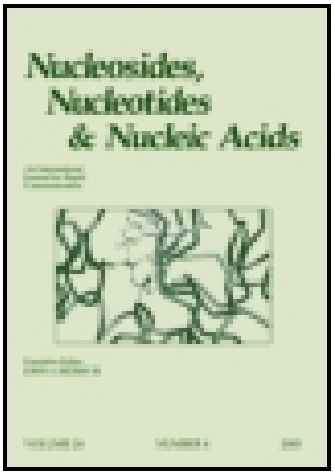


Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lncn20

A Convenient Synthesis of 2′-Deoxy-2-fluoroadenosine; a Potential Prodrug for Suicide Gene Therapy

Abdalla E. A. Hassan [a] , Anita T. Shortnacy-fowler [a] , John A. Montgomery [a] & John A. Secrist III [a]

[a] Drug Discovery Division, Southern Research Institute , P.O. Box 55305, Birmingham, AL, 35255-5305, U. S. A.

Published online: 24 Sep 2006.

To cite this article: Abdalla E. A. Hassan , Anita T. Shortnacy-fowler , John A. Montgomery & John A. Secrist III (2000) A Convenient Synthesis of 2′-Deoxy-2-fluoroadenosine; a Potential Prodrug for Suicide Gene Therapy, Nucleosides, Nucleotides and Nucleic Acids, 19:3, 559-565, DOI: 10.1080/15257770008035007

To link to this article: http://dx.doi.org/10.1080/15257770008035007

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS, 19(3), 559–565 (2000)

A Convenient Synthesis of 2′-Deoxy-2-fluoroadenosine; a Potential Prodrug for Suicide Gene Therapy

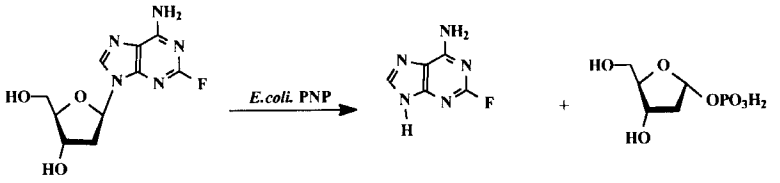
Abdalla E. A. Hassan, Anita T. Shortnacy-Fowler, John A. Montgomery, and John A. Secrist III*

Drug Discovery Division, Southern Research Institute, P.O. Box 55305, Birmingham, AL, U.S.A. 35255-5305

Abstract: A convenient synthesis of 2′-deoxy-2-fluoro-adenosine (**1**) is described. Deaminative fluorination of 2-aminoadenosine (**2**) followed by silylation of the 3′, 5′-hydroxyl groups gave the corresponding 2-fluoroadenosine derivative **4** in good yield. Thiocarbonylation of **4** to thiocarbonylimidazolyl derivative **5a** followed by treatment with an excess of tris(trimethylsilyl)silane (TTMSS) and *tert*-butyl peroxide in toluene at 80 °C was found to affect an efficient deoxygenation to the corresponding 2′-deoxy derivative **6**. Desilylation of **6** by Et_4NF in CH_3CN afforded **1** in high yield.

Suicide gene therapy is a novel approach among those explored for selectively killing tumor cells without harming normal cells.[1] We have developed a strategy that is based on the selective expression of *Escherichia coli* purine nucleoside phosphorylase (*E. coli* PNP) in tumor cells, making them sensitive to otherwise nontoxic agents.[2] *E. coli* PNP, unlike mammalian PNP, accepts not only 6-oxopurine analogs, but also 6-aminopurine (adenine) analogs as substrates, and hence can be used to selectively cleave certain nontoxic purine nucleosides to very toxic purines or purine analogs. For example, 2′-deoxy-2-fluoroadenosine (dFAdo, **1**)[3] is cleaved efficiently by (*E. coli* PNP) to the toxic agent 2-fluoroadenine (FAde)[4] and has demonstrated excellent *in vivo* activity against tumors expressing *E. coli* PNP[2c] (Figure. 1). FAde inhibits protein, DNA, and RNA syntheses.[4] Consequently, dFAdo is a promising prodrug for cancer gene therapy.

