Supporting Information

Synthesis of 2',5'-Dideoxy-2-fluoroadenosine and 2',5'-dideoxy-2,5'-difluoroadenosine: Potent P-site inhibitors of adenylyl cyclase.

Song Ye,¹ Martha M. Rezende,¹ Wei-Ping Deng,¹ Brian Herbert,¹ John W. Daly,¹ Roger A. Johnson² and Kenneth L. Kirk¹

¹Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, DHHS, Bethesda MD 20892 and
²Department of Physiology and Biophysics, State University of New York at Stony Brook, Stony Brook NY 11794-8661

Supporting Information.

Methyl 3-O-benzyl-2,5-dideoxy-D-erythro-pentofuranoside (6). To a solution of 4 (3.06 g, 23 mmol) in dry THF (60 mL) in an ice bath was added sodium hydride (60% dispersion in mineral oil, 1.016 g, 42.3 mmol). Stirring was continued for 15 minutes under N₂ and TBAI (0.86 g, 2.3 mmol) was added followed by dropwise addition of benzyl bromide (3.0 ml, 25.2 mmol). The reaction mixture was stirred under N₂ for 2 hours at rt. After addition of methanol (10 mL) the solvent was evaporated under reduced pressure and the crude product was separated by silica gel chromatography (Hex/EtOAc, 9.5:0.5) to afford 5.14 g of a mixture of α and β anomers of 6 as a colorless oil (70% yield).¹¹H NMR: (CDCl₃, 300 MHz) (α and β); δ: 1.25 (d, 3H, J₄,₅= 6.3 Hz, H-5), 1.30 (d, 3H, J₄,₅= 6.6 Hz, H-5), 1.96 (ddd, 1H, J₁,₂a= 2.1 Hz, J₂a,₃= 4.0 Hz, J₂a,₂b= 13.9 Hz, H-2a), 2.11(dt, 1H, J₁,₂a= 13.3; J₁,₂b= J₂b,₃= 5.7 Hz, H-2b), 2.23 (ddd, 1H, J₁,₂a= 2.1 Hz; J₂a,₃= 5.7 Hz, J₂a,₂b= 13.4 Hz, H-2a), 2.31 (ddd, J₁,₂b= 5.7 Hz, J₂b,₃= 8.2 Hz, J₂a,₂b= 13.4 Hz, H-2b), 3.34 (s, 3H, OCH₃), 3.37 (s, 3H, OCH₃), 3.62 (ddd, 1H, J₂b,₂₃= 8.2 Hz; J₂a,₂₃= 5.7 Hz; J₂₃,₄= 4.2 Hz; H-3), 3.95 (td, 1H, J₀,₃= 4.2 Hz; J₂a,₂₃= 5.7 Hz, H-3), 4.08 - 4.20 (m, 1H, H-4), 4.48 e 4.57 (2d, 2H, J₃,₂₃= 12.0 Hz, OCH₂Ar), 4.98 (dd, 1H, J₁,₂a= 2.1 Hz, J₁,₂b= 5.7 Hz, H-1), 5.05 (dd, 1H, J₁,₂a= 2.1 Hz, J₁,₂b= 5.7 Hz, H-1); 7.25 - 7.35 (m, 5H, H-arom.).¹³C NMR: (CDCl₃, 75 MHz) (α and β); δ: 19.04 and 21.3 (C-5), 39.04 and 39.50 (C-2), 55.13 and 55.16 (OCH₂), 71.89 and 71.99 (OCH₂Ar), 78.02 and 78.05 (C-3), 83.36 and 83.39 (C-4), 104.64 and 105.39 (C-1), 127.98 - 128.71 (C-arom.); 138.48 (C-arom.). IR (CCl₄): 2962 (m), 2905 (w), 2829 (w), 196 (w), 1469 (w), 1362 (w), 1260 (s), 1209 (w), 1097 (s), 1023 (s), 937 (w), 877 (w), 798 (s), 738 (w), 698 (m), 666 (w). MS (EI, 70 eV): 91 (100), 190 (5), 105 (20), 59 (90). MS (Cl, NH₃): 240 ([M + NH₄]⁺, 22), 208 (100), 118 (13), 91 (10). Analysis, calcd for C₁₃H₁₈O₃: C, 70.24; H, 8.16. Found: C, 70.22; H, 8.37.

