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Addition of Difluorocarbene to 3′,4′-Unsaturated Nucleosides: Synthesis of 2′-Deoxy Analogues with a 2-Oxabicyclo[3.1.0]hexane Framework[1]

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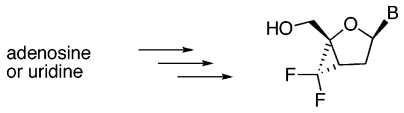

B = adenin-9-yl, cytosin-1-yl, uracil-1-yl

Treatment of protected 2′-deoxy-3′,4′-unsaturated nucleosides derived from adenosine and uridine with difluorocarbene [generated from bis(trifluoromethyl)mercury and sodium iodide] gave fused-ring 2,2-difluorocyclopropane compounds. Stereoselective α-face addition to the dihydrofuran ring resulted from hindrance by the protected β-anomeric nucleobases. A protected uracil compound was converted smoothly into the cytosine derivative via a 4-(1,2,4-triazol-1-yl) intermediate. Removal of the protecting groups gave new difluorocyclopropane-fused nucleoside analogues. The solid-state conformation of the nearly planar furanosyl ring in the uracil compound had a shallow ^{2}E pucker, and a more pronounced $_{1}$E conformation was present in the furanosyl ring of the cytosine derivative.

Introduction

Nucleosides constitute a steadily growing family of small molecules with demonstrated therapeutic potential. A variable that adds complexity to interpretations of structure−activity relationships with nucleoside analogues is their inherent flexibility. Various conformational forms of naturally occurring nucleosides are in rapid equilibrium. Furanosyl rings have pseudorotational mobility, and relationships were defined for two extreme forms of ring pucker [i.e., the north (*N*) and south (*S*) pseudorotational ranges].[2] Conformational preferences are determined by the interplay of anomeric, gauche, and steric effects.[3] Design and synthesis of conformationally restricted nucleoside analogues has been pursued to probe enzyme preferences for the *N* versus *S* (or other) forms. Marquez and co-workers have shown that ring-fused cyclopropane−cyclopentane rings provide carbocyclic bicyclo[3.1.0]hexane scaffolds that can be constrained in either N[4] or S[5] ranges. Selectivities for binding with several enzymes[6] and subtypes of adenosine receptors[7] have been demonstrated with such constrained nucleoside analogues. Syntheses of carbocyclic nucleoside analogues require multiple steps, and the resulting surrogates lack a furanosyl oxygen atom (O4′), which affects hydrogen bond accepting as well as anomeric and gauche effects.

Very recently, Simmons−Smith cyclopropanation of enol ether **B** (derived from L-xylose) was used to prepare a 2-oxabicyclo[3.1.0]hexane-based precursor for nucleoside analogue **A**[8] (Figure 1). We had anticipated[9] that electron-rich alkenes derived from nucleoside enol ethers such as **D** would undergo addition of difluorocarbene to produce 2-oxabicyclo-

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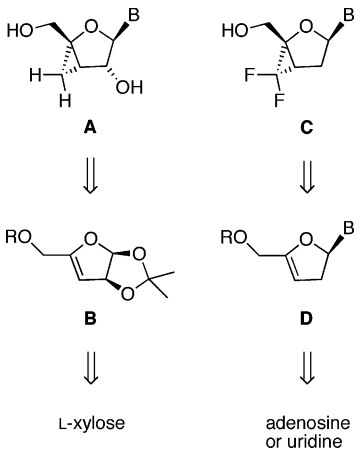

FIGURE 1. 2-Oxabicyclo[3.1.0]hexane analogues.

[3.1.0]hexane nucleosides analogues, **C**, that would resemble 2′-deoxynucleosides with a difluoromethylene bridge spanning the C3′−C4′ bond. Isosteric replacement of hydrogen by fluorine (with the accompanying stereoelectronic effects) could contribute insights for correlations of sugar ring conformation restraint and biological activity. The potent electron-withdrawing effects of fluorine might enhance stability against acid- and enzyme-catalyzed glycosyl bond hydrolysis, and fluorine-substituted analogues usually exhibit increased lipophilicity and altered protein binding. We now report syntheses of the adenine, cytosine, and uracil 2′-deoxy analogues, **C**, of 3′,4′-difluoromethylene insertion compounds derived from adenosine and uridine.

Results and Discussion

We recently developed mild methods for the synthesis of compounds with difluorocyclopropane fused with rings containing nitrogen or oxygen by addition of difluorocarbene to enamines[9] or vinyl ethers.[10] The ultimate goal was synthesis of nucleoside analogues whose furanosyl rings were conformationally restricted by fusion with a difluorocyclopropane ring. Reported procedures in fluorine chemistry usually employed conditions that are incompatible with the sensitivity of glycosyl bonds, and functional groups (including 3-NH of uracil and 6-NH_2 of adenine)[10] in nucleoside derivatives can interact unfavorably with organometallic-based reagents. Suitable protection of the base and sugar components allowed successful addition of difluorocarbene [generated from Seyferth's reagent ($PhHgCF_3$)] to the vinyl ether of 4′,5′-unsaturated nucleosides, and good to high yields of spirodifluorocyclopropane products were obtained.[10] With the present analogues, interference by oxygen-containing groups vicinal to the 3′,4′ carbon−carbon double bond during addition of difluorocarbene (possibly associated with mercury/iodine species) was precluded by prior C2′ deoxygenation. Seyferth's reagent is convenient to use, but its preparation is expensive and somewhat involved and dangerous.[11] Dolbier's reagent (trimethylsilyl fluorosulfonyldifluoroacetate, TFDA) is moisture sensitive, and generation of CF_2 required heating TFDA with sodium fluoride at ≥90 °C[12] (3′,4′-unsaturated nucleosides would decompose upon heating with adventitious HF). Therefore, we generated difluorocarbene (carbenoid) from the inexpensive and readily prepared bis-(trifluoromethyl)mercury[13] (**CAUTION**)[14] and sodium iodide in THF at 60 °C.

