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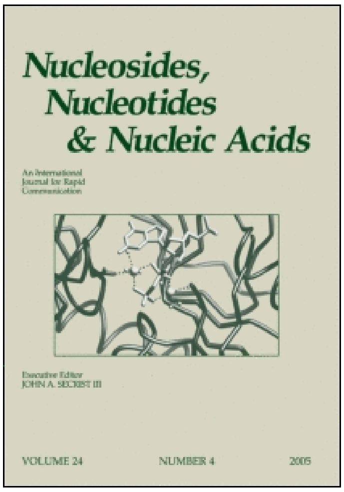

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NUCLEOSIDES & NUCLEOTIDES, 18(11&12), 2433–2442 (1999)

SYNTHESIS OF 8-SUBSTITUTED ANALOGUES OF 2'-DEOXY-2'-FLUOROADENOSINE

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ABSTRACT: After 3',5'-di-O-protection of 8-bromoadenosine, the product was converted to the arabinoside, which was successively treated with diethylaminosulfur trifluoride (DAST) and acid to afford 8-bromo-2'-deoxy-2'-fluoroadenosine. However, the formation of an 8,2'-anhydro compound was noted by treatment of the arabinoside with alkali. Finally, the 8-oxo analog was obtained from the 8-bromo congener.

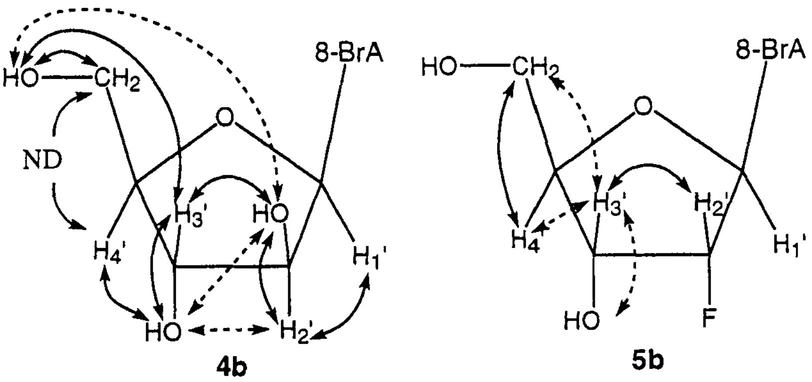
Introduction

A series of 2'-deoxy-2'-fluoronucleosides has been prepared by several ways.[1] One of these, 2'-deoxy-2'-fluorocytidine (dCfl), exhibited antiviral activity against herpes simplex virus (HSV).[2] Tuttle *et al.*[3] reported the enzymatic synthesis and anti-influenza virus activity of purine 2'-deoxy-2'-fluororibosides. Also polymers consisting of 2'-deoxy-2'-fluororibosides have exhibited interesting biological activities such as a primer-template of reverse transcriptase,[4] as codon for mRNA[5] and as interferon inducer.[6] Recently 8-oxo-2'-deoxyguanosine was identified as a unusual nucleoside of the injured DNA[7] and demonstrated to cause miscoding with adenine other than cytosine.[8] Also oligodeoxyribonucleotides containing 2'-deoxy- 8-oxyadenosine[9,10] or its N6-methyl analog11,12 have been shown to form a triple helix as protonated deoxycytidine analogs. This background prompted us to investigate oligodeoxyribonucleotides containing 2'-

deoxy-2'-fluoro-8-oxoadenos- ine. In this paper, a synthetic route to prepare 8-substituted analogs of 2'-deoxy- 2'-fluoroadenosine is described.

