (s, 1H), 5.84 (dd, *J* = 2.2, 8.1 Hz, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 7.67 (t, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ 136.2 (dm, *J* = 164.8 Hz, 1F), 144.9 (ddd, *J* = 7.3, 14.6, 164.8 Hz, 1F); ^{13}C NMR (Me_2CO-d_6) δ 17.4 (t, *J* = 10.7 Hz), 25.1, 26.3, 73.8 (t, *J* = 9.1 Hz), 79.4, 85.0, 98.1, 102.9, 109.5 (dd, *J* = 291.5, 299.8 Hz), 113.6, 129.1, 130.6, 130.9, 135.3, 143.3, 149.6, 161.8, 168.1; MS *m*/*z* 420 ([M^+], 100), 405, 377, 361, 241, 205, 188, 162; HRMS ($C_{20}H_{18}F_2N_2O_6$) calcd 420.1133, found 420.1130. Anal. Calcd for $C_{20}H_{18}F_2N_2O_6$: C, 57.14; H, 4.32; N, 6.66. Found: C, 57.30; H, 4.50; N, 6.64.

1-[(*S*)-4,4-*C*-(1,1-Difluoroethane-1,2-diyl)-β-D-erythrofuranosyl]uracil (5). To a stirred solution of **3a**/**3b** (0.75 g, 1.79 mmol) in THF (10 mL) was added HCl/H_2O (3 M, 10 mL), and stirring was continued until the deprotection was complete (∼6 h; TLC, EtOAc). Volatiles were evaporated in vacuo, and the residue was neutralized (solid $NaHCO_3$) and extracted (EtOAc, 5 × 10 mL). The combined extract was applied to a silica gel column, and elution (EtOAc/hexanes, 1:1 → EtOAc) gave 3-benzoyl-1-[(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-erythrofuranosyl]uracil (**4**) (0.49 g, 72%). This material was dissolved (MeOH, 12 mL), NH_3/H_2O (30%, 4 mL) was added, and the solution was stirred at ambient temperature for 1 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc, then MeOH) to give a syrup that was recrystallized (EtOH) to give **5** (0.31 g, 87%) as colorless needles: mp 225−226 °C; UV_{max} 260 nm (ϵ 10 200), min 230 nm (ϵ 2800); ^{1}H NMR (Me_2CO-d_6) δ 1.60−1.66 (m, 1H), 1.85−1.91 (m, 1H), 2.88 (s, 1H), 2.91 (s, 1H), 4.39 (d, *J* = 4.9 Hz, 1H), 4.67 (dd, *J* = 4.9, 5.9 Hz, 1H), 5.69 (d, *J* = 8.3 Hz, 1H), 6.07 (d, *J* = 5.9 Hz, 1H), 7.65 (d, *J* = 8.3 Hz, 1H); ^{19}F NMR (Me_2CO-d_6) δ 134.4 (dm, *J* = 163.9 Hz, 1F), 141.9 (ddd, *J* = 7.3, 14.5, 163.0 Hz, 1F); ^{13}C NMR (Me_2CO-d_6) δ 18.5 (t, *J* = 9.8 Hz), 68.8, 71.4 (t, *J* = 9.6 Hz), 74.9, 91.1, 103.5, 111.3 (dd, *J* = 292.5, 298.4 Hz), 141.5, 151.6, 163.4; FAB-MS *m*/*z* 321 ([M^+ − H + 2Na], 15), 299 ([M^+ + Na], 10), 277, 271, 259, 237 (100), 217, 213; HRMS ($C_{10}H_{10}F_2N_2O_5Na$) calcd 299.0455, found 299.0448. Anal. Calcd for $C_{10}H_{10}F_2N_2O_5$: C, 43.49; H, 3.64; N, 10.14. Found: C, 43.49; H, 3.82; N, 10.19.

1-[(*S*)-4,4-*C*-(1,1-Difluoroethane-1,2-diyl)-β-D-erythrofuranosyl]cytosine (8). A solution of NH_3/H_2O (30%, 5 mL) was added to a stirred solution of **3a** (0.71 g, 1.71 mmol) in MeOH (20 mL), and stirring was continued at ambient temperature for 1 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:2) to give 1-[(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]uracil (**6**) (0.53 g, 99%) as a syrup.

Et_3N (2.34 mL, 1.71 g, 16.9 mmol) was added dropwise to a stirred, cooled (∼0 °C) mixture of 1,2,4-triazole (1.22 g, 17.8 mmol), $POCl_3$ (0.35 mL, 0.57 g, 3.72 mmol), and acetonitrile (10.5 mL). A solution of **6** (0.53 g, 1.69 mmol) in acetonitrile (6.6 mL) was added to this mixture, and stirring was continued at ambient temperature for 2 h. Et_3N (1.59 mL, 1.16 g, 11.5 mmol) and H_2O

(38) Yuan, C.-S.; Liu, S.; Wnuk, S. F.; Robins, M. J.; Borchardt, R. T. In *Advances in Antiviral Drug Design*; De Clercq, E., Ed.; JAI Press: Greenwich, CT, 1996; Vol. 2, pp 41−88.

(39) See the Supporting Information for general experimental details.

