Unsaturated Acyclic Analogues of 2′-Deoxyadenosine and Thymidine Containing Fluorine: Synthesis and Biological Activity[1]

Ze-Qi Xu,[†,‡] Yao-Ling Qiu,[†] Sudhichai Chokekijchai,[§] Hiroaki Mitsuya,[§] and Jiri Zemlicka*,[†]

Department of Chemistry, Michigan Cancer Foundation, and Departments of Internal Medicine and Biochemistry, Wayne State University School of Medicine, Detroit, Michigan 48201, and The Experimental Retrovirology Section, Medicine Branch, National Cancer Institute, Bethesda, Maryland 20892

Received November 14, 1994[⊗]

The syntheses and biological activities of fluorobutynol **11** and (*E*)- and (*Z*)-fluorobutenols **8a,d** and **9a,d** are described. Alkylation of adenine with bromofluorobutyne **13a** afforded intermediate **14** which was converted to fluorobutynol **11**. Aldehyde **16a** and (carbethoxyfluoromethyl)-triphenylphosphonium bromide furnished (*E*)- and (*Z*)-fluorobutenoates **19a** and **20a** accompanied by regioisomer **21a**. A similar reaction of compound **16d** afforded *Z*- and *E*-esters **19d** and **20d**. Reduction of the mixture of **19a** and **20a** with DIBALH gave (*E*)- and (*Z*)-fluoroalkenols **8a** and **9a**. Similarly, the *Z*-ester **19d** gave (*Z*)-fluoroalkenol **9d**. Both **19d** and **20d** were reduced with $NaBH_4$ to give (*Z*)- and (*E*)-fluoroalkenols **9d** and **8d**. Hydrogenation of **19a** and **20a** afforded fluoro ester **23**. A similar reduction of **8a** and **9a** led to fluoro alcohol **24** and the defluorinated product **25** which were separated by chromatography on a Bio-Rad AG 1-X2 (OH^-) column. (*Z*)-Fluorobutenol **9a** is a substrate for adenosine deaminase, whereas the *E*-isomer **8a** is inert toward the enzyme. By contrast, analogue **8a** inhibited the replication and cytopathic effect of HIV-1 in ATH8 cells with an IC_{50} of approximately 100 μM, but the *Z*-isomer **9a** was inactive. This effect was accompanied by 36% cytotoxicity at 100 μM. Compounds **11** and **8d** inhibited the growth of murine leukemia L1210 culture with IC_{50} = 89 and 60 μM, respectively.

Unsaturated acyclic nucleoside analogues have been a focus of several recent studies.[2] The most important compounds of this series are allenic analogues[3] **1a,b** which are strong inhibitors of HIV-1 and HIV-2 in culture. Other types of compounds which were investigated include butynols **2** and (*E*)- and (*Z*)-butenols **3–6** as well as alkenediols **7**. Thus, analogues[4–7] **4c** and **7a,c** are antiviral agents. Adenine analogues **1a–6a** are substrates for adenosine deaminase of varying efficiency.[2,8,9]

Because replacement of hydrogen with fluorine in biologically important molecules leads often to compounds useful in chemotherapy,[10] we became interested in the synthesis and biological evaluation of unsaturated acyclic nucleoside analogues containing fluorine. Molecular modeling indicated some similarities between the *E*- and *Z*-isomers **8a** and **9a** and 2′,3′-dideoxy-3′-fluoroadenosine (**10a**). Analogues **10a–d**, particularly thymine derivative **10d**, exhibit potent antiviral activity.[11] Thus, the distance between the base and the hydroxymethyl group in nucleoside **10a** ($N_9–C_{5'}$ = 4.46 Å) is better approximated in the *Z*-isomer **9a** ($N_9–C_{4'}$ = 4.53 Å) than in the *E*-isomer **8a** (3.07 Å). The opposite is true for distances between the base and the fluoro atom of **8a** and **9a** (**10a**, $N_9–F$ = 4.66 Å; **8a**, 4.33 Å; **9a**, 3.11 Å). The syntheses and biological evaluation of the first five analogues of this new group of potential nucleoside mimics are the subjects of this communication.

Synthesis

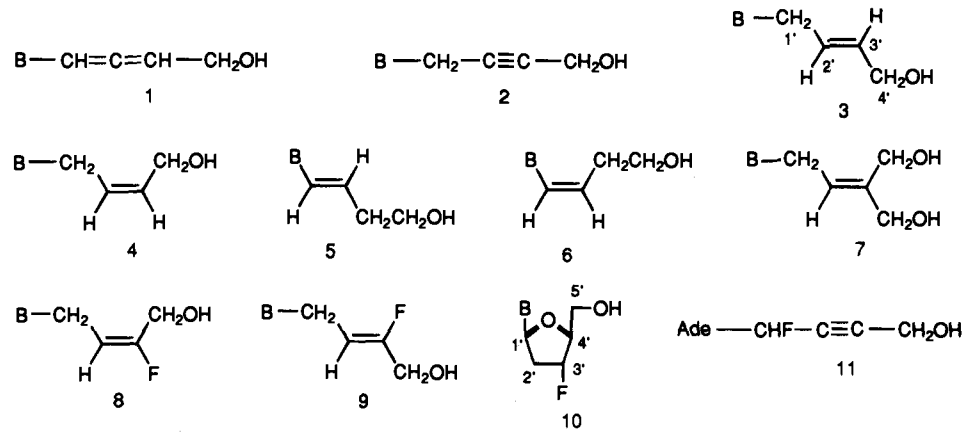
The synthetic approach to fluorobutynol **11** was as follows (Scheme 1). The protected propargyl alcohol **12** was alkylated with dibromofluoromethane to give intermediate **13a** in 32% yield. Alkylation of adenine with **13a** using K_2CO_3 in dimethyl sulfoxide (DMSO) afforded compound **14** in 25% yield. More favorable was the reaction with the sodium salt of adenine in dimethylformamide (DMF) furnishing **14** in 56% yield. Attempted alkylations of adenine with chloro fluoro,[12] bromo difluoro, and iodo difluoro[13] derivatives **13b–d** were fruitless. The tetrahydropyranyl (THP) group of **14** could not be removed by pyridinium *p*-toluenesulfonate[14] in methanol or 5% acetic acid (AcOH) in ethanol at 60 °C. More vigorous treatment such as 2 M HCl in tetrahydrofuran (THF)–MeOH (9:1) caused decomposition to adenine. The optimum conditions for deprotection were found in AcOH–THF–H_2O (4:2:1) at 65 °C for 2 h, and fluorobutynol **11** was obtained in 87% yield.

The IR spectra of fluorinated acetylenes **11**, **13a**, and **14** exhibit a double C≡C frequency at 2230 and 2285 or 2300 cm^{-1}. A similar phenomenon was observed in some polyfluorinated acetylenes.[15,16] The IR absorption of **13a** at 2300 cm^{-1} relative to that at 2230 cm^{-1} was weak, whereas both bands were of comparable intensity in compounds **11** and **14**. It is also of interest to note that ^{19}F NMR signals showed two sets of a doublet of triplets in compounds **13a** and **14**. This can be explained by diastereoisomerism caused by the presence of the THP group. Both molecules have two centers of asymmetry. More difficult to interpret is a doubling of H_2 and H_8 peaks in the ^1H NMR spectrum of fluorobutynol **11**. However, both signals were transformed to single peaks after addition of D_2O. The latter observation may suggest some involvement of hydrogen bonding

* Send correspondence to this author at the Michigan Cancer Foundation, 110 E. Warren Ave., Detroit, MI 48201-1379. Telephone: (313) 833-0715, ext. 312. Fax: (313) 831-8714. e-mail: jiriz@mcf.roc.wayne.edu.
† Wayne State University School of Medicine.
‡ Present address: MediChem Research, Inc., Lemont, IL.
§ National Cancer Institute.
⊗ Abstract published in *Advance ACS Abstracts*, February 15, 1995.

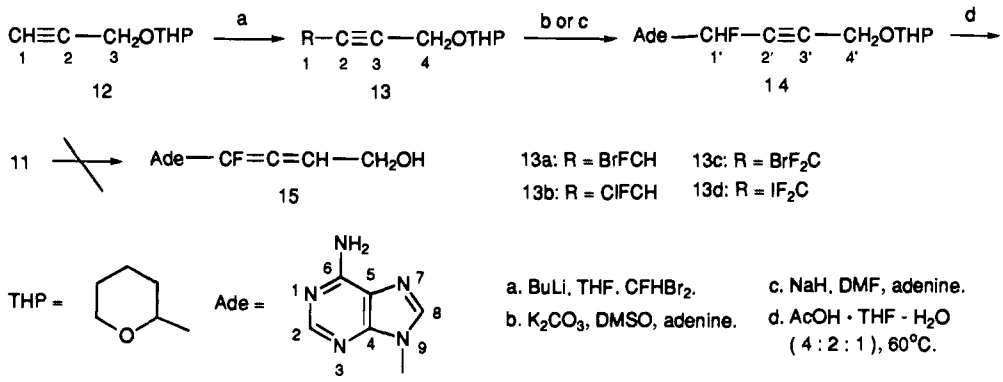
0022-2623/95/1838-0875$09.00/0

Chart 1[a]

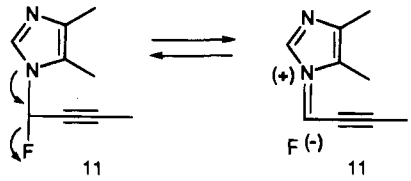


[a] B = nucleic acid base. Series a: B = Ade (adenin-N^9-yl). Series b: B = Cyt (cytosin-N^1-yl). Series c: B = Gua (guanin-N^9-yl). Series d: B = Thy (thymin-N^1-yl).

Scheme 1



Scheme 2



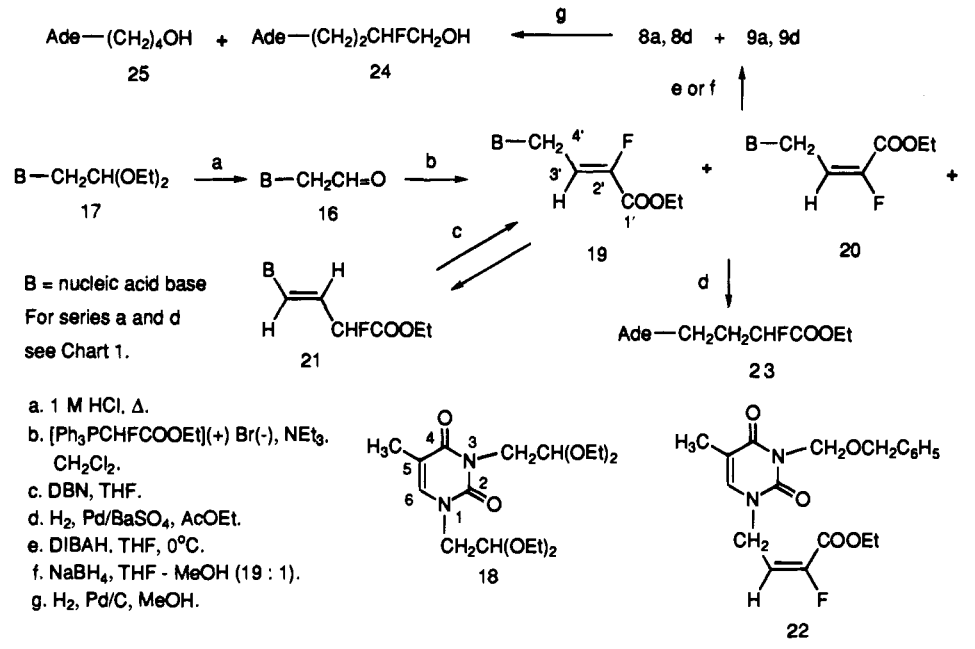
in this phenomenon. The rest of spectroscopic data was in full agreement with the proposed structures **11**, **13a**, and **14**.