Cyclopropylcarbinyl−allylcarbinyl rearrangements that occur upon generation of radicals vicinal to such cyclopropane rings[15] preclude radical-mediated removal of the 2′-hydroxyl group at later stages in the synthesis. Protection of N3 of (2′,5′ and 3′,5′)-bis-*O*-TBSuridine[16] by 4-methoxybenzylation,[17] and treatment of the resulting mixture of (2′,5′ and 3′,5′)-bis-*O*-TBS-3-(4-methoxybenzyl)uridines (**2a**/**2b**) (1:1) with NaH/CS_2 and MeI gave a 2′-enhanced mixture of xanthates **3a**/**3b** (4:1). Equilibration of TBS groups between O2′ and O3′ under basic conditions is well-known, and migration to the more basic O3′ is thermodynamically favored. The **3a**/**3b** mixture was subjected to Barton deoxygenation, and **4a** was isolated by chromatography (52% yield for 3 steps) (Scheme 1).

TBS groups were removed[18] from **4a,** which was converted into 5′-*O*-TBS derivative **6a** (76% for two steps). Replacement of a secondary hydroxyl group by iodide (I_2/Ph_3P/imidazole)[19] usually proceeds with inversion of configuration. However, such treatment of **6a** gave a mixture of inverted product **7a** and epimer **7b** (2.4:1, 81%). Diastereomers **7a** and **7b** had closely similar properties, but both isomers were separated and characterized after removal of the TBS groups with NH_4F/MeOH.[18] Participation of O2 on the uracil ring might have contributed to formation of the doubly inverted isomer **7b**.

We had reported syntheses of 3′,4′-unsaturated nucleoside containing an oxygen atom at C2′ by elimination of H4′ and iodide from C3′ with AgOAc/pyridine and DBN/benzene.[20] However, treatment of the **7a**/**7b** mixture by either of these procedures resulted in predominant or exclusive elimination of H2′/H2″ to give the 2′,3′-unsaturated isomer **8a**. In contrast, heating **7a**/**7b** in a solution of DABCO in benzene at reflux gave **8a**/**8b** (1:2, 99% total). It is noteworthy that no cis-elimination of H4′ and iodide (and neither cis- nor trans-elimination of H2′/H2″ and iodide) was observed with the erythro isomer **7b,** which was recovered from the reaction mixture.

Because separation of **8a**/**8b** was found to be impractical, we treated the mixture with $(CF_3)_2Hg$ and NaI in THF at 60 °C. Adducts were not formed with the less reactive 2′,3′-alkene **8a**, whereas the electron-rich enol ether **8b** underwent addition of difluorocarbene under these mild conditions. Deprotection of the mixture (NH_4F/MeOH) and chromatography allowed separation of the major adduct **9** (65%) from the 2′,3′-alkene, minor adduct, and other byproducts. Benzoylation of **9** gave **10** (99%), excess CAN in CH_3CN/H_2O at reflux removed the 4-methoxybenzyl group to give **11** (82%), and debenzoylation

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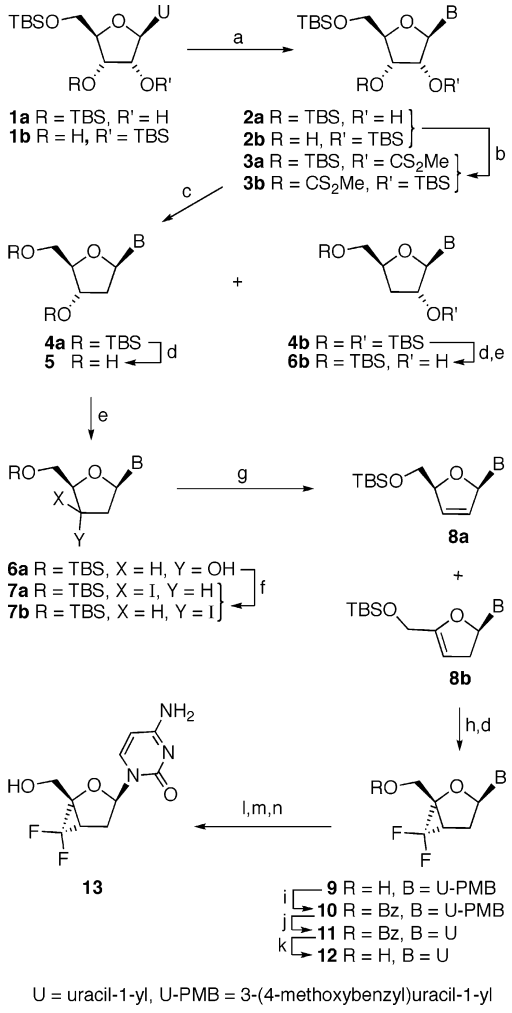
SCHEME 1[a]

