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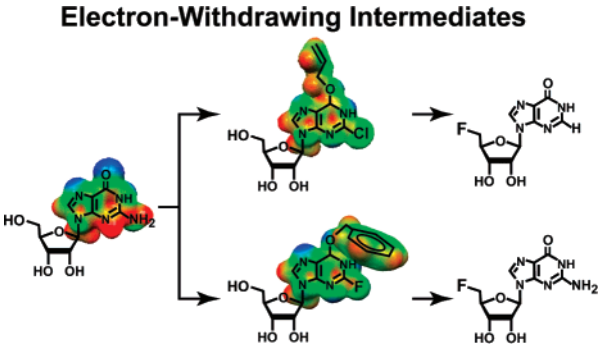
Efficient Syntheses of 5′-Deoxy-5′-fluoroguanosine and -inosine

Robert C. Spitale,[†] Moriah G. Heller,[‡] Amanda J. Pelly,[‡,§] and Joseph E. Wedekind*[,†,‡]

Department of Biochemistry & Biophysics, University of Rochester Medical Center, 601 Elmwood Avenue, Box 712, Rochester, New York 14642, and Department of Chemistry, Biological Chemistry Cluster, University of Rochester, RC Box 270216, Rochester, New York 14627-0216

joseph.wedekind@rochester.edu

Received July 19, 2007



Substitution of oxygen with a weak hydrogen bond acceptor such as fluorine provides a single-atom modification that can have grave effects on the chemical and medicinal properties of nucleoside analogues. To that end, we present a simple and high-yielding method for the novel synthesis of 5′-deoxy-5′-fluoroguanosine and 5′-deoxy-5′-fluoroinosine utilizing an intramolecular electron-withdrawing approach. The properties of the resulting modified nucleosides, as well as the halogenated intermediates, are notable for their similarity to nucleoside analogues used in the treatment of cancer, as well as enzyme inhibitors designed to target parasitic protozoa.

As many as 20% of pharmaceuticals on the market contain fluorine, including half of the top ten drugs sold in 2005.[1] Introducing fluorine into a molecule presents unique problems in terms of selectivity, facility, and safety. Nucleosides are the building blocks of DNA, RNA, many essential vitamins and serve as regulatory molecules in all cells. Fluorinated nucleoside analogues have been employed to study the chemical and metabolic properties of biological systems via ^{19}F NMR[2−6] as anti-sense probes for positron emission tomography studies[7] and as inhibitors of biochemical reactions.[8−10] Functional group transformation at the 5′-position of nucleosides has historically been an area of intense interest, due primarily to the biological importance of this position in phosphoryl transfer.[11−15] Derivatives of adenosine such as 5′-deoxy-5′-fluoroadenosine (5′-F-A) are rare in nature but can be produced enzymatically with high yield and in a single step.[16,17] Here, we describe the first synthesis of 5′-deoxy-5′-fluoroguanosine (5′-F-G) and 5′-deoxy-5′-fluoroinosine (5′-F-I). Alteration of the 5′-substituent to fluorine renders the nucleoside inert to enzymatic phosphorylation and unreactive as a nucleophile, while retaining a size comparable to oxygen, as well as the capacity for modest hydrogen bonding in the appropriate environment.[23−25]

In general, synthetic strategies used to produce nucleoside analogues must overcome unique challenges arising from the reactivity of nucleobase functional groups. Toward this end, the fluorination of nucleoside derivatives has been accomplished either by direct incorporation from a fluoride source or by attachment chemistry involving a fluorinated building block. The chemical synthesis of 5′-F-A has been achieved (i) by fluorination of a primary 5′-alcohol,[18−20] (ii) enzymatic synthesis from *S*-adenosyl-L-methionine,[21] or (iii) use of Vörbruggen's conditions in combination with method (i).[22] Selective fluorination at the 2′- and 3′-positions has been realized as well, but with high step count and low individual yields.[26−29]

[†] University of Rochester.
[‡] University of Rochester Medical Center.
[§] Present address: Department of Chemistry, Cornell University, Hungerford Hill Rd, Ithaca, New York 14853.