Fluorobutynol **11** is relatively stable to nonaqueous bases such as triethylamine (NEt_3), K_2CO_3, or pyridine in DMF. An exposure to strong bases such as fluoride ion, potassium *tert*-butoxide (tBuOK) in THF (DMF), or 0.1 M NaOH led to decomposition and formation of adenine. It is then not surprising that all attempts to isomerize **11** to allenol **15** were unsuccessful. Fluorobutynol **11** is hydrolyzed in phosphate buffer at pH 7 and room temperature to adenine with a half-life of 16 h. This property could adversely affect biological assays with compound **11**. It should be noted that the presence of a strongly basic α-nitrogen atom generally destabilizes organic fluorides toward both acids and bases. This effect can be offset by N-acylation of the respective fluoroamine.[17,18] Adenine ring is a weak base, and it is entirely possible that a similar effect (Scheme 2) can be responsible for a lesser stability of compound **11**.

An approach based on the Wittig reaction was adopted for the synthesis of fluoroalkenols **8a,d** and **9a,d**. Both starting aldehydes **16a,d** were obtained by a modification of the known procedures[19] from the respective acetals **17a,d** (Scheme 3). In contrast to the literature data,[19] alkylation of thymine with diethyl bromoacetate using 2 equiv of NaH in DMF gave only 17% of monoalkylated product **17d** and 10% of dialkyl derivative **18**. Reaction catalyzed by *dry* K_2CO_3 led to improved yields of both **17d** (44%) and **18** (24%). Aldehyde **16a** was reacted with 3 equiv of (carbethoxyfluoromethyl)triphenylphosphonium bromide[20] using NEt_3 in THF. The reaction proceeded without difficulty despite the fact that aldehyde **16a** is predominantly hydrated as shown by ^1H NMR spectra. A mixture of *Z*- and *E*-isomers of fluoro esters **19a** and **20a** (**19a/20a** = 4/1) was obtained in 80% yield accompanied by regioisomer **21a** (5%). Unlike adenine aldehyde **16a**, thymine derivative **16d** exists predominantly as a free aldehyde. The Wittig reaction of **16d** with (carbethoxyfluoromethyl)triphenylphosphonium bromide[20] afforded *Z*- and *E*-esters **19d** and **20d** separable by column chromatography in 87 and 9% yields, respectively. The regioisomer **21d** was absent. The Wittig–Horner reaction of aldehyde **16d** with triethyl 2-fluoro-2-phosphoethanoate and NaH, under conditions which favor the formation of *cis*-unsaturated fluoro esters,[21] gave indeed only the *E*-ester **20d** but in a low yield (15%).

It is interesting to note that isomerization of the mixture of **19a** and **20a** using 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in THF at 0 °C for 3 h led to an increase of fluoroester **21a** (ratio of **19a/20a**:**21a** was 7:3 as determined by ^1H NMR). Compound **21a** was isolated in 31% yield, and the isomeric ratio of the starting materials **19a/20a** (recovered in 66% yield) was unchanged. The amount of **21a** increased further (ratio of **19a/20a**:**21a** was approximately 1:1) when the isomerization was performed at room temperature for 24 h. These experi-

Scheme 3



ments indicate that the ratio of **19a/20a** is thermodynamically controlled whereas the extent of formation of **21a** depends on the base and reaction conditions employed. With strong base (tBuOK at 0 °C for 1 h) the isomerization of **19a** and **20a** to **21a** was accompanied by elimination of adenine. An isomerization of the nonfluorinated analogue of **21a** had been described,[22] but stereochemistry of neither the starting material nor the reaction product was established.

Reduction of the mixture of **19a** and **20a** with diisobutylaluminum hydride (DIBALH in THF at 0 °C furnished (*E*)- and (*Z*)-fluoroalkenols **8a** and **9a** which were separated by column chromatography in 78 and 19% yields, respectively. A similar reduction of thymine *Z*-ester **19d** gave smoothly (*Z*)-fluoroalkenol **9d** (70%). Surprisingly, this method failed with the *E*-isomer **20d** or its N^3-protected derivative[23] **22**, giving several products which were not further investigated. By contrast, reduction of both *Z*- and *E*-esters **19d** and **20d** with $NaBH_4$ in THF–MeOH gave fluoroalkenols **9d** and **8d** without difficulty in 90 and 88% yields, respectively.

The stereochemistry of the double bond was in all cases unequivocally established by the coupling constants of olefinic protons and fluorine. Thus, the *E*-ester **21a** had $J_{H\text{-}3',H\text{-}4'}$ = 14 Hz which indicated a *trans* relationship of both protons. The $J_{H,F}$ and $J_{F,H}$ of *Z*-esters **19a,d** ranged between 31 and 34 Hz, whereas those of *E*-esters **20a,d** were 18–20 Hz. The values for the corresponding alkenols were slightly higher: 36–37.5 Hz for *Z*-alkenols **9a,d** and 19–21 Hz for *E*-isomers **8a,d**.

Hydrogenation of the mixture of **19a** and **20a** over 5% $Pd/BaSO_4$ in ethyl acetate afforded fluoro ester **23** in 70% yield, whereas alkenols **8a** and **9a** were hydrogenated over Pd/C catalyst in MeOH to fluorinated and defluorinated products **24** and **25** (ratio of 4:1) in almost quantitative yield. Reductive removal of the fluorine atom is a frequent complication observed during catalytic hydrogenation of fluoro olefins.[25-28] It was not possible to separate both products by TLC or column chromatography on silica gel. Because ionization constants of fluorinated and nonfluorinated alcohols differ appreciably,[29] a separation on an anion exchange Bio-Rad AG 1-X2 (OH^-) column[30] was attempted. A resolution (Figure 1) was achieved in 5% MeOH to give **24** and **25** in 68 and 15% yields, respectively. The latter procedure has a potential as a general method for separation of fluorinated and nonfluorinated alcohols.

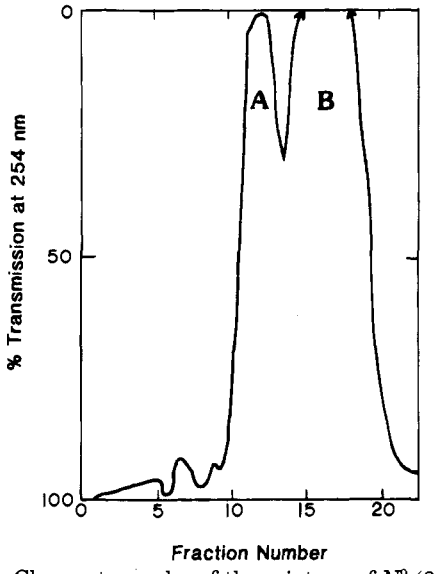


Figure 1. Chromatography of the mixture of N^9-(3-fluoro-4-hydroxybut-1-yl)adenine (**24**; peak B) and N^9-(4-hydroxybut-1-yl)adenine (**25**; peak A) on a Bio-Rad AG1 OH(−) column. For details, see the Experimental Section.

Biological Activity

The *Z*-isomer **9a** is deaminated by adenosine deaminase from calf intestine as determined by a standard procedure.[2] The deamination was 80% complete after 24 h. The *E*-isomer **8a** was not deaminated. It should be noted that TLC alone was unsuitable as a method for following the reaction because fluoroalkenol **9a** is not separated from the product of deamination in CH_2Cl_2–MeOH (9:1 and 4:1) solvent systems. Therefore, paper electrophoresis at pH 3.5 in combination with UV spectroscopy was employed. The activity trend *trans*-*Z*-isomer **9a** > *cis*-*E*-isomer **8a** followed a pattern[2] observed for the corresponding nonfluorinated analogues: *trans*-*E*-isomer **3a** > *cis*-*Z*-isomer[31] **4a**.

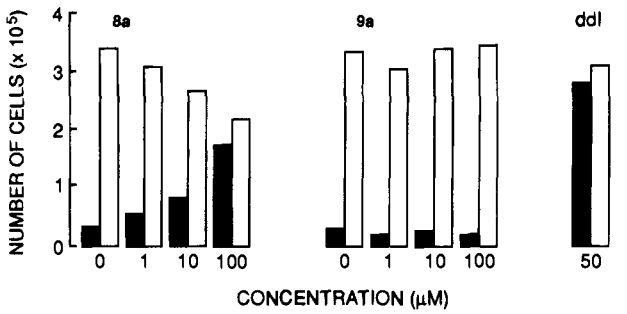


Figure 2. Inhibition of the infectivity and the cytopathic effect of HIV-1 in ATH8 cells by *E*- and *Z*-alkenols **8a** and **9a**. Virus-exposed cells are indicated as solid bars and virus-unexposed cells as open bars. 2′,3′-Dideoxyinosine (ddI) served as a positive control. For details, see the Experimental Section.

The anti-HIV activity was determined in the ATH8 cell assay system using HIV-1_{LAI} as a source of infectious virions. (*E*)-Fluoroalkenol **8a** inhibited the replication and cytopathic effect of HIV-1 with an IC_{50} of approximately 100 μM (Figure 2). Analogue **8a** showed cytotoxicity in a dose–response fashion, and it yielded a 36% reduction in the number of viable cells at 100 μM as compared to the cell population without analogue. Compounds **8d**, **9a,d**, and **24** were inactive and nontoxic. The reference compound 2′,3′-dideoxyinosine (ddI) provided a virtually complete inhibition of the cytopathic effect of HIV-1 at 50 μM without detectable toxicity. The nonfluorinated analogue **4a** did not display any activity or toxicity.[32] Thus, the biological effects of **8a** are attributable to the presence of fluorine atom. The anti-HIV activity of **8a** is roughly comparable to that of 2′,3′-dideoxy-3′-fluoroadenosine (**10a**) in MT-4 cells[33] (IC_{50} = 50 μM), although the latter analogue is less toxic.