Results

The introduction of a fluorine atom at the 2'-carbon of 8-bromoadenosine (**1a**) was attempted according to the method of an earlier report.[13] Starting material **1a**[14] was reacted with 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane and subsequently treated with trifluoromethanesulfonyl chloride in the presence of 4-dimethylamino- pyridine to give the 2'-O-triflate (**1c**). The product **1c** was subjected to an SN2 displacement with acetate in DMF but the 2'(S)(ara)-O-acetate **2a** could not be obtained. When HMPA was employed as a solvent and the reaction time was prolonged for 2 days, the desired product (**2a**) was obtained in low yield. These results indicate that the 8-bromo group causes steric hindrance on the top face of the furanose ring.[15] A trial to improve the yield is under investigation. The protecting groups of **2a** were converted to tetrahydropyran-2-yl groups by the conventional method[13] to give **2c**. However, treatment of **2c** with ammonia in MeOH gave the 8,2'-anhydro compound 3,16 suggesting that intramolecular attack by the 2'-alkoxide ion at 8-carbon had occurred. In general, the formation of 8-anhydro purine nucleosides might be performed by nucleophilic attack of the 8-oxo group on the electrophilic carbon of the sugar moiety.[17] One exception to this rule is the synthesis of 8,2'-anhydro-8-oxo-9-(α-D-xylofuranosyl)adenine.[18] The present method provides an alternative synthetic route for 8,2'-O-cycloadenosine, which is a key compound for the synthesis of nucleoside analogs with a modified base and/or sugar moiety. Thus, conditions which did not produce an 2'-alkoxide ion were explored. Reductive removal of the 2'(S)(ara)-O-acetate (**2c**) was carried out with LiAlH4 in dry THF at –50°C, then carefully neutralized with AcOH after treatment with AcOEt. After separation of the mixture by silica gel chromatography, the arabinoside **4a** was obtained in 61% yield along with **3** (7%). Since compound **4a** is a mixture of four diastereoisomers, this compound was deprotected with pyridinium p-toluene-sulfonate (PPTS) for analysis. The structure of the product **4b** was identified by elemental analysis as wll as by spectroscopic methods including two-dimensional NOE (NOESY) spectra (Fig). Compound **4a** was subjected to the reaction with diethylaminosulfur trifluoride



4b

5b

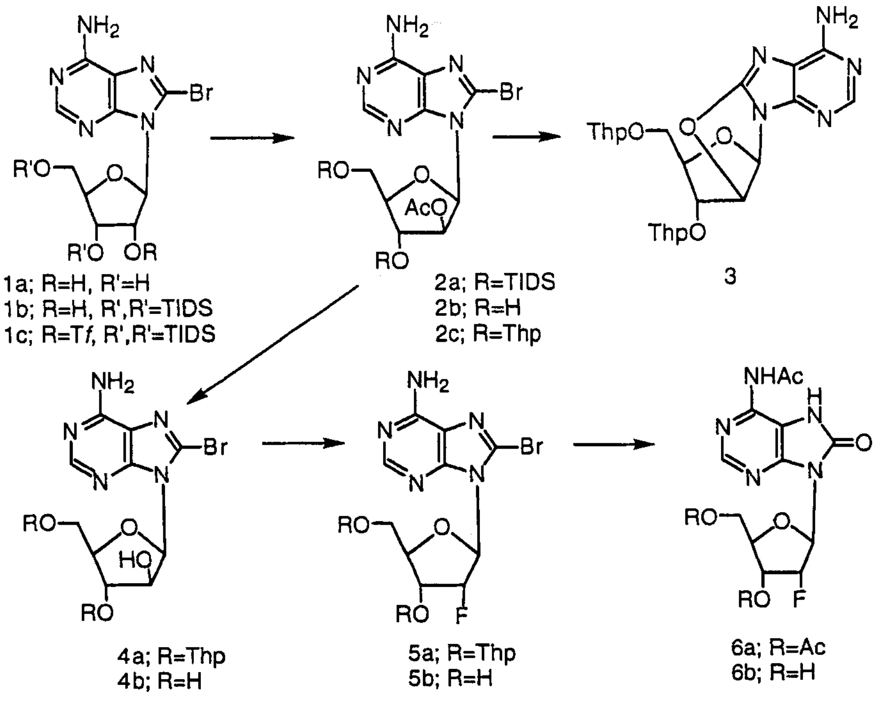
ND; not determined

Fig. NOESY Experiment of Compounds **4b** and **5b** in DMSO-d_6.

(DAST) in the presence of pyridine in CH_2Cl_2 to give **5a**, which was treated with PPTS to give 8-bromo-2'-deoxy-2'-fluoroadenosine (**5b**). The structure of **5b** was confirmed by its 1H-NMR spectrum in which the signal attributable to the 2'-proton appeared at low field (5.85 ppm) and showed a large H2'-C-F geminal coupling (53.57 Hz). The conformation of **5b** was studied with two-dimensional NOE (NOESY) spectrum. A strong NOE contact was observed between H-2' and H-3' in **5b**, whereas protons in trans disposition (H-1' and H-2' or H-3' and H-4') showed a weak NOE. Compound **5b** was also obtained by an alternative method, in which 2'-deoxy-2'-fluoroadenosine was treated with bromine in acetate buffer. The spectroscopic data and physical properties were identical to those of the former sample, therefore the structure of **5b** was finally determined. Nucleophilic substitution of **5b** with NaOAc in Ac2O-AcOH gave the triacetate 6a in 81% yield. A partial deprotection of 6a was carried out in 1 M NaOH in MeOH to afford N6-acetyl-2'-deoxy-2'-fluoro-8-oxoadenosine (**6b**) in good yield (Scheme).

