# Synthesis and Antiviral Activities of 8-Alkynyl-, 8-Alkenyl-, and 8-Alkyl-2′-deoxyadenosine Analogues

Gyula Sági,*,† László Ötvös,† Satoru Ikeda,‡ Graciela Andrei,‡ Robert Snoeck,‡ and Erik De Clercq‡

*Central Research Institute for Chemistry of the Hungarian Academy of Sciences, H-1525 Budapest, P.O. Box 17, Hungary, and the Rega Institute for Medical Research, Katholieke Universiteit Leuven, B-3000 Leuven, Belgium*

*Received November 29, 1993*•

Palladium-catalyzed cross-coupling of 8-bromo-2′-deoxyadenosine with terminal alkynes in the presence of copper(I) iodide in dimethylformamide resulted in a series of 8-(1-alkyn-1-yl)-2′-deoxyadenosines. Hydrogenation of alkynyl derivatives over 10% Pd/C under atmospheric pressure gave 8-*n*-alkyl analogues in nearly quantitative yields. On partial saturation of heptynyl, pentynyl, and propynyl derivatives over Lindlar catalyst, the corresponding *cis*-olefins were obtained along with minor amounts of trans isomers. Of the analogues tested, the following showed some activity, i.e. they were found to be active at concentrations that were at least 3-fold lower than the cytotoxic concentrations: the 8-heptynyl derivative against vaccinia virus (VV), vesicular stomatitis virus (VSV), cytomegalovirus (CMV), and respiratory syncytial virus (RSV); the 8-propyl derivative against varicella-zoster virus (VZV) and CMV; the 8-pentyl derivative against CMV; the 8-heptyl derivative against VV, CMV, RSV, and influenza A; and the 8-heptenyl derivative against VV, RSV, and influenza A. The unsubstituted 2′-deoxyadenosine did not show any antiviral effect, except against RSV. Except for 8-propyl-dA, the antivirally active dA analogues were rather inhibitory to the growth of human embryonic lung cells. The most cytotoxic was the 8-ethynyl derivative.

## Introduction

Numerous base-modified analogues of 2′-deoxyuridine bearing alkyl, alkenyl, or alkynyl substituents at the C-5[1] and C-6[2] positions were synthesized and tested in the last 2 decades. Several members of this series exhibit really significant antiviral or antitumor activity. For example, (*E*)-5-(2-bromovinyl)-2′-deoxyuridine (BVDU) is known as one of the most potent antiherpetic agents,[3] while the 5-isopropyl derivative was also found to be effective against HSV-1 and HSV-2.[4] In the alkynyl series, 5-ethynyl-dU proved to be the most potent, but due to its lack of selectivity it cannot be used as an antiviral agent.[5]

Among the purine nucleosides having C-substituents at C-2, C-6, or C-8 position, a systematic structure–activity study has so far not been done yet. Recently, Matsuda *et al.* have investigated the adenosine receptor binding activities of many 2-alkynyladenosines.[6] They found that 2-(1-hexyn-1-yl)- and 2-(1-octyn-1-yl)adenosine had potent and long-lasting antihypertensive activity.[7] In addition, these derivatives were completely resistant to adenosine deaminase,[6] which is the primary catabolic enzyme for adenine nucleosides and nucleotides. The C-6 and C-8-octynyl analogues were also prepared, but they did not show any antihypertensive activity.[7]

Further C-6 and C-8 alkynyl derivatives of nebularine and adenosine were also synthesized by palladium-catalyzed couplings of terminal alkynes with acetylated ribofuranosides of 6-chloropurine and 8-bromoadenine, respectively; however, no biological data have been reported for these compounds.[8] Several 8-alkyladenosines have also been prepared with different methods: e.g., by palladium-catalyzed coupling of 8-bromoadenosine with Grignard reagents,[9] by condensation of protected 8-lithio-6-chloropurine ribofuranoside with alkyl halogenides,[10] and by a multistep synthesis[11] in which 8-[(ethoxycarbonyl)methyl]adenosine was the key intermediate.