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10.1021/jo7015778 CCC: $37.00
Published on Web 09/29/2007

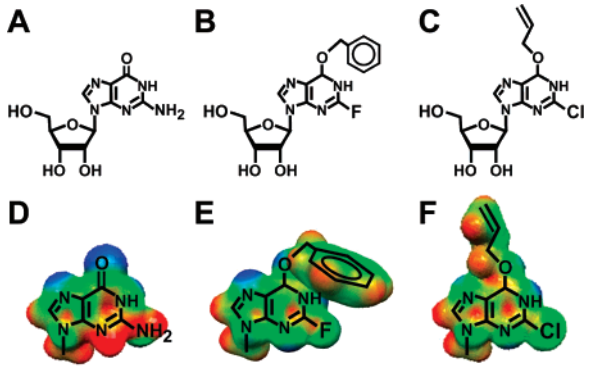
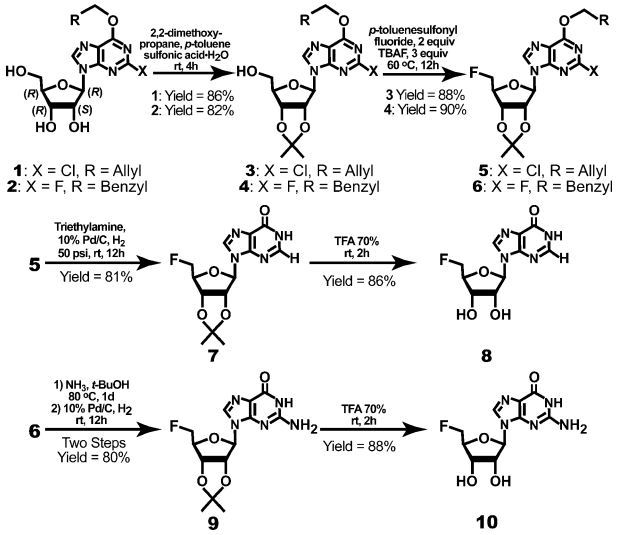


FIGURE 1. Electron-withdrawing substrates with space-filling surface and mapped electrostatic potential: (A) guanosine, (B) O6-benzyl-2-fluoroinosine, 2-F-I, (C) O^6-allyl-2-chloroinosine; 2-Cl-I. (D-F) GAMESS (electrostatic potential) maps calculated for nucleoside bases in parts A−C, respectively. Key: red denotes high electron density; blue denotes low electron density.

At present, the syntheses of 5′-F-G and 5′-F-I have not been reported, although 5′-F-I has been reported as a side product of 5′-F-A production in bacterial extracts derived from *Streptomyces cattleya*.[30] Here we describe the chemical syntheses of 5′-F-G and 5′-F-I utilizing an electron-withdrawing-intermediate approach first employed for 5′-F-A.[18] Earlier attempts at 5′-carbon modification by S_N2 strategies proved unrewarding, due to intramolecular cyclization that formed a 7-membered ring between the N-3 nitrogen and the 5′-carbon.[31−34] To decrease N-3 basicity and alleviate intramolecular cyclization, we hypothesized that a strong electron-withdrawing substituent at the C-2 position would lead to the desired displacement of the tosylated 5′-oxygen by fluoride. A precedent for this approach came from the observation that incorporation of chlorine at the C-6 position of adenosine avoided cyclization, augmented the stability of the tosylated intermediate, and enhanced fluorination yields.[18] This strategy appeared more attractive since the production of both C2-fluorinated and C2-chlorinated inosine have been reported with low step count and high yield. These syntheses utilized a protecting group on the O-6 oxygen, which is normally susceptible to tautomerization and hence could be vulnerable to tosylation (Figure 1). As such, 2-F-I and 2-Cl-I were both attractive starting materials because the benzyl and allyl protecting groups were shown previously to be stable under the conditions to be employed for protection and fluorination. In addition, their deprotection on similar guanosine compounds