(0.66 mL) were added, and stirring was continued for 10 min. Volatiles were evaporated, and the residue was partitioned [ice-cold, saturated $NaHCO_3/H_2O$ (30 mL)//CH_2Cl_2 (30 mL)]. The aqueous phase was extracted (CH_2Cl_2, 30 mL), and the combined organic phase was washed (brine, 50 mL) and dried ($MgSO_4$). Volatiles were evaporated to give 1-[(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2-one (**7**) (0.60 g, 97%) as a yellow foam: UV max 314, 251 nm (ϵ 5500, 14 000), min 280, 232 nm (ϵ 2300, 6600); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 3H), 1.57 (s, 3H), 1.74−1.81 (m, 1H), 1.84−1.92 (m, 1H), 5.12 (d, *J* = 5.9 Hz, 1H), 5.35 (d, *J* = 5.9 Hz, 1H), 5.73 (s, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 1H), 8.13 (s, 1H), 9.27 (s, 1H); ^{19}F NMR ($CDCl_3$) δ 135.8 (ddd, *J* = 5.5, 14.6, 164.8 Hz, 1F), 143.6 (ddd, *J* = 7.3, 14.6, 164.8 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 17.7 (t, *J* = 11.1 Hz), 25.4, 26.4, 74.6 (t, *J* = 9.2 Hz), 79.1, 85.3, 95.2, 99.1, 109.5 (dd, *J* = 292.2, 299.8 Hz), 113.6, 143.4, 149.4, 154.0, 154.5, 160.0; EI-MS *m*/*z* 367 ([M$^+$], 8), 352, 308, 216, 204, 188, 164 (100), 162, 148; HRMS ($C_{15}H_{15}F_2N_5O_4$) calcd 367.1092, found 367.1099.

A solution of NH_3/H_2O (30%, 2.2 mL) was added to a stirred solution of **7** in 1,4-dioxane (7 mL), and stirring was continued at ambient temperature for 19 h. Volatiles were evaporated, and the residue was dissolved (TFA/H_2O, 3.0:0.4 mL). The solution was stirred overnight, and volatiles were evaporated in vacuo (<30 °C). H_2O (20 mL) and $NaHCO_3$ were added to the residue, and the mixture was extracted (EtOAc, 10 × 100 mL). Evaporation of volatiles gave **8** as yellow oil. A solution of this material in MeOH was treated with 5% HCl/H_2O and filtered. The filtrate was concentrated, and excess HCl was removed by repetitive addition and evaporation of $MeOH/H_2O$. The resulting red oil was recrystallized (EtOH) to give **8**·HCl·0.5H_2O (0.40 g, 79%) as a white powder: mp 218−220 °C; UV_{max} 278 nm (ϵ 10 600), min 245 nm (ϵ 4600); ^{1}H NMR (D_2O) δ 1.79−1.87 (m, 1H), 1.92−2.01 (m, 1H), 4.40 (d, *J* = 4.9 Hz, 1H), 4.74 (t, *J* = 5.3 Hz, 1H), 6.04 (d, *J* = 5.9 Hz, 1H), 6.25 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H); ^{19}F NMR (D_2O) δ 135.0 (ddd, *J* = 5.5, 14.6, 164.8 Hz, 1F), 142.0 (ddd, *J* = 7.3, 16.5, 164.8 Hz, 1F); ^{13}C NMR (D_2O) δ 17.5 (t, *J* = 10.3 Hz), 68.5, 70.9 (dd, *J* = 8.6, 11.1 Hz), 74.5, 91.8, 95.8, 109.7 (dd, *J* = 290.6, 299.6 Hz), 144.9, 148.5, 159.4; FAB-MS (thioglycerol) *m*/*z* 298 ([M$^+$ + Na], 100); HRMS ($C_{10}H_{11}F_2N_3O_4$-Na) calcd 298.0615, found 298.0616. Anal. Calcd for $C_{10}H_{11}F_2N_3O_4$·HCl·0.5H_2O: C, 37.45; H, 4.09; N, 13.10. Found: C, 37.14; H, 4.40; N, 12.92.

9-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)purine[27] **(10).** A solution of 2′,3′-*O*-isopropylideneadenosine (**9**) (1.00 g, 3.26 mmol) in 2,5-hexanedione (4 mL) was heated at 150 °C for 2 days. Volatiles were evaporated in vacuo, and the oily residue was chromatographed (EtOAc/hexanes, 1:1) to give **10** (0.70 g, 56%) as an orange oil: UV_{max} 283 nm (ϵ 12 100), min 247 nm (ϵ 4200); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.69 (s, 3H), 2.22 (s, 6H), 3.82−3.88 (m, 1H), 4.02 (dd, *J* = 1.5, 12.7 Hz, 1H), 4.60 (s, 1H), 5.17 (dd, *J* = 1.5, 5.8 Hz, 1H), 5.31 (dd, *J* = 4.4, 5.8 Hz, 1H), 5.46 (d, *J* = 10.7 Hz, 1H), 6.00 (s, 2H), 6.03 (d, *J* = 4.4 Hz, 1H), 8.22 (s, 1H), 8.93 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0, 24.7, 26.9, 62.2, 81.2, 83.6, 86.2, 92.3, 108.6, 113.6, 128.8, 129.2, 144.2, 149.8, 151.6, 152.1; MS *m*/*z* 385 ([M$^+$], 80), 370, 354, 296, 213 (100), 198; HRMS ($C_{19}H_{23}N_5O_4$) calcd 385.1750, found 385.1753.

