Pergamon

Tetrahedron, Vol. 53, No. 15, pp. 5389-5396, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00233-0

Unsaturated Fluoro Analogues of Adenine Nucleotides. Unusual Eliminations of Hydrogen Halides in α,α-Difluorophosphonates Containing a Heterocyclic Base

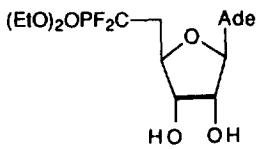
Ze-Qi Xu[1] and Jiri Zemlicka*

Department of Chemistry, Experimental and Clinical Chemotherapy Program, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, Michigan 48201-1379, U. S. A.

Abstract: *Reaction of bromodifluoromethyl phosphonate* ***3*** *with zinc and propynyl chloride led to allenyl phosphonate* ***4*** *which was brominated to give dibromophosphonate* ***6****. Alkylation of adenine* ***7*** *with* ***6*** *afforded Z- and E- difluorophosphonates* ***8*** *and* ***9****. Hydrogenation of* ***8*** *furnished saturated difluorophosphonate* ***10a*** *which was dealkylated to the corresponding phosphonic acid* ***10b****. Reaction of* ***8*** *with tetrabutylammonium fluoride gave fluoroenyne phosphonate* ***11*** *whereas* ***9*** *and 1,5-diazabicyclo[4.3.0]non-5-ene furnished bromofluorodiene phosphonate* ***16****. Hydrogenation of* ***11*** *afforded phosphonates* ***13*** *and* ***14*** *in addition to defluorinated product* ***15****.* © 1997 Elsevier Science Ltd.

INTRODUCTION

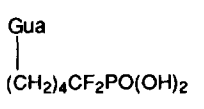
Fluoroalkyl phosphonate analogues of biologically important phosphates have been a subject of much recent interest[2]. Particularly important are oligonucleotide analogues[3] and nucleotide mimics comprising an intact ribofuranose ring (compound **1**)[4] or ω-phosphonylated fluoroalkyl derivatives of nucleic bases such as phosphonate[5] **2**. The latter compound is a strong inhibitor of purine nucleoside phosphorylase. By contrast,



1

Ade = adenin-9-yl

Gua = guanin-9-yl



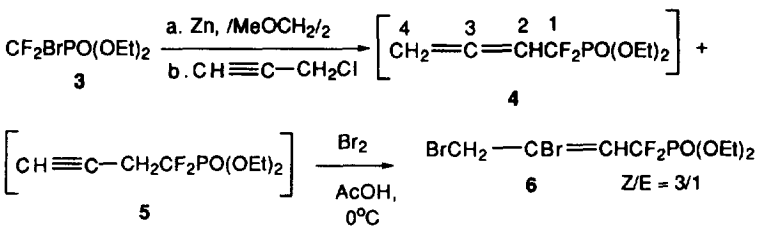
2

little attention was paid to unsaturated acyclic phosphonates containing fluorine and nucleic acid base although similar non-fluorinated analogues exhibit significant biological activities[6-9]. For these reasons, we became interested in the development of synthetic approaches to fluoroalkene analogues of nucleotides. A special emphasis was put on obtaining analogues with multiple bonds between the heterocyclic base and phosphonate moiety.

SYNTHESIS, STRUCTURE ASSIGNMENT AND NMR SPECTRA

At the outset, we preferred to alkylate a nucleic acid base with a suitable alkylating agent comprising a preformed phosphonate moiety. This approach offers more versatility because such an agent can be used for alkylation of several nucleic acid bases. Thus, commercially available diethyl bromodifluoromethylphosphonate **3** was converted by reaction with zinc and propynyl chloride[10] to a mixture of diethyl 1,1-difluoro-2,3-butadiene-1-phosphonate **4** (86 %) and diethyl difluoro-3-butyne-1-phosphonate **5** (6 %, Scheme 1). This