SCHEME 1. Synthetic Steps for 5′-F-G and 5′-F-I Production



had been demonstrated to occur in high yield.[35,36] To assess how the addition of fluorine or chlorine at the C-2 position of guanosine or inosine would affect the basicity of the N-3 nitrogen, we subjected the nucleobase of each in the absence and presence of electron-withdrawing substituents to electrostatic potential calculations using GAMESS software.[37] Structures were minimized with the B3LYP density function using the 6-31G(d) basis set. The results showed a significant loss in electron density at the N-3 position when accompanied by an adjacent halogen (Figure 1D versus Figure 1E,F). This observation further corroborates the concept that the N-3 nitrogen was activated by the adjacent exocyclic amine in the parental guanine base. This calculation is also illustrative of the differences in amine activation of adenosine[18] but is expected to be absent in inosine. Given the strategy of starting with a C-2-halogenated adduct, efforts proceeded with protection of the *cis*-diols of O^6-benzyl-2-fluoroinosine and O^6-allyl-2-chloroinosine with 2,2-dimethoxypropane under acidic conditions (Scheme 1). Each protected nucleoside yielded a product with a single primary 5′-alcohol for displacement (Scheme 1, compounds **3** and **4**). Previous fluorination attempts on nucleic acid derivatives employed a two-step procedure in which tosylation occurred in high yield (52−83%), but fluorination was poor (35−46%).[19,20,22] In contrast, we fluorinated the respective 5′-positions of guanosine and inosine with facility in a single step (Scheme 1). This was accomplished by generating the tosylated alcohol in situ and then fluorinating with excess fluoride providing high yields of **5** and **6** (88% and 90%) with no intramolecular cyclization.

To create a hydrogen atom at the C-2 position of **5**, we conducted Pd-catalyzed reduction under basic conditions (Scheme 1). The allylic protecting group, as well as chlorine, were each removed in high yield (81%) giving **7**. Finally, the isopropylidene group was removed in 86% yield, generating 5′-deoxy-5′-fluoroinosine, **8**, in 52% overall yield in four steps.

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Efforts to produce 5′-F-G from chlorinated inosine intermediate **3**, via displacement with ammonia, proved unsuccessful; specifically, displacement succeeded using dibenzylamine, but palladium-catalyzed reduction did not. Therefore, we were pleased to observe amination of **6** in 98% yield (Scheme 1) as indicated by the presence of a broad peak at 5 ppm in crude ^{1}H NMR, which integrated to 2 H. Without need for chromatographic purification, the aminated product was reduced readily under catalytic conditions producing **9** (Scheme 1) in 80% yield over two steps. Thus, **10** was produced subsequently after deprotection in 52% yield from **2** in five overall steps.

Selective fluorination of purine nucleosides has become an important aspect of medicinal chemistry because the C−F bond is refractory to cellular modifications and can enhance biostability.[38] Purine analogues of adenine such as fludarabine and cladribine exhibit fluorine or chlorine at their base C-2 positions and have received FDA approval in the treatment of neoplasias.[39] In contrast, the site-specific modification of immunocillin-H (i.e., an inosine derivative harboring iminoribitol) with a 5′-deoxy-5′-fluoro adduct results in a potent inhibitor of purine nucleoside phosphorylase (PNP).[40] The toxicity of this compound with respect to the malarial parasite is likely due to inhibition of PNP-mediated hypoxanthine production, which appears to serve as a primary purine source for *Plasmodium falciparum*.[41] Thus, selective and high-yielding fluorination of inosine (**8**) and guanosine (**10**), as well as precursors **5** and **6** presented here, should be of broad interest not only as agents that target cancer but also as potential inhibitors of parasitic protozoa.

