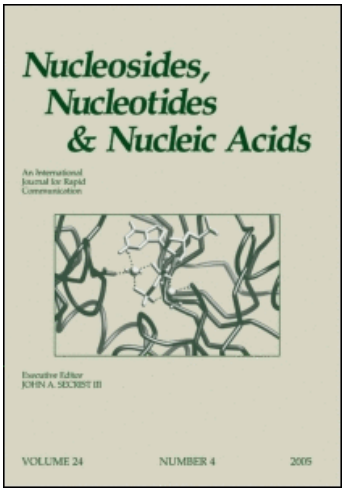

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A Novel Method for the Synthesis of ddA and F-ddA Via Regioselective 2'-O-Deacetylation of 9-(2,5-DI-O-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine

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A NOVEL METHOD FOR THE SYNTHESIS OF ddA AND F-ddA VIA REGIOSELECTIVE 2'-*O*-DEACETYLATION OF 9-(2,5-DI-*O*-ACETYL-3-BROMO-3-DEOXY-β-D-XYLOFURANOSYL)ADENINE†

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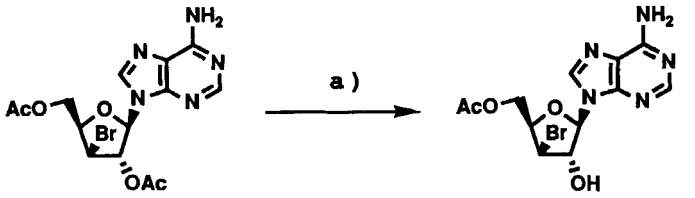
ABSTRACT: Regioselective 2'-*O*-deacetylation of 9-(2,5-di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**1**) is achieved by treatment of **1** with β-cyclodextrin (β-CyD) / aq. $NaHCO_3$ or $N_2H_4 \cdot H_2O$ / EtOH. The 9-(5-*O*-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**2**) obtained is a common intermediate for the synthesis of 2',3'-dideoxy-adenosine (ddA) (**7**) and 9-(2-fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)-adenine (F-ddA) (**9**).

2',3'-Dideoxynucleosides are known as highly potent and selective anti-HIV agents.[1] 2',3'-Dideoxyadenosine (ddA),[2] 2',3'-dideoxyinosine (ddI),[3] and 2',3'-dideoxycytidine (ddC)[4] are undergoing clinical trials in patients with AIDS. Recently, it has been reported that 9-(2-fluoro-2,3-dideoxy-β-D-*threo*-pentofuranosyl)adenine (F-ddA) is more stable than ddA under acidic conditions, and as active and potent as ddA in protecting ATH cells against the cytopathic effect of HIV under substantial viral excess.[5]

In order to develop a convenient synthetic route to these types of nucleosides, especially ddA (**7**) and F-ddA (**9**), we considered 9-(5-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (**2**) as a key intermediate. Our strategy consists of regioselective 2'-*O*-deacetylation of **1** followed by transformation of the resulting 2'-hydroxy group. **1** is readily obtained from adenosine in high yield by the method reported by Moffatt *et al.*[2a] or its modification.[6] The product contains 5-10 % of the regioisomer of **1** at 2' and 3' position but this isomer is easily removed by recrystallization from acetonitrile.

† Dedicated to the memory of Professor Tohru Ueda.



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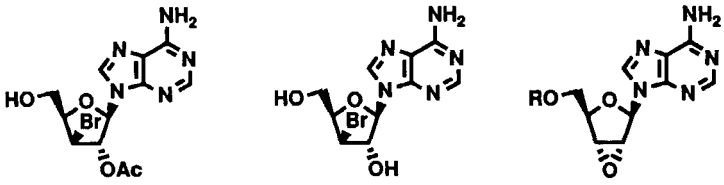
reagents: a) (aqueous) β-CyD, aq $NaHCO_3$
(non-aqueous) $N_2H_4 \cdot H_2O$, EtOH



3 4 5a, R=H
5b, R=Ac

FIG. 1.

Regioselective hydrolysis of nucleoside derivatives has become a target of important studies in recent years with a view to selective cleavage of nucleic acids or selective deprotection of nucleosides.[7-10] We describe in this paper a novel method for the regioselective 2'-*O*-deacetylation of **1**, which leads to a practical synthesis of ddA (**7**) and F-ddA (**9**).