9-[(*S*)-4,4-*C*-(1,1-Difluoroethane-1,2-diyl)-β-D-erythrofuranosyl]adenine (14). A solution of **10** (4.5 g, 11.7 mmol) in dried pyridine (22 mL) was cooled to −20 °C, and TsCl (3.4 g, 17.8 mmol) was added. Stirring was continued for 6 h at −20 °C, and the mixture was allowed to warm to 15 °C overnight. H_2O (100 mL) was added with stirring, and the solution was extracted (CH_2Cl_2, 2 × 50 mL). The combined organic phase was dried ($MgSO_4$), and volatiles were evaporated to give 9-(2,3-*O*-isopropylidene-5-*O*-tosyl-β-D-ribofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)purine (**11**) (6.0 g, 95%) as a yellow syrup: UV_{max} 284 nm (ϵ 12 500), min 247 nm (ϵ 4300); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 3H), 1.63 (s, 3H), 2.22 (s, 6H), 2.42 (s, 3H), 4.25−4.31 (m, 2H), 4.50−4.54 (m, 1H), 5.08 (dd, *J* = 2.9, 6.3 Hz, 1H), 5.42 (dd, *J* = 2.4, 6.3 Hz, 1H), 6.00 (s, 2H), 6.23 (d, *J* = 2.9 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 8.19 (s, 1H), 8.87 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.9, 20.8, 24.5, 26.3, 68.6, 80.6, 83.4, 83.6, 90.0, 108.3, 113.8, 127.1, 128.3, 129.0, 129.2, 131.4, 134.8, 144.7, 149.3, 151.4, 152.1; MS *m*/*z* 539 ([M$^+$], 40), 524, 403, 367, 212 ([M$^+$ − $C_{11}H_{10}N_5$], 100); HRMS ($C_{26}H_{31}N_5O_6S$) calcd 539.1838, found 539.1829.

A solution of potassium *tert*-butoxide (1.8 g, 16.7 mmol) in dried THF (40 mL) was added to a stirred, cooled (−10 °C) solution of **11** (6.0 g, 11.1 mmol) in dried THF (40 mL), and the dark solution was protected from moisture and stirred for 30 min at −10 °C. The reaction mixture was deposited on silica gel and chromatographed (EtOAc/hexanes, 1:4) to give 9-(5-deoxy-2,3-*O*-isopropylidene-β-D-*erythro*-pent-4-enofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)purine (**12**) (2.6 g, 68%) as a pale yellow oil: UV_{max} 284 nm (ϵ 13 500), min 246 nm (ϵ 4400); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 3H), 1.61 (s, 3H), 2.21 (s, 6H), 4.56 (d, *J* = 2.4 Hz, 1H), 4.69 (d, *J* = 2.4 Hz, 1H), 5.38 (d, *J* = 5.9 Hz, 1H), 5.61 (d, *J* = 5.9 Hz, 1H), 5.99 (s, 2H), 6.36 (s, 1H), 8.12 (s, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.0, 25.1, 26.2, 79.1, 82.1, 88.0, 90.0, 108.6, 113.6, 128.4, 129.2, 143.6, 149.7, 151.9, 152.1, 161.2; MS *m*/*z* 367 ([M$^+$], 60), 352, 226, 212 ([M$^+$ − $C_{11}H_{10}N_5$], 100); HRMS ($C_{19}H_{21}N_5O_3$) calcd 367.1644, found 367.1656.

Treatment of **12** (1.14 g, 3.1 mmol) in dried DME (8 mL) with the reagent prepared from NaI (1.4 g, 9.3 mmol) and $PhHgCF_3$ (2.19 g, 6.3 mmol) (according to the procedure described for **2** → **3a**/**3b**) gave a mixture that was deposited on silica gel and chromatographed (EtOAc/hexanes, 1:4 → 1:1) to give recovered **12** (0.26 g, 20%) plus a mixture of 9-[(*R*/*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-2,3-*O*-isopropylidene-β-D-erythrofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (**13a**/**13b**) (∼15:1; 0.78 g, 60%) as a yellow oil: ^{1}H NMR ($CDCl_3$, major isomer) δ 1.50 (s, 3H), 1.65 (s, 3H), 1.65−1.95 (m, 2H), 2.21 (s, 6H), 5.43 (d, *J* = 5.9 Hz, 1H), 5.74 (d, *J* = 6.1 Hz, 1H), 6.00 (s, 2H), 6.29 (s, 1H), 8.13 (s, 1H), 8.94 (s, 1H); ^{19}F NMR ($CDCl_3$) δ 135.6 (ddd, *J* = 5.5, 14.6, 163.0 Hz, 1F), 145.3 (ddd, *J* = 7.3, 14.6, 163.0 Hz, 1F); EI-MS *m*/*z* 417 ([M$^+$], 80), 212, 77 (100); HRMS ($C_{20}H_{21}F_2N_5O_3$) calcd 417.1612, found 417.1617.