Due to low overall yields, none of these procedures seems suitable for the economical preparation of 8-alkylpurine nucleosides. Recently, a few versatile syntheses of some 8-alkyl- and alkenylpurine nucleosides were reported. The common feature of these strategies is the application of metal–organic reagents as alkyl donors: e.g., tetraalkyltins,[12] tributylalkyltins,[13] and trialkylaluminums.[14] These methods, contrary to the earlier ones, were successfully used for the 8-alkylation of ribo-, 2′-deoxyribo-, and 2′,3′-dideoxyribopurine nucleosides, irrespective of the number of hydroxy groups in the sugar moiety. This is of special importance considering the well-known antiretroviral effects of 2′,3′-dideoxynucleosides.[15]

However, these approaches have certain limitations. Metal–organic reagents of such type with long (more than four C-atoms) alkyl or alkenyl groups are not commercially available. The necessary high reaction temperature results in partial decomposition of the more sensitive products,[12] isomerization of the double bond,[12] and partial dehalogenation of the starting materials.[12,13]

Since the effect of C-8 substitution on the antiviral activity was studied only in the case of acyclovir analogues,[16] we were interested in developing an economical synthesis of several 8-alkynyl-, alkenyl-, and alkyl-2′-deoxyadenosines for their antiviral evaluation.

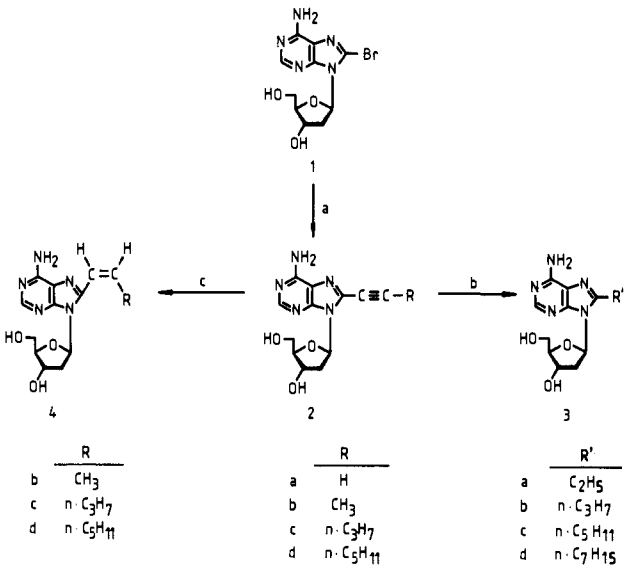
## Results and Discussion

**Chemistry.** Palladium-catalyzed cross-coupling of iodo nucleosides with terminal alkynes is a well-known method for the synthesis of different alkynyl derivatives of pyrimidine and purine nucleosides. In most of these couplings sugar hydroxy groups were protected by acylation and triethylamine was used as the solvent.[1,8] Recently, Hobbs[17] and Robins *et al.*[18] achieved some successful alkynylations in DMF, which eliminated the undesirable secondary intramolecular cyclizations. Al-

† Hungarian Academy of Sciences.
‡ Rega Institute for Medical Research.
• Abstract published in *Advance ACS Abstracts*, April 1, 1994.

0022-2623/94/1837-1307$04.50/0 

**Scheme 1**[a]




[a] (a) (i) HC≡CR (R = $SiMe_3$, $CH_3$, $n$-$C_3H_7$, $n$-$C_5H_{11}$) $(Ph_3P)_2PdCl_2$, CuI, $NEt_3$, DMF, 20 °C, 2–6 h, (ii) Amberlite IRA-400 [$HCO_3^-$], MeOH, $CHCl_3$, (iii) if R = $SiMe_3$, 5% $NH_3$/MeOH–$H_2O$, 20 °C, 45 min, (iv) DCFC; (b) $H_2$/10% Pd/C, EtOH (if R′ = $C_5H_{11}$ or $C_7H_{15}$) MeOH–$H_2O$ (if R′ = $C_2H_5$ or $C_3H_7$); 1 atm, 20 °C, 1–14 h; (c) (i) $H_2$/Lindlar catalyst, MeOH + 2% quinoline (if R = $C_3H_7$ or $C_5H_{11}$), MeOH/$H_2O$ + 2% quinoline (if R = $CH_3$), 1 atm, 20 °C, 2.5–4 h, (ii) DCFC.

though in our case the formation of such byproducts was excluded, application of this solvent seemed to be a good choice, since all components were highly soluble in DMF.