Phenyl 3-O-benzyl-2,5-dideoxy-1-thio-α,β-D-erythro-pentofuranoside (8).

To a solution of 6 (1.5 g, 6.3 mmol) in dry dichloromethane (60 mL) were added zinc iodide (4.0 g, 12.59 mmol), benzenethiol (1.46 mL, 13.46 mmol), and tetrabutylammonium iodide (0.5 g, 1.35 mmol). This suspension was kept under N₂ and was refluxed with stirring. After 7 h, the reaction mixture was filtered and the filtrate was washed with saturated aqueous NaHCO₃ (10 mL) and extracted with CH₂Cl₂. The organic layer was dried over Na₂SO₄ and evaporated in vacuo. The residue was purified
by silica gel chromatography with Hex/EtOAc (99:1) to give 2.0 g (68% yield) of a mixture of α and β anomers of 8 as a colorless syrup. \(^1\)H NMR (CDCl\(_3\), 300 MHz) (α and β); δ: 1.28 (d, 6H, J\(_{4,5}\) = 6.6 Hz, H-5 (major)), 1.30 (d, 6H, J\(_{4,5}\) = 6.6 Hz, H-5 (minor))2.06 (dt, 1H, J\(_{1,2a}\) = 2J\(_{2a,3}\) = 4.8 Hz, J\(_{2a,2b}\) = 13.8 Hz, H-2b (major)), 2.16 (ddd, 1H, J\(_{1,2a}\) = 7.8 Hz, J\(_{2a,3}\) = 6.0 Hz, J\(_{2a,2b}\) = 13.8 Hz, H-2a (minor)), 2.43 (ddd, 1H, J\(_{2b,3}\) = 3.0 Hz, J\(_{1,2b}\) = 6.3 Hz, J\(_{2a,2b}\) = 14.0 Hz, H-2b (minor)), 2.70 (dt, 1H, J\(_{1,2a}\) = J\(_{2a,3}\) = 7.8 Hz, J\(_{2a,2b}\) = 14.0 Hz, H-2a (major)), 3.66 (ddd, 1H, J\(_{1,2a}\) = 7.8 Hz, J\(_{2b,3}\) = 4.8 Hz, J\(_{3,4}\) = 6.0 Hz, H-3 (major)), 3.80 (dt, 1H, J\(_{2a,3}\) = 6.0 Hz, J\(_{2b,3}\) = J\(_{3,4}\) = 3.0 Hz, H-3 (minor)), 4.21 (qd, 1H, J\(_{1,3}\) = 3.0 Hz, J\(_{4,5}\) = 6.6 Hz, H-4 (minor)), 4.30 (quintet, 1H, J\(_{1,4}\) = 6.0 Hz, J\(_{4,5}\) = 6.3 Hz, H-4 (major)), 4.51 (d, 2H, J\(_{gem}\) = 12.0 Hz, OCH\(_2\)Ar (major)), 4.61 (d, 2H, J\(_{gem}\) = 12.0 Hz, OCH\(_2\)Ar (minor)), 5.57 (dd, 1H, J\(_{1,2a}\) = 6.3 Hz, J\(_{1,2b}\) = 7.8 Hz, H-1 (major)), 5.65 (dd, 1H, J\(_{1,2b}\) = 4.2 Hz, J\(_{1,2a}\) = 7.8 Hz, H-1 (minor)).