Compounds **11** and **8d** are moderate inhibitors of the growth of murine leukemia L1210 as determined by a clonogenic assay[2] (IC_{50} = 89 and 60 μM, respectively). As in the case of adenine analogues **8a** and **9a**, the *E*-isomer **8d** was more cytotoxic than the *Z*-isomer **9d**. Modest inhibitory effect of **11** was also seen in disk diffusion assay[2] with L1210 and mouse tumors C38 and M17 as well as human tumors H-8 and H116. As mentioned above, this analogue is of limited stability under the conditions of the assays (pH 7). Compounds **8a**, **9a,d**, and **24** and the mixture of **19a** and **20a** exhibited no antitumor activity.

It is evident that adenosine deaminase on one side and anti-HIV potency as well as antileukemic activity on the other exhibit different selectivity for geometrical isomers **8a,d** and **9a,d**. A similar differential effect of enantiomers although at a higher activity level was reported before.[34,35] Thus, the presence of fluorine atom in **9a** does not influence substantially the activity toward adenosine deaminase, whereas the distance between the base and the hydroxymethyl group does. Shorter distances (see compounds **4a**[2] and **8a**) are less favorable. The opposite is true for the anti-HIV and antileukemic effects of **8a,d** which probably depend on phosphorylation ability of a particular analogue. The fact that *Z*-analogue **4c** exhibits an antiherpetic activity[4-6] whereas *E*-analogue **3c** is inactive is also in accord with such a reasoning.

Experimental Section

General Methods. See refs 8 and 36. The NMR spectra were recorded at the following frequencies unless stated otherwise: ^{1}H NMR, 300.095; ^{13}C NMR, 75.47; ^{19}F NMR, 282.314; and ^{31}P NMR, 121.47 MHz. Molecular modeling was performed using Chem 3D Plus 3.1.1 software (Cambridge Scientific Computing, Inc., Cambridge, MA) with standard parameters. All structures were energy-minimized.

Starting Materials. 3-[(2-Tetrahydropyranyl)oxy]-1-propyne (12). A mixture of propargyl alcohol (2.8 g, 50 mmol), dihydropyran (6.3 g, 74.9 mmol), and pyridinium *p*-toluenesulfonate (PPTS; 125 mg, 5 mmol) was stirred at room temperature in CH_2Cl_2 (15 mL) for 19 h under N_2. The resultant solution was diluted with ether, it was washed with water and dried (Na_2SO_4), and the solvents were evaporated. The crude product was chromatographed on a silica gel column using CH_2Cl_2 as eluent to give compound **12** (6.5 g, 93%) as an oil: IR (neat) 2110 cm^{-1} (s, C≡C); ^{1}H NMR corresponded to that described in the literature;[37] ^{13}C NMR ($CDCl_3$) δ 18.87, 25.22, 30.09, 53.88, 96.71 (THP), 61.87 (C_3), 73.93 (C_1), 79.68 (C_2).

(Carbethoxyfluoromethyl)triphenylphosphonium Bromide. The reaction was performed as described[20] on a half-scale (yield 75%): mp 104–106 °C (dec); ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3, CH_3), 4.03 (m, 2, CH_2), 7.63–7.94 (m, 15, C_6H_5), 9.29 (dd, 1, $^2J_{H,F}$ = 41.9 Hz, $^2J_{H,P}$ = 5.9 Hz CFH). The ^{19}F and ^{31}P NMR spectra were identical with those reported.[20]

***N*^{9}-(2,2-Diethoxyethyl)adenine (17a).** The described procedure[22] was modified as follows. A mixture of adenine (6.5 g, 48.1 mmol), K_2CO_3 (7.3 g, 52.8 mmol), and bromoacetaldehyde diethyl acetal (8.7 mL, 57.8 mmol) in DMF (80 mL) was stirred at 140 °C (bath temperature) for 23 h. The mixture was filtered while hot, and the filter cake was washed with DMF (50 mL). The filtrate was concentrated to ca. 20 mL and cooled to 0 °C. The precipitated product was collected by filtration and dried in vacuo to give the title compound (10 g, 82.7%) as a light yellow solid. Recrystallization from EtOH furnished white crystals of **17a** (7.0 g, 58%): mp 221–223 °C (lit.[19,22] mp 212 and 218–219 °C, respectively).

2-(Adenin-*N*^{9}-yl)ethanal Hydrochloride Dihydrate (16a). A modification of the described procedure[19] was employed. A solution of acetal **17a** (4.4 g, 17.5 mmol) in 1 M HCl (50 mL) was stirred at 100 °C for 1 h whereupon it was evaporated to dryness. The resultant solid residue was washed successively with 50% ethanol (3 mL), CH_2Cl_2 (50 mL), and ether (50 mL) to give white solid **16a** (4.2 g, 96%) after drying at 100 °C/0.1 mmHg for 3 days, mp >300 °C corresponded to that reported.[19]

***N*^{1}-(2,2-Diethoxyethyl)thymine (17d) and *N*^{1},*N*^{3}-Bis(2,2-diethoxyethyl)thymine (18). Method A. Using 2 Equiv of NaH.** Sodium hydride (60%, 4.5 g, 113 mmol) was added into a stirred suspension of thymine (7 g, 55.5 mmol) in DMF (70 mL) under N_2. After evolution of H_2 ceased, bromoacetaldehyde diethyl acetal (11.0 g, 55.8 mmol) was added. The resulting mixture was heated at 80 °C for 16 h and at 140 °C for 1 h, whereupon it was cooled. The reaction was quenched with AcOH, the solution was evaporated in vacuo, and the residue was extracted with AcOEt (total 150 mL). The organic phase was washed with water (200 mL) and dried ($MgSO_4$). The crude product obtained by evaporation was chromatographed on a silica gel column using CH_2Cl_2–MeOH (49:1) to give compound **18** (3.42 g, 17%) as a syrup which solidified on standing and 1.30 g (10%) of **17d** as a solid: mp 106–109 °C after recrystallization from cyclohexane–benzene (lit.[19] mp 76–78 °C); UV_{max} (EtOH) 269 nm (ϵ 8300), 210 (ϵ 7800); IR (KBr) 3200 cm^{-1} (s, NH), 2900 (s, CH), 1630–1730 (vs, thymine); ^{1}H NMR ($CDCl_3$) δ 1.17 (t, 6, CH_3 of Et), 1.89 (d, 3, CH_3 of thymine), 3.46–3.56 (m, 2, CH_2), 3.69–3.77 (m, 4, CH_2 of Et), 4.61 (t, 1, J = 5.3 Hz, CH of acetal), 7.07 (d, 1, H_6), 9.50 (br s, 1, NH); ^{13}C NMR δ 15.23 (CH_3 of Et), 50.77 (NCH_2), 64.25 (CH_2 of Et), 100.28 (CH of acetal), 12.15, 109.83, 142.03, 151.19 and 164.52 (thymine); EI-MS 243 (0.6, M + H), 242 (1.1, M), 197 (19.0, M – OEt), 169 (10.4, M – OEt – C_2H_4), 126 (5.8, thymine), 103 (100.0, $CH(OEt)_2$), 75 (63.2, $CH(OEt)_2$ – C_2H_4); CI-MS 243 (100.0, M + 1), 242 (1.1, M), 197 (66.0, M – OEt), 103 (54.5, $CH(OEt)_2$), 75 (11.5, $CH(OEt)_2$ – C_2H_4); HRMS M – OEt calcd 197.0926, found 197.0930.

Bis-acetal 18: mp 55–58 °C; UV_{max} (EtOH) 270 nm (ϵ 9200), 210 (ϵ 8600); IR (KBr) 2900–2995 cm^{-1} (s, CH), 1650, 1675 and 1720 (s, thymine); ^{1}H NMR ($CDCl_3$) δ 1.06 and 1.10 (2t, 12, CH_3 of Et), 1.83 (s, 3, CH_3 of thymine), 3.41–3.46 (m,

4), 3.63–3.71 (m, 6, NCH_2 + CH_2 of Et), 4.05 (d, 2, NCH_2, J = 5.7 Hz), 4.54 (t, 1, J = 5.1 Hz), 4.85 (t, 1, J = 5.7 Hz, CH of acetal), 7.00 (s, 1, H_6); ^{13}C NMR δ 15.14 (CH_3), 42.39 (N^3-CH_2), 51.81 (N^1-CH_2), 61.46 (N^3-OCH_2), 64.07 (N^1-OCH_2), 98.29 (N^3-CH of acetal), 100.27 (N^1-CH of acetal), 12.78, 108.74, 140.09, 151.59 and 163.64 (thymine); EI-MS 358 (0.6, M), 313 (7.0, M – EtO), 267 (8.7, M – EtO – EtOH), 211 (8.3, M – 2 × EtO – 2 × C_2H_4 – H), 103 (100.0, $CH(OEt)_2$), 75 (53.2, $CH(OEt)_2$ – C_2H_4); CI-MS 313 (100.0, M – EtO), 267 (2.8, M – EtO – EtOH), 103 (34.4, $CH(OEt)_2$), 75 (3.7, $CH(OEt)_2$ – C_2H_4); HRMS M calcd 358.2103, found 358.2111. Anal. ($C_{17}H_{30}N_2O_6$) C, H, N.

Method B. Using Dry K_2CO_3. The reaction was carried out under similar conditions to those reported in the literature[19,22] for adenine. A mixture of thymine (10.0 g, 79.0 mmol), K_2CO_3 (11.0 g, 79.0 mmol; both compounds were freshly dried at 100 °C/0.01 mmHg for 5 h), and bromoacetaldehyde diethyl acetal (16.0 g, 81.0 mmol) in DMF (100 mL) was heated at 130 °C with stirring for 10 h. The solids were filtered while the mixture was still hot and washed with $CHCl_3$ (2 × 20 mL). The organic phase was washed with water (2 × 50 mL) and dried (Na_2SO_4). The crude product obtained by evaporation was triturated with ether–petroleum ether (1:2, 20 mL) to give compound **17d** (5 g). Evaporation of the organic phase left a reddish residue, which was chromatographed on a silica gel column. Elution with CH_2Cl_2–MeOH (99:1) gave 6.86 g (24% yield) of bis-acetal **18**. Continuing elution with CH_2Cl_2–MeOH (49:1) afforded additional acetal **17d** (3.33 g, total yield 43.5%). Both compounds were identical with the samples obtained by Method A. When K_2CO_3 was not freshly dried, the yields of **17d** and **18** were 19 and 40%, respectively.