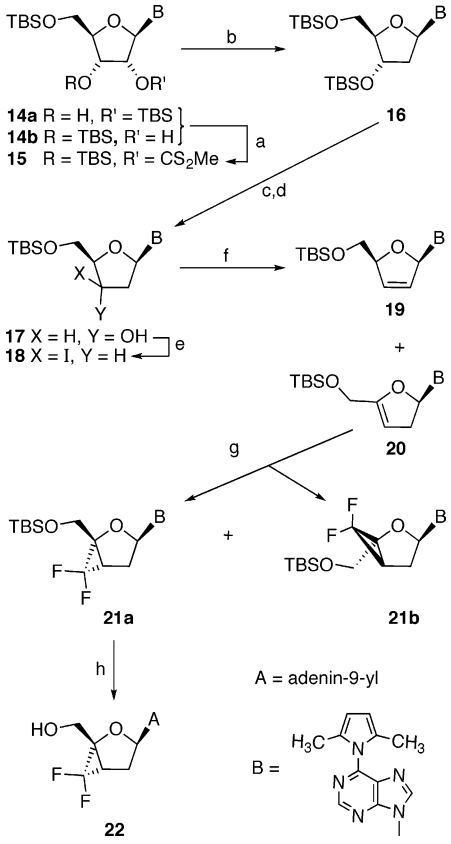


[a] Reagents and conditions: (a) PMBCl/K_2CO_3/DMF; (b) (i) NaH/CS_2/DMF/0 °C, (ii) MeI; (c) Bu_3SnH/AIBN/toluene/90 °C; (d) NH_4F/MeOH/65 °C; (e) TBSCl/pyridine; (f) Ph_3P/I_2/imidazole/toluene/70 °C; (g) DABCO/benzene/80 °C; (h) $(CF_3)_2Hg$/NaI/THF/60 °C; (i) PhCOCl/Et_3N/DCM; (j) CAN/CH_3CN/H_2O/70 °C; (k) NH_3/MeOH/60 °C; (l) $POCl_3$/1,2,4-triazole/Et_3N/CH_3CN; (m) NH_3/H_2O/1,4-dioxane; (n) NH_3/MeOH.

(NH_3/MeOH) gave the 2′-deoxyuridine analogue **12** (86%). Treatment of **11** with $POCl_3$/1,2,4-triazole/Et_3N/CH_3CN[21] gave the 4-(1,2,4-triazol-1-yl) intermediate (93%), which was subjected to ammonolysis (NH_3/H_2O/dioxane) and debenzoylation (NH_3/MeOH) to give 2′-deoxycytidine analogue **13**. Purification [Dowex 1 × 2 (OH^-)] and acidification (HBr/H_2O) gave the crystalline hydrobromide salt of **13** (60% for 3 steps).

A parallel approach was used for the synthesis of adenine analogue **22** (Scheme 2), but differences are noteworthy. We made TBS derivatives of the 6-(2,5-dimethylpyrrol-1-yl)purine nucleosides **14a** and **14b** to overcome difficulties encountered with other 6-amino protecting groups[22] in the presence of organomercury reagents. In contrast with the uridine derivatives **2a**/**2b**, treatment of **14a**/**14b** with NaH/CS_2 and MeI gave highly predominant formation of the 2′-xanthate **15** (86%), presumably resulting from enhanced migration of the TBS group to the more basic O3′ and attack of the O2′ anion on CS_2. Barton

SCHEME 2[a]



[a] Reagents and conditions: (a) (i) NaH/CS_2/DMF/0 °C, (ii) MeI; (b) Bu_3SnH/AIBN/toluene/90 °C; (c) NH_4F/MeOH/65 °C; (d) TBSCl/pyridine; (e) Ph_3P/I_2/imidazole/toluene/70 °C; (f) DABCO/benzene/80 °C; (g) $(CF_3)_2Hg$/NaI/THF/60 °C; (h) TFA/H_2O/0 °C.

deoxygenation gave **16** (62%), which was desilylated and then selectively protected at O5′ to give **17** (69% for 2 steps). Treatment of **17** with Ph_3P/I_2/imidazole gave crystalline **18** (74%), whose structure was confirmed by X-ray analysis.[23] Formation of the single stereoisomer contrasts with our results with **6a** → **7a**/**7b**, and also with a report[24] in which a 1:3 epimeric mixture of iodides was obtained with an analogue lacking protection at N6. Epimerization by iodide displacement of iodide at C3′ was invoked with that unprotected analogue,[24] and neighboring group participation (by O2 of the uracil moiety) might also occur in the **6a** → **7a**/**7b** transformation. The enhanced solubility of **17** in toluene [resulting from masking the amino group as a 6-(2,5-dimethypyrrol-1-yl) moiety] might limit epimerization by reducing reaction times at elevated temperatures.

DABCO in refluxing benzene converted **18** into a mixture of elimination products **19**/**20** (1:2, 97% total), which is in harmony with the parallel reaction with **7a**. The desired regioisomer **20** was isolated and subjected to $(CF_3)_2Hg$/NaI at 60 °C to give the diastereomeric difluorocyclopropanes **21a**/**21b** (~9:1, 51% total). Treatment of **21a**/**21b** with TFA/H_2O (9:1) effected hydrolytic cleavage of both the 2,5-dimethylpyrrole ring and the TBS ether. ^{19}F NMR chemical shifts and

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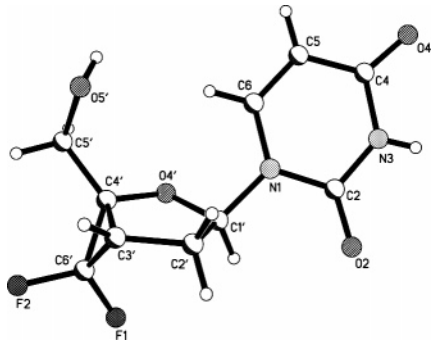

FIGURE 2. X-ray crystal structure of **12**.

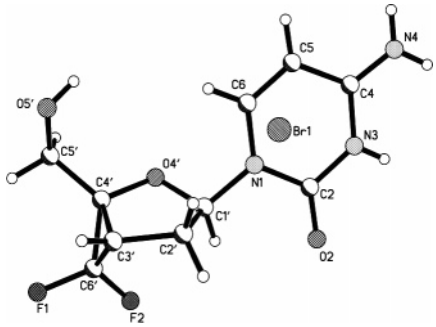

FIGURE 3. X-ray crystal structure of **13**·HBr.

couplings of the microcrystalline major isomer **22** (54%) were parallel with those of the major uracil **12** and cytosine **13** analogues.

X-ray Structures. Crystals of **12** and **13**·HBr were suitable for X-ray analysis. The nearly planar furanosyl ring[25] in **12** (ν_{max} = 10.1°) has a pseudorotation-cycle angle of P = 159.8° (a shallow ^{2}E conformational preference), and the rotation angle of the base about the glycosyl bond is in the anti range (χ = −148.1°) (Figure 2). The furanosyl moiety in **13**·HBr has a larger maximum puckering amplitude (ν_{max} = 25.3°), P = 135.6° ($_1$E conformation range), and the base rotation also is anti (χ = −138.7°) (Figure 3). Thus, changes in the nucleobase and charge (hydrobromide salt) caused only minimal alterations in preferred conformations of these constrained 2-oxabicyclo-[3.1.0]hexane nucleoside analogues.