**General Procedure for the Coupling Reaction with 2,6-Diacetamidopurine.**

Silylated 2,6-diacetamidopurine was prepared by a modification of two methods reported in the literature and used in situ without any further purification.\(^1\) Suspension of 2,6-diacetamidopurine (468 mg, 2.02 mmol) in hexamethyldisilazane (20 mL) and a catalytic amount of (NH\(_4\))\(_2\)SO\(_4\) was heated at reflux for 3 h under N\(_2\). The resulting clear solution was allowed to cool to room temperature. Excess hexamethyldisilazane was removed under reduced pressure. The residue and the thioglycoside (1 mmol) were dissolved in dry CH\(_2\)Cl\(_2\) (12 mL) under N\(_2\), and then 500 mg of powdered molecular sieves 4Å was added. After 20 min, NBS (1.15 mmol) was added to the solution, and the progress of the reaction was followed by TLC (CHCl\(_3\)/CH\(_3\)OH, 95:5). After 72 h aqueous Na\(_2\)S\(_2\)O\(_3\) was added, the solution was filtered and then extraction with CH\(_2\)Cl\(_2\). The organic layer was dried over MgSO\(_4\) and evaporated in vacuo. The residue was purified by silica gel chromatography using 0-5% CH\(_2\)Cl\(_2)/\text{CH}_3\text{OH} \text{gradient} to obtain the desired compound in 48% to 52% yield.

**2-Acetamido-N\(^6\)-Acetyl-9-(3-O-acetyl-2,5-dideoxy-\alpha,\beta-D-erythro-pentofuranosyl)adenine (9).** \(^1\)H NMR (DMSO-d\(_6\), 300 MHz) (α: β = 1.25:1); δ: 1.25 (d, 3H, J\(_{4,5}\) = 6.6 Hz, H-5 (α)), 1.35 (d, 3H, J\(_{4,5}\) = 6.6 Hz, H-5 (β)), 1.96 (s, 3H, CH\(_3\)COO-(α)), 2.09 (s, 3H, CH\(_3\)COO-(β)), 2.24 (s, 3H, CH\(_3\)CONH-(α)), 2.32 (s, 3H, CH\(_3\)CONH-(β)), 2.43-2.52 (m, 2H, H-2′a, H-2′b) DMSO-d\(_6\) overlapping; (β)), 2.65 (dt, 1H, J\(_{1,2a}\) = J\(_{2a,3}\) = 2.7 Hz, J\(_{2a,2b}\) = 14.7 Hz, H-2′a (α)), 2.95 (ddd, 1H, J\(_{1,2b}\) = 7.2 Hz, J\(_{2b,3}\) = 7.0 Hz, J\(_{2a,2b}\) = 14.7 Hz, H-2′b (α)), 4.16 (qd, 1H, J\(_{3,4}\) = 2.4 Hz, H-4′ (β)), 4.54 (qd, 1H, J\(_{3,4}\) = 2.4 Hz, H-4′ (α)), 4.99 (dt, 1H, J\(_{2a,3}\) = J\(_{3,4}\) = 2.4 Hz, J\(_{2b,3}\) = 7.0 Hz, H-3′ (α)), 5.17 (dt, 1H, J\(_{2a,3}\) = J\(_{3,4}\) = 2.4 Hz, J\(_{2b,3}\) = 6.6 Hz, H-3′ (β)), 6.30 (dd, 1H, J\(_{1,2a}\) = 6.0 Hz, J\(_{1,2b}\) = 7.95 Hz, H-1′ (β)), 6.39 (dd, 1H, J\(_{1,2a}\) = 2.7 Hz, J\(_{1,2b}\) = 7.2 Hz, H-1′ (α)), 8.40 (s, 1H, H-8 (α)), 8.54 (s, 1H, H-8 (β)), 10.38 (s, 1H, NHCOCH\(_3\) (β)).
10.55 (s, 1H, NHCOCH₃, (α)). ¹³C NMR (DMOS-d₆, 75 MHz) (α:β=1.25:1); δ: 18.77 and 19.27 (C-5'), 20.80 and 20.92 (CH₃CONH), 24.66 and 24.70 (CH₃COO), 34.68 and 36.06 (C-2'), 77.29 and 77.99 (C-4'), 80.46 and 81.02 (C-3'), 83.21, 83.64 (C-1'), 119.69 and 119.89 (C-5), 141.13 and 141.89 (C-8), 149.27 and 149.45 (C-4), 151.89 and 151.93 (C-6 or C-2), 152.17 (C-2 or C-6), 168.86 and 169.12 (CON-), 169.20 and 169.29 (CON-), 169.74 and 169.83 (COO). IR (KBr): 3263 (m), 3215 (m), 3143 (m), 2984 (m), 1740 (s), 1666 (s), 1620 (s), 1597 (s), 1451 (m), 1371 (s), 1290 (s), 1184 (m), 1111 (w), 1057 (m), 1020 (m), 936 (w), 640 (w), 544 (w). MS (EI, 70eV): 134 (30), 192 (90), 150 (55), 83 (100). MS (Cl, NH₃): 377 ([M + H]⁺, 100), 335 (20), 235 (20) HRMS (Cl, NH₃): Caled for C₁₆H₂₀N₆O₅: 376.37; found: 376.1495. Analysis Caled. for C₁₆H₂₀N₆O₅: C, 51.06; H, 5.36; N, 22.33. Found: C, 51.13, H, 5.53, N, 22.06.