2-(Thymin-N^1-yl)ethanal (16d). The method used for preparation of aldehyde **16a** was modified as follows. Acetal **17d** (4.55 g, 19.0 mmol) was suspended in 1 M HCl (80 mL), and the mixture was stirred at 100 °C for 45 min. The clear solution was evaporated to dryness to give 3.53 g (100%) of colorless solid **16d**, mp 200–210 °C (lit.[19] mp >300 °C). The ^1H and ^{13}C NMR indicated the presence of 70% free aldehyde and 30% hydrate. Amount of monohydrate increased to 90% after addition of D_2O: UV_{max} (pH 7) 270 nm (ϵ 9400), 217 (ϵ 7200), (pH 12) 270 (ϵ 9100), 208 (ϵ 9900); IR (KBr) 3340 cm^{-1} (s), 3180 (s), 3070 (s), 1650–1720 (vs, thymine); ^1H NMR (CD_3SOCD_3, free aldehyde) δ 1.71 (s, 3, CH_3), 4.56 (s, 2, CH_2), 7.37 (s, 1, H_6), 9.51 (s, 1, CH=O), 11.36 (s, 1, NH); ^{13}C NMR δ 56.56 (CH_2), 11.96, 108.51, 141.68, 151.06, 164.39 (thymine), 197.51 (CH=O); ^1H NMR (+D_2O, 500 MHz, monohydrate) δ 1.68 (s, 3, CH_3), 3.50 (d, 2, CH_2, ^3J = 5.4 Hz), 4.88 (t, 1, C*H*$(OH)_2$, ^3J = 5.4 Hz), 7.30 (s, 1, H_6); ^{13}C NMR (+D_2O, 125 MHz) δ 53.61 (CH_2), 87.27 ($CH(OH)_2$), 12.16, 108.37, 143.46, 151.49 and 165.14 (thymine); EI-MS 168 (25.3, M), 140 (82.9, M – CHO + H), 139 (32.9, M – CHO), 126 (4.6, thymine), 96 (100, M – CONHCO – H); CI-MS 169 (100, M + H), 140 (3.1, M – CHO + H), 127 (5.6, thymine + H); HRMS M calcd 168.0535, found 168.0532.

1-Bromo-1-fluoro-4-[(2-tetrahydropyranyl)oxy]-2-butyne (13a). The BuLi in hexane (2 M, 15 mL, 30 mmol) was added dropwise into a solution of compound **12** (4.0 g, 28.5 mmol) in THF (40 mL) at −55 °C under N_2. The mixture was stirred for 0.5 h and then cooled to −78 °C. A solution of $CHBr_2F$ (13.6 g, 71.3 mmol) in THF (10 mL) was then added dropwise at such a rate that the temperature did not exceed −55 °C. The resultant black mixture was stirred at −78 °C for 2 h. The temperature was then gradually increased to −10 °C. Saturated aqueous NH_4Cl and CH_2Cl_2 were added, and the organic layer was washed with water, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on a silica gel column using CH_2Cl_2–hexane (1:1) as eluent to give product **13a** (2.3 g, 32%) as a colorless liquid: IR (neat) 2230 cm^{-1} (s, C≡C), 2300 (w, C≡C); ^1H NMR ($CDCl_3$) δ 1.5–1.8 (m, 6), 3.53 and 3.82 (2m, 2), 4.78 (t, 1, THP), 4.38 (d, 2, H_4, $^5J_{4,F}$ = 6.0 Hz), 6.81 (d, 1, H_1, $^2J_{1,F}$ = 51.3 Hz); ^{13}C NMR δ 18.91, 25.35, 30.17, 53.91, 97.32 (THP), 62.08 (C_4), 73.88 (d, 1, C_1, $^1J_{1,F}$ = 246.3 Hz), 79.63 (d, C_2, $^2J_{2,F}$ = 28.8 Hz), 89.59 (d, C_3, $^3J_{3,F}$ = 6.2 Hz); ^{19}F NMR δ −123.45 (dt, $^2J_{F,H-1}$ = 51.1 Hz, $^5J_{F,H-4}$ = 5.8 Hz), −123.46 (dt, $^2J_{F,H-1}$ = 51.4 Hz, $^5J_{F,H-4}$ = 5.7 Hz); EI-MS 251, 249 (1.6, 1.8, M), 171 (20.3, M – Br), 151, 149 (13.2, 14.5, M – OTHP – H), 85 (100, THP). Anal. ($C_9H_{12}BrFO_2$) C, H, F.

N^9-[1-Fluoro-4-[(2-tetrahydropyranyl)oxy]-2-butyn-1-yl]adenine (14). A. From Sodium Salt of Adenine. Sodium hydride (250 mg, 60% dispersion in mineral oil, 6.3 mmol) was added into a suspension of adenine (860 mg, 6.4 mmol) in DMF (50 mL) at room temperature under N_2. The mixture became thick, and gas evolution ceased in about 1 h. A solution of compound **13a** (1.6 g, 6.4 mmol) in DMF (15 mL) was then added. The resultant mixture was stirred at room temperature for 18 h whereupon it was evaporated. The crude product was chromatographed on a silica gel column using AcOEt–MeOH (95:5) as eluent to give **14** (1.1 g, 56%). For analysis compound **14** was recrystallized from benzene: mp 154–156 °C (dec); UV_{max} (EtOH) 257 nm (ϵ 15 200), 209 (ϵ 18 400); IR (KBr) 2230 cm^{-1} (w, C≡C), 2285 (w, C≡C); ^1H NMR ($CDCl_3$) δ 1.57–1.83 (m, 6), 3.55 and 3.84 (m and t, 2), 4.81 (s, 1, THP), 4.43 (m, 2, $H_{4'}$), 6.19 (s, 2, NH_2), 7.19 (d, 1, $H_{1'}$, $^2J_{1',F}$ = 50.4 Hz), 8.28 and 8.39 (2s, 2, H_2 and H_8); ^{13}C NMR δ 18.80, 25.14, 30.06, 53.87, 97.55 (THP), 62.08 ($C_{4'}$), 76.07 (d, $C_{2'}$, $^2J_{2',F}$ = 35.8 Hz), 79.16 (d, $C_{1'}$, $^1J_{1',F}$ = 200.6 Hz), 87.74 (d, $C_{3'}$, $^3J_{3',F}$ = 6.4 Hz), 119.35, 138.43, 149.26, 153.91, 155.87 (adenine); ^{19}F NMR δ −118.31 (dt, $^2J_{F,H-1'}$ = 51.4 Hz, $^5J_{F,H-4'}$ = 5.1 Hz), −118.35 (dt, $^2J_{F,H-1'}$ = 51.4 Hz, $^5J_{F,H-4'}$ = 5.2 Hz); EI-MS 305 (0.8, M), 220 (15.9, M – THP), 205 (100, M – OTHP + H), 135 (24.3, adenine). Anal. ($C_{14}H_{16}FN_5O_2$) C, H, N, F.

B. Using K_2CO_3 in DMSO. A mixture of adenine (290 mg, 2.1 mmol), butyne **13a** (530 mg, 2.1 mmol), and K_2CO_3 (890 mg, 6.4 mmol) in DMSO (20 mL) was stirred at room temperature for 12 h. The solvent was removed in vacuo (oil pump) at 65 °C (bath temperature), and the residue was extracted with CH_2Cl_2–MeOH (9:1). Evaporation gave crude product which was chromatographed on a silica gel column using AcOEt–MeOH (95:5) as an eluent to give **14** (158 mg, 25%), identical with the compound prepared by method A.

N^9-(1-Fluoro-4-hydroxy-2-butyn-1-yl)adenine (11). A solution of compound **14** (300 mg, 0.98 mmol) in a mixture of acetic acid (60 mL), THF (30 mL), and water (15 mL) was heated for 2 h at 65 °C. The progress of reaction was followed by TLC in CH_2Cl_2–MeOH (9:1). After the reaction was completed, the solvents were evaporated. The crude product was washed with CH_2Cl_2 and chromatographed on a silica gel column using CH_2Cl_2–MeOH (9:1) as eluent to give fluorobutynol **11** (190 mg, 87%). The analytical sample was recrystallized from MeOH, but it had no definite melting point (gradual decomposition starting from 125 °C): UV_{max} (EtOH) 257 nm (ϵ 14 000), 209 (ϵ 19 000); IR (KBr) 2235 cm^{-1} (w, C≡C), 2285 (w, C≡C); ^1H NMR (CD_3SOCD_3) δ 4.24 (apparent s, 2, $H_{4'}$, d after addition of D_2O, $^5J_{4',F}$ = 4.8 Hz), 5.50 (br s, 1, OH), 7.40 (d, 1, $H_{1'}$, $^2J_{1',F}$ = 51.3 Hz), 7.49 (s, 2, NH_2), 8.20 and 8.49 (2d, 2, H_2 and H_8, splitting = 2.4 Hz), after addition of D_2O 8.17 and 8.47 (2s, 2); ^{13}C NMR δ 49.29 ($C_{4'}$), 75.13 (d, $C_{2'}$, $^2J_{2',F}$ = 34.9 Hz), 80.44 (d, $C_{1'}$, $^1J_{1',F}$ = 139.4 Hz), 91.66 (d, $C_{3'}$, $^3J_{3',F}$ = 8.5 Hz), 119.06, 139.04, 149.12, 153.98, 156.63 (adenine); ^{19}F NMR δ −117.28 (dt, $^2J_{F,H-1'}$ = 51.4 Hz, $^5J_{F,H-4'}$ = 5.6 Hz); EI-MS 221 (39.7, M), 220 (100, M – H), 135 (39.1, adenine), 108 (36.5, adenine – HCN). Anal. ($C_9H_8FN_5O \cdot {}^1/_6H_2O$) C, H, F, N.

Ethyl (*Z*)- and (*E*)-4-(Adenin-N^9-yl)-2-fluoro-2-butenoate (19a and 20a) and Ethyl (*E*)-4-(Adenin-N^9-yl)-2-fluoro-2-butenoate (21a). Triethylamine (5.6 mL, 40 mmol) was added dropwise with stirring into a suspension of aldehyde **16a** (2.0 g, 8.0 mmol) and (carbethoxyfluoromethyl)triphenylphosphonium bromide (10.8 g, 24.0 mmol) in THF (100 mL) within 20 min at room temperature under N_2. The progress of the reaction was followed by TLC in CH_2Cl_2–MeOH (9:1), and the mixture was stirred at room temperature for 16 h. The precipitate was filtered off and washed with THF (20 mL). The filtrate was evaporated, and the residue was chromatographed on a silica gel column. Elution with ethyl acetate gave triphenylphosphine oxide (6.1 g, 91%), and AcOEt–MeOH (95:5) afforded the *E*-ester **21a** (106 mg, 5%) and a mixture of (*Z*)- and (*E*)-2-butenoates **19a** and **20a** (**19a**/**20a** = 4/1, 1.7 g, 80%).