In summary, we have reported the first synthesis of 5′-deoxy-5′-fluoroguanosine and -inosine. By use of an electron-withdrawing halogen at the C-2 base position, we developed short, inexpensive syntheses to generate high yields of 5′-fluorinated products. This method provides the first framework to introduce weak nucleophiles at the 5′-position of guanosine- and inosine-related nucleosides. The C-2 halogenated intermediates (**5** and **6**) are also attractive products because their electrophilic character facilitates the incorporation of varied functional groups at the C-2 position, which is suitable for the preparation of a 5′-fluorinated library. Such nucleosides have potential in the treatment of cancer or infection by purine-scavenging parasites.

Experimental Section

The procedures for the production of compounds (**3**) through (**10**) are as follows:

***O*^{6}-Allyl-2-chloro-2′,3′-*O*-ispropylideneguanosine (3).** *O*^{6}-Allyl-2-chloroguanosine (**1**) (0.550 g, 1.6 mmol) was placed in a dry 0.25 L round-bottom flask. To the solution was added 10.5 mL of freshly distilled acetone with 0.978 mL of 2,2-dimethoxypropane; 0.864 g of *p*-toluenesulfonic acid monohydrate was added, and the solution was stirred for 4 h at 24 °C. The solution was neutralized with concentrated sodium bicarbonate and extracted exhaustively with dichloromethane. Organic extracts were dried (sodium sulfate) and purified on silica gel (10:90 ether/dichloromethane) yielding 0.528 g of **3**, which appeared as a viscous colorless solid in 86% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.10 (s, 1H), 6.11−6.01 (m, 1H), 5.86 (d, 1H, J = 4.8), 5.44 (d, 1H, J = 17.2), 5.29 (d, 1H, J = 10.4), 5.11 (d, 1H, J = 5.6), 5.05 (d, 1H, J = 5.6), 4.44 (s, 1H), 3.94 (d, 1H, J = 12.8), 3.79 (d, 1H, J = 12.8), 1.58 (s, 3H) 1.31 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 160.9, 153.0, 151.9, 142.2, 131.3, 121.7, 119.6, 114.2, 93.3, 86.1, 83.2, 81.4, 68.8, 63.1, 27.4, 25.2. IR ν^{max} (cm^{-1}): 3524−3345, 2990, 1647, 1319, 1216, 1110, 1078. High-resolution mass spectroscopy (HRMS) was performed for all compounds: ($C_{16}H_{19}ClN_4O_5$) calcd 382.1044, obsd 382.1047.

2-Fluoro-*O*^{6}-benzyl-2′,3′-*O*-isopropylideneguanosine (4). 2-Fluoro-*O*^{6}-benzylguanosine (2) (0.860 g, 2.27 mmol) was placed in a dry round-bottom flask. Freshly distilled acetone (15 mL) was added with 1.5 mL of 2,2-dimethoxypropane; 0.464 g of *p*-toluenesulfonic acid monohydrate was added. The solution was stirred for 4 h and then neutralized with concentrated sodium bicarbonate followed by exhaustive extraction with dichloromethane. The extracts were dried (sodium sulfate) and purified on silica gel (10:90 ether/dichloromethane) generating 0.776 g of **4** as a colorless solid in 82% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.11 (s, 1H), 7.46 (m, 2H), 7.29 (m, 3H), 5.93 (s, 1H), 5.69 (d, 2H, J = 4.0), 5.09 (d, 1H, J = 5.6), 5.00 (d, 1H, J = 6.0), 4.38 (s,1H), 3.86 (d, 1H, J = 12.4), 3.67 (d, 1H, J = 12.4), 1.61 (s, 3H), 1.57 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.6 (d, J_{CF} = 14), 158.5 (d, J_{CF} = 173), 152.2 (d, J_{CF} = 14), 142.0, 134.9, 128.7, 128.6, 128.5, 128.1, 120.7 (d, J_{CF} = 4), 114.2, 93.0, 86.2, 83.4, 81.4, 69.8, 62.9, 27.4, 25.3. ^{19}F NMR ($CDCl_3$) δ (ppm): 13.4 (s). IR ν^{max} (cm^{-1}): 3628−3233, 2987, 2359, 1635, 1375, 1231, 1076. HRMS ($C_{20}H_{21}FN_4O_5$): calcd 416.1496, obsd 416.1491.