2-Acetamido-N⁶-Acetyl-9-(3-O-benzyl-2,5-dideoxy-α,β-D-erythro-pentofuranosyl)adenine (10). ¹H NMR (DMSO-d₆, 300 MHz) (α and β= 4:1); δ: 1.30, 6 (d, 3H, J₄,₅=6.6 Hz, H-5'(α)), 1.40 (d, 3H, J₄,₅=6.6 Hz, H-5'(β)), 2.53 (s, 3H, CH₃CON-), 2.64 (s, 3H, CH₃CON-), 2.62 (dt, J₁,₂a= J₂a,b= 2.1 Hz, J₂a₂b = 14.7 Hz, H-2'a (α)), 2.72 - 2.83 (m, 2H, H-2'a e H-2'b (β)), 2.85 (ddd, 1H, J₁,₂₂a = 7.2 Hz, J₂₂₂b = 6.3 Hz, J₂₂b₂ = 14.7 Hz, H-2²b (α)), 3.97 (dt, 1H, J₁,₂₄= J₂₂₂₂a = 2.1 Hz, J₂₂₂₂b = 6.3 Hz, H-3² (α)), 4.06 - 4.12 (m, 1H, H-3²(β)), 4.52 - 4.60 (m, 3H, OCH₂Ar and H-4² (α e β)), 6.28 (t, 1H, J₁,₂₂a = J₂₂₂₂a = 6.3 Hz, H-1² (β)), 6.41 (dd, 1H, J₁,₂₂a = 2.1 Hz, J₁,₂₂b = 7.2 Hz, H-1² (α)), 7.21 - 7.32 (m, 5H, H-arom.), 8.32 (s, 1H, H-8 (α)), 8.36 (s, 1H, H-8 (β)), 10.30 (bs, 1H, -NHCOCH₃), 10.60 (bs, 1H, -NHCOCH₃). ¹H NMR (DMSO-d₆, 300 MHz) (α); δ: 1.22 (d, 3H, J₄,₅=6.6 Hz, H-5'), 2.25, 2.30 (2s, 3H, CH₃CON-), 2.70 (dt, 1H, J₁,₂₂a = J₂a₁₂₂ = 2.4, J₂₂₂₂b = 14.7 Hz, H-2²a), 2.82 (m, 1H, H-2²b), 4.02 (dt, 1H, J₂₂₂₂a = J₃₂₄ = 2.4 Hz, J₂₂₂₂b = 6.3 Hz, H-3²), 4.55 (m, 3H, OCH₂Ar and H-4²), 6.37 (dd, 1H, J₁,₂₂a = 2.4 Hz, J₁,₂₂b = 7.3 Hz, H-1²), 7.28 - 7.29 (m, 5H, H-arom.), 8.40 (bs, 1H, H-8-H), 10.36 (bs, 1H, NHCOCH₃ ), 10.55 (bs, 1H, NHCOCH₃). ¹³C NMR (DMSO-d₆, 75 MHz) (α); δ: 19.34 (C-5'), 24.69 (2 CH₃CONH), 36.24 (C-2'), 70.61 (OCH₂Ar), 80.89 (C-4'), 82.70 (C-3'), 83.18 (C-1'), 119.00 (C-5), 127.47 - 128.20 (C-arom.) 137.84 (C-arom.), 141.41 (C-8), 149.32 (C-4), 151.90 (C-6), 152.00 (C-2), 169.32 (2 -COO). IR (KBr): 3273 (m), 3217 (m), 2970 (m), 2870 (m), 1722 (m), 1665 (s), 1620 (s), 1594 (s), 1489 (m), 1453 (m), 1373 (s), 1315 9 (m), 1289 (s), 1105 (m), 1019 (m), 993 (w), 932 (w), 796 (w), 698 (w). MS (EI, 70 eV): 424 (M⁺, 7), 310 (95), 235 (90), 192 (100), 150 (100), 91(100). MS (Cl, NH₃): 425 ([M + H]⁺, 100), 134(100) HRMS (Cl, NH₃): Caled for C₂₁H₂₄N₆O₄: 424.45. Found: 424.1859. Analysis Caled. for C₂₁H₂₄N₆O₄: C, 59.42; H, 5.70; N 19.80. Found C, 59.42; H, 5.72; N, 20.02.