Compound 21a: mp 171–173 °C after recrystallization from benzene; UV_{max} (EtOH) 231 nm (ϵ 33 000), shoulders at 261 (ϵ 16 200) and 280 (ϵ 9500); IR (KBr) 3350 cm^{-1}, 3190 (s, NH_2), 1745 (s, C=O), 1655, 1605, 1580 (s, adenine); ^1H NMR

(CD_3SOCD_3) δ 1.19 (t, 3, CH_3), 4.19 (m, CH_2), 5.80 (dd, 1, $H_{2'}$, $^2J_{2',F}$ = 46.8 Hz, $^3J_{2',3'}$ = 8.1 Hz), 6.85 (ddd, 1, $H_{3'}$, $^3J_{3',4'}$ = 14.3 Hz, $^3J_{3',F}$ = 11.0 Hz, $^3J_{3',2'}$ = 8.1 Hz), 7.30 (s, 2, NH_2), 7.60 (dd, 1, $H_{4'}$, $^2J_{4',3'}$ = 14.3 Hz, $^4J_{4',F}$ = 4.1 Hz), 8.19 and 8.48 (2s, 2, H_2 and H_8); ^{13}C NMR δ 14.35 (CH_3), 62.00 (CH_2), 87.27 (d, $C_{2'}$, $^1J_{2',F}$ = 178.4 Hz), 111.64 (d, $C_{3'}$, $^2J_{3',F}$ = 20.3 Hz), 128.20 (d, $C_{4'}$, $^3J_{4',F}$ = 13.9 Hz), 119.53, 139.62, 149.20, 153.79, 156.53 (adenine), 168.37 (d, $C_{1'}$, $^2J_{1',F}$ = 26.6 Hz); ^{19}F NMR δ −178.17 (dd, $^2J_{F,H-2'}$ = 46.5 Hz, $^3J_{F,H-3'}$ = 10.0 Hz); EI-MS 266 (22.0, M + H) 265 (93.7, M), 192 (100, M − CO_2Et), 172 (19.7, 192 − HF), 145 (46.2, 172 − HCN). Anal. ($C_{11}H_{12}FN_5O_2$) C, H, F, N.

Z- and E-Isomers 19a and 20a: mp 174−183 °C after recrystallization from benzene; UV_{max} (EtOH) 260 nm (ϵ 15 100), 213 (ϵ 26 200); IR (KBr) 3360 cm^{-1}, 3160 (s, NH_2), 1730 (s, C=O), 1650, 1600 (s, adenine); ^1H NMR ($CDCl_3$) *E*-isomer **20a** δ 1.40 (t, 3, CH_3), 4.39 (q, 2, OCH_2), 5.34 (dd, 2, $H_{4'}$, $^3J_{4',3'}$ = 7.2 Hz, $^4J_{4',F}$ = 1.8 Hz), 5.79 (br s, 2, NH_2), 6.17 (dt, 1, $H_{3'}$, $^3J_{3',F}$ = 18.0 Hz, $^3J_{3',4'}$ = 7.2 Hz), 7.88 and 8.37 (2s, 2, H_2 and H_8); ^{19}F NMR δ 116.47 (dt, $^3J_{F,H-3'}$ = 17.8 Hz, $^4J_{F,H-4'}$ = 2.0 Hz); ^1H NMR ($CDCl_3$) *Z*-isomer **19a** δ 1.32 (t, 3, CH_3), 4.30 (q, 2, OCH_2), 5.04 (dd, 2, $H_{4'}$, $^3J_{4',3'}$ = 7.1 Hz, $^4J_{4',F}$ = 1.9 Hz), 5.79 (br s, 2, NH_2), 6.35 (dt, 1, $H_{3'}$, $^3J_{3',F}$ = 30.9 Hz, $^3J_{3',4'}$ = 7.2 Hz, $H_{3'}$), 7.81 and 8.38 (2s, 2, H_2 and H_8); ^{19}F NMR δ −122.58 (dt, $^3J_{F,H-3'}$ = 31.1 Hz, $^4J_{F,H-4'}$ = 1.7 Hz); ^{13}C NMR (CD_3SOCD_3)[38] δ 14.13 (CH_3), 37.64 ($C_{4'}$), 62.50 (OCH_2), 115.08 (d, $C_{3'}$, $^2J_{3',F}$ = 9.7 Hz), 148.41 (d, $C_{2'}$, $^1J_{2',F}$ = 259.6 Hz), 118.65, 141.40, 149.57, 152.85, 155.86 (adenine), 159.84 (d, $C_{1'}$, $^2J_{1',F}$ = 35.6 Hz); EI-MS 266 (2.3, M + H), 265 (3.9, M), 220 (2.7, M − OEt), 192 (100.0, M − CO_2Et), 165 (9.4, 192 − HCN), 145 (7.6, 165 − HF); CI-MS 266 (100.0, M + H), 192 (53.8, M − CO_2Et). Anal. ($C_{11}H_{12}FN_5O_2$) C, H, F, N.

Isomerization of Fluoro Esters 19a, 20a, and 21a. A. Fluoro Esters 19a and 20a and DBN in THF. A mixture of esters **19a** and **20a** (80 mg, 0.3 mmol) and DBN (37 μL, 0.3 mmol) was stirred for 3 h in THF (15 mL) at room temperature. The reaction was quenched with AcOH, and the solution was evaporated. The crude product was chromatographed on a preparative layer of silica gel in AcOEt−MeOH (95:5) to give esters **21a** (25 mg, 31%) and **19a** and **20a** (53 mg, 66%, ratio of 4:1) identical with authentic samples prepared as described above.

B. Fluoro Ester 21a and DBN in THF. A mixture of fluoro ester **21a** (11 mg, 0.04 mmol) and DBN (5.1 μL, 40 μmol) in THF (3 mL) was stirred for 24 h at room temperature. After quenching with AcOH and evaporation, the crude product was flash-chromatographed in CH_2Cl_2−MeOH (9:1) to give a mixture of **19a**, **20a**, and **21a** (10 mg, 91%) in the ratio of 4:1:5 as determined by ^1H NMR spectroscopy.

C. Fluoro Esters 19a and 20a and tBuOK in DMF. A mixture of esters **19a** and **20a** (10 mg, 40 μmol) and tBuOK (4 mg, 40 μmol) in DMF (2 mL) was stirred for 1 h at room temperature. The reaction was quenched with AcOH, and the solution was evaporated. A TLC of the crude product (CH_2Cl_2−MeOH, 9:1) showed the presence of **21a**, **19a** and **20a**, and adenine in the order of decreasing mobility.

Ethyl (Z)-4-(Thymin-N^1-yl)-2-fluoro-2-butenoate (19d) and Ethyl (E)-4-(Thymin-N^1-yl)-2-fluoro-2-butenoate (20d). The procedure for preparation of adenine derivatives **19a** and **20a** was followed. A mixture aldehyde **16d** (100 mg, 0.54 mmol), (carbethoxyfluoromethyl)triphenylphosphonium bromide, and Et_3N (0.3 mL, 2.15 mmol) in THF (20 mL) was stirred at room temperature overnight. The crude product was chromatographed on a silica gel column using petroleum ether−THF (3:1) as eluent. First, the *E*-ester **20d** (12 mg, 9%) was obtained followed by the *Z*-ester **19d** (120 mg, 87%).

***(E)*-Ester 20d**: mp 137−138 °C after recrystallization from cyclohexane−AcOEt (1:2); UV_{max} (EtOH) 269 nm (ϵ 10 500), 211 (ϵ 18 400); IR (KBr) 3160 cm^{-1} (s, NH), 3040 (s), 1720 (vs, C=O), 1670−1640 (vs, C=C and thymine); ^1H NMR (CD_3SOCD_3, 500 MHz) δ 1.27 (t, 3, CH_3), 1.73 (3H, s, 5-CH_3), 4.27 (q, 2, OCH_2), 4.67 (dd, 2, $H_{4'}$, $^3J_{4',3'}$ = 6.0 Hz, $^4J_{4',F}$ = 2.5 Hz), 6.20 (dt, 1, $H_{3'}$, $^3J_{3',F}$ = 19.6 Hz, ^3J = 6.4 Hz), 7.49 (s, 1, H_6), 11.27 (s, 1, NH); ^{13}C NMR (125 MHz) δ 12.38 (CH_3), 43.67 (d, $C_{4'}$, $^3J_{4',F}$ = 7.4 Hz), 62.24 (OCH_2), 119.92 (d, $C_{3'}$, $^2J_{3',F}$ = 20.4 Hz), 147.50 (d, $^1J_{2',F}$ = 256.2 Hz), 160.31 (d, $C_{1'}$, $^2J_{1',F}$ = 36.2 Hz), 14.31, 109.28, 141.47, 151.31 and 164.77 (thymine); ^{19}F NMR δ −120.44 (dt, $^3J_{F,H-3'}$ = 20.0 Hz, $^4J_{F,H4'}$ = 2.7 Hz); EI-MS 257 (10.8, M + H), 256 (66.8, M), 227 (45.7, M − Et), 210 (15.4, M − OEt − H), 184 (100.0, M − CO_2Et + H), 183 (24.2, M − CO_2Et), 182 (36.8, M − CO_2Et − H), 103 (58.2, CH_2-CH=$CFCO_2H$); HRMS M calcd 256.0859, found 256.0854. Anal. ($C_{11}H_{13}FN_2O_4$) C, H, F, N.

***Z*-Ester 19d**: mp 153−155 °C after recrystallization from cyclohexane−AcOEt (1:2); UV_{max} (EtOH) 269 nm (ϵ 10 000), 211 (ϵ 17 900); IR (KBr) 3160 cm^{-1} (s, NH), 1720 (s, C=O), 1670−1640 (vs, C=C and thymine); ^1H NMR (CD_3SOCD_3) δ 1.21 (t, 3, CH_3), 1.71 (s, 3, 5-CH_3), 4.19 (q, 2, OCH_2), 4.45 (dd, 2, $H_{4'}$, $^3J_{4',3'}$ = 6.5 Hz, $^4J_{4',F}$ = 2.3 Hz), 6.21 (dt, 1, $H_{3'}$, $^3J_{3',F}$ = 33.9 Hz, $^3J_{3',4'}$ = 6.5 Hz), 7.50 (s, 1, H_6), 11.29 (s, 1, NH); ^{13}C NMR δ 11.93 (CH_3), 41.91 (d, $C_{4'}$, $^3J_{4',F}$ = 3.0 Hz), 61.81 (OCH_2), 115.59 (d, $C_{3'}$, $^2J_{3',F}$ = 8.5 Hz), 147.84 (d, $C_{2'}$, $^1J_{2',F}$ = 259.0 Hz), 13.89, 108.96, 141.06, 150.81 and 164.31 (thymine), 159.42 (d, $C_{1'}$, $^2J_{1',F}$ = 31.8 Hz); ^{19}F NMR δ −126.23 (dt, $^3J_{F,H-3'}$ = 33.9 Hz); EI-MS 257 (19.6, M + H), 256 (87.5, M), 227 (59.6, M − Et), 210 (20.7, M − OEt − H), 184 (100.0, M − CO_2Et + H), 183 (32.0, M − CO_2Et), 182 (50.9, M − CO_2Et − H), 103 (83.2, CH_2CH=$CFCO_2H$); HRMS M calcd 256.0860, found 256.0859. Anal. ($C_{11}H_{13}FN_2O_4$) C, H, F, N.