Scheme 1

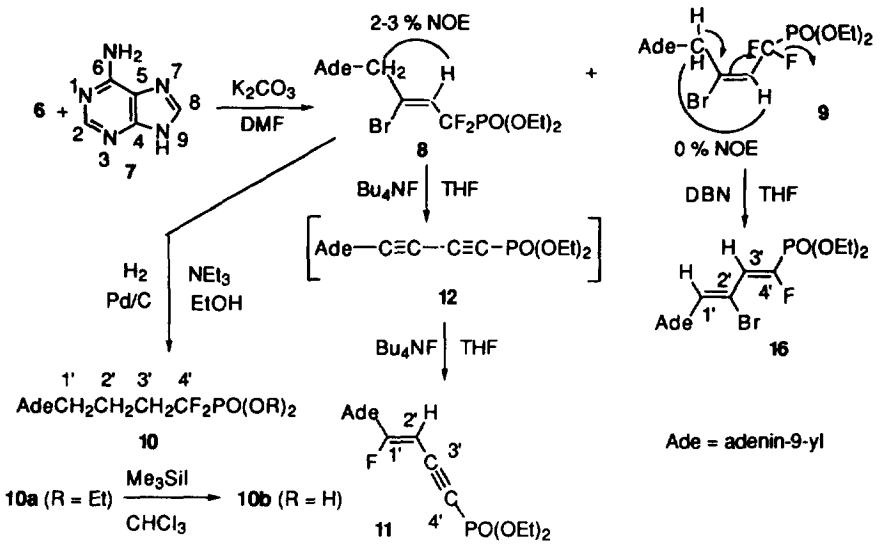


product was brominated[11] in acetic acid at 0°C to give diethyl 1,1-difluoro-3,4-dibromo-2-butene-1-phosphonate **6** as a mixture of *Z*- and *E*-isomers in the ratio of 3 : 1 and 60 % overall yield.

Compound **6** was used for alkylation of a model nucleic acid base, adenine **7**, in the presence of K_2CO_3 and N,N-dimethylformamide (DMF) as a solvent at room temperature to give *Z*- and *E*-isomers **8** and **9** in 13 and 14 % yield, respectively (Scheme 2). A 28 % of the starting material **6** was recovered. Prolonged reaction time or excess of K_2CO_3 led to decomposition. The less polar *E*-isomer **9** was of limited stability and it could not be satisfactorily purified by crystallization or chromatography. By contrast, product **8** was readily crystallized from benzene. The structures of both products followed from the NMR spectra and NOE measurements. Thus, *Z*-isomer **8** exhibited 2 - 3 % NOE enhancement of the $H1'$ and $H3'$ resonances whereas no effect was seen in *E*-isomer **9**. It is also of interest that although the UV spectra were similar, absorbancy of the E-isomer **9** was significantly higher than that of *Z*-isomer **8**. Catalytic hydrogenation of **8** afforded saturated difluorophosphonate **10a** in 82 % yield. The latter was smoothly dealkylated using Me_3SiI in chloroform[6] to give the corresponding phosphonic acid **10b** (80 % yield).

Base-catalyzed elimination of hydrogen halides from alkenes **8** and **9** provided interesting unsaturated phosphonates (Scheme 2). Reaction of the *Z*-isomer **8** with NBu_4F in tetrahydrofuran (THF) resulted in an elimination of the elements of HBr and HF with a formal transposition of one of the 4'-fluoro atoms to the 1' position of alkene system to give fluoroalkene **11** in 49 % yield. This process is best explained by invoking an intermediary formation of butadiyne derivative **12**. A 1',2' addition of fluoride then leads to **11**. The structure of **11** was confirmed by ^1H and ^{19}F NMR spectra which indicate that fluorine and $H2'$ are in a *trans* arrangement ($^3J_{H\text{-}2',F}$ = 35.1 and $^3J_{F,H\text{-}2'}$ = 31.6) and the hydrogen atom ($H2'$) as well as fluorine are

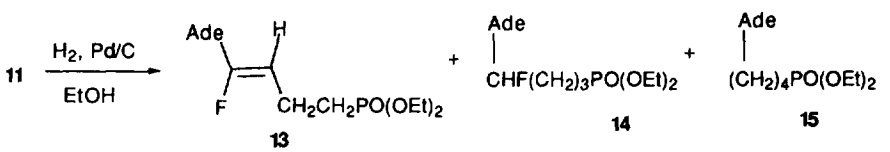
Scheme 2



remote from phosphorus ($^4J_{H\text{-}2',P}$ = 2.7, $^5J_{P,F}$ = 2.1). In addition, the ^{13}C NMR spectrum showed both acetylenic carbons $C_{3'}$ and $C_{4'}$ at 75.60 and 85.02 ppm are coupled to fluorine and phosphorus ($^2J_{3',P}$ = 9.9, $^3J_{3',F}$ = 6.8 and $^1J_{4',P}$ = 293.6, $^4J_{4',F}$ = 4.3, respectively). By contrast, alkene carbons $C_{1'}$ and $C_{2'}$ at 154.73 and 90.93 ppm are coupled only to fluorine ($^1J_{1',F}$ = 274.0 and $^2J_{2',F}$ = 53.1, respectively). These data rule out the structure of an isomeric 3',4'-adduct of HF. It is likely that the primary driving force for elimination of HBr and HF from both **8** and **9** is the formation of a conjugated system between the heterocyclic base (adenine) and phosphonate group. The importance of this factor was also recognized in isomerization of some adenine phosphonates containing multiple bonds[6].

