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Syntheses of Pyridine C-Nucleosides as Analogues of the Natural Nucleosides dC and dU

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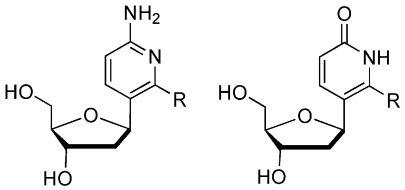

The syntheses of four pyrimidine C-nucleosides are described. These derivatives are designed as mimics of dC and dU, and in that respect, each can form two hydrogen bonds with complementary dG or dA residues. The minor groove O2 carbonyl in each derivative is replaced by a fluorine or a methyl group. The key carbon−carbon bond connecting the heterocycle to the carbohydrate is formed using a Heck-type palladium-mediated coupling reaction.

Introduction

Nucleoside analogues can be used to probe a variety of enzyme substrate interactions, including those involving polymerase dNTP recognition or protein-DNA targeting. They can also be incorporated into nucleic acid sequences using conventional synthesis protocols to probe the structural and functional aspects of DNA or RNA. Two classes of DNA analogues that have been described recently include those in which specific functional groups have been deleted from the pyrimidine residues[1−3] and those in which hydrophobic isosteres have the desired molecular shape. In the latter cases, −F replaces the carbonyls and $-CH_3$ replaces the exocyclic amino groups in the nucleobase heterocycles.[4−6]

Results and Discussion

Here we describe four pyrimidine nucleoside analogues (**1**−**4**) in which the heterocycles are substituted in a pattern similar to the native residues dC and dU (Figure 1).

The hydrogen-bonding faces of these analogues are designed to function as bidentate acceptors/donors to form base pairs with dA or dG (Figure 2) but use isosteric fluorine and methyl group to replace the substituents bound to the C2 carbons (the minor groove functional groups).

To maintain the correct tautomeric forms for base pairing, or other recognition processes using the Watson−Crick functional groups, it was necessary to prepare the derivatives as pyridine C-nucleosides. Derivatives such as **2** and **4** can form essentially normal base pairs with dA such that the exocyclic fluorine or methyl group is placed into the minor groove. Derivatives such as **1** and **3** can form two hydrogen bonds with dG. The third hydrogen bond is lost due to the substitution of the −F or $-CH_3$ for the O2 carbonyl.

The desired pyridine heterocycles necessary for the syntheses of **1**−**4** were obtained from the readily available 2,6-substituted pyridines **5**, **12**, or **14** (Scheme 1a−c). The iodo heterocycles were prepared in each case to generate the carbon−carbon bond of the C-nucleosides by a palladium-mediated Heck-type coupling. The heterocycle for **3** was obtained by simple iodination of readily available 2-amino-6-methylpyridine (→ **13**).[7] Compound **9**, which is necessary to prepare nucleoside **1**, was obtained by iodination of 2,6-diaminopyridine. Subsequent monoacetylation generated solely the 6-acetamido derivative **7**, which could be converted to the 2-fluoro compound **8** in the presence of $HBF_4/NaNO_2$; deacetylation resulted in the desired **9**. Pyridine **11** was easily obtained from **9** by diazotization (→ **10**), followed by the protection of the carbonyl as the *p*NPE derivative **11**. The fourth heterocycle could be obtained from **14** by simple *p*NPE protection (→ **15**) and subsequent iodination (→ **16**). To convert the pyridine heterocycles to the corresponding C-nucleosides we employed a palladium-mediated Heck-type coupling[8,9] involving the glycal **17**, which we obtained in three steps from thymidine.[10] Each coupling reaction yielded only the β anomer in part because the bulky silyl protecting group at the 3′-hydroxyl precludes addition of the heterocycle from the "lower" face of the sugar. We had difficulty in separating the initial coupling products from the starting glycal, so the simplest procedure was to remove the silyl group from the initial coupling products so that compounds **18**−**21** could be purified. Stereospecific reduction of the carbohydrate[11] and removal of the *p*NPE protecting group, where necessary (e.g., for **22** and **23**), resulted in the target compounds **1**−**4** (Scheme 2). Nuclear Overhauser enhancement studies confirmed the presence of solely the β anomers for all four compounds. Crystallographic analysis (data not shown) of **9** also confirmed the presence of the β nucleoside.