We chose 8-bromo-dA (1) as a starting material which can readily be prepared by direct bromination of dA in ca. 70% yield.[19] Coupling of 1 with four terminal alkynes in DMF in the presence of 0.1 equiv of $(Ph_3P)_2PdCl_2$, 0.2 equiv of CuI, and 2.0 equiv of $Et_3N$ afforded the corresponding 8-(1-alkyn-1-yl)-dA analogues in 55–85% overall yields (Scheme 1).

Working with the unprotected nucleosides, the synthetic route proved to be advantageous especially in the case of the heptynyl (**2d**) and pentynyl (**2c**) derivatives. These analogues have better solubility in $CHCl_3$ and poorer solubility in water with increasing length of the alkyl chain; thus the majority of copper and triethylammonium salts could be removed from the organic phase by extraction with 5% $Na_2EDTA/H_2O$ solution. According to our earlier experiments, similar aqueous workup of **2a** and **2b** led to a significant loss of products. Therefore, in all cases triethylammonium bromide was first converted to its hydrogen carbonate salt, which decomposed on evaporation in vacuo, at 45 °C. The remaining metal impurities were removed by two chromatographies on a short, dry silica gel column.[20] Desilylation of the 8-[(trimethylsilyl)-ethynyl] intermediate proceeded smoothly in 5% $NH_3$/aqueous MeOH solution to give **2a** in ca. 80% yield after chromatography.

Complete saturation of the triple bonds over 10% Pd/C at atmospheric $H_2$ pressure took place in 1 and 1.5 h for **2a** and **2b**, respectively. At the same time, hydrogenations of **2c** and **2d** required much longer time under the same conditions. This may be due to the increasing steric hindrance caused by the long alkyl chains. However, partial hydrogenations of **2c** and **2d** in the presence of Lindlar catalyst to give the corresponding olefins (**4c** and **4d**) proceeded more rapidly, especially in the case of **2d**, where reduction to **4d** required only 2.5 h. Although similar partial reductions of acetylene derivatives of nucleosides are known to give pure $Z$-olefins,[1,6] we found that in two cases small amounts of $E$-isomers were also formed, as indicated by $^1H$ NMR (400 MHz) spectra. Reduction of **2d** gave **4d** in 86% yield, which contained 3.7% of trans isomer. Also a minor (5%) amount of **3d** was isolated. Similar hydrogenation of **2c** afforded **4c** as a major product, but the proportion of the $E$-isomer (7.0%) was still higher than in the previous case. Trans isomers were unambiguously identified by their larger vicinal coupling constant ($J$ = 15.5 Hz). In addition, their olefinic proton signals appear 0.2–0.3 ppm downfield from those of cis isomers in both cases. Interestingly, partial reduction of **2b** gave pure ($Z$)-8-(propen-1-yl)-dA (**4b**), with no traces of trans isomer, in 75% isolated yield, along with 14% **3b**, which shows the increasing rate of overreduction with decreasing length of alkyl chain.

In spite of the very small $R_f$ differences on TLC, we could completely separate the alkenyl and alkyl derivatives by dry column flash chromatography (DCFC). However, in the case of **4c** and **4d**, we could not separate the minor $E$- and the major $Z$-isomers either by TLC or DCFC.

Structures of the new compounds were confirmed by $^1H$ NMR, UV, and IR spectroscopy. While the UV spectra of the alkyl derivatives are practically identical with that of dA ($\lambda_{max}$ at 214 and 262 nm, $\lambda_{min}$ at 228 nm), introduction of a conjugated double or triple bond into the C-8 position results in a significant red-shift of both maxima of the parent dA.

It should be noted that there are characteristic differences between the UV spectra of alkenyl and alkynyl analogues, as well. Alkynyl compounds have three absorption maxima, at 205, 229, and 292 nm. The $\epsilon$ values for the two main peaks are nearly identical, except for 8-ethynyl-dA, where the difference is somewhat larger. In the case of alkenyl derivatives, we find only two maxima, at 228 and 282 nm, although the first one has a strong shoulder in the 207–212 nm wavelength range. Contrary to what is seen for the alkynyl analogues, in the alkenyl series the second maximum at 282 nm is much weaker ($\epsilon$ = 13 400), compared to the first one ($\epsilon$ = 22 300).