Catalytic hydrogenation of **11** was complex furnishing three products Scheme 3). A mixture of

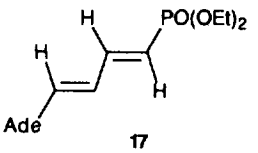
Scheme 3



unsaturated fluorophosphonate **13** and the corresponding saturated derivative **14** was obtained in 20 % yield and 1 : 1 ratio as determined by ^1H NMR which could not be separated by chromatography on silica gel. Phosphonate **15** lacking fluorine (26 %) was also obtained. Reductive removal of fluorine was frequently

observed during hydrogenation of fluoro derivatives[12]. It is interesting to note that a complete saturation of the triple bond (compound **13**) preceded the reduction of alkene moiety (compounds **14** and **15**).

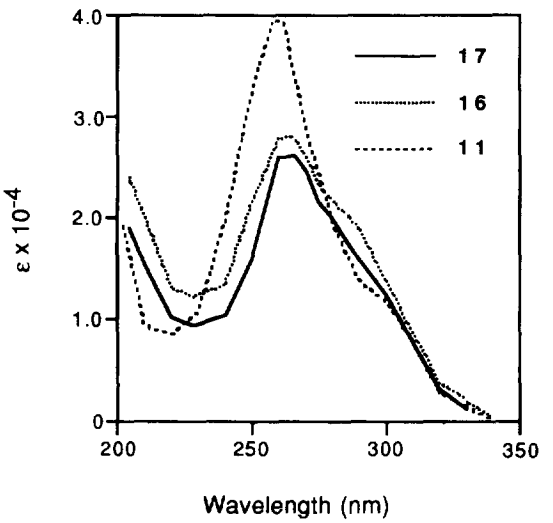
The reaction of *E*-isomer **9** catalyzed with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in THF took a different course. In this case only one mol of HF was eliminated to furnish bromofluorodiene **16** in 21 % yield. The UV spectrum of **16** strongly resembles that of diene phosphonate[5] **17** (Figure 1). The absorption maximum



17

of **11** exhibits a slight hypsochromic shift relative to **16** and **17** but the ε value is significantly higher. This may reflect a more favorable conjugation between adenine and phosphonate moiety. The ^{1}H and ^{19}F NMR spectra of **16** indicate a *trans* arrangement of the H3' and fluorine ($^{3}J_{H\text{-}3',F}$ = 35.1, $^{3}J_{F,H\text{-}3'}$ = 35.3). Large coupling constants ($^{2}J_{P,F}$ = 93.8 and $^{2}J_{F,P}$ = 93.7) suggest a geminal disposition of phosphorus and fluorine.

Figure 1. *UV spectra of phosphonates* **11**, **16** *and* **17** *in ethanol*



EXPERIMENTAL

General Methods. See[6, 12]. UV spectra were determined in ethanol, NMR in $CDCl_3$ and IR as KBr pellets unless stated otherwise. J-Values are given in Hz. For fast-atom bombardment (FAB) mass spectra thioglycerol was used as a matrix.

Diethyl 3,4-Dibromo-1,1-difluoro-2-butene-1-phosphonate 6. Warning! Distillation of the crude product 4 should not be attempted[10]**!** Diethyl bromodifluoromethane phosphonate **3** (20 g, 74.9 mmol) was added within 30 min. into a stirred suspension of zinc powder (acid-washed, 4.9 g, 74.9 mmol) in 1,2-dimethoxyethane (40 mL) at room temperature. The stirring was continued for 24 h. The excess of zinc was filtered off and CuBr (1.1 g, 7.5 mmol) was added to the filtrate. Propynyl chloride (5.5 mL, 76 mmol) was then added over 10 min. into the solution with external ice-cooling. The mixture was allowed to warm to room temperature during a period of 3 h and it was stirred for another 24 h. The inorganic salts were filtered off and the filtrate was evaporated in vacuo at room temperature. The ^{1}H NMR spectrum indicated the crude product contained diethyl 1,1-difluoro-2,3-butadiene-1-phosphonate **4** as the major component[10] along with some diethyl 1,1-difluoro-3-propyne-1-phosphonate **5** and diethyl difluoromethanephosphonate. The spectroscopic data for **4** are as follows: IR (NaCl) 1990 and 1960 cm^{-1} (s, C=C=C). ^{1}H NMR ∂ 1.32 (6 H, m, CH_3), 4.22 (4 H, q, J = 7.2, CH_2O), 5.15 (2 H, qt, H_4, J = 6.4), 5.42 (1 H, m, H_3). ^{19}F NMR -105.18 (ddt, $^2J_{F,P}$ = 122.6, $^3J_{F,H-3}$ = 12.2, $^5J_{F,H-1}$ = 6.8).