These syntheses generate a series of four related pyrimidine-like compounds that can be used directly for studies that probe biological processes involving pyrimidine nucleosides. In principle, they can also be converted to the corresponding triphosphates or phosphoramidites for enzyme-mediated or

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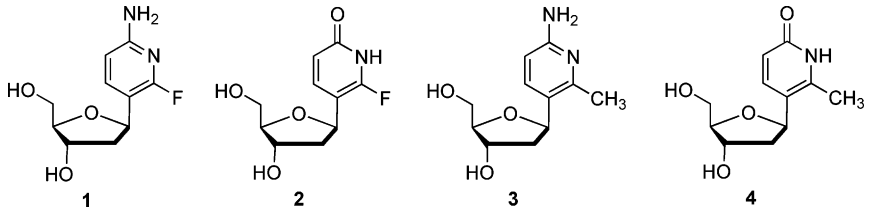


FIGURE 1. Structures of two dU analogues (**1** and **2**) and two dC analogues (**3** and **4**).

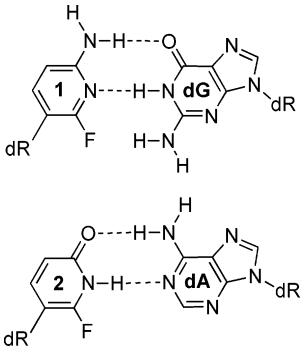


FIGURE 2. Structures of **1**-dG and **2**-dA Watson−Crick-like base pairs.

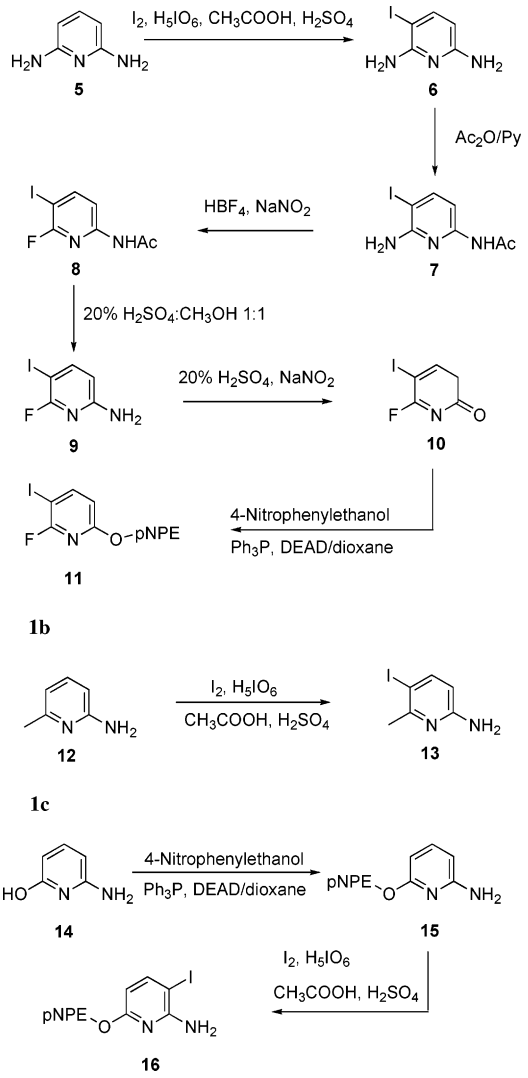
chemical syntheses of modified DNA sequences used in structure and function studies.