In the infrared spectra of alkynyl derivatives (**2b–d**) the $\nu$C≡C bands appear at 2220 $cm^{-1}$ with the usual weak intensity, while the same band of **2a** at 2120 $cm^{-1}$ is somewhat stronger. The similar unambiguous identification of $\nu$C=C bands in the case of alkenyl analogues (**4b–d**) is not possible, since these are overlapped by the very strong bands coming from the scissoring vibration of amino group and skeleton vibrations of heteroaromatic rings appearing in the 1600–1660-$cm^{-1}$ region. These disturbing bands can be separated and differentiated by Raman spectroscopy that enables the unambiguous detection of the $\nu$C=C band, as well.[21]

**Antiviral Activity.** Of the test compounds, the 8-ethynyl derivative (**2a**) was the most cytotoxic: it inhibited the proliferation of HEL cells at an $IC_{50}$ (50% inhibitory concentration) of 2 μg/mL. The 8-heptynyl derivative **2d**, 8-heptyl derivative **3d**, and 8-heptenyl derivative **4d** inhibited HEL cell proliferation at an $IC_{50}$ of 6, 13 and 20 μg/mL, respectively. They exhibited inhibitory activity to some of the test viruses at concentrations that were at least 3-fold lower than the concentration required to reduce host cell growth by 50%; i.e., **2d** inhibited CMV at 3 μg/mL, and **3d** inhibited CMV at

Table 1. Antiviral Activity of 8-Alkynyl-, 8-Alkenyl-, and 8-Alkyl-2'-deoxyadenosine Analogues

| | | minimum inhibitory concentration[a] (μg/mL) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| virus (strain) | cell | 2a | 2b | 2c | 2d | 3a | 3b | 3c | 3d | 4b | 4c | 4d | dA | BVDU | acyclovir | C-c3Ado | ribavirin |
| HSV-1 (KOS) | ESM | >4 | >200 | 100 | >100 | 300 | 200 | 150 | >40 | >100 | >200 | >100 | >400 | 0.02 | 0.07 | >200 | ≥300 |
| HSV-2 (G) | ESM | >4 | ≥200 | 150 | 150 | ≥200 | 70 | 150 | >40 | >100 | >200 | >40 | >400 | 20 | 0.07 | >200 | ≥400 |
| TK-HSV-1 (B2006) | ESM | >4 | 150 | 100 | >100 | 300 | ≥300 | >100 | >40 | >100 | >100 | >40 | >400 | >200 | 100 | >200 | ≥300 |
| VV | ESM | >4 | 300 | 150 | 7 | >400 | 70 | 150 | 20 | >100 | >100 | 20 | >400 | 2 | >400 | 4 | 70 |
| VSV | ESM | >4 | 150 | 70 | 20 | >400 | 400 | 70 | >40 | >100 | >100 | >40 | >400 | >400 | >400 | 10 | >400 |
| VZV (Oka) | HEL | 7 | 40 | 40 | 15 | >100 | 20 | 20 | 10 | >50 | >50 | 15 | >100 | 0.004 | 4 | ND | ND |
| TK-VZV (07/1) | HEL | 4 | 40 | 20 | 8 | 55 | 7 | 20 | 6 | >50 | >50 | 10 | >100 | >10 | 80 | ND | ND |
| CMV (Davis) | HEL | 4 | 20 | 10 | 7 | 70 | 20 | 10 | 4 | >50 | >50 | 20 | >100 | 70 | 50 | ND | ND |
| CMV (AD-169) | HEL | 2 | 20 | 10 | 2 | 70 | 20 | 10 | 4 | >50 | >50 | 30 | >100 | 70 | 35 | ND | ND |
| RSV (Long) | HeLa | >4 | >200 | >100 | 30 | >200 | >200 | >100 | 20 | >200 | 100 | 14 | 20 | ND | ND | ND | ND |
| influenza A (Ishikawa) | MDCK | >20 | >200 | 30 | ≥100 | >200 | >200 | >100 | 20 | >200 | >200 | 12 | >200 | ND | ND | ND | ND |
| influenza B (Singapore) | MDCK | >20 | >200 | >100 | >100 | >200 | >200 | >100 | >100 | >200 | >200 | >100 | >200 | ND | ND | ND | ND |
| morphology | ESM | 10 | >400 | 400 | ≥200 | >400 | >400 | ≥200 | ≥100 | ≥100 | ≥200 | ≥100 | >400 | >400 | >400 | ≥200 | >400 |
| proliferation | HEL | 2 | 40 | 10 | 6 | >200 | 170 | 30 | 13 | >50 | 40 | 20 | ND | >200 | >200 | ND | ND |
| morphology | HeLa | 4 | >200 | 100 | 100 | >200 | >200 | 100 | 100 | >200 | >200 | 100 | 200 | ND | ND | ND | ND |
| morphology | MDCK | 20 | >200 | 100 | 100 | >200 | >200 | 100 | 100 | >200 | >200 | 100 | >200 | ND | ND | ND | ND |