***O*^{6}-Allyl-2-chloro-5′-fluoro-2′,3′-*O*-ispropylideneguanosine (5).** To an oven-dried 100 mL round-bottom flask was added 0.726 g (1.9 mmol) of **3** and dissolved in 28 mL of freshly distilled THF. To the flask was added 0.487 g of *p*-toluenesulfonyl fluoride (2 molar equiv) followed by dropwise addition of 5.7 mL of 1 M TBAF in THF (3 molar equiv). The solution was heated to 60 °C, stirred for 12 h, cooled, concentrated to dryness, and purified by silica gel chromatography using (50:50 ethyl acetate/hexanes) to yield 0.642 g of **5** as a clear oil in 88% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 8.07 (s, 1H), 6.24 (s, 1H), 6.20−6.13 (m, 1H), 5.53 (d, 1H, J = 14), 5.36 (d, 1H, J = 8.4), 5.28 (d, 1H, J = 4.4), 5.14 (d, 2H, J = 4.4), 5.12−5.10 (m, 1H), 4.76 (dd, 1H, J = 11.6, 8.4), 4.66 (dd, 1H, J = 11.6, 8.4), 4.55 (d, 1H, J = 20), 1.66, (s, 3H), 1.42 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 160.7, 153.1, 152.5, 141.2, 131.5, 120.9, 119.4, 114.8, 90.5, 85.5 (d, J_{CF} = 15), 84.4, 83.5 (d, J_{CF} = 136), 80.6 (d, J_{CF} = 6), 68.6, 27.1, 25.3. ^{19}F NMR ($CDCl_3$) δ (ppm): −168.685 (m). IR ν^{max} (cm^{-1}): 2939, 1635, 1310, 1216. HRMS ($C_{16}H_{18}ClFN_4O_4$): calcd 384.1001, obsd 384.1004.

2-Fluoro-5′-fluoro-*O*^{6}-benzyl-2′,3′-*O*-isopropylideneguanosine (6). To an oven-dried 100 mL round-bottom flask was added 0.600 g (1.44 mmol) of **4** and dissolved in 25 mL of freshly distilled THF. To the flask was added 0.500 g of *p*-toluenesulfonyl fluoride (2 molar equiv), followed by dropwise addition of 4.32 mL of 1 M TBAF in THF (3 molar equiv). The solution was heated to 60 °C, stirred overnight, and then cooled and concentrated to dryness. Purification was by silica gel chromatography (50:50 ethyl acetate/hexanes) to produce

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0.542 g of **6** as a clear oil in 90% yield. ^{1}H NMR ($CDCl_3$) δ (ppm): 7.99 (s, 1H), 7.44 (m, 2H), 7.25 (m, 3H), 6.10 (s, 1H), 5.56 (s, 2H), 5.19 (d, 1H, $J = 5.6$), 4.97 (d, 1H, $J = 5.6$), 4.64 (dd, 1H, $J = 10.4, 6.4$), 4.52 (dd, 1H, $J = 10.4, 6.4$), 4.44 (d, 1H, $J = 23.6$), 1.54 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$) δ (ppm): 162.3 (d, $J_{CF} = 14$), 158.6 (d, $J_{CF} = 171$), 152.8 (d, $J_{CF} = 15$), 142.1, 135.1, 128.5, 128.4, 128.4, 128.1, 120.2 (d, $J_{CF} = 4$), 114.6, 90.6, 85.4 (d, $J_{CF} = 15$), 84.2, 83.5 (d, $J_{CF} = 136$), 80.5 (d, $J_{CF} = 5$), 69.5, 27.0, 25.2. ^{19}F NMR ($CDCl_3$) δ (ppm): 13.7 (s, 1F), −166.9 (m, 1F). IR ν^{max} (cm^{-1}): 2987, 1581, 1377, 1225, 1078, 1019. HRMS ($C_{20}H_{20}F_2N_4O_4$) calcd 418.1453, obsd 418.1451.