Decaylation of Diacetamido Coupling Products. A solution of 9 (500 mg, 1.33 mmol) or 10 (500 mg, 1.18 mmol) in 1N methanolic sodium methoxide (100 mL) was stirred under reflux and N₂. After 3h, the reaction mixture was cooled to 0°C, neutralized with acetic acid, and refrigerated overnight. The resulting solid was removed by filtration, washed and dried in vacuo to afford 11 (330 mg; α:β ~ 1:1) and 12 (399 mg; α:β = 4:1) in quantitative yield.

2-Amino-9-(2,5-dideoxy-α,β-D-erythro-pentofuranosyl)adenine (11). Mp(α): 180 - 182°C.

¹H NMR (DMSO-d₆, 300 MHz) (β): 1.23 (d, 3H, J₄,₅=6.4 Hz, H-5'), 1.83 (s, 1H, OH-3²), 2.17 (ddd, 1H, J₁,₂₂b = 6.8 Hz, J₂₂₂₂b = 4.0 Hz, J₂₂₂₂b = 13.2 Hz, H-2²b), 2.67 (ddd,
1H, *J*1,2':a = 6.8 Hz, *J*2,3':b = 6.6 Hz, *J*2,2':b = 13.2 Hz, H-2’a), 3.90 (qd, 1H, *J*3,4 = 3.6 Hz, *J*4,5 = 6.4 Hz, H-4’), 4.10 (dd, 1H, *J*3,4 = 3.6 Hz, *J*2,3 = 4.0 Hz, H-2’a), 3.96 (dt, 1H, *J*2,3 = 3.6 Hz, *J*4,5 = 7.2 Hz, H-3’), 5.77 (bs, 2H, NH2), 6.09 (t, 1H, *J*1,2' = *J*1,2 = 6.8 Hz, H-1’), 6.70 (bs, 2H, NH2), 7.86 (s, 1H, H-8’).

1H NMR (DMSO-d6, 300 MHz) (α): 1.23 (d, 3H, *J*4,5 = 6.4 Hz, H-5’), 2.25 (dt, 1H, *J*1,2 = *J*2,3 = 7.2 Hz, H-2’a), 14.1 Hz, H-2’b), 2.72 (dt, 1H, *J*1,2 = *J*2,3 = 3.6 Hz, H-2’a), 14.2 Hz, H-2’b), 3.96 (dt, 1H, *J*2,3 = 3.6 Hz, *J*4,5 = 7.2 Hz, H-3’), 4.10 (qd, 1H, *J*3,4 = 3.6 Hz, *J*4,5 = 6.4 Hz, H-4’), 5.77 (bs, 2H, NH2), 6.08 (dd, 1H, *J*1,2 = 3.6 Hz, *J*1,2 = 7.2 Hz, H-1’), 6.70 (bs, 2H, NH2), 7.96 (bs, 1H, H-8’).