The solution of crude **4** in acetic acid (50 mL) was cooled in an ice-bath and bromine (3.8 mL, 73.8 mmol) was added dropwise with stirring. The mixture was then stirred at room temperature for 4 h whereupon TLC in CH_2Cl_2 - ethyl acetate (99 : 1) indicated no starting material. The crude product obtained by evaporation was flash-chromatographed on a silica gel column using CH_2Cl_2 - ethyl acetate (99 : 1) to give a colorless liquid (17.5 g, 60.5 %, based on diethyl bromodifluoromethane phosphonate **3**), which was a mixture of *Z*- and *E*-isomers of **6** in the ratio of 3 : 1. IR (NaCl) 1650 cm^{-1} (s, C=C). ^{1}H NMR ∂ 1.3 (6 H, t, CH_3), 4.16 - 4.35 (6 H, m, CH_2O + H_1), 6.44 (1 H, t, H_3, $^3J_{3,F}$ = 13.5). ^{13}C NMR 16.11, 16.18 (2s, CH_3), 37.40 (C_1, *Z*-isomer), 49.40 (C_1, *E*-isomer), 64.79, 64.88 (2s, CH_2O), 115.57 (dt, C_4, $^1J_{4,F}$ = 262.1, $^1J_{4,P}$ = 220.5), 122.65 (dt, C_3, $^2J_{3,F}$ = 23.6, $^2J_{3,P}$ = 14.2, *E*-isomer), 123.64 (dt, C_3, $^2J_{3,F}$ = 23.4, $^2J_{3,P}$ = 13.9, *Z*-isomer), 127.90 - 128.39 (m, C_2). ^{19}F NMR -107.21 (dd, $^2J_{F,P}$ = 108.8, $^3J_{F,H-3}$ = 14.0, *Z*-isomer), -106.90 (ddq, $^2J_{F,P}$ = 109.0, ^{3}JF,H-3 = 14.0, ^{5}JF,H-1 = 1.5 *E*-isomer). ^{31}P NMR 4.62 (t, $^2J_{P,F}$ = 109.1, *Z*-isomer), 4.75 (t, $^2J_{P,F}$ = 109.2, *E*-isomer). Anal. Calcd. for $C_8H_{13}Br_2F_2O_3P$: C, 24.90; H, 3.39; Br, 41.40; F, 9.84; P, 8.02. Found: C, 24.92; H, 3.60; Br, 41.27, F, 9.71; P, 8.22.

Diethyl (Z)-4-(Adenin-9-yl)-3-bromo-1,1-difluoro-2-butene-1-phosphonate 8 and Diethyl (E)-4-(Adenin-9-yl)-3-bromo-1,1-difluoro-2-butene-1-phosphonate 9. A mixture of adenine **7** (4.6 g, 29.6 mmol), K_2CO_3 (6.2 g, 44.8 mmol) and **6** (11.5 g, 29.6 mmol) in DMF (100 mL) was stirred under N_2 at room temperature for 23 h. The reaction was followed by TLC in CH_2Cl_2 - MeOH (9 : 1). The insoluble portion was filtered off and it was washed with CH_2Cl_2 - MeOH (4 : 1, 50 mL). The combined filtrate and washings were evaporated and the residue was chromatographed on a silica gel column using ethyl acetate to recover the starting material **6** (3.2 g, 28 %) followed by ethyl acetate - MeOH (95 : 5) to give *E*-isomer **9** (1.68 g, 13 %) as an amorphous foam and, subsequently, *Z*-isomer **8** (1.87 g, 14 %), m.p. 122-124°C after recrystallization from benzene. UV max nm 260 (ε 16,200), 209 (ε 30,100). IR 3340 and 3200 cm^{-1} (s, NH_2), 1650 and 1600 cm^{-1} (s, C=C and adenine ring). ^{1}H NMR ∂ 1.31 (6 H, t, CH_3), 4.23 (4 H, m, OCH_2), 5.12 (2 H, s, $H_{1'}$), 6.30 (1 H, t, $H_{3'}$, $^3J_{3',F}$ = 13.5 Hz), 6.34 (2 H, s, NH_2), 7.88 and 8.33 (2 H, 2 s, H_2 and H_8, adenine). ^{13}C NMR 16.31, 16.37 (2s, CH_3), 52.20 ($C_{1'}$), 65.06, 65.15 (2s, OCH_2), 115.75 (dt, $C_{4'}$, $^1J_{4',F}$ = 262.5, $^1J_{4',P}$ = 220.1), 123.72 (dt, $C_{3'}$, $^2J_{3',F}$ = 23.6, $^2J_{3',P}$ = 13.9), 127.28 (q, $C_{2'}$, $^3J_{2',F}$ =