5′-Fluoro-2′,3′-*O*-isopropylideneinosine (7). A 0.320 g portion of **5** (0.833 mmol) was added to a round-bottom flask; 15 mL of ethanol was added, followed by 128 μL of triethylamine. The solution was transferred to a hydrogenation pressure bottle. A 138 mg portion of 10% Pd/C was added, and then the bottle was shaken at 50 psi for 12 h. Catalyst was removed by filtering through Celite, and the solution was concentrated and purified on silica gel (10:90 MeOH/DCM) giving 0.209 g of **7** as a colorless solid in 81% yield. ^{1}H NMR (MeOD) δ (ppm): 8.172 (s, 1H), 8.059 (s, 1H), 6.241 (s, 1H), 5.351 (d, 1H, $J = 6$), 5.088 (d, 1H, $J = 6$), 4.688 (m, 1H), 4.552−4.512 (m, 1H), 4.501 (d, 1H, $J = 18.8$), 1.589 (s, 3H), 1.377 (s, 3H). ^{13}C NMR (MeOD) δ (ppm): 157.4, 148.2, 145.5, 139.1, 124.4, 114.1, 90.6, 85.6 (d, $J_{CF} = 15$), 84.5, 83.4 (d, $J_{CF} = 135$), 80.6 (d_{CF}, $J = 5$), 26.0, 24.0. ^{19}F NMR (MeOD) δ (ppm): −168.391 (m). IR ν^{max} (cm^{-1}): 2942, 1695, 1338, 1237, 1108, 1060, 1019. HRMS ($C_{13}H_{15}FN_4O_4$): calcd 310.1077, obsd 310.1075.

5′-Fluoro-5′-deoxyinosine (8). A 10 mL portion of 70% TFA was added to 0.162 g of **7** at 0 °C. The solution was warmed to 24 °C, stirred for 2 h, evaporated to dryness, and coevaporated 3× with toluene. The resulting white solid was recrystallized from methanol to yield 0.121 g of **8** (86% yield) as colorless needles. ^{1}H NMR (DMSO-d_6) δ: 12.47 (br s, 1H), 8.27 (s, 1H), 8.14 (s, 1H), 5.97 (s, 1H), 5.72 (s, 1H), 5.49 (s, 1H), 4.74 (s, 1H), 4.69 (s, 1H), 4.62 (s, 1H), 4.25 (s, 1H), 4.19 (app d, 1H, $J = 12.2$), 4.13 (app d, 1H, $J = 12.2$). ^{13}C NMR (DMSO-d_6) δ (ppm): 157.0, 148.7, 146.48, 138.9, 124.9, 88.13, 83.97 (d, $J = 14.5$), 83.04 (d, $J_{CF} = 134$), 73.96, 69.83 (d, $J_{CF} = 4.6$). ^{19}F NMR (DMSO-d_6) δ (ppm): −169.2 (m). IR ν^{max} (cm^{-1}): 2872, 1680, 1410, 1220, 1110, 960. HRMS ($C_{10}H_{11}FN_4O_4$): calcd 270.0764, obsd [M + H^+] 271.0840.