13C NMR (DMSO-d6, 75 MHz) (α): 21.89 (C-5’), 42.80 (C-2’), 78.73 (C-3’), 85.59 (C-1’), 85.90 (C-4’), 116.30 (C-5), 140.02 (C-8), 154.30 (C-4), 159.20 (C-6), 163.50 (C-2), IR (KBr): 3433 (s), 3335 (s), 3200 (s), 2937 (m), 1705 (s), 1648 (s), 1592 (s), 1533 (m), 1410 (s), 1277 (w), 1218 (w), 1099 (w), 1000 (w), 942 (w), 936 (w), 505 (w). MS (EI, 70 eV): 250 (M+, 22), 177 (37), 150 (100), 108 (15). MS (Cl, NH3): 251 ([M + H]+, 100), 150 (20), 116 (22), 96 (22). HRMS (Cl, NH3): Calcd for C10H14N6O2: 250.26. Found: 250.12.

2-Amino-9-(3-O-benzyl-2,5-dideoxy-α,β-D-erythro-pentofuranosyl)adenine (12). Mp: 220 – 222 °C. 1H NMR (DMSO-d6, 300 MHz) (α:β = 4:1); δ: 1.28 (d, 3H, *J*4,5 = 6.6 Hz, H-5’ (α)), 1.39 (d, 3H, *J*4,5 = 6.6 Hz, H-5’ (β)), 2.08 – 2.16 (m, 2H, H-2’a and H-2’b, (β)); 2.52 (dt, 1H, *J*1,2 = *J*2,3 = 2.1 Hz, H-2’a (α)); 2.73 (dd, 1H, *J*2,3 = 7.2 Hz, *J*1,2 = 7.5 Hz, H-2’a (β)); 3.87 (d, 1H, *J*2,3 = *J*4,5 = 2.1 Hz, H-2’a (β)); 4.02 – 4.05 (m, 1H, H-3’ (α)), 4.24 – 4.28 (m, 1H, H-4’ (β)). 4.47 – 4.54 (m, 3H, OCH2Ar (α) and H-4’), 4.79 (bs, 2H, OCH2Ar (β)), 4.78 – 4.82 (m, 1H, H-4’ (α)), 5.60 (bs, 2H, NH2), 6.20 (t, 1H, *J*1,2 = *J*1,2 = 6.0 Hz, H-1’, (β)), 5.81 (d, 1H, *J*1,2 = 2.4 Hz, H-1’, (β)), 7.0 (bs, 2H, NH2), 7.26 – 7.38 (m, 5H, H-arom.), 8.15 (bs, 1H, H-8 (α and β)). 1H NMR (DMSO-d6, 300 MHz) (α); δ: 1.19 (d, 3H, *J*4,5 = 6.6 Hz, H-5’), 2.44 (dd, 1H, *J*1,2 = 2.7 Hz, *J*2,3 = 6.6 Hz, H-2’a), 2.79 (dt, 1H, *J*1,2 = 7.2 Hz, *J*2,3 = 13.8 Hz, H-2’a), 3.98 (dt, 1H, *J*1,2 = 6.6 Hz, H-3’, *J*3,4 = 12.8 Hz, H-3’), 4.42 (qd, 1H, *J*3,4 = 2.7 Hz, *J*4,5 = 6.6 Hz, H-4’), 4.86 (s, 2H, OCH2Ar), 5.79 (bs, 2H, NH2), 6.17 (dd, 1H, *J*1,2 = 2.7 Hz, *J*1,2 = 7.2 Hz, H-1’), 7.29 – 7.37 (m, 5H, H-arom.), 7.87 (bs, 1H, H-8). 13C NMR (DMSO-d6, 75.4 MHz) (α): 19.20 (C-5’), 36.44 (C-2’), 70.74 (OCH2Ar), 80.15 (C-3’), 81.94 (C-4’), 82.95 (C-1’), 113.18 (C-5), 127.72 – 128.51 (C-arom.), 135.76 (C-arom.), 138.25 (C-8), 151.73 (C-4), 156.34 (C-6), 160.56 (C-2). IR (KBr): 3458 (m), 3327 (m), 3173 (m), 2871 (w), 1655 (m), 1593 (s), 1475 (m), 1364 (s), 1272 (w), 1221 (w), 1061 (m), 967 (w), 791 (w), 740 (w), 699 (w), 635 (w). HRMS (Cl, NH3): Calcd for C17H20N6O2: 340.38; found, 340.1659. Analysis, calcd for C17H20N6O2: C, 59.99; H, 5.92; N, 24.69. Found: C, 60.00; H, 5.97; N, 24.49.