In summary, we have synthesized a new class of 2-oxabicyclo-[3.1.0]hexane-based nucleosides that are conformationally restricted by a difluoromethylene bridge spanning the C3′−C4′ bond. Addition of difluorocarbene (carbenoid) to vinyl ethers within 3′,4′-unsaturated nucleosides derived from adenosine and uridine gave the target structures. Electron-withdrawing effects of two fluorine atoms β to the furanosyl ring oxygen (O4′) in these compounds are expected to confer stability under conditions that result in chemical or enzymatic cleavage of naturally occurring nucleosides. Solid-state conformations of the uracil (^{2}E) and cytosine ($_1$E) analogues were similar, with a less puckered furanosyl ring in the former. Synthesis of other types of difluorocyclopropane-fused nucleoside analogues and collaborative biological testing results will be reported separately.

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Experimental Section[26]

2′-Deoxy-3-(4-methoxybenzyl)uridine (5) and 5′-*O*-TBS-3′-deoxy-3-(4-methoxybenzyl)uridine (6b). (A) Dried K_2CO_3 (11.3 g, 82.0 mmol) and then 4-methoxybenzyl chloride (12.8 g, 11.4 mL, 82.0 mmol) were added to a stirred solution of a mixture[16] of 3′,5′-bis-*O*-TBS-uridine (**1a**) and 2′,5′-bis-*O*-TBS-uridine (**1b**) (19.3 g, 41.0 mmol) in DMF (60 mL), and stirring was continued at ambient temperature overnight. Volatiles were removed in vacuo, and the residue was chromatographed (hexanes → EtOAc/hexanes, 1:3) to give a 1:1 mixture of 3′,5′-bis-*O*-TBS-3-(4-methoxybenzyl)-uridine (**2a**) and 2′,5′-bis-*O*-TBS-3-(4-methoxybenzyl)uridine (**2b**) as a colorless oil (22.8 g, 94%). (B) NaH (1.8 g, 76.9 mmol) and then CS_2 (3.8 mL, 4.9 g, 65.4 mmol) were added to an ice-cold solution of the **2a**/**2b** in DMF (100 mL), and the solution was stirred at 0 °C for 1.5 h. MeI (7.1 mL, 16.2 g, 115.3 mmol) was added, and stirring was continued for 0.5 h. Volatiles were evaporated in vacuo, the residue was partitioned [EtOAc (200 mL)/H_2O (200 mL)], and the aqueous phase was extracted with EtOAc (2 × 200 mL). The combined organic phase was dried ($MgSO_4$), and volatiles were evaporated to give a mixture of xanthates **3a**/**3b** (4:1; 24.1 g, 92%). (C) A deoxygenated solution of this material in toluene (100 mL) was heated to 90 °C, and a solution of AIBN (600 mg, 3.5 mmol) and Bu_3SnH (15.0 mL, 16.2 g, 55.5 mmol) in toluene (20 mL) was added slowly (20 min). Heating and stirring were continued for an additional 30 min, and volatiles were evaporated in vacuo. The residue was chromatographed (hexanes → EtOAc/hexanes, 1:20) to give 3′,5′-bis-*O*-TBS-2′-deoxy-3-(4-methoxybenzyl)uridine (**4a**) (∼12.2 g, 60%) and 2′,5′-bis-*O*-TBS-3′-deoxy-3-(4-methoxybenzyl)uridine (**4b**) (∼3.1 g, 15%) contaminated with tin-containing impurities. (D) A solution of **4a** (6.5 g, 11.3 mmol) and NH_4F (2.5 g, 67.6 mmol) in MeOH (200 mL) was refluxed with stirring for 12 h, and volatiles were evaporated. Chromatography (EtOAc) gave **5** (3.7 g, 94%). Purification by recrystallizations (EtOAc) gave a colorless powder: mp 133−135 °C; UV max 222, 264 nm (ϵ 19 000, 13 200), min 217, 240 nm (ϵ 18 700, 6500); ^{1}H NMR (CD_3OD) δ 2.12−2.21 (m, 1H), 2.31 (ddd, J = 3.4, 5.9, 13.7 Hz, 1H), 3.71 (dd, J = 3.4, 13.2 Hz, 1H), 3.76 (s, 3H), 3.77 (dd, J = 3.4, 13.2 Hz, 1H), 3.91−3.93 (m, 1H), 4.37 (dt, J = 3.4, 5.9 Hz, 1H), 5.00 (s, 2H), 5.78 (d, J = 8.4 Hz, 1H), 6.28 (t, J = 6.6 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 7.32 (d, J = 8.8 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H); ^{13}C NMR (CD_3OD) δ 41.6, 44.7, 55.8, 62.8, 72.2, 87.6, 89.0, 102.2, 114.8, 130.4, 131.1, 140.7, 152.4, 160.6, 165.0; FAB-MS *m*/*z* 371 ([M + Na^+] 100%); HRMS ($C_{17}H_{20}N_2O_6Na$) calcd 371.1219, found 371.1208. (E) Deprotection of **4b** (1.7 g, 2.9 mmol) with NH_4F (0.6 g, 16.2 mmol) as described for **4a** → **5** was followed by treatment with 1.1 equiv of TBSCl in pyridine, evaporation to dryness, and chromatography (EtOAc/hexanes, 1:6 → 1:2) to give **6b** (0.9 g, 70%) as a pale-yellow oil: UV max 222, 264 nm (ϵ 19 000, 13 200), min 217, 240 nm (ϵ 18 700, 6500); ^{1}H NMR (CD_3OD) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 1.88 (ddd, J = 1.5, 5.4, 13.2 Hz, 1H), 2.08−2.14 (m, 1H), 3.68 (dd, J = 1.5, 11.7 Hz, 1H), 3.76 (s, 3H), 3.81 (s, 1H), 4.11 (dd, J = 1.5, 11.7 Hz, 1H), 4.35 (d, J = 4.4 Hz, 1H), 4.51−4.55 (m, 1H), 5.00 (d, J = 13.7 Hz, 1H), 5.07 (d, J = 13.7 Hz, 1H), 5.69 (s, 1H), 5.71 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 7.8 Hz, 1H); ^{13}C NMR (CD_3OD) δ −5.6, −5.5, 18.4, 25.8, 31.9, 43.4, 55.2, 62.9, 77.4, 82.0, 94.0, 100.9, 113.6, 128.9, 130.6, 137.8, 151.4, 159.0, 162.8; FAB-MS *m*/*z* 495 ([M + Na^+] 100%); HRMS ($C_{23}H_{34}N_2O_6SiNa$) calcd 495.2084, found 495.2103.