$^3J_{2',P}$ = 7.1), adenine: 119.25, 140.00, 149.88, 153.39 and 155.80. ^{19}F NMR -106.92 (dd, $^2J_{F,P}$ = 109.0, $^3J_{F,H-3'}$ = 13.6). ^{31}P NMR 4.72 (t, $^2J_{P,F}$ = 108.8). EI-MS m/z 441, 439 (1.1, 1.4, M^+), 360 (10.7, M^+ - Br), 254, 252 /97.5, 100.0, M^+ - $CF_2P(O)(OEt)_2$/, 135 (28.1, adenine). *E*-Isomer **9**: UV max nm 259 nm (ε 27,200), 212 (ε 42,700). IR 3340 and 3160 cm^{-1} (s, NH_2), 1650 and 1600 cm^{-1} (s, C=C and adenine ring). ^1H NMR ∂ 1.41 (6 H, t, CH_3), 4.33 (4 H, m, OCH_2), 5.37 (2 H, s, $H_{1'}$), 6.22 (2 H, s, NH_2), 6.36 (1 H, t, $H_{3'}$, $^3J_{3',F}$ = 13.8, 8.06 and 8.37 (2 H, 2 s, H_2 and H_8, adenine). ^{19}F NMR -102.13 (dd, $^2J_{F,P}$ = 109.7, $^3J_{F,H-3'}$ = 15.1). Anal. Calcd. for $C_{13}H_{17}BrF_2N_5O_3P.0.66\ H_2O$: C, 34.53; H, 4.09; N, 15.49; Br, 17.67; F, 8.40; P, 6.85. Found: C, 34.57; H, 4.25; N, 15.51; Br, 17.71, F, 8.30; P, 6.70.

Diethyl (Z,E)-4-(Adenin-9-yl)-3-bromo-1-fluoro-1,3-butadiene-1-phosphonate 16. DBN (65 μL, 0.52 mmol) was added to a stirred solution of *E*-isomer **9** (230 mg, 0.52 mmol) in THF (20 mL) at room temperature. The stirring was continued for 3 h and the reaction was quenched with acetic acid. The insoluble portion was filtered off and the filtrate was evaporated. The residue was chromatographed on a silica gel column using CH_2Cl_2 - MeOH (95 : 5) to give product **16** (45 mg, 21 %), m.p. 159-161°C after recrystallization from benzene. UV max nm 284 (shoulder, ε 21,000), 265 (ε 28,100), 260 (shoulder, ε 27,800), 204 (ε 24,000). IR 3340 and 3160 cm^{-1} (m, NH_2), 1685, 1660 and 1610 cm^{-1} (s, C=C and adenine ring). ^1H NMR ∂ 0.83 (6 H, m, CH_3), 3.66 (4 H, m, OCH_2), 5.84 (2 H, s, NH_2), 6.08 (1 H, dd, $H_{3'}$, $^3J_{3',F}$ = 35.1, $^3J_{3',P}$ = 8.4), 7.49 (1 H, s, $H_{1'}$), 7.81 and 8.26 (2 H, 2 s, H_2 and H_8, adenine). ^{19}F NMR -118.69 (dd, $^2J_{F,P}$ = 93.7, $^3J_{F,H-3'}$ = 35.3). ^{31}P NMR 3.36 (d, $^2J_{P,F}$ = 93.8). EI-MS m/z 421, 419 (12.3, 12.7, M^+), 340 (24.3, M^+ - Br), 284, 282 (100.0, 82.4).