2-Fluoro-9-(3-O-benzyl-2,5-dideoxy-α,β-D-erythro-pentofuranosyl)adenine (13). The diamino compound 12 (55 mg, 0.22 mmol) was dissolved in 60% HF/pyridine (0.57 mL) at −10 °C by vigorous stirring. To this cloudy solution was added tert-butyl nitrite (30 mL, 0.24 mmol). After 4.5 h at −20 °C, the cold reaction mixture was added dropwise over 10 min to a vigorously stirred mixture of saturated NaHCO3 and ice (80 mL). Small portions of NaHCO3 were added to stabilize the pH at 7 – 8 (monitored with paper). CHCl3 (30 mL) was added, the layers were separated, and the aqueous layer
was separated was extracted with more CHCl₃ (2 x 15 mL). The combined CHCl₃ layers were dried (MgSO₄) and evaporated to dryness. The residue was purified by preparative plate chromatography (CH₂Cl₂/MeOH, 95:5) to afford 7.0 mg of 13 as an anomic mixture (α:β ~ 1:1) (12.6 % yield). Mp: 214 – 216 °C (α anomer from ethanol). ¹H NMR (DMSO-d₆, 300 MHz) (α:β~1:1; δ: 1.21 (d, 3H, J₄,₅ = 6.6 Hz, H-5’ (α)), 1.29 (d, 3H, J₄,₅ = 6.3 Hz, H-5’), 2.46 – 2.73 (m, 2H, H-2’a and H-2’b (α and β) overlapping DMSO-d₆), 2.76 – 2.97 (m, 2H, H-2’a and H-2’b (α and β)), 3.96 – 4.01 (m, 1H, H-3’ (α and β)), 4.12 – 4.51 (m, 1H, H-4’ (α and β), 4.54 (s, 2H, OCH₂Ar (α or β)), 4.56 (s, 2H, OCH₂Ar (α or β)), 6.19 (t, 1H, J₁:₂b = 7.2 Hz, H-1’ (β)), 7.27 – 7.33 (m, 5H, H-arom.), 7.84 (bs, 2H, NH₂), 8.22 (s, 1H, H-8 (α or β)), 8.32 (s, 1H, H-8 (α or β)). ¹H NMR (DMSO-d₆, 300 MHz) (α; δ: 1.21 (d, 3H, J₄,₅ = 6.3 Hz, H-5’), 2.55 – 2.60 (m, 1H, H-2’a), 2.81 (dd, 1H, J₁:₂b = 7.5 Hz, J₂a:₂b = 14.4 Hz, H-2’b’), 4.00 (t, 1H, J₂a:₂b’ = J₃:₄ = 3.0 Hz, H-3’), 4.49 (dd, 1H, J₃:₄ = 3.0 Hz, J₄,₅ = 6.3 Hz, H-4’), 4.56 (d, 2H, J_gem = 12.0 Hz, OCH₂Ar), 6.26 (dd, 1H, J₁:₂a = 2.7 Hz, J₁:₂b = 7.5 Hz, H-1’), 7.28 – 7.38 (m, 5H, H-arom.), 7.81 (bs, 2H, NH₂), 8.22 (s, 1H, H-8). ¹⁹F NMR (DMSO-d₆, 282 MHz) (α and β ~ 1:1; δ: -46.94 and -47.27. ¹⁹F NMR (DMSO-d₆, 282 MHz) (α; δ: -47.27 (2-F). MS (EI, 70 eV): 344 ([M + H]⁺, 15), 237 (100), 191 (25), 180 (75), 154 (100), 107 (100), 91 (100). MS (CI, NH₃): 344 ([M+H]⁺, 100), 154 (10), 108 (30), 91 (60). HRMS (CI, NH₃): Calcd for C₁₇H₁₈F₃N₅O₂: 343.36. Found: 343.14.