Experimental

Melting points (mp) were determined using a Yanagimoto micro-melting point apparatus (hot stage type) and are uncorrected. UV spectra were recorded with a Shimadzu UV-190 digital spectrometer. Low resolution mass spectra were obtained on a



Scheme

Shimadzu-LKB 9000B mass spectrometer in the direct-inlet mode. High resolution mass spectra were obtained on a JMS AX-500 spectrometer in the direct-inlet mode. 1H-NMR spectra were recorded on either Varian UNITY 200 (200 MHz) or Varian UNITY 600 (600 MHz) in $CDCl_3$ (or dimethyl sulfoxide (DMSO)-d_6) with tetramethylsilane as an internal standard. Merck Art 5554 plates precoated with silica gel 60 containing fluorescent indicator F_{254} were used for thin-layer chromatography and silica gel 60 (Merck 7734, 60 - 200 mesh) was employed for column chromatography.

8-Bromo-9-(3,5-O-tetraisopropyldisiloxane-1,3-diyl-β-D-ribo-furanosyl)-adenine (1b) To a solution of 8-bromoadenosine (**1a**) (20 g, 57.7 mmol) and imidazole (17.34 g, 255 mmol) in DMF (290 ml) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (20.23 ml, 64 mmol) at 0 °C and the solution was kept at room temperature for 40 min, then water (20 ml) was added. The solvents were removed under reduced pressure and the residue was partitioned between benzene (900 ml) and water (600 ml). The organic layer was washed with water (600 ml), dried over $MgSO_4$, and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (6.5x42 cm) using 11-50% AcOEt in hexane (5 l). Evaporation of the main fraction gave **1b** as white crystals (26.7 g, 78%). mp 85.7-86.5°C; Anal. Calcd. for $C_{22}H_{38}BrN_5O_0Si_2$: C, 44.89; H, 6.51; N, 11.90. Found: C, 45.12; H, 6.64; N, 11.87. MS m/z: 587, 589 (M^+), 544, 546 ($M^+–C_3H_7$); UV λ_{max} (MeOH) 264 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.17 (1H, s, H2), 6.01 (1H, d, *J* = 1.10 Hz, H1'), 5.64 (2H, br s, NH_2), 5.48-5.51 (1H, m, H3'), 4.96 (1H, ddd, *J* = 5.77, 1.37, 1.10 Hz, H2'), 4.00-4.04 (3H, m, H4', H5'), 3.27 (1H, d, *J* = 1.37 Hz, 2'OH), 1.01-1.20 (28H, m, $(CH_3)_2CHx4$).

8-Bromo-9-(2-O-triflyl-3,5-O-tetraisopropyldisiloxane-1,3-diyl-β-D-ribofuranosyl)adenine (1c) To an ice-cooled solution of **1b** (26.9 g, 45.7 mmol), triethylamine (8.8 ml) and 4-dimethylaminopyridine (7.02 g, 57.5 mmol) in dry CH_2Cl_2 (300 ml) was added trifluoromethanesulfonyl chloride (8.8 ml, 52.2 mmol), and the solution was kept at room temperature for 15 min, then water (20 ml) was added. The solution was diluted with CH_2Cl_2 (900 ml) and the organic layer was washed with water twice (1.2 l), dried over $MgSO_4$, and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (6x30 cm) using 0-2% EtOH in $CHCl_3$ (4 l). Evaporation of the first fraction gave **1c** as a gum (26.7 g, 82%). MS m/z: 676, 678 (M^+-C3H7); UV λ_{max} (MeOH) 263 nm.