[a] Required to reduce virus-induced cytopathicity or cell proliferation by 50%, or required to cause a microscopically detectable alteration of cell morphology.

4 μg/mL. Furthermore, compounds **2d**, **3d**, and **4d** were found to be active against VV, VSV, RSV, and/or influenza A virus at concentrations that were 5–10-fold lower than the concentrations required to alter normal host cell morphology (Table 1).

Some of the compounds (i.e. **2d**, **4b**, **4c**, and **4d**) were also evaluated against other viruses than those listed in Table 1, i.e., PV-3, RV-1, SV, polio 1, Coxs B4, and SFV. However, no activity was noted with any of the compounds against these viruses (data not shown). In comparison with the parent compound (dA), the 8-substituted derivatives clearly showed an increased antiviral potency, particularly against VV, VZV, and CMV. However, the antiviral potency of even the most active dA congeners (**2d** and **3d**) was still significantly lower than that of the established antiviral drugs BVDU and acylclovir.

The mechanism of antiviral action of the 8-alkynyl-, 8-alkenyl-, and 8-alkyl-dA analogues, in particular **2d**, **3d**, and **4d**, remains the subject of further investigation. The possibility that the dA analogues might interact with *S*-adenosylhomocysteine hydrolase was entertained. Yet, neither **2d** and **3d** nor **2a** and **3a** inhibited AdoHcy hydrolase activity (from murine L929 cells) at a concentration of 100 μg/mL, while under the same conditions neplanocin A and 3-deazaneplanocin A, two well-known AdoHcy hydrolase inhibitors, inhibited AdoHcy hydrolase at an $IC_{50}$ of 0.005 and 0.03 μM, respectively (data not shown).

## Experimental Section

**Abbreviations.** HSV-1, herpes simplex virus type 1; HSV-2, herpes simplex virus type 2; VV, vaccinia virus; VSV, vesicular stomatitis virus; CMV, cytomegalovirus; VZV, varicella zoster virus; PV-3, parainfluenza virus type 3; RV-1, reovirus type 1; SV, Sindbis virus; Coxs B4, Coxsackie B4 virus; SFV, Semliki forest virus; RSV, respiratory syncytial virus; ESM, human embryonic skin–muscle cells; HEL, human embryonic lung cells; MDCK, Madin-Darby canine kidney cells; HeLa, (human) carcinoma cells; DCFC, dry column flash chromatography; brs, broad singlet; d, doublet; dd, double of doublets; t, triplet; q, quartet; m, multiplet; sh, shoulder.

**Materials.** Terminal alkynes, CuI, and Lindlar catalyst were purchased from Fluka AG. 2'-Deoxyadenosine was from Pharma-Waldhof GmbH (Düsseldorf, Germany). Dimethylformamide and triethylamine were distilled from $CaH_2$. Bis(triphenylphosphine)palladium(II) chloride was prepared according to the method of Burmeister and Basolo.[22] All coupling reactions were performed under an atmosphere of oxygen-free nitrogen, and the solutions were vigorously deoxygenated with $N_2$ prior to the addition of catalysts and terminal alkynes.

**Spectroscopy.** UV spectra were recorded with a Shimadzu UV-160 spectrometer; maxima are reported in nanometers. IR spectra were recorded with a Nicolet-205 FT-IR spectrometer. $^1H$ NMR spectra were recorded on a Varian XL-400 FT-NMR instrument operating at 400 MHz. Chemical shifts are reported in ppm using $Me_4Si$ as the internal standard. Optical rotation measurements were performed on a Polamat A (Carl Zeiss) polarimeter. Melting points were determined with a Koefler apparatus and were uncorrected.