5′-Fluoro-2′,3′-*O*-isopropylideneguanosine (9). A 1.00 g (2.4 mmol) portion of **6** was placed in a sealed pressure tube and dissolved in 20 mL of dry *tert*-butyl alcohol. Anhydrous ammonia gas was bubbled through the solution at 0 °C, which was then warmed to 80 °C for 24 h. The mixture was extracted exhaustively with chloroform from water and evaporated to produce 0.971 g of a white solid in 98% yield. The solid was dissolved in 0.60 L of 50:50 MeOH/THF, and 390 mg of 10% Pd/C was added. H_2 gas was bubbled through the solution, followed by stirring for 12 h under a balloon. Catalyst was removed by filtering through Celite. The solution was purified by silica gel chromatography (20% MeOH to DCM) and evaporated to dryness to generate 0.620 g of **9**, a colorless solid, in 80% yield over two steps. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.72 (br s, 1H), 7.81 (s, 1H), 6.56 (br s, 1H), 6.01 (s, 1H), 5.21 (s, 1H), 5.10 (s, 1H), 4.62 (app d, 1H, $J = 14.4$), 4.55 (app d, 1H, $J = 15.6$), 4.33 (app d, 1H, $J = 19.6$), 1.49 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (DMSO-d_6) δ (ppm): 157.1, 154.1, 150.9, 136.4, 117.3, 113.8. 88.9, 85.3 (d, $J_{CF} = 15$), 84.2 (d, $J_{CF} = 133$), 84.0, 80.7 (d, $J_{CF} = 6$), 27.4, 25.6. ^{19}F NMR (DMSO-d_6) δ (ppm): −162.7 (m). IR ν^{max} (cm^{-1}): 2984, 1719, 1374, 1203, 1108, 1071, 1000. HRMS ($C_{13}H_{16}F_1N_5O_4$): calcd 325.1186, obsd 325.1187.

5′-Fluoro-5′-deoxyguanosine (10). A 15 mL solution of 70% TFA was added to 0.20 g of **9** at 0 °C. The solution was warmed to 24 °C, stirred for 2 h, evaporated to dryness, and then coevaporated 3× with toluene. The resulting white solid was recrystallized from methanol yielding 0.154 g of **10** (88% yield) as colorless needles. ^{1}H NMR (DMSO-d_6) δ (ppm): 10.74 (br s, 1H), 7.93 (s, 1H), 6.49 (s, 1H), 5.69 (s, 1H), 5.42 (s, 1H), 5.14 (s, 1H), 5.06 (s, 1H), 4.62 (app d, 1H, $J = 10.4$), 4.07 (s, 1H), 3.87 (s, 1H), 3.61 (app d, 1H, $J = 12$), 3.52 (app d, 1H, $J = 12$). ^{13}C NMR (DMSO-d_6) δ (ppm): 157.2, 154.2, 151.8, 135.8, 117.2, 87.2, 84.1(d, $J_{CF} = 133$), 82.7 (d, $J_{CF} = 14.7$), 73.6, 70.0 (d, $J_{CF} = 5.7$). ^{19}F NMR (DMSO-d_6) δ (ppm): −163.0 (m). IR ν^{max} (cm^{-1}): 2950, 1726, 1598, 1367, 1210, 1108, 1071. HRMS ($C_{10}H_{12}F_1N_5O_4$): calcd 285.0873, obsd [M + H^+] 286.0948.

Acknowledgment. We thank Profs. Ben Miller, Bob Boeckman, and Brad Nilsson for helpful discussions. We thank B. McNaughton for assistance with GAMESS software and Dr. A. Bergmann for MS data collection (supported in part by NSF Grant CHE0091977). This investigation was supported in part by grants NIH R01 GM63162 and ACS/PRF 45534-AC4 to J.E.W. This work is dedicated to Prof. Perry A. Frey in honor of his career as a researcher, teacher, mentor, and chemist.

Supporting Information Available: Synthetic methods and ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and spectral assignments. This material is available free of charge via the Internet at http://pubs.acs.org.

JO7015778