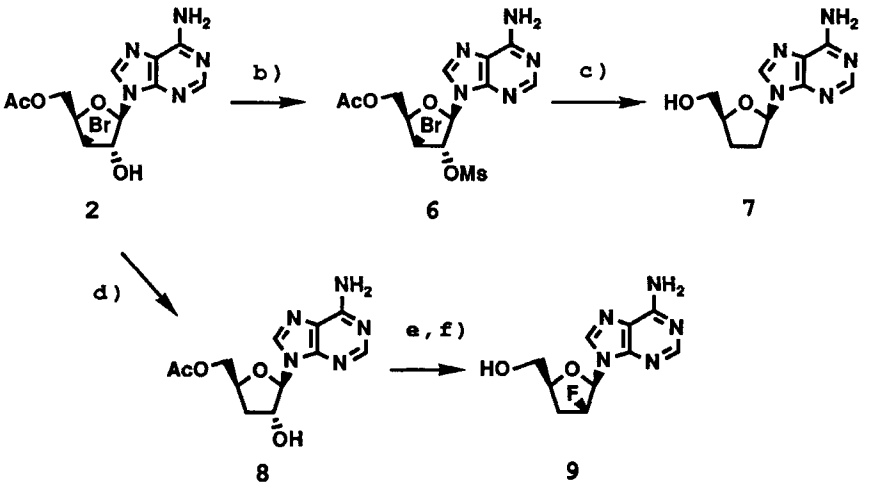
The results of regioselective 2'-*O*-deacetylation were shown in TABLE 1. Under various conditions, four kinds of nucleosides were formed. Base treatment of **1** gave deacetylation products **2**, **3** and **4** together with 2',3'-epoxide **5a** and **5b**. We examined the reaction under aqueous and non-aqueous conditions and found appropriate conditions for the regioselective 2'-*O*-deacetylation in each case. The regioselective P-O(2') or P-O(3') cleavages of 2',3'-cyclic monophosphates of ribonucleosides by the catalyzing action of cyclodextrin was reported by Komiyama *et al.*[7] In our cases, by adding β-cyclodextrin (β-CyD) to the aqueous solution of inorganic salt, 2'-*O*-deacetylation of **1** proceeded regioselectively to give **2.** As is clear from TABLE 1, the best result was obtained by use of the combination of β-CyD and aq. $NaHCO_3$ or Na_2HPO_4. If a salt was used in the same reaction without β-CyD or with α-CyD, the reaction was very slow to proceed at room temperature. Even under heating conditions, the hydrolysis was still slow

TABLE 1. Regioselective 2'-*O*-Deacetylation of Nucleoside (1)

Solvent	Additives (eq.)		Conditions	Products and % yields [d]			
				2	**3**	**4**	**5b (5a)**
H_2O	β-CyD (1.5)	$NaHCO_3$ (1.2)	a	89.1	0.9	1.5	2.4 (0.4)
H_2O	β-CyD (1.5)	Na_2CO_3 (1.2)	a	57.9	0.2	9.8	25.8 (3.8)
H_2O	β-CyD (1.5)	Na_2HPO_4 (1.2)	a	85.9	0.7	1.9	4.0 (0.4)
H_2O	β-CyD (1.5)	AcONa (1.2)	a	15.3	0.4	0.1	0.1 (0.2)
H_2O	β-CyD (1.5)	$(NH_4)_2CO_3$ (1.2)	a	65.9	0.2	9.5	20.1 (2.1)
H_2O	α-CyD (1.5)	$NaHCO_3$ (1.2)	a	17.2	0.5		
H_2O		$NaHCO_3$ (1.2)	b	8.0	6.9	4.3	31.2 (10.8)
H_2O		Na_2CO_3 (1.2)	b	8.5	10.6	2.8	37.1 (16.9)
H_2O		NH_3 (30%)	c				(94.3)
H_2O		$N_2H_4 \cdot H_2O$ (10)	c	50.8	7.4	9.7	21.7 (6.7)
H_2O		HCl (10)	a	9.4	37.3	42.3	
EtOH		NH_3 (sat.)	c	76.5	0.1	5.0	16.7 (1.0)
EtOH		$N_2H_4 \cdot H_2O$ (10)	c	82.3	1.2	2.3	5.9 (0.5)
EtOH		AcONa (1.2)	b	35.7	3.1	4.3	17.5 (1.5)
EtOH		Na_2CO_3 (1.2)	b				26.4 (73.2)
EtOH		$AcONH_4$ (1.2)	b	52.9	3.8	2.5	3.8 (0.9)
EtOH		$NaHCO_3$ (1.2)	b	16.4	2.5	2.7	60.9 (7.7)