8-Bromo-9-(2-O-acetyl-3,5-O-tetraisopropyldisiloxane-1,3-diyl-β-D-arabinofuranosyl)adenine (2a) Compound **1c** (26.62 g, 37 mmol) was dissolved in dry HMPA (160 ml) and anhydrous NaOAc (15.18 g, 185 mmol) was added to the solution, then the mixture was stirred at 50°C for 2 days. The solution was diluted with benzene (900 ml), washed with water (5x400 ml), dried over $MgSO_4$ and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (4x40 cm) using 9-50% AcOEt in hexane (4 l). Evaporation of the fraction gave a residue, which was crystallized from EtOH to afford **2a** as white crystals (6.09 g, 26%). mp 208-210°C; Anal. Calcd. for $C_{24}H_{40}BrN_5O_6Si_2$: C, 45.71; H, 6.39; N, 11.10. Found: C, 45.70; H, 6.39; N, 11.23. MS m/z: 629, 631 (M^+); UV λ_{max} (MeOH) 261 nm. ^{1}H-NMR ($CDCl_3$) δ: 8.24 (1H, s, H2), 6.49 (1H, d, *J* = 7.33 Hz, H1'), 5.82 (1H, t, *J* = 7.69 Hz, H2'), 5.61

(2H, br s, NH_2), 5.42 (1H, dd, *J* = 7.69, 7.33 Hz, H3'), 4.40 (1H, dd, *J* = 11.36, 7.33 Hz, H5'a), 3.98 (1H, dd, *J* = 11.36, 3.30 Hz, H5'b), 3.92 (1H, m, H4'), 1.67 (3H, s, CH_3CO), 0.95-1.37 (28H, m, $(CH_3)_2CH$x4).

8-Bromo-9-(2-O-acetyl-β-D-arabinofuranosyl)adenine (2b) To a solution of **2a** (6.09 g, 9.7 mmol) and AcOH (1.06 ml, 17.65 mmol) in THF (50 ml) was added tetrabutylammonium fluoride (1.0 M solution in THF, 19.4 ml, 19.4 mmol) and the solution was kept at 0°Cfor 1.5 hr. The solvent was concentrated to a small volume and chromatographed over a column of silica gel G (4x40 cm) using 5-12.5% EtOH in $CHCl_3$ (3 l). Evaporation of the fraction gave a residue, which was crystallized from EtOH to afford **2b** as white crystals (3.28 g, 88%). mp 194.3-195.5°C; Anal. Calcd. for $C_{12}H_{14}BrN_5O_5$: C, 37.13; H, 3.64; N, 18.04. Found: C, 37.10; H, 3.60; N, 18.11. MS m/z: 388, 390 (M^{+}+H), 387, 389 (M^{+}), 357, 359 (M^{+}-CH_2O); UV λ_{max} (MeOH) 264 nm. ^{1}H-NMR (DMSO-d_6) δ: 8.13 (1H, s, H2), 7.48 (2H, br s, NH_2), 6.47 (1H, d, *J* = 7.14 Hz, H1'), 5.77 (1H, d, *J* = 5.49 Hz, 3'OH), 5.31 (1H, t, *J* = 7.14 Hz, H2'), 5.04 (1H, dd, *J* = 6.32, 4.94 Hz, 5'OH), 4.86 (1H, m, H3'), 3.75 (1H, ddd, *J* = 8.52, 6.04, 2.47 Hz, H4'), 3.71-3.79 (2H, m, H5'), 1.59 (3H, s, CH_3CO).

8-Bromo-9-(2-O-acetyl-3,5-di-O-tetrahydropyran-2-yl-β-D-arabinofuranosyl)adenine (2c) To an ice-cooled solution of **2b** (3.28 g, 8.45 mmol) and 3,4-dihydro-2H-pyran (7.3 ml, 80 mmol) in dry DMF (66 ml) was added p-toluenesulfonic acid (2.96 g, 8.45 mmol) and the solution was stirred at 0°C for 5 min, then the reaction was continued at room temperature for 90 min. After neutralization with triethylamine (2.2 ml), the solvents were removed under reduced pressure and the residue was partitioned between benzene (400 ml) and water (200 ml). The organic layer was washed with water twice (400 ml), dried over $MgSO_4$, and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (3.2x52 cm) using 0-5% EtOH in $CHCl_3$ (3 l). Evaporation of the fraction gave 2c as a caramel (3.7 g, 76%). MS m/z: 470, 472 (M^{+}-C_5H_9O); UV λ_{max} (MeOH) 264 nm.

8,2'-Anhydro-8-oxy-9-(3,5-di-O-tetrahydropyran-2-yl-β-D-arabinofuranosyl)adenine (3) To an ice-cooled solution of **2c** (100 mg, 0.18 mmol) in MeOH (3 ml) was added ammonia in MeOH (3 ml) and the solution was kept at 0°C overnight. Concentration of the solution gave **3** as white crystals (52 mg, 66%). mp 227.3-228.9°C;

Anal. Calcd. for $C_{20}H_{27}N_5O_6$: C, 55.42; H, 6.28; N, 16.16. Found: C, 54.97; H, 6.32; N, 16.02.; MS m/z: 433 (M^+); UV λ_{max} (MeOH) 256 nm.