Methods available for the synthesis of dFAdo **1**, however, are rather low yielding[3] or non-reproducible[5]. Herein, we report a synthetic method for dFAdo (**1**) based on deoxygenation of the 2′-hydroxyl group of the readily available ribonucleoside derivative **4**.[6] Deaminative fluorination of 2-aminoadenosine (**2**) by reaction with potassium nitrite in the presence of HF/pyridine[7] proceeded in higher yield than the corresponding Schiemann reaction of **2**.[3] The 3′- and 5′-hydroxyl groups of **3** were protected by 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl (TIPDS) group to give the corresponding nucleoside **4** in good yield. Deoxygenation[8] of the 2′-hydroxyl group of **4** was explored under various conditions to optimize the yield of the 2′-



dFAdo, 1 FAde

Figure 1

deoxynucleoside **6** (Scheme 1). First, conversion of the 2′-hydroxyl to its thiocarbonylimidazolyl derivative was accomplished by treatment of **4** with thiocarbonyldiimidazole in the presence of a catalytic amount of DMAP in refluxing 1,2-dichloroethane, giving **5a** in high yield.

The toxicity associated with organotin compounds as well as the difficulty for their complete elimination from the reaction products suggested the use of organosilanes as radical based reducing agents[9]. Deoxygenation of **5a** in neat Et_3SiH in the presence of dibenzoylperoxide (DBP)[8b] gave the 2′-deoxynucleoside **6**[10] in 39% yield, while performing the reaction in toluene at 110 °C raised the yield of **6** to 60%. Scaling up this deoxygenation reaction under the latter conditions, however, required a longer reaction time (6 h), and a substantial amount of the hydrolyzed byproduct **4** was obtained (**6**:**4**, 2:1).

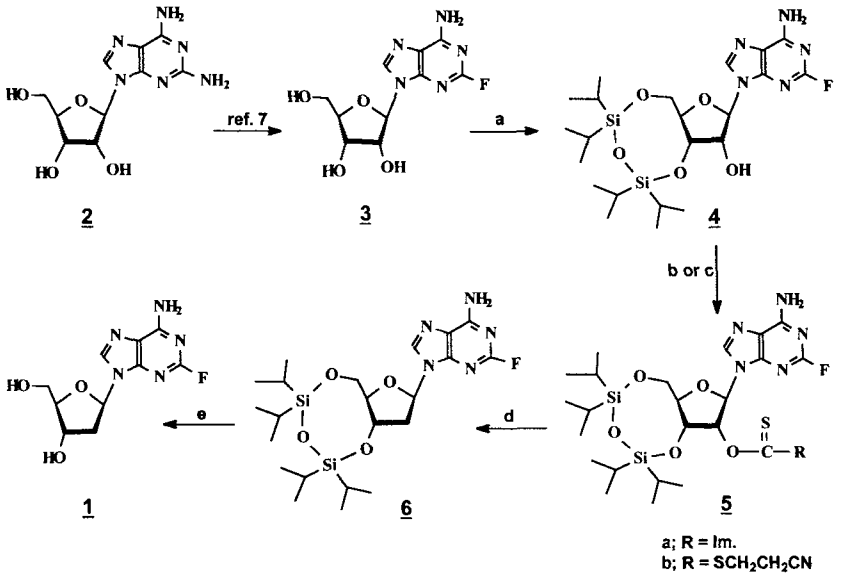
The low yield and the non-reproducibility observed under the above reduction conditions were probably caused by: 1) the lability of 2-fluoroadenosine derivatives **5a** and **6** to prolonged heat treatment, resulting in partial decomposition of **5a** and/or **6**; and 2) the hydrolysis of the thiocarbonylimidazolyl derivative **5a** back to **4**, partly due to the liberation of imidazole as an imidazolyl derivative in the reaction mixture.