(a) at 20 °C for 3 hours
(b) at 40 °C for 24 hours
(c) at 0 °C for 30 minutes
(d) Yields were determined by HPLC analysis of the reaction mixture.

and low selectivity was obtained and undesired formation of epoxide occurred. ^1H NMR study revealed that β-CyD and **1** formed a certain molecular complex. Thus, an upfield shift of the H-3 proton of β-CyD was observed (0.053 ppm when the concentrations of β-CyD and **1** were 10^{-2}M). This result is consistent with the case of β-CyD and the 2',3'-cyclic monophosphates of adenosine.[7a] In the case of α-CyD, no such chemical shifts were observed at all. Hydrolysis by aqueous NaOH or NH_3 did not give satisfactory results on regioselectivity and preferential formation of epoxide was observed, while regioselective 2'-*O*-deacetylation was performed by hydrazine monohydrate[10] or ammonia in ethanol at 0 °C. In the latter case, β-CyD is not effective and the epoxide derivative was formed in larger amount than in the case of aqueous conditions. It is worthy to note that the treatment of **1** with aqueous HCl predominantly gave the 5'-*O*-deacetylation product **3** instead of **2**.



reagents: b) MsCl, Pyridine (91%); c,d) H_2, Pd-C, aq.Na_2CO_3, MeCN (c, 85%, d, 69%); e) DAST, CH_2Cl_2 (10%); f) NH_3 / MeOH (95%).

FIG. 2.

The synthesis of ddA (**7**) from **2** was performed by mesylation of the 2'-hydroxy group of **2**, followed by palladium catalyzed hydrogenation. Moffatt *et al.* reported that almost the same amount of 3'-deoxyadenosine (46%) and **7** (40%) were obtained from the reduction of **1** under similar conditions.[2a] By introducing an electronwithdrawing group at the 2'-position, the reduction proceeded more selectively to give **7** in high yield. Thus, a higher ratio of **7** (85%) to 3'-deoxyadenosine (0.8%) was obtained by the reduction of **6**.

For the synthesis of F-ddA (**9**), regioselectively hydrolyzed nucleoside (**2**) was subjected to hydrogenation in acetonitrile and aqueous sodium carbonate solution in the presence of a palladium catalyst. In this case, simple reduction of the bromide occurred and 3'-deoxy-5'-*O*-acetyladenosine (**8**) was obtained. For the introduction of a fluorine atom in the 2'-"up" position by an S_N2 displacement, we modified Herdewijn's direct method using DAST (*N,N*-diethylaminosulfur trifluoride).[11] The best result was obtained in the reaction at 45 °C for 5 hr in CH_2Cl_2. Following removal of the protective group by NH_3 / MeOH and purification by silica gel column chromatography, **9** was obtained as a crystalline solid.

In summary, a method utilizing a regioselective deacetylation reaction offers a convenient route to the synthesis of ddA and F-ddA.

EXPERIMENTAL

Melting points were measured with a Yamato melting point apparatus and are uncorrected. UV spectra were recorded on a Hitachi U-3200 spectrometer. ^{1}H NMR spectra were obtained on a Varian XL-300 or JEOL JNM-GX 400 spectrometers and are reported as ppm values downfield from Me_4Si (Me_2SO-d_6) or 3-(trimethylsilyl)propanesulfonic acid sodium salt (D_2O). Fast atom bombardment mass spectra were obtained on a JEOL D-300 instrument. HPLC was carried out on a 15 cm YMC A-312 column with a Hitachi 655 system equipped with a Shimadzu C-R4A integrator and Hitachi variable wavelength UV monitor set at 260 nm.