A solution of **13a**/**13b** (0.85 g, 2.0 mmol) in TFA/H_2O (9:1, 20 mL) was stirred at ambient temperature for 3 h. Volatiles were evaporated in vacuo (<30 °C), and saturated $NaHCO_3/H_2O$ (20 mL) was added. The mixture was extracted (EtOAc, 10 × 100 mL), and volatiles were evaporated from the combined organic phase to give a red oil. Chromatography (EtOAc/MeOH, 20:1) gave **14** (0.35 g, 57%) as a syrup: UV_{max} 260 nm (ϵ 12 000), min 229 nm (ϵ 3300); ^{1}H NMR (Me_2CO-d_6) δ 1.59−1.67 (m, 1H), 1.87−1.95 (m, 1H), 2.87 (br s, 2H), 4.63 (d, *J* = 5.4 Hz, 1H), 5.26 (t, *J* = 5.4 Hz, 1H), 6.22 (d, *J* = 5.4 Hz, 1H), 6.64 (br s, 2H), 8.20 (s, 1H), 8.23 (s, 1H); ^{19}F NMR (Me_2CO-d_6) δ 134.5 (ddd, *J* = 5.5, 16.5, 163.0 Hz, 1F), 141.8 (ddd, *J* = 7.3, 16.5, 163.0 Hz, 1F); ^{13}C NMR (DMSO-d_6) δ 17.9 (t, *J* = 8.8 Hz), 68.1, 70.3 (t, *J* = 9.2 Hz), 73.2, 87.6, 110.9 (dd, *J* = 292.2, 299.1 Hz), 119.4, 140.2, 149.9, 153.0, 156.3; MS *m*/*z* 299 ([M$^+$], 7), 270, 178 (100), 148, 136; HRMS ($C_{11}H_{11}F_2N_5O_3$) calcd 299.0830, found 299.0828. This material was recrystallized (pyridine/MeOH/Et_2O) to give yellow-green blades of **14**·pyridine: mp ∼160−166 °C dec; ^{1}H NMR (CD_3OD) δ 1.64 (ddd, *J* = 4.9, 10.3, 15.6 Hz, 1H), 1.89 (ddd, *J* = 7.3, 9.8, 16.1 Hz, 1H), 4.45 (d, *J* = 5.4 Hz, 1H), 5.13 (t, *J* = 5.9 Hz, 1H), 6.19 (d, *J* = 6.3 Hz, 1H), 7.40−7.43 (m, 2H), 7.81−7.85 (m, 1H), 8.20 (s, 1H), 8.23 (s, 1H), 8.51−8.53 (m, 2H); ^{19}F NMR (CD_3OD) δ 134.7 (ddd, *J* = 4.9, 17.1, 163.6 Hz, 1F), 142.3 (ddd, *J* = 7.3, 17.1, 163.6 Hz, 1F); ^{13}C NMR (CD_3OD) δ 17.3 (t, *J* = 10.3 Hz), 68.4, 70.7 (dd, *J* = 8.4, 10.7 Hz), 74.5, 88.7, 110.2 (dd, *J* = 293.0, 297.5 Hz), 119.3, 124.4, 137.2, 140.0, 148.9, 149.8, 152.9, 156.2. X-ray crystallography confirmed the 1:1 complex stoichiometry.

1-[2-Deoxy-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-*glycero*-tetrofuranosyl]uracil (21a). TBS-Cl (0.73 g, 4.8 mmol) was added

to a stirred solution of **5** (0.44 g, 1.6 mmol) in dried pyridine (5 mL), and stirring was continued at ambient temperature for 2 days. Volatiles were evaporated in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:4 → 1:1) to give 1-[2-*O*-*tert*-butyldimethylsilyl-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-erythrofuranosyl]-uracil (**15**) (0.60 g, 97%): mp 175−177 °C; UV_{max} 260 nm (ϵ 10 400), min 229 nm (ϵ 2600); ^1H NMR (Me_2CO-d_6) δ 0.10 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.58−1.70 (m, 1H), 1.82−1.95 (m, 1H), 4.29 (t, *J* = 5.4 Hz, 1H), 4.42 (d, *J* = 5.8 Hz, 1H), 4.82 (t, *J* = 5.7 Hz, 1H), 5.75 (d, *J* = 8.1 Hz, 1H), 6.15 (d, *J* = 5.8 Hz, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 10.25 (s, 1H); ^{19}F NMR (Me_2CO-d_6) δ 134.1 (dm, *J* = ∼163 Hz, 1F), 142.0 (dm, *J* = ∼163 Hz, 1F); ^{13}C NMR (Me_2CO-d_6) δ −4.9, −4.7, 18.5 (t, *J* = 9.8 Hz), 18.7, 26.1, 69.0, 71.2 (dd, *J* = 8.2, 11.5 Hz), 76.2, 90.0, 103.6, 111.1 (dd, *J* = 292.5, 298.4 Hz), 141.1, 151.5, 163.6; FAB-MS *m*/*z* 435 ([M^+ − H + 2Na], 50), 413 ([M^+ + Na], 100), 401, 391; HRMS ($C_{16}H_{24}F_2N_2O_5SiNa$) calcd 413.1320, found 413.1322. Anal. Calcd for $C_{16}H_{24}F_2N_2O_5Si$: C, 49.22; H, 6.20; N, 7.17. Found: C, 49.40; H, 6.06; N, 7.07.