We have examined means to minimize both of these potential problems. In an attempt to circumvent the latter effect, the cyanoethylxanthate derivative **5b** was synthesized as a precursor for the reduction step. Treatment of **4** with CS_2 and NaOH in DMSO[11a] followed by addition of 3-bromopropionitrile gave **5b**, however, only in 17% yield. To avoid prolonged heat treatment in the deoxygenation step, triethylborane (Et_3B) was used as a radical initiator in combination with tris(trimethylsilyl)silane (TTMSS) as a hydride radical donor.

Treatment of **5b** with (TTMSS/Et_3B, Table 1, entry 1) in dry benzene at room temperature for 48 h gave the deoxygenated derivative **6** in 72% yield. Attempts to improve the yield of **5b** or to synthesize of the corresponding 2-methylxanthate derivative under various conditions were unsuccessful due in part to its instability and the lability of the fluorine group at the 2-position to basic conditions.[11b] It is worth noting that application of the above deoxygenation condition on the thiocarbonylimidazolyl derivative **5a** gave **6** and **4** in a ratio of (4:1) in 78 % yield (Table 1, entry 2). Additionally, we found that deoxygenation of **5a** with Et_3B and oxygen in benzene in the presence of either diphenylsilane or TTMSS did not afford **6**.

We reasoned that the more the powerful the hydrogen donor used, the more rapid the radical chain reaction, and the lesser the reaction time, the less hydrolyzed byproduct **4** would be expected. To verify this hypothesis, we examined the deoxygenation of **5a** under different

Scheme 1[a]



[a]**Reagents and Conditions**: a) TIPDSCl$_2$, Im., DMF, r.t., 4h 52%; b) ImC(S)Im, DMAP, ClCH$_2$CH$_2$Cl, reflux, 2h, 81%; c) CS$_2$, 10 M NaOH, DMSO, 3-bromopropionitrile, 17%; d) TTMSS, Bu^{t}OOBu^t, toluene, 80 °C, 30 min, 84%; e) Et$_4$NF•xH$_2$O, CH$_3$CN, 98%.

Table 1 Deoxygenation of 5a and 5b[a,b]

Entry	Substrate	Hydrogen donor	Radical Initiator	Temp./time	yield %	Ratio 6:4[c]
1	5b	TTMSS (1.7 eq.)	Et_3B	r.t., 48 h	72	32 : 1
2	5a	TTMSS (1.7 eq.)	Et_3B	r.t., 48 h	78	4 : 1
3	5a	TTMSS (4 eq.)	Bu^{t}OOBu^t	80 °C, 30 min	75	31 : 1
4	5a	TTMSS (10 eq.)	Bu^{t}OOBu^t	80 °C, 30 min	84	33 : 1
5	5a	TTMSS (20 eq.)	Bu^{t}OOBu^t	80 °C, 5 min	96	39 : 1
6	5a	Ph_2SiH_2 (20 eq.)	Bu^{t}OOBu^t	80 °C, > 8h	SM[d]	----

a) all reactions were performed on 0.13 mmol scale. b) All reactions were performed in dry toluene except for entries 1 and 2, which were performed in dry benzene. c) Ratios of **6** and **4** were determined by HPLC area percent after flash silica gel chromatography. d) Traces of **6** and **4** along with the starting material and decomposition by-products were isolated.

conditions. The use of TTMSS proved to be superior to Et_3SiH in terms of the reaction time (30 min. *vs.* 2 h) and the yield of the deoxygenated product **6** (75% *vs.* 60%), while Ph_2SiH_2[8c] was ineffective as a hydride radical donor under these conditions. Moreover, the molar equivalent of TTMSS showed a positive correlation with the reaction time, yield, and the distribution ratio of **6** and **4**. This implies that the excess of TTMSS besides increasing the rate of deoxygenation step,

blocks the hydrolysis process of **5a** back to **4**. Finally, desilylation of **6** was performed by $Et_4NF{\bullet}xH_2O$ in CH_3CN at room temperature to afford 2′-deoxy-2-fluoroadenosine (**1**) in excellent yield.