Experimental Section

Preparation of 6-Amino-3-(*β*-D-2-deoxy-*erythro*-furanosyl)-2-fluoropyridine (1): To a solution of compound **18** (200 mg, 0.88 mmol, 1.0 equiv) in AcOH (10 mL) and acetonitrile (10 mL) at 0 °C was added sodium triacetoxyborohydride (275 mg, 1.3 mmol, 1.5 equiv). The reaction was complete within 40 min, as revealed by TLC analysis. The reaction was quenched with a 50% aqueous ethanol solution (5 mL). Volatiles were removed under high vacuum, and the product was purified by flash column chromatography with EtOAc/MeOH (9:1) to afford **1** (142 mg, 0.68 mmol, 78%) as a white solid. Mp 152 °C; TLC in DCM/MeOH (20:1), R_f = 0.24. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.57 (dd, J = 8.3, 10.1 Hz, 1H), 6.29 (d, J = 8.2 Hz, 1H), 6.25 (br s, 2H), 5.02−4.99 (m, 2H), 4.71 (t, J = 5.7 Hz, 1H), 4.16 (m, 1H), 3.70 (m, 1H), 3.41 (m, 2H), 1.94 (m, 1H), 1.80 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 159.4 (d, J = 232.7 Hz), 158.2 (d, J = 18.3 Hz), 139.7 (d, J = 5.7 Hz), 107.3 (d, J = 27.7 Hz), 104.6 (d, J = 3.6 Hz), 87.2, 72.5, 72.2, 62.3, 41.5. ϵ ($M^{-1}cm^{-1}$) = 15 665 (237.5 nm), 738 (260.0 nm). Exact mass calculated for [$C_{10}H_{13}N_2O_3FNa^+$] requires m/z 251.0808; found, 251.0806 (ESI^+).

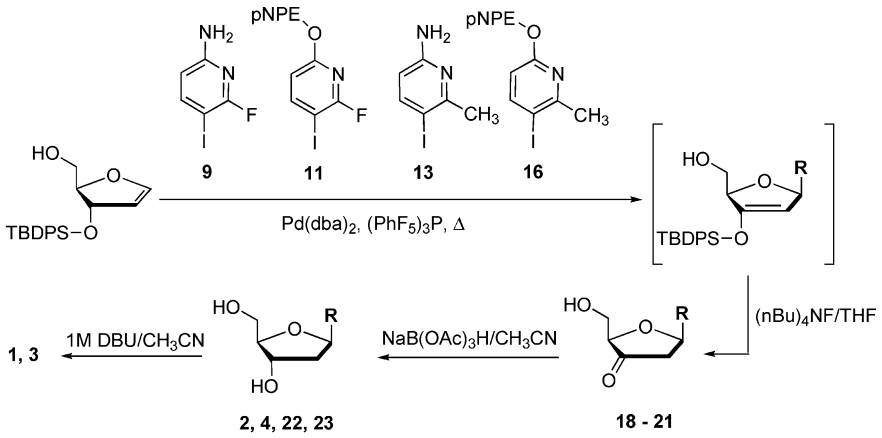
Preparation of 5-(*β*-D-2-Deoxy-*erythro*-furanosyl)-6-fluoropyridone (2): Compound **22** (23 mg, 0.061 mmol) was dissolved in 1 M DBU in dry acetonitrile solution (0.5 mL) and stirred at ambient temperature. The reaction was completed in 2 h, as revealed by TLC analysis. Solvent was removed completely under high vacuum, and the residue was dissolved in DCM (1 mL). The product was purified by flash column chromatography, eluting with 10% MeOH in DCM to give **2** (12 mg, 0.052 mmol, 86%) as a white solid. Mp 207 °C; TLC in 10% MeOH in DCM, R_f = 0.15. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.84 (t, J = 8.4 Hz, 1H), 6.52 (d, J = 8.1 Hz, 1H), 5.08 (dd, J = 5.5, 10.3 Hz, 1H), 4.18 (m, 1H), 3.75 (m, 1H), 3.43 (m, 2H), 2.02 (m, 1H), 1.81 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.8 (d, J = 15.7 Hz), 158.9 (d, J = 236.9 Hz), 142.2 (d, J = 5.4 Hz), 113.3 (d, J = 27.0 Hz), 107.1 (d, J = 4.6 Hz), 88.2, 73.2, 73.0, 63.0, 42.4. ϵ ($M^{-1}cm^{-1}$) = 6847 (216.0 nm), 2027 (260.0 nm). Exact mass calculated for [$C_{10}H_{13}FNO_4^+$] requires m/z 230.0829; found, 230.0833 (ESI^+).