9-(2,5-Di-*O*-acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (1). An analytical sample was obtained by recrystallization from acetonitrile: mp 163-164 °C; $\lambda_{max}(H_2O)$ 259 nm (ε 14 035) , $\lambda_{min}(H_2O)$ 227 nm (ε 2513); ^{1}H NMR (Me_2SO-d_6) δ 2.06 (s, 3H, Ac), 2.11 (s, 3H, Ac), 4.38 (m, 2H, H-5'$_{ab}$), 4.56 (m, 1H, H-4'), 4.92 (dd, 1H, J=2.5, 4.7 Hz, H-3'), 5.90 (t, 1H, J=2.5, 3.1 Hz, H-2'), 6.17 (d, 1H, J=3.1 Hz, H-1'), 7.37 (s, 2H, NH_2), 8.16 (s, 1H, H-8), 8.30 (s, 1H, H-2); fast atom bombardment mass spectrum, *m/z* 414, 416 (MH^+). Anal. Calcd for $C_{14}H_{16}BrN_5O_5$: C, 40.60; H, 3.89; N, 16.91. Found: C, 40.45; H, 3.88; N, 16.88.

9-(5-*O*-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (2).
(Aqueous conditions): A suspension of β-cyclodextrin (41.1 g, 36.2 mmol) in water (1000 mL) was heated to 50 °C to completely dissolve. The clear solution was cooled to room temperature and **1** (10 g, 24.2 mmol) was added to the solution. Then sodium hydrogencarbonate (2.4 g, 29.0 mmol) was added to the reaction mixture over 1 hour. After stirring was continued for further 2 hours, the reaction mixture was extracted 3 times with ethyl acetate (500 mL). The combined organic layers were dried and evaporated. The title compound was crystallized from ethyl acetate: 7.0 g (18.9 mmol, 78% yield); mp 167-169 °C; $\lambda_{max}(H_2O)$ 260 nm (ε 17 053); $\lambda_{min}(H_2O)$ 229 nm (ε 4143); ^{1}H NMR (Me_2SO-d_6) δ 2.06 (s, 3H, Ac), 4.38 (d, 2H, J=5.2 Hz, H-5'$_{ab}$), 4.55-4.65 (m, 2H, H-3', H-4'), 5.01 (m, 1H, H-2'), 5.89 (d, 1H, J=3.9 Hz, H-1'), 6.51 (d, 1H, J=5.1 Hz, OH), 7.33 (brs, 2H, NH_2), 8.17 (s, 1H, H-8), 8.30 (s, 1H, H-2); fast atom bombardment mass spectrum, *m/z* 372, 374 (MH^+). Anal. Calcd for $C_{12}H_{14}BrN_5O_4$: C, 38.73; H, 3.79; N, 18.82. Found: C, 38.86; H, 3.78; N, 18.75.

(Non-aqueous conditions): To a solution of **1** (10 g, 24.2 mmol) in ethanol (100 mL) was added hydrazine monohydrate (12.1 g, 242 mmol). The reaction mixture was stirred for 30 minutes at 0 °C and evaporated to dryness. The residue was purified by silica gel column chromatography (eluent $CHCl_3$/ MeOH, 10/1) to give **2** (6.3 g, 16.9 mmol, 70 % yield) .

9-(2-*O*-Acetyl-3-bromo-3-deoxy-β-D-xylofuranosyl)adenine (3).

A solution of **1** (1 g, 2.4 mmol) in 1N HCl (5 mL) was stirred for 2 days at room temperature. The reaction mixture was evaporated and the resulting residue was purified by silica gel column chromatography (eluent $CHCl_3$/ MeOH, 10/1) to give **3** (340 mg, 38% yield): mp 185-188 °C; $\lambda_{max}(H_2O)$ 259 nm (ε 15 891); $\lambda_{min}(H_2O)$ 227 nm (ε 3140); ^1H NMR (Me_2SO-d_6) δ 2.08 (s, 3H, Ac), 3.77 (m, 2H, H-5'$_{ab}$), 4.34 (dt, 1H, *J*=4.7, 5.6 Hz, H-4'), 4.89 (dd, 1H, J=2.5, 4.7 Hz, H-3'), 5.42 (t, 1H, *J*=5.2 Hz, OH), 5.91 (dd, 1H, *J*=3.1, 2.5 Hz, H-2'), 6.11 (d, 1H, *J*=3.1 Hz, H-1'), 7.38 (brs, 2H, NH_2), 8.16 (s, 1H, H-8), 8.30 (s, 1H, H-2); fast atom bombardment mass spectrum, *m/z* 372, 374 (MH^+). Anal. Calcd for $C_{12}H_{14}BrN_5O_4$: C, 38.73; H, 3.79; N, 18.82. Found: C, 38.63.; H, 3.78; N, 18.72. As by-products in the reaction mixture were detected **2** (7%) and 9-(3-Bromo-3-deoxy-β-D-xylofuranosyl)adenine (**4**) (42%) by HPLC analysis.