Diethyl 4-(Adenin-9-yl)-4-fluoro-3-buten-1-ynephosphonate 11. Bu_4NF in THF (1 M, 3.8 mL, 3.8 mmol) was added dropwise to a stirred solution of *Z-isomer* **8** (840 mg, 1.91 mmol) in THF (80 mL) at 0°C. The reaction was followed by TLC in ethyl acetate - MeOH (95 : 5). Additional Bu_4NF (2 mL) was added in two portions at 1 h intervals. The stirring was continued at 0°C for a total of 5 h, the mixture was then quenched with acetic acid and it was evaporated. The residue was chromatographed on a silica gel column using ethyl acetate - MeOH (97 : 3) to give compound **11** (315 mg, 49 %), m.p. 165 - 168°C after recrystallization from benzene. UV max nm 292 (shoulder, ε 13,300), 257 - 262 (ε 39,400), 202 (ε 19,200). IR 3340 and 3180 cm^{-1} (s, NH_2), 2180 (m, C≡C), 1680, 1605 and 1575 cm^{-1} (s, C=C and adenine ring). ^1H NMR ∂ (DMSO-d_6) 1.26 (6 H, t, CH_3), 4.08 (4 H, apparent qt, OCH_2), 6.48 (1 H, dd, 2', $^3J_{2',F}$ = 35.1, $^4J_{2',P}$ = 2.7), 7.65 (2 H, s, NH_2), 8.25 and 8.48 (2 H, 2 s, H_2 and H_8, adenine). ^{13}C NMR ∂ 16.26, 16.34 (2s, CH_3), 63.43, 63.50 (2s, OCH_2), 75.60 (dd, $C_{3'}$, $^2J_{3',P}$ = 9.9, $^3J_{3',F}$ = 6.8), 85.02 (dd, $C_{4'}$, $^1J_{4',P}$ = 293.6, $^4J_{4',F}$ = 4.3), 90.93 (d, $C_{2'}$, $^2J_{2',F}$ = 53.1, 154.73 (d, $C_{1'}$, $^1J_{1',F}$ = 274.0), adenine: 119.44, 137.10, 148.45, 154.45 and 156.77. ^{19}F NMR ∂ -84.33 (bd, $^3J_{F,H-2'}$ = 31.6). ^{31}P NMR -7.76 (d, $^5J_{P,F}$ = 2.1); EI-MS m/z 339 (36.3, M^+), 312 (8.6), 295 (10.6), 266 (23.9), 203 (100.0), 176 (27.6). Anal. Calcd. for $C_{13}H_{15}FN_5O_3P$: C, 46.02; H, 4.46; N, 20.64; F, 5.60; P, 9.13. Found: C, 46.16; H, 4.43; N, 20.75; F, 5.46; P, 8.91.

Diethyl 4-(Adenin-9-yl)-1,1-difluorobutane-1-phosphonate 10a. *Z-Isomer* **8** (460 mg, 1.04 mmol) was hydrogenated in a Parr apparatus using Pd/C (10 %, 67 mg) in ethanol (100 mL) and triethylamine (4 mL) at 20 psi and room temperature for 2 h. The catalyst was removed by filtration through a Celite pad. The filtrate was evaporated and the residue was chromatographed on a silica gel column using ethyl acetate - MeOH (95 : 5)

to give product **10a** (310 mg, 82 %), m.p. 107 - 109°C after recrystallization from CCl_4. UV max nm 261 (ε 12,700), 209 (ε 17,500). IR 3360 and 3160 cm^{-1} (s, NH_2), 1655, 1605 and 1575 cm^{-1} (s, adenine ring). ^1H NMR ∂ 1.35 (6 H, t, CH_3), 2.01-2.28 (4 H, apparent m, $H_{2'}$ + $H_{3'}$), 4.14-4.30 (6 H, m, OCH_2 + $H_{1'}$), 6.04 (2 H, s, NH_2), 7.81 and 8.35 (2 H, 2 s, H_2 and H_8, adenine). ^{13}C NMR 16.24, 16.30 (2 s, CH_3), 21.82 ($C_{2'}$), 30.93 (q, 3', $^2J_{3',F} = {}^2J_{3',P} = 18.8$), 43.04 ($C_{1'}$), 64.50, 64.58 (2 s, OCH_2), 120.22 (dt, $C_{4'}$, $^1J_{4',F} = 260.3$, $^1J_{4',P} = 216.4$), adenine: 119.58, 140.18, 149.98, 152.97 and 155.69. ^{19}F NMR -111.38 (dt, $^2J_{F,P} = 107.3$, $^3J_{F,H-3'} = 19.0$). ^{31}P NMR 6.86 (t, $^2J_{P,F} = 107.2$). EI-MS m/z 363 (22.1, M^+), 226 (100.0), 176 /41.9, $M^+ - CF_2P(O)(OEt)_2$/, 162 /72.6, $M^+ - CH_2CF_2P(O)(OEt)_2$/, 149 /23.2, $M^+ - (CH_2)_2CF_2P(O)(OEt)_2$/, 135 (25.5, adenine). Anal. Calcd for $C_{13}H_{20}F_2N_5O_3P$: C, 42.98; H, 5.55; N, 19.28; P, 8.53. Found: C, 43.13; H, 5.55; N, 19.35; P, 8.66.