SCHEME 1



Preparation of 6-Amino-3-(*β*-D-2-deoxy-*erythro*-furanosyl)-2-methylpyridine (3): To a solution of compound **20** (360 mg, 1.62 mmol, 1.0 equiv) in AcOH (20 mL) and acetonitrile (20 mL) at 0 °C was added sodium triacetoxyborohydride (0.51 g, 2.43 mmol, 1.5 equiv). The reaction was complete within 50 min, as revealed by TLC analysis. The reaction was quenched with a 50% aqueous ethanol solution (10 mL). Volatiles were removed under vacuum, and the residue was purified by flash column chromatography with EtOAc/MeOH (9:1), affording **3** (300 mg, 1.34 mmol, 83%) as a white color solid. Mp 169 °C; TLC in EtOAc/MeOH (9:1), R_f = 0.2. ^{1}H NMR (400 MHz, D_2O): δ 8.0 (d, J = 9.2 Hz, 1H), 6.83 (d, J = 9.1 Hz, 1H), 5.27 (dd, J = 5.4, 10.5 Hz, 1H), 4.40 (m, 1H), 4.00 (m, 1H), 3.71 (m, 2H), 2.45 (s, 3H), 2.24−2.20 (m, 1H), 2.04−1.97 (m, 1H). ^{13}C NMR (100 MHz, D_2O): δ 153.7, 144.8, 142.4, 123.2, 111.0, 87.3, 75.1, 73.0, 41.0, 16.6, ϵ ($M^{-1}cm^{-1}$)

SCHEME 2 [a]



[a] **R** = pyridine heterocycles corresponding to structures **9**, **11**, **13**, and **16**.

= 11 872 (230.0 nm), 628 (260.0 nm), 4175 (307.0 nm). Exact mass calculated for $[C_{11}H_{17}N_2O_3^+]$ requires *m*/*z* 225.1239; found, 225.1235 (ESI^+).

Preparation of 5-(β-D-2-Deoxy-*erythro*-furanosyl)-6-methylpyridone (4): Compound **23** (70 mg, 0.19 mmol) was dissolved in 1 M DBU in dry acetonitrile solution (2 mL) and stirred at ambient temperature. The reaction was completed in 2 h, as revealed by TLC analysis. Solvent was removed completely under high vacuum, and the residue was dissolved in DCM (3 mL). The product was purified by flash column chromatography, eluting with 10% MeOH in DCM to give **4** (40 mg, 0.18 mmol, 96%) as a white solid. Mp 255 °C; TLC in 10% MeOH in DCM, $R_f = 0.1$. ^1H NMR (400 MHz, DMSO-d_6): δ 7.48 (d, J = 9.4 Hz, 1H), 6.15 (d, J = 9.4 Hz, 1H), 5.03 (br s, 1H), 4.95 (dd, J = 5.3, 10.6 Hz, 1H), 4.75 (br s, 1H), 4.15 (m, 1H), 3.69 (m, 1H), 3.45 (m, 2H), 2.18 (s, 3H), 1.91−1.87 (m, 1H), 1.76−1.69 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 162.3, 139.8, 141.9, 116.6, 115.1, 87.2, 73.9, 72.2, 62.1, 41.3, 15.5. ϵ ($M^{-1}cm^{-1}$) = 14 877 (231.0 nm), 4403 (260.0 nm). Exact mass calculated for $[C_{11}H_{16}NO_4^+]$ requires *m*/*z* 226.1079; found, 226.1077 (ESI^+).