Reaction of Aldehyde Monohydrate 16d with Triethyl 2-Fluoro-2-phosphoethanoate. Sodium hydride (60%, 49 mg, 1.2 mmol) was added to a solution of triethyl 2-fluoro-2-phosphoethanoate (266 mg, 1.1 mmol) in THF (5 mL) at 0 °C under N_2. The resultant mixture was added dropwise to a stirred suspension of aldehyde **16d** (100 mg, 0.54 mmol) in THF (5 mL) at 0 °C under N_2. The reaction mixture was kept at room temperature for 5 h whereupon 6 M HCl (3 mL) and CH_2Cl_2 were added. The organic layer was separated, washed with brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed on a silica gel column using petroleum ether−THF (4:1 and 2:1) as eluent to give the *E*-ester **20d** (20 mg, 14.5%) which was identical with the compound obtained from the previous experiment.

Ethyl 4-(Adenin-N^9-yl)-2-fluorobutanoate (23). A. Hydrogenation in Ethyl Acetate. Fluorobutenoates **19a** and **20a** (100 mg, 0.377 mmol) were hydrogenated in a Parr apparatus using 5% Pd/$BaSO_4$ (80 mg, 0.038 mmol) as a catalyst in AcOEt (70 mL) at 20 psi and room temperature for 96 h. TLC (CH_2Cl_2−MeOH, 9:1) showed approximately 90% conversion to **23**. The catalyst was filtered off with the aid of a Celite pad. The filtrate was evaporated, and the residue was washed with CH_2Cl_2−benzene (1:1, 4 mL) to give fluorobutanoate **23** (71 mg, 70% yield) as a white solid: mp 185−188 °C after recrystallization from benzene−CH_2Cl_2 (1:1, 4 mL); UV_{max} (EtOH) 260 nm (ϵ 14 200), 210 (ϵ 19 600); IR (KBr) 3310 cm^{-1}, 3130 (s, NH_2), 1760 (vs, C=O), 1675, 1600, 1580 (s, adenine); ^1H NMR (CD_3SOCD_3) δ 1.10 (t, 3, CH_3), 2.28−2.43 (m, 2, $H_{3'}$), 4.02 (q, 2, OCH_2), 4.26 (t, 2, $H_{4'}$, $^3J_{4',3'}$ = 6.9 Hz), 5.14 (ddd, 1, $^2J_{2',F}$ = 46.8 Hz, $^3J_{2',3'a}$ = 7.1 Hz, $^3J_{2',3'b}$ = 4.3 Hz, $H_{2'}$), 7.21 (s, 2, NH_2), 8.09 and 8.11 (2s, 2, H_2 and H_8); ^{13}C NMR δ 14.19 (CH_3), 32.10 (d, $C_{3'}$, $^2J_{3',F}$ = 20.7 Hz), 39.24 ($C_{4'}$), 61.60 (OCH_2), 86.90 (d, $C_{2'}$, $^1J_{2',F}$ = 181.7 Hz), 119.17, 141.32, 149.91, 152.82, 156.35 (adenine), 169.05 (d, $C_{1'}$, $^2J_{1',F}$ = 22.0 Hz); ^{19}F NMR δ −192.27 (ddd, $^2J_{F,H-2'}$ = 48.7 Hz, $^3J_{F,H-3'a}$ = 27.1 Hz, $^3J_{F,H-3'b}$ = 22.2 Hz); EI-MS 268 (6.2, M + 1), 267 (38.7, M), 222 (9.8, M − OEt), 194 (33.7, M − CO_2Et), 149 (100.0, M − CH_2CFHCO_2Et + H), 148 (77.9, M − CH_2CFHCO_2-Et), 135 (11.4, adenine). Anal. ($C_{11}H_{14}FN_5O_2$) C, H, F.

B. Hydrogenation in Methanol. The reaction was performed as described in method A in methanol (15 mL) instead of ethyl acetate for 2.5 h. TLC showed a complete disappearance of **19a** and **20a**. The catalyst was filtered off, and the filtrate was evaporated to give a 1:1 mixture (90 mg) of fluoro ester **23** and the corresponding methyl ester as established by ^1H NMR spectra: mp 171−173 °C after crystallization from benzene−CH_2Cl_2 (10:1).

Ethyl (E)-[N^3-[(Benzyloxy)methyl]thymin-N^1-yl]-2-fluoro-2-butenoate (22). A solution of (benzyloxy)methyl chloride (290 mg, 1.85 mmol) in CH_2Cl_2 (5 mL) was added to a solution of the *E*-ester **20d** (390 mg, 1.52 mmol) and *N*-ethyl-*N*,*N*-diisopropylamine[23] (0.92 ml, 7.6 mmol) in CH_2Cl_2 (20 mL) with stirring at room temperature. The mixture was then refluxed for 16 h. The solution was evaporated, and the resultant syrup was partitioned between CH_2Cl_2 (50 mL) and water (2 × 10 mL). The organic phase was dried (Na_2SO_4)

and evaporated. The crude product was chromatographed on a silica gel column using CH_2Cl_2–MeOH (95:5) as eluent to give ester **22** as a syrup (180 mg, 31.5%) and material (0.38 g) containing both **22** and starting compound **20d**. The latter portion was rechromatographed using hexanes–acetone (7:3) to give esters **22** (280 mg, 48.9%) and **20d** (105 mg, 18.4%): UV_{max} (EtOH) 273 nm (ϵ 9100), 212 (ϵ 20 800); ^1H NMR ($CDCl_3$) δ 1.37 (t, 3, CH_3), 1.90 (apparent s, 3, 5-CH_3), 4.34 (q, 2, CH_2, ester), 4.70 (s, CH_2, benzyl), 4.80 (dd, 2, $H_{4'}$, $^3J_{4',3'}$ = 7.2 Hz, $^4J_{4',F}$ = 1.5 Hz), 5.49 (s, 2, N^3-CH_2), 6.00 (dt, 1, $H_{3'}$, $^3J_{3',F}$ = 18.9 Hz, $^3J_{3',4'}$ = 7.5 Hz), 7.05 (d, 1, H_6), 7.30 (m, 6, C_6H_5 + $CHCl_3$); ^{13}C NMR δ 12.99 (CH_3, ester), 44.18 (d, $C_{4'}$, $^3J_{4',F}$ = 7.9), 62.23 (CH_2, ester), 70.67 and 72.26 (CH_2 of $C_6H_5CH_2$ and N_3-CH_2), 116.72 (d, $C_{3'}$, $^2J_{3',F}$ = 21.1 Hz), 127.58, 128.23, 137.98 (C_6H_5), 149.07 (d, $C_{2'}$, $^1J_{2',F}$ = 266.9 Hz), 160.58 (d, $C_{1'}$, $J_{2',F}$ = 34.6 Hz), 14.01, 110.55, 138.73, 151.39, 163.64 (thymine); ^{19}F NMR δ −117.09 (apparent d, $^3J_{F,H\text{-}3'}$ = 18.6 Hz); EI-MS 377 (1.0, M + H), 376 (0.1, M), 270 (100.0, C_6H_5CHO), 91 (76.4, $C_6H_5CH_2$). Anal. ($C_{19}H_{21}FN_2O_5$) C, H, F, N.

(*Z*)-N^9-(3-Fluoro-4-hydroxy-2-buten-1-yl)adenine (9a) and (*E*)-N^9-(3-Fluoro-4-hydroxy-2-buten-1-yl)adenine (8a). A 1.0 M solution of DIBALH in CH_2Cl_2 (10.8 mL, 10.8 mmol) was added dropwise with stirring into a mixture of ethyl fluorobutenoates **19a** and **20a** (704 mg, 2.65 mmol) in THF (100 mL) at 0 °C under N_2 during 10 min. The stirring at 0 °C was continued for 1 h and then for another hour at 20 °C. TLC (CH_2Cl_2–MeOH, 9:1) showed 100% conversion. The reaction mixture was cooled to 0 °C, and saturated aqueous NH_4Cl (10 mL) was added slowly with stirring within 30 min. The resultant solution was evaporated to dryness, and the residue was extracted with CH_2Cl_2–MeOH (4:1, 3 × 30 mL). The organic phase was evaporated, and the crude product was chromatographed on a column of silica gel using CH_2Cl_2–MeOH (9:1) as an eluent.

***Z*-Isomer 9a**: 460 mg (78%); mp 195–196 °C after recrystallization from ethyl acetate; UV_{max} (EtOH) 261 nm (ϵ 14 200), 209 (ϵ 19 600); IR (KBr) 3280 cm^{-1}, 3110 (vs, NH_2 + OH), 1690, 1610, 1580 (vs, adenine); ^1H NMR (CD_3SOCD_3) δ 3.93 (dd, 2, $H_{4'}$, $^3J_{4',F}$ = 12.0 Hz, $^3J_{4',OH}$ = 5.4 Hz), 4.79 (d, 2, $H_{1'}$, $^3J_{1',2'}$ = 7.2 Hz), 5.26 (dt, 1, $H_{2'}$, $^3J_{2',F}$ = 36.2 Hz, $^3J_{2',1'}$ = 7.2 Hz), 5.31 (t, 1, OH, $^3J_{OH,4'}$ = 5.4 Hz), 7.22 (s, 2, NH_2), 8.10 and 8.12 (2s, 2, H_2 and H_8); ^{13}C NMR δ 36.94 (d, $C_{1'}$, $^3J_{1,F}$ = 7.0 Hz), 58.90 (d, $C_{4'}$, $^2J_{4',F}$ = 32.3 Hz), 101.46 (d, $C_{2'}$, $^2J_{2',F}$ = 10.3 Hz), 119.03, 140.81, 149.67, 152.92, 156.34 (adenine), 161.73 (d, $C_{3'}$, $^1J_{3',F}$ = 261.9 Hz); ^{19}F NMR δ −113.37 (dt, $^3J_{F,H\text{-}2'}$ = 36.6 Hz, $^3J_{F,H\text{-}4'}$ = 12.2 Hz); EI-MS 223 (46.4, M), 206 (32.8, M − OH), 192 (100, M − CH_2OH), 136 (32.8, adenine + H), 135 (48.9, adenine), 108 (42.2, adenine − HCN). Anal. ($C_9H_{10}FN_5O_2$) C, H, N, F.