1-(5-*O*-TBS-2,3-dideoxy-3-iodo-β-D-*threo*-pentofuranosyl)-3-(4-methoxybenzyl)uracil (7a) and 5′-*O*-TBS-2′,3′-dideoxy-3′-iodouridine (7b). A solution of **5** (3.7 g, 10.6 mmol) and TBSCl (1.8 g, 11.7 mmol) in pyridine (10 mL) was stirred at ambient temperature for 1.5 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:6 →1:2) to give 5′-*O*-

(26) General experimental details are in the Supporting Information.

TBS-2′-deoxy-3-(4-methoxybenzyl)uridine (**6a**) (4.0 g, 81%) as a pale yellow oil: FAB-MS *m*/*z* 463 ([M + H$^+$] 10%), 307 (100%); HRMS ($C_{23}H_{35}N_2O_6Si$) calcd 463.2264, found 463.2249.

Ph_3P (9.1 g, 34.6 mmol), imidazole (4.7 g, 69.3 mmol), and iodine (8.8 g, 34.6 mmol) were added to a stirred solution of **6a** (8.0 g, 17.3 mmol) in toluene (200 mL) under N_2. Stirring was continued, and the mixture was heated at 70 °C for 2 h and then cooled to ambient temperature. The clear supernatant was decanted, concentrated, and chromatographed (EtOAc/hexanes, 1:4) to give the threo/erythro epimers **7a**/**7b** (2.4:1; 8.1 g, 81%). See the Supporting Information for separation and characterization of the deprotected epimers.

1-[5-*O*-Benzoyl-2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]-3-(4-methoxybenzyl)uracil (10). (A) A solution of **7a**/**7b** (8.0 g, 13.9 mmol) and DABCO (6.0 g, 53.6 mmol) in benzene (200 mL) was stirred at reflux for 6 h, concentrated, and deposited on silica gel. Chromatography (EtOAc/hexanes, 1:20 → 1:3) gave unreacted **7b** (2.2 g, 28%) plus a 1:2 mixture of 1-(5-*O*-TBS-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-3-(4-methoxybenzyl)uracil (**8a**) and (*R*)-2-[(*tert*-butyldimethylsilyloxy)methyl]-5-[3-(4-methoxybenzyl)uracil-1-yl]-4,5-dihydrofuran (**8b**) (total: 4.4 g, 71%). (B) Powdered NaI (3.0 g, 20.0 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 ambient temperature, and a mixture of **8a**/**8b** (1.47 g, 3.3 mmol) and then $(CF_3)_2Hg$[13,14] (1.7 g, 5.0 mmol) in dried THF (10 mL) was injected through a septum (under N_2). The reaction mixture was heated at 60 °C for 1 h, and volatiles were evaporated. Column chromatography (EtOAc/hexanes, 1:4 → 1:1) gave a mixture of unreacted **8a** plus 5′-*O*-TBS-2′,3′-dideoxy-3′,4′-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]-3-(4-methoxybenzyl)uracil. A solution of the mixture (1.40 g) and NH_4F (0.4 g, 10.8 mmol) in MeOH (25 mL) was refluxed overnight. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:4 → 2:1) to give 1-[2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]-3-(4-methoxybenzyl)uracil (**9**) (470 mg, 65%). (C) Et_3N (0.5 mL, 0.4 g, 3.9 mmol) and BzCl (0.3 mL, 0.4 g, 2.6 mmol) were added to a stirred solution of **9** (470 mg, 1.2 mmol) in CH_2Cl_2 (5 mL), and stirring was continued for 1 h. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:6 → EtOAc) to give 1-[5-*O*-benzoyl-2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]-3-(4-methoxybenzyl)uracil (**10**) (590 mg, 99%): UV max 227, 260 nm (ε 25 500, 10 000), min 212, 248 nm (ε 17 700, 8700); ^{1}H NMR ($CDCl_3$) δ 2.30−2.36 (m, 1H), 2.50 (dd, *J* = 7.3, 14.2 Hz, 1H), 2.85 (dd, *J* = 7.8, 11.2 Hz, 1H), 3.76 (s, 3H), 4.80−4.87 (m, 2H), 4.95 (d, *J* = 13.7 Hz, 1H), 4.98 (d, *J* = 13.7 Hz, 1H), 5.56 (d, *J* = 8.3 Hz, 1H), 6.12−6.15 (m, 1H), 6.81 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.61 (t, *J* = 7.3 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 2H); ^{19}F NMR ($CDCl_3$) δ 135.7 (dd, *J* = 15.0, 166.6 Hz, 1F), 155.0 (d, *J* = 166.6 Hz, 1F); ^{13}C NMR ($CDCl_3$) δ 28.0 (t, *J* = 12.2 Hz), 32.1, 43.5, 55.1, 59.8, 70.3 (t, *J* = 11.4 Hz), 89.7 (d, *J* = 4.1 Hz), 102.8, 111.9 (dd, *J* = 296.8, 305.2 Hz), 113.6, 128.6, 128.7, 129.1, 129.6, 130.7, 133.7, 137.2, 150.3, 159.1, 162.1, 165.9; FAB-MS *m*/*z* 507 ([M + Na$^+$] 100%), 485 (100%); HRMS ($C_{25}H_{22}F_2N_2O_6Na$) calcd 507.1344, found 507.1333.