Preparation of 6-Amino-3-(β-D-*glycero*-pentofuran-3′-ulos-1′yl)-2-fluoropyridine (18): A mixture of tris(dibenzylideneacetone)palladium (300 mg, 0.33 mmol) and trispentafluoro phenylphosphine (240 mg, 0.45 mmol) in dry acetonitrile (100 mL) was stirred under argon at ambient temperature for 5 h. Formation of the complex was evidenced by a change of reaction color to deep yellow. *N*,*N*-Diisopropylethylamine (0.22 mL, 5.6 mmol, 2.0 equiv), 1,4-anhydro-deoxy-3-*O*-[(1,1-dimethylethyl)diphenylsilyl]-D-*erythro*-1-enitol compound **17** (1.0 g, 2.8 mmol, 1.0 equiv) and compound **9** (1.0 g, 4.2 mmol, 1.5 equiv) were added, and the reaction mixture was stirred under argon at 55 °C for 48 h. Volatiles were removed under vacuum, and the residue was then passed through a Celite column, eluting with MeOH to remove the palladium catalyst. The filtrate was then treated with 0.5 mL of 1 M *n*-butylammonium fluoride and 0.05 mL AcOH in 5 mL of THF at 0 °C for 30 min. Volatiles were removed, and the product was purified by flash column chromatography, eluting with DCM/MeOH (20:1) to afford the desired product **18** (449 mg, 1.9 mmol 71%). Mp 120 °C; TLC in CH_2Cl_2/MeOH (20:1), $R_f = 0.25$. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, J = 8.2, 9.6 Hz, 1H), 6.46 (dd, J = 1.2, 8.0 Hz, 1H), 5.30 (dd, J = 5.5, 11.1 Hz, 1H), 4.83 (br s, 2H), 4.02 (t, J = 3.0 Hz, 1H), 3.94 (d, J = 3.0 Hz, 2H), 2.83 (dd, J = 6.0, 18.0 Hz, 1H), 2.55 (dd, J = 10.8, 19.2 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.9, 160.3 (d, J = 238.0 Hz), 157.9 (d, J = 18.3 Hz), 140.5 (d, J = 32.0 Hz), 108.2 (d, J = 26.6 Hz), 105.6 (d, J = 30.0 Hz), 82.3, 72.2, 59.4, 44.0. Exact mass calculated for $[C_{10}H_{11}N_2O_3FNa^+]$ requires *m*/*z* 249.0651; found, 249.0643 (ESI^+).

Preparation of 6-[2-(4-Nitrophenylethoxy)]-3-(β-D-*glycero*-pentofuran-3′-ulos-1′yl)-2-fluoropyridine (19): A mixture of tris(dibenzylideneacetone)palladium (300 mg, 0.33 mmol) and trispentafluoro phenylphosphine (240 mg, 0.45 mmol) in dry acetonitrile (100 mL) was stirred under argon at ambient temperature for 5 h. Formation of the complex was evidenced by a change of reaction color to deep yellow. *N*,*N*-Diisopropylethylamine (0.22 mL, 5.6 mmol, 2.0 equiv), compound **17** (1.0 g, 2.8 mmol, 1.0 equiv) and compound **11** (1.6 g, 4.2 mmol, 1.5 equiv) were added, and the reaction mixture was stirred under argon at 90 °C for 48 h. Volatiles were removed under vacuum, and the residue was then passed through a Celite column, eluting with MeOH to remove the palladium catalyst. The filtrate was then treated with 0.5 mL of 1 M *n*-butylammonium fluoride and 0.05 mL AcOH in 5 mL of THF at 0 °C for 30 min. Volatiles were removed, and the product was purified by flash column chromatography, eluting with DCM/MeOH (20:1) to afford the desired product **19** (686 mg, 1.82 mmol, 65%). Mp 125 °C; TLC in CH_2Cl_2/MeOH (20:1), $R_f = 0.63$. ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.7 Hz, 2H), 7.89 (t, J = 9.6 Hz, 1H), 7.44 (d, J = 8.7 Hz, 2H), 6.65 (d, J = 8.84 Hz, 1H), 5.33 (dd, J = 5.9, 10.9 Hz, 1H), 4.54 (t, J = 6.5 Hz, 2H), 4.04 (m, 1H), 3.96 (m, 1H), 3.19 (t, J = 6.5 Hz, 2H), 2.90 (dd, J = 6.3, 18.2 Hz, 1H), 2.50 (dd, J = 10.9, 18.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.7, 162.1 (d, J = 13.6 Hz), 158.9 (d, J = 241.1 Hz), 146.0, 140.7, 140.4, 129.8, 123.6, 112.3 (d, J = 26.2 Hz), 107.8 (d, J = 5.0 Hz), 82.0, 71.5, 66.3, 61.5, 43.9, 35.1. Exact mass calculated for $[C_{18}H_{17}N_2O_6FNa^+]$ requires *m*/*z* 399.0968; found, 399.0963 (ESI^+).