8-Bromo-9-(3,5-di-O-tetrahydropyran-2-yl-β-D-arabinofuranos-yl)adenine (4a) To a suspension of $LiAlH_4$ (280 mg) in dry THF (130 ml) at -50°C was added a solution of **2c** (3.29 g, 5.91 mmol) in dry THF (10 ml) and the solution was stirred at –50°C for 4.5 hr. AcOEt (30 ml), AcOH (2 ml) and water (4 ml) were successively added to the solution and filtered to remove insoluble materials. The filtrate was evaporated and the residue was partitioned between ether (300 ml) and water (300 ml). The organic layer was washed with water (300 ml), dried over $MgSO_4$, and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (2.8x70 cm) using 0-5% EtOH in $CHCl_3$ (4 l). Evaporation of the first fraction gave the starting material as a gum (0.137 mg, 7%). The second fraction was evaporated to afford **4a** as a gum (2.09 g, 61%). MS m/z; 433 (M^+-HBr), 428, 430 (M^+-C_5H_9O), 213, 215 (8-Bromoadenine); UV λ_{max} (MeOH) 264 nm.

9-(β-D-Arabinofuranosyl)-8-bromoadenine (4b) To a solution of **4a** (200 mg, 0.388 mmol) in EtOH (8 ml) was added pyridinium *p*-toluenesulfonate (96.8 mg, 0.385 mmol) and the solution was kept at 80°C overnight. The reaction mixture was evaporated, and the residue was crystallized from EtOH to give **4b** as white crystals (61 mg, 45%). mp 208.5-210.2°C(dec.); Anal. Calcd. for $C_{10}H_{12}BrN_5O_4$: C, 34.70; H, 3.49; N, 20.23. Found: C, 34.95; H, 3.57; N, 20.27. MS m/z: 345, 347 (M^+), 213, 215 (8-bromoadenine); UV λ_{max} (MeOH) 265 nm. ^{1}H-NMR (DMSO-d_6) δ : 8.07 (1H, s, H2), 7.45 (2H, br s, NH_2), 6.24 (1H, d, J = 6.87 Hz, H1'), 5.62 (1H, d, J = 5.77 Hz, 2'OH), 5.47 (1H, d, J = 5.49 Hz, 3'OH), 5.32 (1H, dd, J = 6.32, 4.40 Hz, 5'OH), 4.43-4.47 (1H, dt, J = 7.28(t), 5.49(d) Hz, H3'), 4.34 (1H, m, H2'), 3.72-3.80 (3H, m, H4', H5').

8-Bromo-9-(2-deoxy-2-fluoro-3,5-di-O-tetrahydropyran-2-yl-β-D-ribofuranosyl)adenine (5a) To an ice-cooled solution of **4a** (2.095 g, 4.06 mmol) in a mixture solution of dry CH_2Cl_2 (170 ml) and pyridine (3.1 ml) was added DAST (4.06 ml, 30.7 mmol). The mixture was gradually warmed to room temperature and refluxed for 4 h. The whole was added dropwise to 5% $NaHCO_3$ (400 ml) with stirring, then the organic layer was diluted with CH_2Cl_2 (100 ml), washed with water twice (300 ml), dried over $MgSO_4$, and concentrated to a small volume. The residual solution was chromatographed over a column of silica gel G (2.9x42 cm) using 0-6.3% EtOH in $CHCl_3$ (2 l). Evaporation of the fraction gave **5a** as a gum (1.44 g, 73%). MS m/z: 430, 432 (M^+–C_5H_9O), 346, 348 (M^+ – $C_{10}H_{17}O_2$), 213, 215 (8-Bromoadenine); UV λ_{max} (MeOH) 264 nm.