4-(Adenin-9-yl)-1,1-difluorobutane-1-phosphonic Acid 10b. Trimethylsilyl iodide (0.39 mL, 2.7 mmol) was added dropwise into a stirred solution of diethyl phosphonate **10a** (250 mg, 0.69 mmol) in $CHCl_3$ (25 mL) at -40°C (dry ice - CCl_4 bath). The stirring was continued for 2 h at -40°C and then at room temperature for 30 min. The mixture was evaporated, the residue was stirred in water (20 mL) for 30 min at room temperature and it was kept at 0°C overnight. The precipitated product **10b** was colllected by filtration and it was washed several times with acetone (total 30 mL) to give a white solid (170 mg, 80 %), m.p. 293 - 297°C after recrystallization from water. Mobility on paper electrophoresis at pH 7 relative to adenosine 5'-phosphate 0.83. UV max nm 261nm (ε 15,000), 216 (ε 11,300). IR 3480 - 3100 cm^{-1} (s, NH_2 + OH), 1695, 1645 and 1575 cm^{-1} (s, adenine ring). ^1H NMR ∂ (sodium salt, D_2O) 1.87 (4 H, s, $H_{2'}$ + $H_{3'}$), 3.95 (2 H, s, $H_{1'}$), 7.76 and 7.80 (2 H, 2 s, H_2 and H_8, adenine). ^{19}F NMR -111.58 (dm, $^2J_{F,P} = 85.5$). ^{31}P NMR 5.98 (t, $^2J_{P,F} = 85.9$). FAB-MS m/z (16.1, M^+ + H). Anal. Calcd. for $C_9H_{12}F_2N_5O_3P.1.5\ H_2O$: C, 32.34; H, 4.52; N, 20.95; P, 9.27. Found: C, 32.55; H, 4.39; N, 20.94; P, 9.61.

Hydrogenation of Diethyl 4-(Adenin-9-yl)-4-fluoro-3-buten-1-yne-1-phosphonate 11. Compound **11** (68 mg, 0.2 mmol) was hydrogenated in a Parr apparatus using 10 % Pd/C (13 mg) as catalyst in ethanol (50 mL) at 20 psi for 5 h at room temperature. The catalyst was removed by filtration through a Celite pad. The filtrate was evaporated and the crude product was separated by preparative TLC in CH_2Cl_2 - MeOH (9 : 1) to give a mixture of diethyl 4-(adenin-9-yl)-4-fluoro-3-butane-1-phosphonate **14** and diethyl 4-(adenin-9-yl)-4-fluoro-3-butene-1-phosphonate **13** in the ratio of 1 : 1 (14 mg, ~20 %) as well as diethyl 4-(adenin-9-yl)-butane-1-phosphonate **15** (17 mg, 26 %). Compound **13**: ^1H NMR ∂ 1.15 - 1.30 (6 H, m, CH_3), 2.26 - 2.36 (2 H, m, $H_{4'}$), 2.57 (2 H, sx, $H_{3'}$, $^3J_{3',2'} = 7.7$), 3.95 - 4.14 (4 H, m, OCH_2), 5.73 (1 H, dt, $H_{2'}$, $^3J_{2',F} = 32.2$, $^3J_{2',3'} = 7.7$), 5.90 (2 H, s, NH_2), 7.93 or 7.96 and 8.31 or 8.34 (2 H, 2 s, H_2 and H_8, adenine). ^{19}F NMR -103.23 (d, $^3J_{F,H-2'} = 32.2$). ^{31}P NMR ∂ 32.83 (s) or 33.26 (s). Compound **14**: ^1H NMR ∂ 1.15-1.30 (6 H, m, CH_3), 1.65-2.16 (6 H, m, $H_{3'}$ + $H_{4'}$), 3.95-4.14 (4 H, m, OCH_2), 5.90 (2 H, s, NH_2), 6.51 (1 H, dt, $H_{2'}$, $^2J_{1',F} = 49.2$, $^3J_{2',F} = 7.5$), 7.93 or 7.96 and 8.31 or 7.94 (2 H, 2s, H_2 and H_8). ^{19}F NMR -138.07 (ddd, $^2J_{F,H-1'} = 49.3$, $^3J = 24.6$, $^3J = 10.4$). ^{31}P NMR 32.83 (s) or 33.26 (s). Compound **15**: m.p. 127-129°C after recrystallization from CCl_4. UV max nm 261 (ε 12,700), 210 (ε 17,200). IR 3330 and 3140 cm^{-1} (s, NH_2), 1665, 1605 and 1580 cm^{-1} (s, adenine ring). ^1H NMR ∂ 1.29 (6 H, t, CH_3), 1.60 - 1.83 (4 H, m, $H_{2'}$ + $H_{3'}$), 2.01 (2 H, qt, $H_{4'}$, $^3J = 7.1$), 4.06 (4 H, m, OCH_2), 4.21 (2 H, t, $H_{1'}$, $^3J = 7.1$), 5.95 (2 H, s, NH_2), 7.80 and 8.35 (2 H, 2 s, H_2 and H_8, adenine). ^{31}P NMR 31.34 (s).