A stirred solution of **15** (0.13 g, 0.3 mmol) and 1,1′-thiocarbonyldiimidazole (0.09 g, 0.5 mmol) in dried toluene (2 mL) was heated at 70 °C for 30 min. Volatiles were evaporated in vacuo, and chromatography of the residue (EtOAc/hexanes, 1:2 → 1:1) separated two isomers. The more polar 1-{3-*O*-*tert*-butyldimethylsilyl-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-2-*O*-[(imidazol-1-yl)-thiocarbonyl]-β-D-erythrofuranosyl}uracil (**17a**) (38 mg, 23%) had: UV_{max} 259 nm (ϵ 17 500), min 229 nm (ϵ 6200); ^1H NMR ($CDCl_3$) δ −0.06 (s, 3H), 0.06 (s, 3H), 0.83 (s, 9H), 1.67−1.76 (m, 1H), 1.81−1.90 (m, 1H), 5.02 (d, *J* = 4.9 Hz, 1H), 5.80 (d, *J* = 7.8 Hz, 1H), 5.99 (t, *J* = 4.9 Hz, 1H), 6.18 (d, *J* = 4.9 Hz, 1H), 7.07 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.63 (s, 1H), 8.38 (s, 1H), 10.54 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 135.1 (dm, *J* = 169 Hz, 1F), 141.6 (dm, *J* = 169 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ −5.3, −5.1, 17.7, 17.9 (t, *J* = 10.1 Hz), 25.3, 67.7, 70.2 (dd, *J* = 8.1, 12.1 Hz), 82.6, 89.3, 103.7, 108.9 (dd, *J* = 294.1, 297.6 Hz), 117.9, 131.2, 137.1, 140.2, 150.1, 163.4, 182.5; FAB-MS (glycerol) *m*/*z* 501 ([M^+ + H], 52), 373 (100), 261; HRMS ($C_{20}H_{27}F_2N_4O_5SSi$) calcd 501.1439, found 501.1454. The less polar 1-{2-*O*-*tert*-butyldimethylsilyl-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-3-*O*-[(imidazol-1-yl)thiocarbonyl]-β-D-erythrofuranosyl}uracil (**17b**) (65 mg, 40%) had: mp 205−206 °C dec; UV_{max} 260 nm (ϵ 16 500), min 232 nm (ϵ 6200); ^1H NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.73 (s, 9H), 1.82−1.97 (m, 2H), 4.90 (t, *J* = 5.9 Hz, 1H), 5.86 (dd, *J* = 2.2, 8.3 Hz, 1H), 5.99 (d, *J* = 6.3 Hz, 1H), 6.28 (d, *J* = 5.4 Hz, 1H), 7.11 (s, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 7.68 (s, 1H), 8.15 (s, 1H), 8.41 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 134.7 (ddd, *J* = 4.3, 15.0, 164.5 Hz, 1F), 143.8 (ddd, *J* = 6.4, 15.0, 164.5 Hz, 1F); ^{13}C NMR (Me_2CO-d_6) δ −5.1, −4.9, 18.2, 19.6 (t, *J* = 10.3 Hz), 25.7, 69.0 (t, *J* = 10.3 Hz), 74.8, 79.7, 92.2, 104.0, 110.4 (dd, *J* = 293.4, 298.0 Hz), 119.4, 132.1, 138.0, 142.0, 151.5, 163.2, 185.3; FAB-MS (glycerol) *m*/*z* 501 ([M^+ + H], 20), 443, 373, 353, 261 (100); HRMS ($C_{20}H_{27}F_2N_4O_5SSi$) calcd 501.1439, found 501.1437.

Bu_3SnH (0.6 g, 2.0 mmol) was added to a solution of **17a** (0.25 g, 0.5 mmol) and AIBN (20 mg, 0.1 mmol) in dried, deoxygenated toluene. The mixture was heated at 90 °C for 50 min, and volatiles were evaporated. The residual oil was chromatographed (EtOAc/hexanes, 1:4 → 1:2) to give 1-[3-*O*-*tert*-butyldimethylsilyl-2-deoxy-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-*glycero*-tetrofuranosyl]-uracil (**19a**) (0.12 g, 64%): UV_{max} 260 nm (ϵ 10 200), min 229 nm (ϵ 2500); ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.91 (s, 9H), 1.68−1.76 (m, 2H), 2.35 (dt, *J* = 6.3, 14.2 Hz, 1H), 2.59 (ddd, *J* = 2.4, 6.3, 14.2 Hz, 1H), 4.51 (dd, *J* = 2.4, 5.9 Hz, 1H), 5.79 (d, *J* = 8.3 Hz, 1H), 6.38 (t, *J* = 6.3 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 8.47 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 135.0 (dm, *J* = 164 Hz, 1F), 142.1 (dm, *J* = 165 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ −5.2, −4.9, 17.7 (t, *J* = 10.1 Hz), 17.8, 25.5, 42.3, 69.0, 72.2 (dd, *J* = 7.8, 10.5 Hz), 86.5, 103.0, 110.1 (dd, *J* = 294.8, 299.3 Hz), 139.0, 150.3, 163.6; FAB-MS (thioglycerol) *m*/*z* 397 ([M^+ + Na], 100), 375, 263, 243, 237; HRMS ($C_{16}H_{24}F_2N_2O_4SiNa$) calcd 397.1371, found 397.1375.

Bu_4NF/THF (1 M; 2.0 mL, 2.0 mmol) was added to a stirred solution of **19a** (0.60 g, 1.6 mmol) in THF (10 mL), and stirring was continued for 1 h. 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 (1:3)] and evaporation of volatiles from UV-active fractions gave **21a** (0.36 g, 87%) as colorless crystals. An analytically pure sample was obtained by several recrystallizations (EtOH): mp 205−206 °C; UV_{max} 260 nm (ϵ 9700), min 229 (ϵ 3600); ^1H NMR (Me_2CO-d_6) δ 1.65−1.72 (ddd, *J* = 4.9, 10.3, 16.6 Hz, 1H), 1.83−1.90 (ddd, *J* = 6.8, 9.8, 17.1 Hz), 2.54−2.59 (ddd, *J* = 2.4, 6.8, 14.2 Hz, 1H), 2.66−2.72 (dt, *J* = 14.2, 6.6 Hz, 1H), 4.59 (dd, *J* = 2.0, 6.3 Hz, 1H), 5.67 (d, *J* = 8.3 Hz, 1H), 6.48 (t, *J* = 6.8 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H); ^{19}F NMR (CD_3OD) δ 134.6 (ddd, *J* = 5.4, 16.5, 163.0 Hz, 1F), 141.9 (ddd, *J* = 7.3, 16.5, 163.0 Hz, 1F); ^{13}C NMR (CD_3OD) δ 17.9 (t, *J* = 10.3 Hz), 41.8, 69.9, 73.9 (dd, *J* = 7.6, 10.7 Hz), 88.4, 103.3, 112.2 (dd, *J* = 292.2, 299.1 Hz), 142.2 (d, *J* = 1.8 Hz), 152.5, 166.6; EI-MS *m*/*z* 260 ([M^+], 5), 232, 188, 167, 149, 128, 113, 96 (100); HRMS ($C_{10}H_{10}F_2N_2O_4$) calcd 260.0608, found 260.0598. Anal. Calcd for $C_{10}H_{10}F_2N_2O_4$: C, 46.16; H, 3.87; N, 10.77. Found: C, 46.30; H, 3.85; N, 10.60.