In conclusion, we have developed an efficient method for thiocarbonylation and deoxygenation of the 2′-hydroxyl group of the base and heat labile nucleoside **4** under mild conditions and utilized it for the synthesis of the potential prodrug for gene therapy, 2′-deoxy-2-fluoroadenosine (**1**).

EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Nicolet NT 300NB spectrometer operating at 300.635 MHz (^1H) or 75.6 MHz (^{13}C). Chemical shifts were expresses in parts per million from tetramethylsilane. The hydrogen-decoupled ^{13}C NMR were assigned by comparison of the J_{CH} values obtained from hydrogen-coupled ^{13}C NMR spectra, and when necessary, selective hydrogen decoupling was performed in order to confirm the assignments. The NOE experiments were conducted in degasses solution of $CDCl_3$. To minimize the effects of magnetic perturbations with the sample nonspinning, eight FID's were recorded with the decoupler set to a desired frequency and eight FID's were recorded with the decoupler off-resonance. Ultraviolet absorption spectra were determined on Perkin-Elmer Lambda 9 spectrometer by dissolving each compound in methanol or water and diluting 10-fold with 0.1 *N* HCl, pH 7 buffer, and 0.1 *N* NaOH. Mass spectra were recorded on a Varian/MAT 311A double-focusing mass spectrometer in the fast atom bombardment (FAB) mode (glycerol matrix). HPLC analysis were carried out on a Hewlett-Packard 1100 series liquid chromatograph with a Phenomenex Sphenclone 5 μ ODS (1) column (4.6 mm x 25 cm) with UV monitoring (254 nm). All flash column chromatography used 230-400 mesh silica gel from E. Merck. TLC was done on Analtech precoated (250 μm) silica gel (GF) plates.

2-Fluoro-2′-*O*-[(1-imidazolyl)thiocarbonyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (5a). A mixture of **4** (3.73 g, 7.06 mmol), 1,1′-thiocarbonyldiimidazole (2.1 g, 10.59 mmol) and DMAP (0.43 g, 3.35 mmol) in $ClCH_2CH_2Cl$ (90 mL) was heated under reflux for 2 h, by which time the starting material was completely consumed (TLC). The solvent was removed *in vacuo* and the residue was purified by flash silica gel column chromatography. Elution of the column by 2% MeOH in CH_2Cl_2 afforded 3.6 g. (81%) of **5a** as a white solid: mp 135-137 °C; MS *m/z* 638 $(M+1)^+$, 510 $(M+H\text{-}HOC(S)Im)^+$, 485 $(M+H\text{-}2FAde)^+$, UV λ_{max} (pH 1) 262, λ_{max} (pH 7) 273, λ_{max} (pH 13) 263; ^1H NMR ($CDCl_3$) δ 8.39 (1H, t, Im, J = 0.9 Hz), 7.87 (1H, s, H-8), 7.67 (1H, br t, Im), 7.09 (1H, dd, Im, J = 0.9, J = 1.8 Hz), 6.37 (1H, dd, H-2′, J = 0.9, J = 5.3 Hz), 6.07 (1H, d, H-1′, J = 0.9 Hz), 5.87 (2H, br s, 6-NH_2), 5.41 (1H, dd, H-3′, J = 5.7, J = 8.8 Hz), 4.20-4.05 (3H, m, H-4′, H-5′a, and H-5′b), 1.18-0.96 (28H, m, *i*Pr).