**Chromatography.** Precoated TLC plates (Kieselgel 60 $F_{254}$, 0.2 mm) were purchased from Merck; compounds were detected by UV light. Kieselgel 60 H by Stahl (Merck) was used for preparative DCFC.[20]

The solvent systems (v/v) used for TLC and DCFC were (A) $CHCl_3$/MeOH = 9:1, (B) EtOAc/MeOH = 9:1, and (C) $CHCl_3$/MeOH = 19:1.

**2'-Deoxy-8-ethynyladenosine (2a).** 8-Bromo-2'-deoxyadenosine (1)[19] (0.99 g, 3.0 mmol) was dissolved in dry DMF, and then absolute $Et_3N$ (0.83 mL, 6.0 mmol), $(PPh_3)_2PdCl_2$ (210 mg, 0.3 mmol), CuI (114 mg, 0.6 mmol), and (trimethylsilyl)acetylene (1.7 mL, 12.0 mmol) were added. The mixture was stirred under $N_2$ at ambient temperature. After 2.5 h TLC (in system A) showed that the reaction was complete. The solvent was removed by evaporation and the brown, oily residue obtained was taken up in MeOH/$CHCl_3$ (40/40 mL). Amberlite IRA-400 in [$HCO_3^-$] form (5 mequiv) was added and the mixture was stirred for 15 min. After filtration the ion-exchange treatment was repeated, and the resin was filtered and washed with MeOH.

The combined filtrate was evaporated to dryness (finally at 45 °C, 1 mm), dissolved in $CHCl_3$ (5 mL), and applied to a column made of Kieselgel H (45 g). The apolar yellow impurities were first eluted with $CHCl_3$. Further elution with C and A systems afforded 0.72 g (2.07 mmol, 69%) of 8-[(trimethylsilyl)ethynyl]-dA as a pale yellow foam which was pure according to TLC ($R_f$ (A) = 0.31). Subsequent desilylation of this intermediate in 5% $NH_3$/MeOH–$H_2O$ (50 mL) at 20 °C took place in 45 min, then 5.0 g of Kieselgel H was added to the solution and the mixture was carefully evaporated to dryness. The residue obtained was put on a Kieselgel H column (35 g) and eluted with systems C and A.

The appropriate fractions were combined and evaporated to give 0.43 g (1.57 mmol, 76%) of 8-ethynyl-dA (**2a**) as a pale yellow powder that was recrystallized from MeOH/$H_2O$: mp >360 °C;

$R_f$ (B) = 0.23; $[\alpha]^{24}_D$ = −23° [c 0.5, MeOH/$H_2O$ (1:1)], UV $\lambda_{max}$ (MeOH) 205 (ε 10 939), 229 (ε 20 247), 292 (ε 16 846), 303 sh (ε 13 000); UV $\lambda_{min}$ (MeOH) 210 (ε 10 176), 246 (ε 2939); IR (KBr) νC≡C 2120 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$ + $CDCl_3$) δ 2.27 (1H, m, H-2′a), 2.99 (1H, m, H-2′b), 3.67–3.90 (2H, m, H-5′ab), 4.15 (1H, m, H-4′), 4.19 (1H, s, C≡C*H*), 4.62 (1H, m, H-3′), 5.22 (1H, d, 3′-OH), 6.49 (1H, m, 5′-OH), 6.59 (1H, dd, H-1′, $J^3_{1',2'a}$ = 5.8 Hz, $J^3_{1',2'b}$ = 9.5 Hz), 7.14 (2H, brs, $NH_2$), 8.20 (1H, s, H-2). Anal. ($C_{12}H_{13}N_5O_3$) C, H, N.