1-[3-Deoxy-4-(1,1-difluoroethyl)-β-D-*glycero*-tetr-3-enofuranosyl]uracil (21b). Treatment of **17b** (0.25 g, 0.5 mmol) with Bu_3SnH/AIBN/toluene (as described for **17a** → **19a**) gave 1-[2-*O*-*tert*-butyldimethylsilyl-3-deoxy-4-(1,1-difluoroethyl)-β-D-*glycero*-tetr-3-enofuranosyl]uracil (**19b**) (0.16 g, 83%): UV_{max} 259 nm (ϵ 10 300), min 231 nm (ϵ 3700); ^1H NMR ($CDCl_3$) δ 0.07 (s, 3H), 0.10 (s, 3H), 0.87 (s, 9H), 1.81 (t, *J* = 18.8 Hz, 3H), 4.97 (s, 1H), 5.46 (s, 1H), 5.78 (d, *J* = 7.8 Hz, 1H), 6.32 (s, 1H), 7.02 (d, *J* = 7.8 Hz, 1H), 10.09 (br s, 1H); ^{19}F NMR ($CDCl_3$) δ 92.9 (dq, *J* = 18.3, 265.5 Hz, 1F), 97.4 (dq, *J* = 18.3, 265.5 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ −4.81, −4.76, 17.9, 21.9 (t, *J* = 26.5 Hz), 25.5, 79.8, 94.0, 102.7, 103.6, 116.2 (t, *J* = 236.6 Hz), 138.8, 149.8, 155.6 (dd, *J* = 30.2, 36.6 Hz), 163.4; FAB-MS (thioglycerol) *m*/*z* 397 ([M^+ + Na], 100), 375, 359, 339, 317, 263; HRMS ($C_{16}H_{24}F_2N_2O_4$-SiNa) calcd 397.1371, found 397.1372.

Bu_4NF/THF (1 M; 1.4 mL, 1.4 mmol) was added to a stirred solution of **19b** (0.26 g, 0.695 mmol) in THF (5 mL), and stirring was continued for 15 min. Volatiles were evaporated, and the residue was dissolved (H_2O, 10 mL) and applied to a column of Dowex 1 × 2 (OH^-) resin (in H_2O). Elution [H_2O → MeOH → AcOH/MeOH (1:3)], and evaporation of volatiles from UV-active fractions gave **21b** (0.15 g, 82%) as an oil that crystallized upon standing. An analytically pure sample was obtained by several recrystallizations (EtOH): mp 148−150 °C; UV_{max} 260 nm (ϵ 9800), min 231 nm (ϵ 2800); ^1H NMR (CD_3OD) δ 1.82 (t, *J* = 18.6 Hz, 3H), 5.05 (m, 1H), 5.60 (m, 1H), 5.73 (d, *J* = 8.3 Hz, 1H), 6.30 (d, *J* = 2.9 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H); ^{19}F NMR (Me_2CO-d_6) δ 94.1 (dqm, *J* = 18.8, 264.2 Hz, 1F), 94.7 (dqm, *J* = 18.8, 264.2 Hz, 1F); ^{13}C NMR (Me_2CO-d_6) δ 22.4 (t, *J* = 26.5 Hz), 79.0, 95.0, 104.1, 104.2 (t, *J* = 4.1 Hz), 117.6 (t, *J* = 236.3 Hz), 151.1, 155.9 (t, *J* = 32.5 Hz), 163.5; EI-MS *m*/*z* 261 (MH^+, 35), 242, 231, 199, 167, 148, 113 (100); HRMS ($C_{10}H_{11}F_2N_2O_4$) calcd 261.0687, found 261.0694. Anal. Calcd for $C_{10}H_{10}F_2N_2O_4$: C, 46.16; H, 3.87; N, 10.77. Found: C, 46.31; H, 3.96; N, 10.60.