2-Fluoro-2′-*O*-[(cyanoethylthio)thiocarbonyl]-3′,5′-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (5b). A mixture of **4** (380 mg, 0.72 mmol) and carbon disulfide (0.34 mL, 5.65 mmol) in DMSO (5mL) was treated with 10 M NaOH (0.2 mL, 2 mmol). The reaction mixture was stirred at room temperature for 30 min then treated with 3-bromopropionitrile (0.2 mL, 2.4

mmol) and stirring was continued for further 18 h. The solvent was evaporated *in vacuo* and the residue was dissolved in EtOAc and washed with water and brine. The organic phase was dried ($MgSO_4$) and evaporated. The residual yellow oil was purified by flash silica gel column chromatography (5% MeOH in CH_2Cl_2) and preparative TLC (eluate, 5% MeOH in CH_2Cl_2) to give (80 mg, 17%) as a white solid after crystallization from 2-propanol: mp 201-203°C; MS *m/z* 663 $(M+Li)^+$, 510 $(M+H-HOC(S)SCH_2CH_2CN)^+$, 504 $(M+H-2FAde)^+$, UV λ_{max} (MeOH) 270, 263; ^1H NMR ($CDCl_3$) δ 7.87 (1H, s, H-8), 6.52 (1H, dd, H-2', $J_{1',2'}$ = 0.9, $J_{2',3'}$ = 5.5 Hz), 6.01 (1H, d, H-1', $J_{1',2'}$ = 1 Hz), 5.78 (2H, br s, 6-NH_2), 5.27 (1H, dd, H-3', $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 8.8 Hz), 4.17-4.02 (3H, m, H-4' and H-5'a, b), 3.41 (2H, m, SCH_2CH_2CN), 2.87 (2H, t, SCH_2CH_2CN, J = 6.8 Hz), 1.26-0.96 (28H, m, *i*Pr). Anal. Calcd for $C_{26}H_{41}FN_6O_5S_2Si_2$: C, 47.54; H, 6.29; N, 12.79. Found: C, 47.28; H, 6.36; N, 12.86.

2'-Deoxy-2-fluoro-3',5'-*O*-(tetraisopropyldisiloxane-1,3-diyl)adenosine (6).

Deoxygenation of 5a using (TTMSS, Bu^{t}OOBu^t): A solution of *tert*-butyl peroxide (0.7 mL, 1.4 mmol) in dioxane (10 mL) was added dropwise to a preheated mixture of **5a** (2.0 g, 3.91 mmol) and TTMSS (12.1 mL, 39.1 mmol) in 30 mL toluene at 80 °C. After being stirred for 15 min, TLC showed that the starting material was completely consumed. The mixture was cooled down to room temperature and the solvent was evaporated in *vacuo*. The residue was purified by a flash silica gel column, elution of the column by 2% EtOH in $CHCl_3$ affording (1.67 g, 84%) of **6** as a white solid: mp (>187 °C dec.); MS *m/z* 512.1 $(M+1)^+$, UV λ_{max} (pH 1) 262; (pH 7) 261, λ_{max} (pH 13) 261; ^1H NMR ($CDCl_3$) δ 7.98 (1H, s, H-8), 6.20 (1H, dd, H-1', J = 2.9, J = 6.9 Hz), 5.28 (2H, br s, 6 NH_2), 4.91 (1H, ddd, H-3', J = 8.9, J = 7.6, J = 1.3 Hz), 4.09-3.99 (2H, m, 5'a and 5'b), 3.87 (1H, m, H-4'), 2.72-2.56 (2H, m, H-2'a and H-2'b), 1.12-1.03 (28H, m, *i*-Pr); ^{13}C NMR ($CDCl_3$) δ 159 (d, C2, $^1J_{F2,C2}$ = 211 Hz), 157 (d, C6, $^3J_{F2,C6}$ = 20 Hz), 150.4 (d, C4, $^3J_{F2,C4}$ = 19 Hz), 139.3 (d, C8, $^5J_{F2,C8}$ = 2.8 Hz), 118.5 (d, C5, $^4J_{F2,C5}$ = 3.9 Hz), 85.3 (C4'), 83.3 (C1'), 69.8 (C3'), 61.8 (C5'), 40.0 (C2'), 17.5-16.8 (8s, *i*-Pr-methyl), 13.4-12.6 (4s, *i*Pr-methyl), NOE: irradiate (H-1'), observe H-2'a (5 %), H-4' (2 %); irradiate H-3', observe H-8 (2 %), H-2'b (4 %); irradiate H-4', observe H-1' (2 %), H-5' (2 %); irradiate H-8, observe H-3' (3 %).