1-[2,3-Dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]uracil (12). (A) CAN (8.5 g, 15.5 mmol) in H_2O (18 mL) was added to a solution of **10** (1.9 g, 3.9 mmol) in CH_3CN (180 mL), the mixture was heated at 70 °C for 1.5 h, and H_2O was added. The diluted reaction mixture was extracted with EtOAc (5 × 50 mL), and the combined organic phase was concentrated and deposited on silica gel. Chromatography (EtOAc/hexanes, 1:4 → 2:1) gave 1-[5-*O*-benzoyl-2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]uracil (**11**) (1.17 g, 82%). (B) A solution of **11** (1.68 g, 4.6 mmol) in NH_3/MeOH (14%, 20 mL) in a sealed flask was heated at 60 °C overnight. Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:3 → EtOAc) to give crystalline material (1.03 g, 86%) that was recrystallized (MeOH) to give **12**: mp 168−170 °C dec; UV max 259 nm (ε 9900), min 229 nm (ε 2700); ^{1}H NMR (CD_3OD) δ 2.44−2.53 (m, 2H), 2.78 (dd, *J* = 7.8, 13.7 Hz, 1H), 3.89 (d, *J* = 13.2 Hz, 1H), 4.06 (dd, *J* = 3.4, 13.2 Hz, 1H), 5.72 (d, *J* = 8.3 Hz, 1H), 6.10−6.16 (m, 1H), 7.81 (d, *J* = 8.3 Hz, 1H); ^{19}F NMR (CD_3OD) δ 135.7 (dd, *J* = 15.0, 164.5 Hz, 1F), 151.0 (d, *J* = 164.5 Hz, 1F); ^{13}C NMR (CD_3OD) δ 28.9 (t, *J* = 12.2 Hz), 32.7, 58.5, 74.4 (t, *J* = 11.1 Hz), 90.9 (dd, *J* = 3.3, 7.9 Hz), 103.4, 114.8 (dd, *J* = 295.3, 303.7 Hz), 142.9, 152.0, 166.2; MS *m*/*z* 260 ([M$^+$] 3%), 229, 202, 158, 138 (100%); HRMS ($C_{10}H_{10}F_2N_2O_4$) calcd 260.0608, found 260.0602. Anal. Calcd for $C_{10}H_{10}F_2N_2O_4$: C, 46.16; H, 3.87; N 10.77. Found: C, 46.23; H, 4.11; N 11.06.

1-[2,3-Dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]cytosine Hydrobromide (13·HBr). Et_3N (7.28 mL, 3.86 g, 38.2 mmol) was added dropwise to a stirred, cooled (∼0 °C) mixture of $POCl_3$ (1.11 mL, 1.77 g, 11.54 mmol), 1,2,4-triazole (3.80 g, 55.1 mmol), and MeCN (32.8 mL). A solution of **11** (1.92 g, 5.25 mmol) in MeCN (20.5 mL) was added, and stirring was continued at ambient temperature for 2 h. Et_3N (5.08 mL, 3.70 g, 36.6 mmol) and H_2O (2.05 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 (60 mL)//CH_2Cl_2 (60 mL)]. The aqueous phase was extracted (CH_2Cl_2, 60 mL), and the combined organic phase was washed (brine, 100 mL) and dried ($MgSO_4$). Evaporation of volatiles gave 1-[5-*O*-benzoyl-2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]-4-(1,2,4-triazol-1-yl)pyrimidin-2-one (2.04 g, 93%) as colorless crystals, which were dissolved in 1,4-dioxane (30 mL) and stirred with a solution of NH_3/H_2O (30%, 10 mL) at ambient temperature for 12 h. Volatiles were evaporated and the residue was dissolved and filtered through silica gel (EtOAc/MeOH, 2:1). Volatiles were evaporated, and the residue was stirred in NH_3/MeOH (14%, 10 mL) at 80 °C for 90 min. Volatiles were evaporated and the residue was dissolved in H_2O and applied to a column of Dowex 1 × 2 (OH^-) resin (in H_2O). Elution (H_2O) and evaporation of volatiles from UV-active fractions gave 1-[2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]cytosine (**13**) (520 mg, 60%) as a pale-yellow oil that was dissolved in MeOH (10 mL) and 48% HBr/H_2O (1 mL) was added. Volatiles were evaporated, and the residue was recrystallized (MeOH) to give **13**·HBr as colorless crystals: mp 170−174 °C dec; UV max 280 nm (ε 11 400), min 245 nm (ε 3000); ^{1}H NMR (CD_3OD) δ 2.51−2.64 (m, 2H), 2.86 (dd, *J* = 7.8, 13.7 Hz, 1H), 3.91 (d, *J* = 13.2 Hz, 1H), 4.10 (dd, *J* = 3.4, 13.2 Hz, 1H), 6.09−6.13 (m, 1H), 6.15 (d, *J* = 7.8 Hz, 1H), 8.26 (d, *J* = 7.8 Hz, 1H); ^{19}F NMR (CD_3OD) δ 136.1 (dd, *J* = 15.0, 164.5 Hz, 1F), 152.0 (d, *J* = 164.5 Hz, 1F); ^{13}C NMR (CD_3OD) δ 28.9 (t, *J* = 12.2 Hz), 33.3, 58.3, 75.3 (t, *J* = 11.2 Hz), 92.3 (br s), 95.2, 114.5 (dd, *J* = 294.5, 302.9 Hz), 147.0, 148.3, 161.5; FAB-MS *m*/*z* 282 ([M + Na$^+$] 90%), 239, 237 (100%); HRMS ($C_{10}H_{11}F_2N_3O_3Na$) calcd 282.0666, found 282.0678.