2-Fluoro-9-(2,5-dideoxy-α-L-erythro-pentofuranosyl)adenine (1a). The diamino compound 11 (91.8 mg, 0.37 mmol) was dissolved in 60% HF/pyridine (1.32 mL) at -10 °C by vigorous stirring. To this cloudy solution was added tert- butyl nitrite (0.51 µL, 0.41 mmol). After 4 h more tert- butyl nitrite (0.26 µL, 0.21 mmol) was added at -20 °C to -30 °C, and the reaction was held at -20 to -30 °C for an additional 2 h. The cold reaction mixture was added dropwise over 10 min to a vigorously stirred mixture of saturated NaHCO₃ and ice (100mL). Small portions of NaHCO₃ were added to stabilize the pH at 7 – 8 (monitor with paper). CHCl₃ (50 mL) was added, the layers were separated and the aqueous layer was separated was extracted with CHCl₃. The combined CHCl₃ layers were dried (MgSO₄) and evaporated to dryness. The residue was purified by preparative plate chromatography (CH₂Cl₂/MeOH, 95:5) to afford 11 mg of 1 (11.8 % yield). Mp: ~194 °C (dec). ¹H NMR (DMSO-d₆, 300 MHz): 1.17 (d, 3H, J₄,₅ = 6.6 Hz, 5’-H), 2.34 (dt, 1H, J₁:₂a = J₂a:₂b = 4.0 Hz, J₂a:₂b’ = 14.1 Hz, H-2’a), 2.77 (dt, 1H, J₁:₂b = 7.2 Hz, J₂a:₂b’ = 14.1 Hz, H-2’b’), 4.003 – 4.015 (m, 1H, H-3’), 4.18 (qqd, 1H, J₃:₄ = 4.2 Hz, J₄,₅ = 6.6 Hz, H-4’), 5.49 (d, 1H, J_H/3’OH = 3.6 Hz OH-3’), 6.19 (dd, 1H, J₁:₂a = 4.0 Hz, J₁:₂b = 7.2 Hz, H-1’), 7.82 (bs, 2H, NH₂), 8.33 (s, 1H, H-8). ¹³C NMR (DMSO-d₆, 75 MHz): 18.61 (C-5’), 41.15 (C-2’), 74.64 (C-3’), 82.44 (C-1’ or C-4’), 82.54 (C-4’ or C-1’), 117.12 (J:C₅,F₂ = 3.99, C-5), 139.63 (C-8), 150.12 (C-4, J:C₄,F₂ = 20.3), 157.35 (C-6, J:C₆,F₂ = 21.11), 158.34 (C-2, J:C₂,F₂ = -203.2). ¹⁹F NMR (DMSO-d₆, 282 MHz): -47.3. IR (KBr): 3435 (s), 2963 (m), 1650 (w), 1383 (w), 1261 (s), 1095 (s), 1022 (s), 802 (s), 700 (w). MS (EI, 70 eV): 253 (M⁺, 40), 237 (30), 180 (100), 154 (100), 101 (100), 83 (100), 57 (100). HRMS (CI, NH₃): Calcd for C₁₀H₁₂F₃N₅O₂F: 253.23. Found: 253.098.
References:

[in vacuo means in a vacuum. I think we should either use the latin in vacuo or the English under vacuum, but not in vacuum. Because the change was easier, I changed in vacuum to in vacuo in this Supplemental Information and in the paper as appropriate.]