9-(3-Bromo-3-deoxy-β-D-xylofuranosyl)adenine (4).

A solution of **1** (1 g, 2.4 mmol) in 6N HCl (10 mL) was stirred for 24 hours at room temperature. The reaction mixture was evaporated and the resulting residue was purified by column chromatography (synthetic adsorption resin SP-207, eluent 30-50% MeOH) to give **4** (580 mg, 73 % yield) : mp 152-153 °C; $\lambda_{max}(H_2O)$ 260 nm (ε 13 957); $\lambda_{min}(H_2O)$ 229 nm (ε 2813); ^1H NMR (Me_2SO-d_6) δ 3.74-3.84 (m, 2H, H-5'$_{ab}$), 4.35 (dt, 1H, *J*=4.7, 5.6 Hz, H-4'), 4.56 (dd, 1H, J=4.9, 4.7 Hz, H-3'), 4.92 (dd, 1H, *J*=4.4, 4.9 Hz, H-2'), 5.43 (t, 1H, *J*=6.2 Hz, OH), 5.85 (d, 1H, *J*=4.4 Hz, H-1'), 6.40 (d, 1H, *J*=5.3 Hz, OH), 7.36 (brs, 2H, NH_2), 8.17 (s, 1H, H-8), 8.30 (s, 1H, H-2); fast atom bombardment mass spectrum, *m/z* 330, 332 (MH^+). Anal. Calcd for $C_{10}H_{12}BrN_5O_3$: C, 36.38; H, 3.66; N, 21.21. Found: C, 36.30; H, 3.65; N, 21.17.

2',3'-Anhydroadenosine (5a).

A solution of **1** (5 g, 12.1 mmol) in 28 % NH_3 in water (50 mL) was stirred for 1 hour at room temperature. After evaporation of the solvent, the residue was purified by column chromatography (synthetic adsorption resin SP-207, eluent 30 % MeOH) to give **5a** (2.4 g, 9.7 mmol, 80 % yield): mp 169-171 °C; $\lambda_{max}(H_2O)$ 259 nm (ε 15 955); $\lambda_{min}(H_2O)$ 226 nm (ε 3139); ^1H NMR (Me_2SO-d_6) δ 3.52 (m, 2H, H-5'$_{ab}$), 4.18 (t, 1H, *J*=5.2 Hz, H-4'), 4.22 (d, 1H, *J*=2.7 Hz, H-3'), 4.46 (d, 1H, *J*=2.7 Hz, H-2'), 5.09 (brs, 1H, OH), 6.20 (s, 1H, H-1'), 7.31 (brs, 2H, NH_2), 8.17 (s, 1H, H-8), 8.33 (s, 1H, H-2); fast atom bombardment mass spectrum, *m/z* 250 (MH^+). Anal. Calcd for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 47.99; H, 4.44; N, 27.99.

5'-*O*-Acetyl-2',3'-anhydroadenosine(5b).

To a suspension of **5a** (1.0 g, 4.0 mmol) in anhydrous pyridine (10 mL) was added acetic anhydride (610 mg). The reaction mixture was stirred for 3 hours at room temperature and evaporated. The residue was coevaporated with toluene (10mL), $CHCl_3$ (30mL) was

added and the solution was washed with 10% aqueous copper sulfate (10 mL). The organic layer was dried, evaporated and purified by silica gel column chromatography (eluent $CHCl_3$/ MeOH, 10/1) to give **5b** (1.1 g, 3.8 mmol, 95 % yield): mp 172-173 °C; $\lambda_{max}(H_2O)$ 260 nm (ε 13 674); $\lambda_{min}(H_2O)$ 226 nm (ε 2781); ^1H NMR (Me_2SO-d_6) δ 1.93 (s, 3H, Ac), 4.18 (m, 2H, H-5'$_{ab}$), 4.30 (d, 1H, J=2.6 Hz, H-3'), 4.39 (t, 1H, J=4.8 Hz, H-4'), 4.56 (d, 1H, J=2.6 Hz, H-2'), 6.24 (s, 1H, H-1'), 7.34 (brs, 2H, NH_2), 8.17 (s, 1H, H-8), 8.31 (s, 1H, H-2). fast atom bombardment mass spectrum, *m/z* 292 (MH^+). Anal. Calcd for $C_{12}H_{13}N_5O_4$: C, 49.48; H, 4.50; N, 24.04. Found: C, 49.49; H, 4.50; N, 23.95.