8-Bromo-9-(2-deoxy-2-fluoro-β-D-ribofuranosyl)adenine (5b) *Method A* To a solution of **5a** (1.44 g, 2.79 mmol) in EtOH (59 ml) was added pyridinium p-toluenesulfonate (698 mg, 2.77 mmol) and the solution was kept at 80°C overnight, then concentrated to 5 ml. The crystals were collected by filtration and the filtrate was evaporated to give a residue, which was chromatographed over a column of silica gel G (2.3x33 cm) using 3.2-14.3% EtOH in $CHCl_3$ (1 l). Crystals obtained after evaporation of the main fraction were combined with the initial crop of crystals to give **5b** (0.746 g, 76%). mp 208.4°C(dec.); Anal. Calcd. for $C_{10}H_{11}BrFN_5O_3$: C, 34.50; H, 3.18; N, 20.12. Found: C, 34.84; H, 3.33; N, 19.99. MS m/z: 347, 349 (M^+); UV λ_{max} (MeOH) 264 nm. ^{1}H-NMR (DMSO-d_6) δ: 8.13 (1H, s, H2), 7.57 (2H, br s, NH_2), 6.05 (1H, dd, J = 20.60, 3.02 Hz, H1'), 5.85 (1H, ddd, J = 53.57, 4.95, 3.02 Hz, H2'), 5.76 (1H, d, J = 6.32 Hz, 3'OH), 5.11 (1H, br s, 5'OH), 4.68 (1H, m, H3'), 3.95 (1H, br s, H4'), 3.70 (1H, d, J = 12.36 Hz, H5'a), 3.49 (1H, m, H5'b).

Method B A solution of 2'-deoxy-2'-fluoroadenine (0.69 g, 2.56 mmol) in a mixture of 0.5 M acetate buffer (14 ml), AcOH (14 ml) and bromine water (30 ml) was kept at room temperature overnight, then the solution was partitioned between benzene (100 ml) and water (50 ml). The aqueous layer was washed with benzene twice (100 ml) and evaporated to give a residue, which was crystallized from water to afford white crystals (0.5 g, 56%).

N6,O3',O5'-Triacetyl-2'-deoxy-2'-fluoro-8-oxoadenosine (6a) To a solution of **5b** (400 mg, 1.15 mmol) in a mixture solution of AcOH (6 ml) and Ac_2O (3 ml) was added anhydrous NaOAc (0.81 g, 9.88 mmol) and the solution was refluxed overnight. The solution was evaporated and the residue was crystallized from a mixture solution of EtOH (9 ml) and water (18 ml) to give white crystals (386 mg, 81%). mp 188.7-190.2°C; Anal. Calcd. for $C_{16}H_{18}FN_5O_7$: C, 46.72; H, 4.41; N, 17.02. Found: C, 46.82; H, 4.47; N, 17.05. MS m/z: 411 (M^+); UV λ_{max} (MeOH) 288 nm. ^{1}H-NMR (DMSO-d_6) δ: 10.91 (1H, br s, N-H), 10.44 (1H, br s, N-H), 8.45 (1H, br s, H2), 6.06 (1H, d, J

= 23.81 Hz, H1'), 5.90 (1H, dd, J = 52.56, 4.95 Hz, H2'), 5.56-5.72 (1H, m, H3'), 4.08-4.43 (3H, m, H4', H5'), 2.15 (6H, s, Acx2), 1.97 (3H, s, Ac).

N6-Acetyl-2'-deoxy-2'-fluoro-8-oxoadenosine (6b). To an ice-cooled solution of **6a** (325 mg, 0.79 mmol) in pyridine (10 ml) was added 1 M NaOH (8 ml) and cold water was added until the solution became clear. The solution was stirred at 0┼Ú for 13 min then neutralized with AcOH (0.5 ml). Concentration of the solution gave white crystals (257 mg, 92%). mp 243.5-245.9°C; Anal. Calcd. for $C_{12}H_{14}FN_5O_5.1/2H_2O$: C, 42.86; H, 4.50; N, 20.83. Found: C, 42.92; H, 4.44; N, 20.91.; MS m/z: 327 (M^+); UV λ_{max} (MeOH) 288 nm, λ_{max} (0.1 M NaOH) 307 nm. ^{1}H-NMR (DMSO-d_6) δ: 10.89 (1H, br s, N-H), 10.39 (1H, br s, N-H), 8.43 (1H, d, J = 0.92 Hz, H2), 5.96 (1H, d, J = 22.89 Hz, H1'), 5.61 (1H, dd, J = 54.03, 4.21 Hz, H2'), 5.60 (1H, d, J = 6.59 Hz, 3'OH), 4.81 (1H, t, J = 6.04 Hz, 5'OH), 4.48-4.68 (1H, m, H3'), 3.85 (1H, br s, H4'), 3.65-3.74 (1H, m, H5'a), 3.41-3.53 (1H, m, H5'b), 2.14 (3H, s, Ac).

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