9-[3,5-Bis-*O*-TBS-2-*O*-(thiomethoxythiocarbonyl)-β-D-ribofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (15). NaH (1.42 g, 59.3 mmol) and then CS_2 (3.0 mL, 3.8 g, 50.4 mmol) were added to a cold (ice/water bath) stirred solution of **14a**/**14b**[22] (17.0 g, 29.7 mmol) in DMF (100 mL). Stirring was continued for 1.5 h at ∼0 °C, MeI (5.5 mL, 12.6 g, 89.0 mmol) was added, and stirring was continued for 0.5 h. Volatiles were evaporated in vacuo (<50 °C), the residue was partitioned (EtOAc/H_2O), the aqueous phase was extracted (EtOAc, 3 × 100 mL), and the combined organic phase was dried ($MgSO_4$). Volatiles were evaporated, and the residue was chromatographed (EtOAc/hexanes, 1:20 → 1:4) to give xanthate **15** (17.0 g, 86%). Recrystallizations of a sample (toluene/hexanes) gave colorless needles: mp 158−160 °C; UV max 283 nm (ε 20 200), min 248 nm (ε 4700); ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.12 (s, 3H), 0.13 (s, 3H), 0.89 (s, 9H), 0.95 (s, 9H), 2.21 (s, 6H), 2.56 (s, 3H), 3.82 (dd, *J* = 2.4, 11.7 Hz, 1H), 3.97 (dd, *J* = 2.9, 11.7 Hz, 1H), 4.23−4.25 (m, 1H), 4.96 (dd, *J* = 2.9,

4.9 Hz, 1H), 5.98 (s, 2H), 6.44 (t, J = 5.4 Hz, 1H), 6.51 (d, J = 5.9 Hz, 1H), 8.36 (s, 1H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.6, −5.5, −5.1 (2C), 13.5, 17.9, 18.3, 19.2, 25.6, 25.9, 62.4, 70.3, 82.6, 85.6, 86.8, 108.8, 128.9, 129.6, 143.4, 150.2, 152.3, 153.2, 215.0; FAB-MS m/z 686 ([M + Na^+] 67%), 664, 451 (100%), 421, 343, 291; HRMS ($C_{30}H_{49}N_5O_6S_2Si_2Na$) calcd 686.2662, found 686.2669.

9-[5-*O*-TBS-2-deoxy-β-D-*erythro*-pentofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (17). A solution of **15** (17.0 g, 25.6 mmol) in dried toluene (50 mL) was deoxygenated (N_2) and heated with stirring at 100 °C. A solution of Bu_3SnH (14.0 mL, 15.0 g, 51.3 mmol) and AIBN (0.8 g, 4.9 mmol) in dried toluene (20 mL) was added over 40 min, and stirring was continued at 100 °C for 20 min. Volatiles were evaporated, and the residue was chromatographed (hexanes → EtOAc/hexanes, 1:6) to give 9-[3,5-bis-*O*-TBS-2-deoxy-β-D-*erythro*-pentofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (**16**) (8.8 g, 62%) as an orange oil, which was dissolved in MeOH (100 mL). NH_4F (3.4 g, 91.5 mmol) was added, the solution was stirred at reflux overnight, and volatiles were evaporated. The residue was chromatographed (EtOAc) to give 9-[2-deoxy-β-D-*erythro*-pentofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (5.2 g, 93%) as an orange oil, which was dissolved in pyridine (14 mL). TBS−Cl (2.63 g, 17.4 mmol) was added, and the solution was stirred for 1 h. Volatiles were evaporated in vacuo, and the residue was chromatographed (EtOAc/hexanes, 1:6 → EtOAc) to give **17** (5.0 g, 71%) as an orange oil: UV max 283 nm (ϵ 12 200), min 245 nm (ϵ 3800); ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 2.19 (s, 6H), 2.53−2.58 (m, 1H), 2.67−2.73 (m, 1H), 3.16 (br s, 1H), 3.85 (dd, J = 3.9, 11.2 Hz, 1H), 3.90 (dd, J = 3.9, 11.2 Hz, 1H), 4.09−4.10 (m, 1H), 4.62−4.66 (m, 1H), 5.94 (s, 2H), 6.60 (t, J = 6.3 Hz, 1H), 8.45 (s, 1H), 8.91 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, 13.4, 18.3, 25.9, 41.1, 63.3, 72.0, 84.6, 87.4, 108.9, 129.0, 129.6, 143.4, 150.0, 152.1, 153.0; FAB-MS m/z 443 ([M^+] 100%); HRMS ($C_{22}H_{33}N_5O_3Si$) calcd 443.2352, found 443.2360.

9-[5-*O*-TBS-2,3-dideoxy-3-iodo-β-D-*threo*-pentofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (18). Ph_3P (3.9 g, 14.9 mmol), imidazole (2.0 g, 29.8 mmol), and iodine (3.8 g, 15.0 mmol) were added to a stirred solution of **17** (2.2 g, 5.0 mmol) in toluene (70 mL) under N_2. The mixture was stirred and heated at 70 °C for 2 h, and allowed to cool to ambient temperature. The clear supernatant was decanted, concentrated, and chromatographed (EtOAc/hexanes, 1:4) to give **18** (2.0 g, 74%). Recrystallizations (CH_2Cl_2/MeOH) gave colorless needles: mp 116−118 °C dec; UV max 283 nm (ϵ 13 500), min 245 nm (ϵ 4400); ^{1}H NMR ($CDCl_3$) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.89 (s, 9H), 0.91 (s, 9H), 2.21 (s, 6H), 3.10 (dt, J = 4.6, 14.6 Hz, 3H), 3.33 (dt, J = 6.9, 14.6 Hz, 1H), 3.73−3.76 (m, 1H), 3.91 (dd, J = 4.4, 10.7 Hz, 1H), 4.09 (dd, J = 4.9, 10.7 Hz, 1H), 4.54−4.58 (m, 1H), 5.98 (s, 2H), 6.50 (dd, J = 4.7, 7.0 Hz, 1H), 8.62 (s, 1H), 8.90 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.3 (2C), 13.5, 18.2, 20.0, 25.9, 43.8, 67.8, 82.7, 84.5, 108.9, 129.0, 129.7, 143.4, 150.1, 152.1, 152.8; FAB-MS m/z 553 ([M^+] 30%); HRMS ($C_{22}H_{32}IN_5O_2Si$) calcd 553.1329, found 553.1360.