***E*-Isomer 8a**: 115 mg (19%); mp 176–178 °C after recrystallization from ethyl acetate; UV_{max} (EtOH) 261 nm (ϵ 15 100), 210 (ϵ 19 600); IR (KBr) 3460 cm^{-1} (sharp s, OH), 3110 (br s, NH_2), 1660 (vs, br), 1600, 1580 (s, adenine); ^1H NMR (CD_3SOCD_3) δ 4.26 (d, 2, $H_{4'}$, $^3J_{4',F}$ = 21.3 Hz), 4.81 (d, 2, $H_{1'}$, $^3J_{1',2'}$ = 7.8 Hz), 5.45 (dt, 1, $H_{2'}$, $^3J_{2',F}$ = 19.2 Hz, $^3J_{2',1'}$ = 7.9 Hz), 5.48 (apparent s, 1, OH), 7.24 (s, 2, NH_2), 8.09 and 8.12 (2s, 2, H_2 and H_8); ^{13}C NMR δ 38.62 (d, $C_{1'}$, $^3J_{1',F}$ = 12.8 Hz), 56.17 (d, $C_{4'}$, $^2J_{4',F}$ = 29.8 Hz), 103.85 (d, $C_{2'}$, $^2J_{2',F}$ = 24.0 Hz), 119.13, 140.76, 149.52, 152.82 and 156.37 (adenine), 163.08 (d, $C_{3'}$, $^1J_{3',F}$ = 257.8 Hz); ^{19}F NMR δ −104.08 (q, $^3J_{F,H\text{-}2'}$ = $^3J_{F,H\text{-}4'}$ = 20.9 Hz); EI-MS 223 (46.9, M), 206 (33.6, M − OH), 192 (100, M − CH_2OH), 136 (46.4, adenine + H), 135 (57.2, adenine), 108 (50.3, adenine − HCN). Anal. ($C_9H_{10}FN_5O_2$) C, H, N, F.

(*Z*)-4-(Thymin-N^1-yl)-2-fluoro-2-buten-1-ol (9d). A. Reduction of the *Z*-Ester 19d with DIBALH. The reaction was carried out under the same conditions as those used for the preparation of analogue **9a**. The *Z*-ester **19d** (70 mg, 0.27 mmol) was reacted with DIBALH (1 M in CH_2Cl_2, 0.8 mL, 0.8 mmol) in THF (10 mL) at 0 °C under N_2 for 1 h and then at room temperature for another hour. TLC showed 100% conversion. After the usual workup and chromatography using AcOEt followed by AcOEt–MeOH (95:5), 40 mg (70%) of compound **9d** was obtained: mp 139–141 °C; UV_{max} (EtOH) 270 nm (ϵ 9000), 209 (ϵ 9600); IR (KBr) 3495 cm^{-1} (m, OH), 3160 (w, NH), 1695–1650 (vs, C=C and thymine); ^1H NMR (CD_3SOCD_3, 500 MHz) δ 1.73 (s, 3, CH_3), 3.93 (d, 2, $H_{4'}$, $^3J_{4',F}$ = 12.0 Hz), 4.28 (d, 2, $H_{1'}$, $^3J_{1',2'}$ = 6.5 Hz), 5.06 (dt, 1, $H_{2'}$, $^3J_{2',F}$ = 37.5 Hz, $^3J_{2',1'}$ = 7.0 Hz), 5.28 (br s, 1, OH), 7.45 (s, 1, H_6), 11.22 (s, 1, NH); ^{13}C NMR (125 MHz) δ 40.91 (d, $C_{1'}$, $^3J_{1',F}$ = 6.5 Hz), 58.49 (d, $C_{4'}$, $^2J_{4',F}$ = 32.4 Hz), 100.82 (d, $C_{2'}$, $^2J_{2',F}$ = 10.2 Hz), 161.39 (d, $C_{3'}$, $^1J_{3',F}$ = 260.8 Hz), 11.85, 108.79, 149.83, 150.66 and 164.18 (thymine); ^{19}F NMR δ −114.44 (dt, $^3J_{F,H\text{-}2'}$ = 37.4 Hz, $^3J_{F,H\text{-}4'}$ = 12.4 Hz); EI-MS 214 (57.2, M), 198 (22.5, M − OH + H), 196 (62.4, M − H_2O), 127 (100, thymine + H), 126 (83.9, thymine), 125 (41.2, thymine − H); HRMS M calcd 214.0754, found 214.0756. Anal. ($C_9H_{11}FN_2O_3$) C, H, F, N.

B. Reduction of the *Z*-Ester 19d with $NaBH_4$. Solid $NaBH_4$ (142 mg, 3.76 mmol) was added to a solution of the *Z*-ester **19d** (240 mg, 0.94 mmol) in THF–MeOH (19:1, 20 mL) at 0 °C with stirring. The stirring was continued for 3.5 h whereupon the reduction was complete. Saturated aqueous NH_4Cl (4 mL) was then added, and after 30 min the solvents were evaporated. The residue was chromatographed on a silica gel column using petroleum ether–THF (55:45 containing 0.5–1% MeOH) to give analogue **9d** (180 mg, 90%), mp 144–146 °C after recrystallization from AcOEt, which was identical with the sample obtained by method A.

(*E*)-4-(Thymin-N^1-yl)-2-fluoro-2-buten-1-ol (8d). The procedure described for analogue **9d** (method B) was followed on a 0.58 mmol scale of the *E*-ester **20d** to give compound **8d** (110 mg, 88%): mp 137–138 °C after recrystallization from AcOEt; UV_{max} (EtOH) 269 nm (ϵ 8800), 212 (ϵ 6300); IR (KBr) 3450 cm^{-1} (br m, OH), 1710–1650 (vs, C=C and thymine); ^1H NMR (CD_3SOCD_3, 500 MHz) δ 1.70 (s, 3, CH_3), 3.33 (br s, 1, OH), 4.16 (d, 2, $H_{4'}$, $^3J_{4',F}$ = 21.5 Hz), 4.29 (d, $H_{1'}$, 2, $^3J_{1',2'}$ = 8.0 Hz), 5.24 (dt, 1, 2', $^3J_{2',F}$ = 19.5 Hz, $^3J_{2',1'}$ = 8.0 Hz), 7.43 (d, 1, H_6); ^{13}C NMR (125.7 MHz) δ 42.95 (d, $C_{1'}$, $^3J_{1',F}$ = 13.1 Hz), 55.78 (d, $C_{4'}$, $^2J_{4',F}$ = 29.7 Hz), 103.67 (d, $C_{3'}$, $^2J_{3',F}$ = 23.2 Hz), 162.75 (d, $C_{3'}$, $^1J_{3',F}$ 257.2 Hz), 12.25, 109.65, 141.28, 151.33 and 165.12 (thymine); ^{19}F NMR δ −105.43 (q, $^3J_{F,H\text{-}2'}$ = $J_{F,H\text{-}4'}$ = 21.2 Hz); EI-MS 214 (41.1, M), 196 (52.6, M − H_2O), 127 (100.0, thymine + H), 126 (82.5, thymine), 125 (34.4, thymine–H); HRMS M calcd 214.0754, found 214.0748. Anal. ($C_9H_{11}FN_2O_3$) C, H, F, N.

N^9-(3-Fluoro-4-hydroxybut-1-yl)adenine (24) and N^9-(4-Hydroxybut-1-yl)adenine (25). A mixture of (*Z*)- and (*E*)-fluorobutenols **9a** and **8a** (63 mg, 0.28 mmol) was hydrogenated in a Parr apparatus using 10% Pd/C as a catalyst in MeOH (50 mL) at 20 psi and room temperature for 4.5 h. TLC showed 100% conversion. The catalyst was removed by filtration through a Celite pad. The filtrate was evaporated to give 62.6 mg (99%) of white solid, which was recrystallized from AcOEt–MeOH (87:13) or 2-propanol, mp 217–223 °C. The ^1H NMR indicated that it was a mixture of **24** and **25** in the ratio of 4:1. A portion (35 mg) of this material was dissolved in 30% aqueous MeOH (2 mL) and the solution applied on a column of Bio-Rad AG 1-X2 (OH^-, 200–400 mesh, 20 mL). The column was eluted with 5% MeOH at a flow rate of 1 mL/min (Figure 1). Both UV absorbing peaks were pooled, and the appropriate fractions were evaporated. Peak A gave compound **25** (5 mg, 15%), mp 196–199 °C, identical with that reported.[8] IR and TLC (CH_2Cl_2–MeOH, 9:1) were also indistinguishable from an authentic sample.[8] Peak B furnished fluoro alcohol **24** (24 mg, 68%): mp 226–227 °C after recrystallization from 30% MeOH; UV_{max} (EtOH) 261 nm (ϵ 14 600), 211 (ϵ 18 400); IR (KBr) 3280 and 3100 cm^{-1} (vs br, NH_2), 1690, 1610 and 1580 (vs, adenine); ^1H NMR (CD_3SOCD_3) δ 2.09 (apparent dq, 2, $H_{2'}$, $^3J_{2',F}$ = 21.6 Hz, $^3J_{2',1'}$ = 7.1 Hz), 3.46 (apparent dt, 2, $H_{4'}$, $^3J_{4',F}$ = 24.3 Hz, $^3J_{4',3'}$ = $^3J_{4',OH}$ = 5.4 Hz), 4.23 (t, 2, $H_{1'}$, $^3J_{1',2'}$ = 7.2 Hz), 4.43 (dsxt, 1, $H_{3'}$, $^2J_{3',F}$ = 49.5 Hz, $^3J_{3',4'}$ = 5.3 Hz), 4.93 (t, 1, OH, $^3J_{OH,4'}$ = 5.6 Hz), 7.19 (s, 2, NH_2), 8.11 (s, 2, H_2 and H_8); ^{13}C NMR δ 31.72 (d, $C_{2'}$, $^2J_{2',F}$ = 20.5 Hz), $C_{1'}$ overlapped with CD_3SOCD_3 signal, 63.15 (d, $C_{4'}$, $^2J_{4',F}$ = 21.8 Hz), 92.84 (d, $C_{3'}$, $^1J_{3',F}$ = 169.6 Hz), 119.36, 141.42, 150.11, 152,99, 156.54 (adenine); ^{19}F NMR δ −187.48 (dqt, $^2J_{F,H\text{-}3'}$ = 49.0 Hz, $^3J_{F,H\text{-}4'}$ = 24.5 Hz); EI-MS 225 (18.8, M), 208 (29.6, M − OH), 194 (11.7, M − CH_2OH), 149 (97.9, M − CH_2CFHCH_2OH + H), 148 (100.0, M − CH_2CFHCH_2OH), 136 (34.0, adenine + H), 135 (39.8, adenine), 108 (28.4, adenine − HCN). Anal. ($C_9H_{10}FN_5O_2$) C, H, F, N.

Adenosine Deaminase Assay. Compound **8a** or **9a** (0.6–0.7 mg, 2.6–3 μmol) was dissolved in 0.05 M Na_2HPO_4 (pH 7.5, 0.2 mL), adenosine deaminase (calf intestine, type VIII, Sigma Chemical Co., St. Louis, MO; 0.4 unit, 0.2 mL in the same buffer) was added, and the solution was kept at room

temperature for 24 h. The reaction was followed by paper electrophoresis (flat-bed instrument, Whatman No. 1 paper, 15 °C, 0.05 M citrate buffer, pH 3.5, 40 V/cm, 1 h) and UV spectroscopy. After 24 h (*Z*)-fluorobutenol **9a** was deaminated from 80% whereas the *E*-isomer **8a** was unchanged.