EI-MS m/z 327 (20.9, M^+), 190 /56.7, M^+ - P(O)(OEt)2/, 162 /63.9, M^+ - $(CH_2)_2P(O)(OEt)_2$/, 149 /26.2, M^+ - $(CH_2)_3P(O)(OEt)_2$/, 135 (18.4, adenine), 121 (10.9), 119 (98.5), 117 (100.0). HRMS calcd. for $C_{13}H_{22}N_5O_3P$ M^+ 327.1460. Found M^+ 327.1454. Anal. Calcd. for $C_{13}H_{22}N_5O_3P$: 47.70; H, 6.77; N, 21.40. Found: C, 47.46; H, 6.57; N, 21.16.

Acknowledgments. Thanks are due to the Central Instrumentation Facility, Department of Chemistry, Wayne State University (Dr. R. J. Hood, Director) and, particularly, to Drs. M. B. Ksebati and M. B. Kempff for NMR and mass spectra. The work described herein was supported in part by grant CA32779 from the National Cancer Institute, Bethesda, Maryland, U. S. A. and in part by an institutional grant to the Barbara Ann Karmanos Cancer Institute from the United Way of Southeastern Michigan.

REFERENCES AND NOTES

1. Present address: MediChem Research, Inc., Lemont, Illinois, U. S. A.
2. For a useful compilation of pertinent literature see: Berkowitz, D. B.; Sloss, D. G. *J. Org. Chem.* **1995**, 60, 7047.
3. Bergstrom, D. E.; Shum, P. W. *J. Org. Chem.* **1988**, 53, 3953.
4. Matulic-Adamic, J.; Usman, N. *Tetrahedron Lett.* **1994**, 35, 3227.
5. Halazy, S.; Ehrhard, A.; Danzin, C. *J. Am. Chem. Soc.* **1991**, 113, 315.
6. Megati, S.; Phadtare, S.; Zemlicka, J. *J. Org. Chem.* **1992**, 57, 2320.
7. Harnden, M. R.; Parkin, A.; Parratt, M. J.; Perkins, R. M. *J. Med. Chem.* **1993**, 36, 1343.
8. Shirokova, E. A.; Tarussova, N. B.; Shipitsin, A. V.; Semizarov, D. G.; Krayevsky, A. A. *J. Med. Chem.* **1994**, 37, 3739.
9. Casara, P. J.; Altenburger, J.-M.; Taylor, D. L.; Tyms, A. S.; Kenny, M.; Nave, J. F. *Bioorg. Med. Chem. Lett.* **1995**, 5, 1275.
10. D. J. Burton, D. J.; Sprague, L. G. *J. Org. Chem.* **1989**, 54, 613.
11. Padwa, A.; Austin, D. J.; Ishida, M.; Muller, C. L.; Murphree, S. S.; Yeske, P. E. *J. Org. Chem.* **1992**, 57, 1161.
12. Xu, Z.-Q.; Qiu, Y.-L.; Chokekijchai, S.; Mitsuya, H.; Zemlicka, J. *J. Med. Chem.* **1995**, 38, 875 and references 25 - 28 cited therein.

(*Received in USA* 6 *January* 1997; *revised* 18 *February* 1997; *accepted* 20 *February* 1997)