**2′-Deoxy-8-(propyn-1-yl)adenosine (2b).** Compound 1 (2.00 g, 6.04 mmol) was dissolved in dry DMF (36 mL), and then absolute $Et_3N$ (1.68 mL, 12.08 mmol), $(Ph_3P)_2PdCl_2$ (423 mg, 0.60 mmol), and CuI (230 mg, 1.20 mmol) were added. Then propyne, which was previously generated and collected according to the method of Hurd *et al.*,[23] was introduced with stirring at room temperature. After 4 h, TLC (in system B) indicated that the reaction was complete and the solvent was removed by evaporation under vacuum. The residue was dissolved in MeOH (100 mL) and the ion-exchange treatment described for the preparation of **2a** was applied. The crude product thus obtained was dissolved in MeOH (100 mL), 12 g of Kieselgel H was added, and the mixture was slowly evaporated to dryness. The dry silica residue was placed onto the top of a column made of Kieselgel H (60 g). The column was eluted with EtOAc containing MeOH (1 → 5%). The main product in most fractions was accompanied by a more polar byproduct. The repeated DCFC afforded 1.02 g (3.52 mmol, 58%) of chromatographically pure **2b** as a white solid that was then recrystallized from EtOH: mp 214 °C; $R_f$ (B) = 0.19; $[\alpha]^{23}_D$ = −33° (c 0.5, MeOH); UV $\lambda_{max}$ (MeOH) 206 (ε 14 902), 229 (ε 22 941) 283 sh (ε 19 700), 290 (ε 20 673), 303 sh (ε 15 000); UV $\lambda_{min}$ (MeOH), 212 (ε 12 700), 246 (ε 3700); IR (KBr) νC≡C 2240 cm$^{-1}$, $\nu_{as}CH_3$ 2950 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$ + $CDCl_3$) δ 2.18 (3H, s, $CH_3$), 2.27 (1H, m, H-2′a), 2.98 (1H, m, H-2′b), 3.68–3.96 (2H, m, H-5′ab), 4.17 (1H, brs, H-4′), 4.66 (1H, brs, H-3′), 5.15 (1H, d, 3′-OH), 6.52 (1H, m, 5′-OH), 6.60 (1H, dd, H-1′, $J^3_{1',2'a}$ = 5.5 Hz, $J^3_{1',2'b}$ = 9.5 Hz), 6.78 (2H, brs, $NH_2$), 8.37 (1H, s, H-2). Anal. ($C_{13}H_{15}N_5O_3$) C, H, N.

**2′-Deoxy-8-(1-pentyn-1-yl)adenosine (2c).** Compound 1 (2.00 g, 6.04 mmol) was dissolved in dry DMF (36 mL), and then absolute $Et_3N$ (1.68 mL, 12.08 mmol), $(Ph_3P)_2PdCl_2$ (423 mg, 0.60 mmol), CuI (230 mg, 1.20 mmol), and 1-pentyne (2.38 mL, 24.16 mmol) were added.

The mixture was stirred at 20 °C for 3 h and evaporated to dryness. The oily residue obtained was dissolved in $CHCl_3$ (120 mL) and washed with 5% $Na_2EDTA/H_2O$ (3 × 40 mL), and the combined aqueous phase, which contained a little product as evidenced by TLC, was reextracted with $CHCl_3$ (2 × 40 mL). The combined organic phase was concentrated in vacuo, dissolved in $CHCl_3$/MeOH (50/50 mL), and treated with anion-exchange resin in the usual way.

After evaporation in vacuo and dissolution of the residue in $CHCl_3$ (~6 mL), the crude product was applied to a column (60 g). DCFC using $CHCl_3$/MeOH (1 → 5%) as the eluant resulted in 1.64 g (5.17 mmol, 86%) of **2c** as a TLC-homogeneous white solid that was recrystallized from EtOH/$Et_2O$: mp 119–121 °C; $R_f$ (B) = 0.27; $[\alpha]^{24}_D$ = −13° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 206 (ε 11 297), 229 (ε 20 503), 284 sh (ε 17 900), 292 (ε 19 281), 303 sh (ε 13 700); UV $\lambda_{min}$ (MeOH), 212 (ε 9265), 246 (ε 2958); IR (KBr) νC≡C 2220 cm$^{-1}$, $\nu_{as}CH_2$ 2920 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 1.05 (3H, t, $CH_3$), 1.70 (2H, m, $CH_2CH_3$), 2.33 (1H, m, H-2′a), 2.51 (2H, t, C≡CC*H*$_2$), 2.98 (1H, m, H-2′b), 3.76–4.02 (2H, m, H-5′ab), 4.27 (1H, brs, H-4′), 4.82 (1H, m, H-3′), 6.08 (2H, brs, $NH_2$), 6.64 (1H, dd, H-1′, $J^3_{1',2'a}$ = 5.5 Hz, $J^3_{1',2'b}$ = 9.5 Hz), 6.74 (1H, d, 5′-OH), 8.29 (1H, s, H-2). Anal. ($C_{15}H_{19}N_5O_3$) C, H, N.