Preparation of 6-Amino-3-(β-D-*glycero*-pentofuran-3′-ulos-1′yl)-2-methylpyridine (20): A mixture of tris(dibenzylideneacetone)palladium (300 mg, 0.33 mmol) and trispentafluoro phenylphosphine (240 mg, 0.45 mmol) in dry acetonitrile (100 mL) was stirred under argon at ambient temperature for 5 h. Formation of the complex was evidenced by a change of reaction color to deep yellow. *N*,*N*-Diisopropylethylamine (0.22 mL, 5.6 mmol, 2.0 equiv), compound **17** (1.0 g, 2.8 mmol, 1.0 equiv), and compound **13**[7] (see also Supporting Information; 1.0 g, 4.3 mmol, 1.5 equiv) were added, and the reaction mixture was stirred under argon at 55 °C for 48 h. Volatiles were removed under high vacuum, and the residue was then passed through a Celite column, eluting with MeOH to remove the palladium catalyst. The filtrate was then treated with 0.5 mL of 1 M *n*-butylammonium fluoride and 0.05 mL AcOH in 5 mL of THF at 0 °C for 30 min. Volatiles were removed, and the product was purified by flash column chromatography, eluting with DCM/MeOH (98:2) to afford the desired product **20** (416 mg, 1.9 mmol, 67%). Mp 136 °C; TLC in CH_2Cl_2/MeOH (9:1), $R_f = 0.1$. ^1H NMR (400 MHz, acetone-d_6): δ

7.68 (d, $J = 8.4$ Hz, 1H), 6.41 (d, $J = 8.4$ Hz, 1H), 5.42 (br s, 2H), 5.33 (dd, $J = 5.5, 11.1$ Hz, 1H), 3.97 (t, $J = 3.0$ Hz, 1H), 3.83 (d, $J = 3.0$ Hz, 2H), 2.80 (dd, $J = 5.5, 17.4$ Hz, 1H), 2.34 (s, 3H), 2.30 (dd, $J = 11.1, 17.9$ Hz, 1H) ppm. ^{13}C NMR (100 MHz, acetone-d_6): δ 213.9, 158.7, 153.8, 135.8, 122.8, 105.9, 83.2, 74.0, 61.3, 44.5, 21.3. Exact mass calculated for $[C_{11}H_{15}N_2O_3^+]$ requires *m*/*z* 223.1083; found, 223.1080 (ESI^+).

Preparation of 6-[2-(4-Nitrophenylethoxy)]-3-(*β*-D-*glycero*-pentofuran-3′-ulos-1′yl)-2-methylpyridine (21): A mixture of tris(dibenzylideneacetone)palladium (300 mg, 0.33 mmol) and trispentafluoro phenylphosphine (240 mg, 0.45 mmol) in dry acetonitrile (100 mL) was stirred under argon at ambient temperature for 5 h. Formation of the complex was evidenced by a change of reaction color to deep yellow. *N*,*N*-Diisopropylethylamine (0.22 mL, 5.6 mmol, 2.0 equiv), compound **17** (1.0 g, 2.8 mmol, 1.0 equiv), and compound **16** (1.6 g, 4.2 mmol, 1.5 equiv) were added, and the reaction mixture was stirred under argon at 90 °C for 48 h. Volatiles were removed under vacuum, and the residue was then passed through a Celite column, eluting with MeOH to remove the palladium catalyst. The filtrate was then treated with 0.5 mL of 1 M *n*-butylammonium fluoride and 0.05 mL AcOH in 5 mL of THF at 0 °C for 30 min. Volatiles were removed under high vacuum, and the residue was purified by flash column chromatography, eluting with DCM/MeOH (20:1) to afford the desired product **21** (595 mg, 1.6 mmol, 57%). Mp 88 °C; TLC in CH_2Cl_2/MeOH (98:2), $R_f = 0.7$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, $J = 8.8$ Hz, 2H), 7.74 (d, $J = 8.4$ Hz, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 6.60 (d, $J = 8.4$ Hz, 1H), 5.33 (dd, $J = 5.6, 11.2$ Hz, 1H), 4.56 (t, $J = 7.2$ Hz, 2H), 4.04 (m, 1H), 3.96 (m, 1H), 3.19 (t, $J = 6.8$ Hz, 2H), 2.85 (dd, $J = 5.7, 18.0$ Hz, 1H), 2.47 (s, 3H), 2.40 (dd, $J = 11.0, 18.0$ Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.0, 162.4, 153.5, 146.8, 136.5, 130.0, 126.1, 123.8, 108.7, 82.5, 74.2, 65.7, 61.9, 44.6, 35.8, 22.2. Exact mass calculated for $[C_{19}H_{21}N_2O_6^+]$ requires *m*/*z* 373.1400; found, 373.1395 (ESI^+).