Deoxygenation of 5a using (Et_3SiH, BzOOBz): To a solution of **5a** (82 mg, 0.13 mmol) in dry toluene (2 mL) was added Et_3SiH (1 mL, 6.26 mmol) and the mixture was heated at 110 °C. Solid benzoyl peroxide (15 mg, 22 μmol) was added in one portion and the mixture was stirred for 30 min. Another portion of benzoyl peroxide was added and stirring was continued for 1.5 h. The reaction mixture was cooled down to room temp. and the solvent was evaporated *in vacuo*. The residue was purified by flash silica gel column (1% EtOH/$CHCl_3$) to give (41 mg, 60%) of **6** as a white solid; HPLC 98.4%.

Deoxygenation of 5b using (TTMSS, Et_3B): To a mixture of **5b** (50 mg, 76.2 μmol), and triethylborane (1 M in hexanes, 115 μL), in dry benzene (2 mL), TTMSS (40 μL, 130 μmol) was added dropwise at room temperature and the reaction mixture was stirred under nitrogen atmosphere for 48 h. The solvent was evaporated and the residue was purified by flash silica gel column (1% EtOH/$CHCl_3$) to give (28 mg, 72%) of **6** as a white solid: HPLC 97%.

Deoxygenation of 5a using (TTMSS, Et_3B): To a mixture of **5a** (82 mg, 0.13 mmol), and triethylborane (1 M in hexanes, 0.2 mL) in dry benzene (3 mL), TTMSS (70 μL, 0.25 mmol) was added dropwise at room temperature and the reaction mixture was stirred under nitrogen atmosphere for 48 h. The solvent was evaporated and the residue was purified on a flash silica gel column (1% EtOH/$CHCl_3$) to give 53 mg (78%), of **6** and **4** as a white solid: HPLC (**6**:**4**, 4:1).

2′-Deoxy-2-fluoroadenosine (1). To a solution of **5** (1 g, 1.9 mmol) in CH_3CN (30 mL) at room temperature was added $Et_4NF•xH_2O$ (603 mg, 4.22 mmol) in one portion. The reaction mixture was stirred for 30 min, a white solid was collected and washed with cold CH_3CN. After crystallization from hot EtOH and drying over night under vacuum at room temperature, (0.51 g, 98 %) of **1** was obtained as a white solid: mp (>210 °C indefinite), MS *m/z* 270 $(M+1)^+$, UV λ_{max} (pH 1) 262, λ_{max} (pH 7) 261, λ_{max} (pH 13) 261; ^1H NMR (DMSO-d_6) δ 8.31 (1H, s, H-8), 7.85 (2H, br s, 6-NH_2), 6.22 (1H, dd, H-1′, J = 7.0, J = 6.6 Hz), 5.31 (1H, d, 3′-OH, J = 4.2 Hz), 4.95 (1H, t, 5′-OH, J = 5.5 Hz), 4.95 (1H, m, H-3′), 3.85 (1H, m, H-4′), 3.62-3.47 (2H, m, H-5′a,b), 2.66 (1H, ddd, H-2′a, J = 3.3 Hz, J = 6.2 Hz, J = 9.5 Hz); Anal. Calcd. for $C_{10}H_{12}O_3N_4F$: C, 44.61; H, 4.49; N, 24.01. Found: C, 44.74; H, 4.82; N 24.06.

Acknowledgments. This investigation was supported by a National Cooperative Drug Discovery Grant (U19CA67763) from the National Cancer Institute. We Thank Dr. J. M. Riordan, Mr. M. D. Richardson, and Mrs. J. C. Bearden of the Molecular Spectroscopy Section of Southern Research Institute for analytical and spectral data and Mrs. S. Campbell for HPLC analyses.