9-(5-*O*-TBS-2,3-dideoxy-β-D-*glycero*-pent-2-enofuranosyl)-6-(2,5-dimethylpyrrol-1-yl)purine (19) and (*R*)-2-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[6-(2,5-dimethylpyrrol-1-yl)purin-9-yl]-4,5-dihydrofuran (20). A solution of **18** (2.7 g, 4.9 mmol) and DABCO (3.0 g, 26.8 mmol) in benzene (60 mL) was stirred and heated at 80 °C under N_2 for 14 h, allowed to cool to ambient temperature, and concentrated. Filtration through silica (EtOAc/hexanes, 1:3) gave a mixture of **19**/**20** (1:2; 2.0 g, 97%). Separation and purification (PTLC; EtOAc/hexanes, 1:3) gave **19**: ^{1}H NMR ($CDCl_3$) δ 0.026 (s, 3H), 0.031 (s, 3H), 0.86 (s, 9H), 2.19 (s, 6H), 3.81−3.91 (m, 2H), 5.12−5.16 (m, 1H), 5.97 (2H), 6.10−6.12 (m, 1H), 6.44−6.46 (m, 1H), 7.23−7.25 (m, 1H), 8.38 (s, 1H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.5, −5.4, 13.5, 18.5, 25.9, 64.6, 88.0, 88.4, 108.8, 125.1, 128.8, 129.7, 135.0, 143.5, 150.0, 152.3, 153.3; MS m/z 448 ([M + Na^+] 100%), 426 (50%); HRMS ($C_{22}H_{31}N_5O_2SiNa$) calcd 448.2145, found 448.2150. Enol ether **20** was obtained as a pale yellow oil: UV max 283 nm (ϵ 11 800), min 246 nm (ϵ 3800); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 2.21 (s, 6H), 3.03−3.06 (m, 1H), 4.41−4.48 (m, 1H), 4.23−4.31 (m, 2H), 5.17 (s, 1H), 5.98 (s, 2H), 6.96 (dd, J = 2.9, 9.3 Hz, 1H), 8.27 (s, 1H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4 (2C), 13.5, 18.3, 25.7, 36.8, 58.2, 84.3, 95.2, 108.9, 128.5, 129.7, 142.1, 150.2, 152.5, 152.7, 157.0; MS m/z 425 ([M^+] 55%), 213 (100%); HRMS ($C_{22}H_{31}N_5O_2Si$) calcd 425.2247, found 425.2249.

9-[2,3-Dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]adenine (22). Treatment of **20** (2.5 g, 5.9 mmol) in dried THF (25 mL) with the reagent prepared from NaI (5.3 g, 35.3 mmol) and $(CF_3)_2Hg$[13,14] (3.0 g, 8.8 mmol) (according to the procedure described for **7a** → **8**) gave a mixture that was deposited on silica gel and chromatographed (EtOAc/hexanes, 1:10 → 1:7). The eluted red oil contained a mixture of 9-[5-*O*-TBS-2,3-dideoxy-3,4-*C*-(difluoromethylene)-β-D-*erythro*-pentofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (**21a**) and 9-[5-*O*-TBS-2,3-dideoxy-3,4-*C*-(difluoromethylene)-α -L-*erythro*-pentofuranosyl]-6-(2,5-dimethylpyrrol-1-yl)purine (**21b**) (~9:1; 1.43 g, 51%), which was dissolved in cold (~0 °C) TFA/H_2O (9:1, 20 mL) and stirred at ~0 °C for 3 h. Volatiles were evaporated in vacuo (<30 °C), saturated $NaHCO_3$/H_2O (20 mL) was added, the mixture was extracted (EtOAc, 4 × 50 mL), the organic phase was combined, and volatiles were evaporated. Chromatography of the resulting red oil (EtOAc/MeOH, 20:1) gave **22** (460 mg, 54%) as a syrup that was crystallized (MeOH) to give **22** as an analytically pure white powder: mp 188−190 °C dec; UV max 259 nm (ϵ 14 000), min 227 nm (ϵ 2500); ^{1}H NMR (CD_3OD) δ 2.66 (dd, J = 6.1, 14.9 Hz, 1H), 2.91−3.02 (m, 2H), 3.89 (d, J = 13.2 Hz, 1H), 4.03 (dd, J = 3.4, 13.2 Hz, 1H), 6.38 (t, J = 6.1 Hz, 1H), 8.20 (s, 1H), 8.32 (s, 1H); ^{19}F NMR (CD_3OD) δ 135.1 (dd, J = 15.0, 164.5 Hz, 1F), 152.0 (d, J = 164.5 Hz, 1F); ^{13}C NMR (CD_3OD) δ 29.5 (t, J = 12.6 Hz), 33.4, 58.9, 74.9 (t, J = 11.4 Hz), 90.5, 103.4, 114.8 (dd, J = 294.5, 302.9 Hz), 120.7, 141.2, 150.2, 154.1, 157.6; MS m/z 283 ([M^+] 3%), 226, 135; HRMS ($C_{11}H_{11}F_2N_5O_2$) calcd 283.0880, found 283.0890. Anal. Calcd for $C_{11}H_{11}F_2N_5O_2$: C, 46.65; H, 3.91; N 24.73. Found: C, 46.43; H, 4.05; N, 24.80.

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Supporting Information Available: General experimental details, separation and characterization of the products of deprotection of **7a**/**7b**, NMR spectra of compounds for which elemental analyses were not obtained, and CIF data for the crystal structures of **12** (code number XL519) and **13**·HBr (code number XL528). This material is available free of charge via the Internet at http://pubs.acs.org.

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