Inhibition of HIV-Induced Cytopathic Effect. The assay was performed as described.[39] The CD_4 + ATH8 cells (2×10^5) were exposed to a laboratory HIV-1 strain (HIV-1_{LAI} at a 1000 tissue culture inhibition dose, $TCID_{50}$) and incubated in the presence of analogues at 37 °C in 5% CO_2-containing humidified air. 2′,3′-Dideoxyinosine (ddI) was used as a positive control at 50 μM. Control cells were treated similarly, but they were not exposed to the virus. On day 7 of the culture, the total viable cells were counted in a hemocytometer under microscope by the trypan blue dye exclusion method. The results are summarized in Figure 2.

Acknowledgment. Thanks are due to the Central Instrumentation Facility (Dr. R. J. Hood, Director), Department of Chemistry, Wayne State University, and, particularly, to Drs. M. B. Ksebati and M. B. Kempff for NMR and mass spectra. The antitumor assays were performed by Dr. D. Kessel (clonogenic assays), Department of Pharmacology, and Dr. T. H. Corbett (disk diffusion assays), Department of Internal Medicine, Wayne State University School of Medicine. The work described herein was supported in part by Grant CA 32779 from the National Cancer Institute, Bethesda, MD, and in part by an institutional grant to the Michigan Cancer Foundation from the United Way of Southeastern Michigan.

References

(1) Presented in part at the 206th American Chemical Society National Meeting, Chicago, IL, August 22–27, 1993; Abstract 134.
(2) Phadtare, S.; Kessel, D.; Corbett, T. H.; Renis, H. E.; Court, B. A.; Zemlicka, J. Unsaturated and Carbocyclic Nucleoside Analogues: Synthesis, Antitumor, and Antiviral Activity. *J. Med. Chem.* **1991**, *34*, 421–429 and references cited therein.
(3) Zemlicka, J. Allenols Derived from Nucleic Acid Bases - a New Class of Anti-HIV Agents: Chemistry and Biological Activity. In: *Nucleosides and Nucleotides as Antitumor and Antiviral Agents*; Chu, C. K., Baker, D. C., Eds., Plenum Publishing Corp.: New York, 1993; pp 73–100.
(4) Johansson, K. N.-G.; Lindborg, B. G.; Noren, J.-O. Novel Derivatives of Guanine. Eur. Patent 146 516, 1985.
(5) Larsson, A.; Stenberg, K.; Ericson, A.-C.; Haglund, U.; Yisak, W.-A.; Johansson, N. G.; Oberg, B.; Datema, R. Mode of Action, Toxicity, Pharmacokinetics, and Efficacy of Some Antiherpes Virus Analogs Related to Buciclovir. *Antimicrob. Agents Chemother.* **1986**, *30*, 598–605.
(6) Ashton, W. T.; Meurer, L. C.; Cantone, C. L.; Field, A. K.; Hannah, J.; Karkas, J. D.; Liou, R.; Patel, G. F.; Perry, H. C.; Wagner, A. F.; Walton, E.; Tolman, R. L. Synthesis and Antiherpetic Activity of (+)-9-[[(*Z*)-2-(Hydroxymethyl)cyclopropyl]-methyl]-guanine and Related Compounds. *J. Med. Chem.* **1988**, *31*, 2304–2315.
(7) Haines, D. R.; Tseng, C. K. H.; Marquez, V. E. Synthesis and Biological Activity of Unsaturated Carboacyclic Purine Nucleosides Analogues. *J. Med. Chem.* **1987**, *30*, 943–947.
(8) Phadtare, S.; Zemlicka, J. Nucleic Acid Derived Allenols: Unusual Analogues of Nucleosides with Antiretroviral Activity. *J. Am. Chem. Soc.* **1989**, *111*, 5925–5931.
(9) Phadtare, S.; Zemlicka, J. Synthesis of (Z)- and (E)-N^9-(Hydroxy-1-buten-1-yl)adenine - New Unsaturated Analogues of Adenosine. *Tetrahedron Lett.* **1990**, *31*, 43–46.
(10) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1991.
(11) DeClercq, E. HIV Inhibitors Targeted at Reverse Transcriptase. *AIDS Res. Hum. Retroviruses* **1992**, *8*, 119–134.
(12) Castelhano, A. L.; Krantz, A. A Novel Route to Allenyl Fluorides. Synthesis of Amino-7-fluorohepta-5,6-dienoic Acid, the First Fluoroallenyl Amino Acid. *J. Am. Chem. Soc.* **1987**, *109*, 3491–3493.
(13) Kwok, P.-Y.; Muellner, F. W.; Chen, C. K.; Fried, J. Total Synthesis of 7,7-, 10,10-, and 13,13-Difluoroarachidonic Acids. *J. Am. Chem. Soc.* **1987**, *109*, 3684–3692.
(14) Miyashita, N.; Yoshikoshi, A.; Grieco, P. A. Pyridinium p-Toluenesulfonate. A Mild and Efficient Catalyst for the Tetrahydropyranylation of Alcohols. *J. Org. Chem.* **1977**, *42*, 3772–3774.
(15) Henne, A. L.; Nager, M. Trifluoropropyne. *J. Am. Chem. Soc.* **1951**, *73*, 1042–1043.
(16) Henne, A. L.; Finnegan, W. G. Perfluoro 2-Butyne and Its Hydrogenation Products. *J. Am. Chem. Soc.* **1949**, *71*, 298–300.
(17) Bailey, P. D.; Boa, A. N.; Crofts, G. A. Asymmetric Synthesis of Protected α-Fluoroglycines. *Tetrahedron Lett.* **1989**, *30*, 7457–7460.
(18) Takeuchi, Y.; Nabetani, M.; Takagi, K.; Hagi, T.; Koizumi, T. Synthetic Studies for Novel Structure of α-Nitrogenously Functionalized α-Fluorocarboxylic Acids. Part 1. The First Synthesis and Reactions of N-Protected α-Fluoroglycines. *J. Chem. Soc., Perkin Trans. 1* **1991**, 49–53.
(19) Doel, M. T.; Jones, A. S.; Taylor, N. An Approach to the Synthesis of Peptide Analogues of Oligonucleotides (Nucleopeptides). *Tetrahedron Lett.* **1969**, 2285–2288.
(20) Thenappan, A.; Burton, D. J. Alkylation of (Fluorocarbethoxymethylene)tri-n-butylphosphorane: A Facile Entry to α-Fluoroalkanoates. *J. Org. Chem.* **1990**, *55*, 2311–2317.
(21) Thenappan, A.; Burton, D. J. Reduction-Olefination of Esters: A New and Efficient Synthesis of α-Fluoro α,β-Unsaturated Esters. *J. Org. Chem.* **1990**, *55*, 4639–4642.
(22) Holy, A.; Votruba, I.; De Clercq, E. Synthesis and Antiviral Activity of Stereoisomeric Eritadenines. *Collect. Czech. Chem. Commun.* **1982**, *47*, 1392–1407.
(23) This compound was prepared according to the method[24] described for the introduction of the N^3-[2-(trimethylsilyl)ethoxy]-methyl group. Inadvertently, NEt_3 was mentioned as the base employed.[24] In both procedures, *N*-ethyl-*N*,*N*-diisopropylamine was used.
(24) Phadtare, S.; Zemlicka, J. *Synthesis* of N^1-(4-Hydroxy-1,2-butadien-1-yl)thymine, an Analogue of 3′-Deoxythymidine. *J. Org. Chem.* **1989**, *54*, 3675–3679.
(25) Hudlicky, M. Hydrogenolysis of Carbon-Fluorine Bonds in Catalytic Hydrogenation. *J. Fluorine Chem.* **1979**, *14*, 189–199.
(26) Butina, D.; Hudlicky, M. The Synthesis of γ-Fluoroisoleucine. *J. Fluorine Chem.* **1980**, *16*, 301–323.
(27) Hudlicky, M. Hydrogenolysis of Carbon-Fluorine Bond in Catalytic Hydrogenation. II. *J. Fluorine Chem.* **1983**, *22*, 241–259.
(28) Allmendinger, T.; Dandois, C.; Walliser, B. The Hydrogenation of Fluoroolefins. *Tetrahedron Lett.* **1991**, *32*, 2735–2736.
(29) *Handbook of Biochemistry*, 2nd ed.; Sober, H. A., Ed.; CRC Press: Cleveland, OH, 1970; J-196.
(30) Gin, J. B.; Dekker, C. A. The Preparation and Properties of O-Methylated Adenosine Derivatives. *Biochemistry* **1968**, *7*, 1413–1420.
(31) The apparent changes in *E*- and *Z*-stereoselectivity are artifacts of *E*,*Z*-nomenclature.
(32) Hayashi, S.; Phadtare, S.; Zemlicka, J.; Matsukura, M.; Mitsuya, H.; Broder, S. Adenallene and Cytallene: Acyclic Nucleoside Analogues that Inhibit Replication and Cytopathic Effect of Human Immunodeficiency Virus in Vitro. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 6127–6131.
(33) Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; De Clercq, E. Synthesis and Anti-HIV Activity of Various 2′- and 3′-Substituted 2′,3′-Dideoxyadenosines: A Structure - Activity Analysis. *J. Med. Chem.* **1987**, *30*, 2131–2137.
(34) Megati, S.; Goren, Z.; Silverton, J. V.; Orlina, J.; Nishimura, H.; Shirasaka, T.; Mitsuya, H.; Zemlicka, J. (*R*)-(−)- and (*S*)-(+)-Adenallene: Synthesis, Absolute Configuration, Enantioselectivity of Antiretroviral Effect, and Enzymic Deamination. *J. Med. Chem.* **1992**, *35*, 4098–4104.
(35) Chang, C.-N.; Doong, S.-L.; Zhou, J. H.; Beach, J. W.; Jeong, L. S.; Chu, C. K.; Tsai, C.-H.; Cheng, Y.-C. Deoxycytidine Deaminase-Resistant Stereoisomer Is the Active Form of (±)-2′,3′-Dideoxy-3′-thiacytidine in the Inhibition of Hepatitis B Virus Replication. *J. Biol. Chem.* **1992**, *267*, 13938–13942.
(36) Megati, S.; Phadtare, S.; Zemlicka, J. Unsaturated Phosphonates as Acyclic Nucleotide Analogues. Anomalous Michaelis-Arbuzov and Michaelis-Becker Reactions with Multiple Bond Systems. *J. Org. Chem.* **1992**, *57*, 2320–2327.
(37) Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S. A Simple and Practical Method for Tetrahydropyranylation of Alcohols and Phenols. *Synthesis* **1979**, 618–620.
(38) The signals of the less abundant *E*-isomer were not detected.
(39) Richman, D. D.; Johnson, V. A.; Mayers, D. L.; Shirasaka, T.; O'Brien, M. C.; Mitsuya, H. In Vitro Evaluation of Experimental Agents for Anti-HIV Activity. In *Current Protocols in Immunology*; Colligan, J. E., Kruisbeek, A. M., Margulies, D. H., Shevach, E. M., Strober, W., Eds.; Wiley Interscience: New York, 1993; pp 12.9.1–12.9.21.

JM9407623