9-(5-*O*-Acetyl-3-bromo-3-deoxy-2-*O*-methanesulfonyl-β-D-xylofuranosyl)adenine (6).

A mixture of **2** (1g, 2.7mmol) and methanesulfonyl chloride (340mg, 1.1 eq) in anhydrous pyridine (10 mL) was stirred for 3 hours at room temperature. The reaction mixture was evaporated and co-evaporated with toluene (10mL). $CHCl_3$ (30 mL) was added and the mixture was washed with 10% aqueous copper sulfate (5 ml). The organic layer was dried, evaporated and purified by silica gel column chromatography (eluent $CHCl_3$/MeOH, 10/1) to give **6** (1.1 g, 2.4 mmol, 90% yield): mp 162-164 °C; $\lambda_{max}(H_2O)$ 259 nm (ε 15 284); $\lambda_{min}(H_2O)$ 227 nm (ε 4838); ^1H NMR (Me_2SO-d_6) δ 2.07 (s, 3H, CH_3), 3.38 (s, 3H, Ms), 4.37-4.41 (m, 2H, H-5'$_{a,b}$), 4.61-4.66 (m, 1H, H-4'), 5.05-5.10 (m, 1H, H-3'), 5.99 (d, 1H, J=5.5 Hz, H-2'), 6.18 (d, 1H, J=4.5 Hz, H-1'), 7.43 (brs, 2H, NH_2), 8.19 (s, 1H, H-8), 8.37 (s, 1H, H-2). fast atom bombardment mass spectrum, *m/z* 450, 452 (MH^+).Anal. Calcd for $C_{13}H_{16}BrN_5O_6S$: C, 34.68; H, 3.58; N, 15.55. Found: C, 34.54; H, 3.56; N, 15.15.

2',3'-Dideoxyadenosine (7).

To a solution of **6** (1.0 g, 2.2 mmol) in acetonitrile (50 mL) was added aqueous solution of sodium carbonate (360 mg, 3.4 mmol in 10 mL of water) and 10% palladium on carbon (120 mg on a dry basis, 0.11 mmol). The mixture was stirred for 2 hours at room temperature under a hydrogen atmosphere at 1 atm. After disappearance of starting material, the catalyst was removed by filtration and the filtrate was evaporated. The residue was treated with 10 % NaOH (adjusted to pH 12) for 1 hour at room temperature and neutralized by 1N HCl. The mixture was purified by column chromatography (synthetic adsorption resin SP-207, eluent 30 % MeOH) to give **7** (439 mg, 1.9 mmol, 85 % yield). A small amount of 3'-deoxyadenosine was detected (4.4 mg, 0.02 mmol, 0.8%) by HPLC analysis of the reaction mixture. By recrystallization from water, an analytical sample was obtained: mp 187-188 °C; $\lambda_{max}(H_2O)$ 261 nm (ε 15 450); $\lambda_{min}(H_2O)$ 227 nm (ε 2327); ^1H NMR (D_2O) δ 2.04 (m, 1H, H-3'$_a$), 2.24(m, 1H, H-3'$_b$), 2.55 (m, 2H, H-2'$_{ab}$), 3.67 (dd, 1H, J=5.1, 12.5 Hz, H-5'$_a$), 3.84 (dd, 1H, J=3.2, 12.5 Hz, H-5'$_b$), 4.36 (m, 1H,

H-4'), 6.27 (dd, 1H, J=3.5, 6.6 Hz, H-1'), 8.13 (s, 1H, H-8), 8.28 (s, 1H, H-2); fast atom bombardment mass spectrum, m/z 236 (MH^+). Anal. Calcd for $C_{10}H_{13}N_5O_2$: C, 51.06; H, 5.57; N, 29.77. Found: C, 51.05; H, 5.57; N, 29.78.

5'-*O*-Acetyl-3'-deoxyadenosine (8).