Preparation of 6-[2-(4-Nitrophenylethoxy)]-3-(*β*-D-2-deoxy-*erythro*-furanosyl)-2-fluoropyridine (22): To a solution of compound **19** (400 mg, 1.06 mmol, 1.0 equiv) in AcOH (20 mL) and acetonitrile (20 mL) at 0 °C was added sodium triacetoxyborohydride (0.32 g, 1.5 mmol, 1.5 equiv). The reaction was complete within 40 min, as revealed by TLC analysis. The reaction was quenched with a 50% aqueous ethanol solution (10 mL). Volatiles were then removed under vacuum, and the residue was separated by column chromatography with EtOAc/MeOH (9:1) to afford **22** (320 mg, 0.85 mmol, 80%) as a white solid. Mp 100 °C; TLC in DCM/MeOH (20:1), $R_f = 0.2$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, $J = 8.6$ Hz, 2H), 7.73 (dd, $J = 8.3, 9.7$ Hz, 1H), 7.41 (d, $J = 8.5$ Hz, 2H), 6.56 (d, $J = 8.1$ Hz, 1H), 5.24 (dd, $J = 5.6, 10.2$ Hz, 1H), 4.51 (t, $J = 6.5$ Hz, 2H), 4.45 (m, 1H), 3.98 (m, 1H), 3.75 (m, 2H), 3.16 (t, $J = 6.5$ Hz, 2H), 2.27 (dd, $J = 5.7, 13.2$ Hz, 1H), 2.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7 (d, $J = 13.6$ Hz), 158.6 (d, $J = 239.0$ Hz), 147.1, 147.0, 141.5, 130.4, 123.5, 115.3 (d, $J = 26.7$ Hz), 107.5 (d, $J = 5.0$ Hz), 88.3, 73.3, 73.2, 66.4, 63.1, 42.9, 35.0. Exact mass calculated for $[C_{18}H_{19}N_2O_6FNa^+]$ requires *m*/*z* 401.1125; found, 401.1120 (ESI^+).

Preparation of 6-[2-(4-Nitrophenylethoxy)]-3-(*β*-D-2-deoxy-*erythro*-furanosyl)-2-methylpyridine (23): To a solution of compound **21** (400 mg, 1.06 mmol, 1.0 equiv) in AcOH (20 mL) and acetonitrile (20 mL) at 0 °C was added sodium triacetoxyborohydride (0.32 g, 1.5 mmol, 1.5 equiv). The reaction was complete within 40 min, as revealed by TLC analysis. The reaction was quenched with a 50% aqueous EtOH solution (10 mL). Volatiles were then removed under high vacuum, and the residue was purified by flash column chromatography, eluting with 5% MeOH in DCM to afford **23** (345 mg, 0.92 mmol, 87%) as a white solid. Mp 102 °C; TLC in DCM/MeOH (20:1), $R_f = 0.2$. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.17 (d, $J = 8.7$ Hz, 2H), 7.74 (d, $J = 8.5$ Hz, 1H), 7.59 (d, $J = 8.7$ Hz, 2H), 6.58 (d, $J = 8.5$ Hz, 1H), 5.13 (dd, $J = 5.4, 10.3$ Hz, 1H), 5.06 (d, $J = 4.1$ Hz, 1H), 4.50 (t, $J = 4.5$ Hz, 2H), 4.19 (m, 1H), 3.76 (m, 1H), 3.46 (m, 2H), 3.17 (t, $J = 6.6$ Hz, 2H), 2.37 (s, 3H), 2.10−2.06 (m, 1H), 1.68−1.63 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 161.8, 152.5, 147.9, 146.8, 137.6, 130.8, 129.3, 124.0, 108.3, 88.2, 75.9, 73.0, 65.7, 62.9, 42.7, 35.2, 22.1. Exact mass calculated for $[C_{19}H_{23}N_2O_6^+]$ requires *m*/*z* 375.1556; found, 375.1554 (ESI^+).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all procedures and compounds, CIF file for **1**, and synthetic procedures for compounds in Scheme 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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