REFERENCES

1. For reviews on this topic see: a) Moolten, F. L. *Cancer Gene Ther.*, **1994**, *4*, 279-287. b) Kramm, C. M.; Sena-Esteves, M.; Barnett, F. H.; Rainov, N. G.; Schuback, D. E.; Yu, J.S.; Pechan, P. A.; Paulus, W.; Chiocca, E. A.; Breakefield, X. O. *Brain Pathol.*, **1995**, *5*, 345-381. c) Anderson, W. F. *Science*, **1992**, *256*, 808-813. d) Miller, A. D. *Nature*, **1992**, *357*, 455-460.
2. a) Sorscher, E. J.; Peng, S.; Bebok, Z.; Allan, P. W.; Bennett, L. L., Jr.; Parker, W. B. *Gene Ther.*, **1994**, *1*, 233-238. b) Parker, W. B.; King, S. A.; Allan, P. W.; Bennett, L. L., Jr.; Secrist, J. A., III; Montgomery, J. A.; Gilbert, K. S.; Waud, W. R.; Wells, A. H.; Gillespie, G. Y.; Sorscher, E. J. *Hum. Gene Ther.*, **1997**, *8*, 1637-1644. c) Waud, W. R.; Gilbert, K. G.; Parker, W. B.; Secrist, J. A., III; Montgomery, J. A.; Bennett, L. L., Jr.; Sorscher, E. J. *Proc. Amer. Assoc. Cancer Res.*, **1998**, *39*, 512.
3. Montgomery, J. A.; Hewson, K. *J. Med. Chem.*, **1969**, *12*, 498-504.
4. Parker, W. B.; Allan, P. W.; Shaddix, S. C.; Rose, L. M.; Speegle, H. F.; Gillespie, G. Y.; Bennett, L. L., Jr. *Biochem. Pharmacol.*, **1998**, *55*, 1673-1681.
5. Huang, M.-C.; Hatfield, K.; Roetker, A. W.; Montgomery, J.A.;. Blakley, R. L. *Biochem. Pharmacol.*, **1981**, *30*, 2663-2671.
6. Secrist, J. A., III; Shortnacy, A. T.; Montgomery, J. A. *J. Med. Chem.*, **1988**, *31*, 405-410.

7. a) Krolikiewicz, K.; Vorbruggen, H. *Nucleosides Nucleotides,* **1994**, *13*, 673-678. b) Olah, G. A., Welch, J. T., Vankar, Y. D., Nojima, M., Kerekes, I., Olah, J. A. *J. Org. Chem.* **1979**, *44,* 3872-3881.
8. a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc. Chem. Perkin Trans. 1,* **1975**, 1574-1585. b) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.*, **1991**, *32*, 7187-7190. c) Barton, D. H. R.; Jang, D. O.; Jaszberenyi, J. C. *Tetrahedron Lett.*, **1992**, *33*, 6629-6632.
9. Chatgilialoglu, C. *Acc. Chem. Res.*, **1992**, *25*, 188-194.
10. The structure of **6** was assigned on the basis of the following: a) The ^{1}H NMR spectra showed the presence of two protons resonating at 2.72-2.56 corresponding to H-2'$_{a,b}$; b) The signal of the H-1' proton appeared as a doublet of doublets, confirming the 2'-deoxy derivative, which was further confirmed by NOE experiments; c) The large $^{1}J_{CF}$ and the long range $^{2}J_{CF}$, $^{3}J_{CF}$, $^{4}J_{CF}$, $^{5}J_{CF}$ observed in ^{13}C-NMR spectra.
11. a) Chen, Y.; Bauman, J. G.; Chu, C. K. *Nucleosides Nucleotides,* **1992**, *11*, 693-705, and references cited therein. b) Sakata, S.; Yonei, S.; Yoshino, H. *Chem. Pharm. Bull.*, **1982**, *30*, 2583-2585.

Received 10/11/99
Accepted 10/11/99