1-[2-Deoxy-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-*glycero*-tetrofuranosyl]cytosine (23). Treatment of **19a** (1.10 g, 2.54 mmol) by the sequence described for the conversion of **6** → **8**, followed by deprotection as described for **19a** → **21a**, gave an acetate salt after chromatography with Dowex 1 × 2 (OH^-) resin [H_2O → MeOH → AcOH/MeOH (1:3)]. The salt was neutralized (Na_2CO_3/H_2O), and the mixture was extracted (EtOAc). The combined organic phase was concentrated and subjected to PTLC (EtOAc/MeOH, 10:1) to give **23** (0.56 g, 74%). Recrystallization (MeOH) gave an analytical sample as colorless needles: mp 217−218 °C dec; UV_{max} 271 nm (ϵ 8900), min 255 nm (ϵ 8000); ^1H NMR (CD_3OD) δ 1.65−1.89 (m, 2H), 2.38−2.48 (dt, *J* = 6.5, 14.2 Hz, 1H),

2.57−2.65 (ddd, J = 2.2, 6.3, 14.2 Hz, 1H), 4.56 (dd, J = 2.2, 6.1 Hz, 1H), 4.87 (s, 3H), 5.91 (d, J = 7.6 Hz, 1H), 6.45 (t, J = 6.6 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H); ^{19}F NMR (CD_3OD) δ 135.0 (ddd, J = 5.5, 16.5, 163.0 Hz, 1F), 142.2 (ddd, J = 7.3, 16.5, 163.0 Hz, 1F); ^{13}C NMR (CD_3OD) δ 18.8 (t, J = 10.3 Hz), 42.7, 70.0, 73.8 (dd, J = 7.6, 10.7 Hz), 89.0, 96.6, 112.3 (dd, J = 292.6, 299.5 Hz), 141.9 (d, J = 2.3 Hz), 158.3, 167.8; EI-MS m/z 259 (M^+, 3), 230, 222, 207, 179, 138, 128 (100); HRMS ($C_{10}H_{11}F_2N_3O_3$) calcd 259.0768, found 259.0759. Anal. Calcd for $C_{10}H_{11}F_2N_3O_3$: C, 46.34; H, 4.27; N, 16.21. Found: C, 46.29; H, 4.31; N, 16.12.

1-[3-Deoxy-4-(1,1-difluoroethyl)-β-D-*glycero*-tetr-3-enofuranosyl]cytosine (24). Treatment of **19b** (0.37 g, 1.0 mmol) by the sequence described for conversion of **6** → **8**, followed by deprotection as described for **19a** → **21a**, gave a residue after chromatography with Dowex 1 × 2 (OH^-) resin (H_2O → MeOH). Extraction (EtOAc) followed by PLTC (EtOAc/MeOH, 10:1) of the concentrated extract gave a product that was recrystallized (EtOH/Et_2O) to give **24** (0.20 g, 76%) as colorless plates: mp 197−198 °C; UV_{max} 270 nm (ϵ 8700), min 259 (ϵ 8400); ^{1}H NMR (CD_3OD) δ 1.83 (t, J = 18.8 Hz, 3H), 4.88 (s, 3H), 4.95−4.98 (m, 1H), 5.57−5.60 (m, 1H), 5.91 (d, J = 7.3 Hz, 1H), 6.34 (d, J = 2.9 Hz, 1H), 7.31 (d, J = 7.3 Hz, 1H); ^{19}F NMR (CD_3OD) δ 93.8 (dq, J = 18.3, 265.5 Hz, 1F), 95.3 (dq, J = 18.3, 265.5 Hz, 1F); ^{13}C NMR (CD_3OD) δ 22.5 (t, J = 26.7 Hz), 79.8, 96.5, 97.3, 104.0 (t, J = 3.8 Hz), 117.9 (t, J = 235.4 Hz), 141.8, 156.8 (dd, J = 31.5, 34.1 Hz), 157.8, 167.8; EI-MS m/z 259 (M^+, 2), 241, 230, 166, 123, 112 (100); HRMS ($C_{10}H_{11}F_2N_3O_3$) calcd 259.0768, found 259.0780. Anal. Calcd for $C_{10}H_{11}F_2N_3O_3$: C, 46.34; H, 4.27; N, 16.21. Found: C, 46.12; H, 4.48; N, 16.01.

1-[2-Deoxy-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-*glycero*-tetrofuranosyl]adenine (22a). TBSCl (0.76 g, 5.02 mmol) was added to a stirred solution of **14** (0.50 g, 1.67 mmol) in dried pyridine (5 mL), and stirring was continued at ambient temperature for 1 day. Volatiles were evaporated in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:2 → 1:1) to give 1-[2-*O*-*tert*-butyldimethylsilyl-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-erythrofuranosyl]adenine (**16**) (0.54 g, 78%). This material (0.45 g, 1.09 mmol) and 1,1′-thiocarbonyldiimidazole (0.29 g, 1.63 mmol) were dissolved in dried toluene/THF (10:4, 14 mL) and heated at 65 °C for 5 h. Volatiles were evaporated in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:1 → EtOAc) to give **18a**/**18b** (1:2; 0.44 g, 77%). This material and AIBN (34 mg, 0.21 mmol) were dissolved in dried toluene (15 mL), and the solution was deoxygenated (N_2). Bu_3SnH (0.68 mL, 0.73 g, 2.5 mmol) was added, and the solution was heated at 100 °C for 1 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:1 → EtOAc) to give 1-[3-*O*-*tert*-butyldimethylsilyl-2-deoxy-(*S*)-4,4-*C*-(1,1-difluoroethane-1,2-diyl)-β-D-*glycero*-tetrofuranosyl]adenine (**20a**) (0.10 g, 31%): ^{19}F NMR ($CDCl_3$) δ 134.6 (dm, J = 164 Hz, 1F), 142.2 (dm, J = 164 Hz, 1F); EI-MS m/z 397 ([M^+], 17), 340, 320, 304, 262, 242 (100), 205, 162, 135, 115; HRMS ($C_{17}H_{25}F_2N_5O_2Si$) calcd 397.1745, found 397.1739; and 1-[2-*O*-*tert*-butyldimethylsilyl-3-deoxy-4-(1,1-difluoroethyl)-β-D-*glycero*-tetr-3-enofuranosyl]adenine (**20b**) (0.22 g, 65%): UV_{max} 259 nm (ϵ 15 100), min 230 nm (ϵ 3700); ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.86 (s, 9H), 1.80 (t, J = 18.5 Hz, 3H), 5.37−5.40 (m, 1H), 5.58 (dd, J = 2.0, 2.9 Hz, 1H), 6.44 (d, J = 2.9 Hz, 1H), 6.62 (br s, 2H), 7.84 (s, 1H), 8.37 (s, 1H); ^{19}F NMR ($CDCl_3$) δ 94.1 (dq, J = 18.3, 265.5 Hz, 1F), 96.6 (dq, J = 18.3, 265.5 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ −5.0, −4.9, 17.7, 21.8 (t, J = 26.8 Hz), 25.3, 79.5, 92.4, 102.1, 116.1 (t, J = 236.4 Hz), 119.3, 137.3, 149.2, 153.1, 155.1 (t, J = 33.6 Hz), 156.2; FAB-MS (thioglycerol) m/z 420 ([M^+ + Na], 75), 398 (100), 382, 340, 266; HRMS ($C_{17}H_{25}F_2N_5O_2SiNa$) calcd 420.1643, found 420.1647.