To a solution of **2** (5 g, 13.4 mmol) in acetonitrile (100 ml) was added an aqueous solution of sodium carbonate (2.1 g, 20.1 mmol in 10 mL of water) and 10% palladium on carbon (715 mg on dry basis, 0.67 mmol). The mixture was stirred for 2 hours at room temperature under a hydrogen atmosphere at 3.5 atm. The catalyst was removed by filtration and the filtrate was evaporated. The residue was purified by silica gel column chromatography (eluent $CHCl_3$/MeOH, 10/1) to give **8** (2.7 g, 9.2 mmol, 69% yield): mp 166-167 °C; $\lambda_{max}(H_2O)$ 260 nm (ε 15 713); $\lambda_{min}(H_2O)$ 227 nm (ε 2864); ^1H NMR (Me_2SO-d_6) δ 2.00 (s, 3H, Ac), 2.01 (m, 1H, H-3'$_a$), 2.32 (m, 1H, H-3'$_b$), 4.19 (dd, 1H, J=12.0, 3.2 Hz, H-5'$_a$), 4.26 (dd, 1H, J=12.0, 5.9 Hz, H-5'$_b$), 4.53 (m, 1H, H-4'), 4.70 (brs, 1H, OH), 5.75 (d, 1H, J=3.9 Hz, H-2'), 5.92 (d, 1H, J=1.7 Hz, H-1'), 7.29 (brs, 2H, NH_2), 8.16 (s, 1H, H-8), 8.25 (s, 1H, H-2); fast atom bombardment mass spectrum, m/z 294 (MH^+). Anal. Calcd for $C_{12}H_{15}N_5O_4$: C, 49.14; H, 5.16; N, 23.88. Found: C, 48.99; H, 5.16; N, 23.80.

9-(2-Fluoro-2,3-dideoxy-β-D-threo-pentofuranosyl)adenine (9).

To a suspension of **8** (6 g, 20.5 mmol) in dichloromethane (200 mL) was added 10 mL (4 eq.) of DAST (*N,N*-diethylaminosulfur trifluoride). The reaction mixture was gently heated to reflux for 5 hours. After cooling to room temperature, the reaction mixture was washed with 10 % aqueous sodium hydrogencarbonate (600 mL) and the aqueous layer was extracted twice with dichloromethane (1000 mL). The combined organic layers were dried and evaporated. The residue was purified by silica gel column chromatography (eluent, $CHCl_3$/MeOH, 24/1) to give 9-(5-*O*-acetyl-2,3-dideoxy-2-fluoro-β-D-threo-pentofuranosyl)adenine (600 mg, 2.0 mmol, 10 % yield); ^1H NMR (Me_2SO-d_6) δ 2.05 (s, 3H, Ac), 2.20-2.37 (m, 1H, H-3'), 2.61-2.82 (m, 1H, H-3'), 4.21-4.44 (m, 3H, H-4', H-5'), 5.42 (dm, 1H, $J_{2',F}$=54.3 Hz), 6.37 (1H, dd, $J_{1',2'}$=3.3 Hz, $J_{1',F}$=18.3 Hz, H-1'), 7.32 (brs, 2H, NH_2), 8.15 (d, 1H, J=2.7 Hz, H-8), 8.18 (s, 1H, H-2); fast atom bombardment mass spectrum, m/z 296 (MH^+).

The 9-(5-*O*-acetyl-2,3-dideoxy-2-fluoro-β-D-threo-pentofuranosyl)adenine (500mg, 1.7 mmol) obtained was treated with NH_3 saturated methanol (100 mL) for 2 hours at room temperature. The reaction mixture was evaporated, and the resulting residue was chromatographed on silica gel ($CHCl_3$/MeOH, 12/1) to give **9** (410 mg,1.6 mmol, 95 % yield): mp 224-227 °C; $\lambda_{max}(H_2O)$ 259 nm (ε 15 537); $\lambda_{min}(H_2O)$ 226 nm (ε 2655); ^1H NMR (Me_2SO-d_6) δ 2.48-2.67 (m, 1H, H-3'), 2.19-2.36 (m, 1H, H-3'), 3.56-3.69 (m, 2H, H-5'), 4.19 (m, 1H, H-4'), 5.06 (brs, 1H, OH) 5.43 (dm, 1H, $J_{2',F}$=54.6 Hz, H-

2'), 6.33 (dd, 1H, $J_{1',2'}$=3.9 Hz, $J_{1',F}$=16.2 Hz, H-1'), 7.31 (brs, 2H, NH_2), 8.16 (s, 1H, H-2), 8.27 (d, 1H, J=2.1 Hz , H-8), fast atom bombardment mass spectrum, *m/z* 254 (MH^+) Anal. Calcd for $C_{10}H_{12}FN_5O_2$: C, 47.43; H, 4.78; N, 27.66. Found: C, 47.29; H, 4.80; N, 27.60.

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