Treatment of **20a** (0.29 g, 0.73 mmol) with Bu_4NF/THF, as described for **19a** → **21a**, and chromatography with Dowex 1 × 2 (OH^-) resin (H_2O → MeOH) gave a residue that was purified by PTLC (EtOAc/MeOH, 19:1). This material (0.18 g, 87%) was recrystallized (EtOH) to give **22a** as tiny colorless needles: mp 208−209 °C; UV_{max} 259 nm (ϵ 14 900), min 226 nm (ϵ 2200); ^{1}H NMR (CD_3OD) δ 1.65−1.73 (ddd, J = 4.9, 10.3, 16.3 Hz, 1H), 1.79−1.88 (ddd, J = 7.3, 10.3, 16.1 Hz, 1H), 2.70−2.77 (ddd, J = 2.9, 7.3, 14.2 Hz, 1H), 3.24−3.31 (ddd, J = 5.4, 6.8, 14.2 Hz, 1H), 4.77 (dd, J = 2.9, 6.8 Hz, 1H), 6.63 (dd, J = 5.4, 7.3 Hz, 1H), 8.20 (s, 1H), 8.21 (s, 1H); ^{19}F NMR (CD_3OD) δ 135.1 (ddd, J = 5.2, 15.7, 162.2 Hz, 1F), 142.1 (ddd, J = 6.9, 15.7, 162.3 Hz, 1F); ^{13}C NMR (CD_3OD) δ 17.5 (t, J = 10.7 Hz), 41.9, 69.9, 73.5 (dd, J = 8.0, 10.3 Hz), 86.1, 112.2 (dd, J = 293.4, 297.9 Hz), 120.6, 140.9, 150.7, 154.1, 157.4; EI-MS m/z 283 ([M^+], 10), 265, 190, 163, 162, 136, 135 (100%), 108; HRMS ($C_{11}H_{11}F_2N_5O_2$) calcd 283.0880, found 283.0888. Anal. Calcd for $C_{11}H_{11}F_2N_5O_2$: C, 46.65; H, 3.91; N, 24.73. Found: C, 46.72; H, 3.89; N, 24.70.

1-[3-Deoxy-4-(1,1-difluoroethyl)-β-D-*glycero*-tetr-3-enofuranosyl]adenine (22b). Deprotection of **20b** (0.57 g, 1.44 mmol) (as described for **19b** → **21b**) and chromatography with Dowex 1 × 2 (OH^-) resin [(H_2O → MeOH → AcOH/MeOH (1:3)] gave an acetate salt. The salt was neutralized (Na_2CO_3/H_2O), and the mixture was extracted (EtOAc). PTLC (EtOAc/MeOH, 10:1) of the concentrated organic phase gave material (0.39 g, 96%) that was recrystallized (EtOH) to give **22b** as colorless cubes: mp 185−186 °C; UV_{max} 259 nm (ϵ 15 300), min 230 nm (ϵ 3800); ^{1}H NMR (Me_2CO-d_6) δ 1.80 (t, J = 18.8 Hz, 1H), 5.29 (br s, 1H), 5.56−5.60 (m, 1H), 5.76−5.80 (m, 1H), 6.53 (d, J = 2.9 Hz, 1H), 6.84 (br s, 2H), 8.12 (s, 1H), 8.23 (s, 1H); ^{19}F NMR (Me_2CO-d_6) δ 94.5 (qm, J = 18.9 Hz, 2F); ^{13}C NMR (Me_2CO-d_6) δ 22.5 (t, J = 26.5 Hz), 78.9, 93.4, 104.1 (t, J = 4.1 Hz), 117.7 (t, J = 235.3 Hz), 120.3, 139.4, 150.6, 154.3, 155.4 (t, J = 35.7 Hz), 157.3; EI-MS m/z 283 ([M^+], 17), 266, 218, 190, 136 (100); HRMS ($C_{11}H_{11}F_2N_5O_2$) calcd 283.0880, found 283.0876. Anal. Calcd for $C_{11}H_{11}F_2N_5O_2$: C, 46.65; H, 3.91; N, 24.73. Found: C, 46.80; H, 3.66; N, 24.91.

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Supporting Information Available: Experimental details, NMR spectra of selected intermediates, and X-ray crystal structures and CIF data for compounds **3a**, **14**·pyridine, and **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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