**2′-Deoxy-8-(1-heptyn-1-yl)adenosine (2d).** Compound 1 (495 mg, 1.50 mmol) was dissolved in dry DMF (9 mL), and absolute $Et_3N$ (0.42 mL, 3.00 mmol), $(Ph_3P)_2PdCl_2$ (105 mg, 0.15 mmol), CuI (57 mg, 0.30 mmol), and 1-heptyne (0.78 mL, 6.00 mmol) were added.

The complete reaction required 6 h, as indicated by TLC. The mixture was allowed to stand at 4 °C overnight. After workup it was purified as described for the preparation of **2c**. Impure fractions were rechromatographed to give a total of 419 mg (1.21 mmol, 81%) of pure **2d** as a white solid which was recrystallized from EtOH/$Et_2O$: mp 112–114 °C; $R_f$ (B) = 0.30; $[\alpha]^{22}_D$ = −28° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 205 (ε 10 260), 229 (ε 20 211), 285 sh (ε 17 800), 292 (ε 19 458), 303 sh (ε 13 700); UV $\lambda_{min}$ (MeOH) 212 (ε 8042), 246 (ε 2666); IR (KBr) νC≡C 2220 cm$^{-1}$, $\nu_{as}CH_2$ 2920 cm$^{-1}$ $^1$H; NMR ($CDCl_3$) δ 0.92 (3H, t, $CH_3$), 1.36–1.45 (6H, m, $(CH_2)_3$), 2.30 (1H, m, H-2′a), 2.52 (2H, t, C≡CC*H*$_2$), 2.98 (1H, m, H-2′b), 3.76–4.04 (2H, m, H-5′ab), 4.28 (1H, brs, H-4′), 4.80 (1H, m, H-3′), 6.46 (2H, brs, $NH_2$), 6.64 (1H, dd, H-1′, $J^3_{1',2'a}$ = 5.5 Hz, $J^3_{1',2'b}$ = 9.5 Hz), 6.76 (1H, d, 5′-OH), 8.27 (1H, s, H-2). Anal. ($C_{17}H_{23}N_5O_3$) C, H, N.

**General Procedure for the Preparation of 8-*n*-Alkyl-2′-deoxyadenosines (3a–d).** Compound **2a** or **2b** (1.5–1.5 mmol) was dissolved in MeOH/$H_2O$ (3:1) (16 mL) while **2c** or **2d** (1.0–1.0 mmol) was dissolved in EtOH (12 mL). These solutions of alkynes were added to the suspension of 100–150 mg of prehydrogenated 10% Pd–C in the given solvent (~5 mL), and the resulting mixtures were shaken in a $H_2$ atmosphere at a slight positive pressure. Complete hydrogenation of **2a** and **2b** took place within 2 h while in the case of **2c** and **2d** the full saturation of the triple bonds required 10 and 14 h, respectively. After the $H_2$ consumption and TLC (in system B) had indicated that the reaction was complete, the catalyst was filtered through an asbestos pad and washed with a few portions of the appropriate solvent. The combined filtrate was evaporated to give the corresponding 8-alkyl-2′-deoxyadenosines (**3a–d**) as white solids in 85–95% yield.

**2′-Deoxy-8-ethyladenosine (3a):** yield 94%; mp 210–211 °C (from EtOH) (lit. mp 216 °C,[12] 234–235 °C,[14] $R_f$ (B) = 0.11 $[\alpha]^{22}_D$ = −21° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 210 (ε 17 079), 262 (ε 17 426); UV $\lambda_{min}$ (MeOH), 228 (ε 2392); IR (KBr) $\nu_{as}CH_2$ 2936 cm$^{-1}$, $\nu_{as}CH_3$ 2974 cm$^{-1}$; $^1$H NMR data were practically identical with those reported in the literature.[14] Anal. ($C_{12}H_{17}N_5O_3$) C, H, N.

**2′-Deoxy-8-propyladenosine (3b):** yield 91%; mp 164–166 °C; $R_f$ (B) = 0.15 $[\alpha]^{22}_D$ = −21° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 210 (ε 14 005), 262 (ε 12 254); UV $\lambda_{min}$ (MeOH) 228 (ε 1156); IR (KBr) $\nu_{as}CH_2$ 2930 cm$^{-1}$, $\nu_{as}CH_3$ 2970 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$) δ 1.10 (3H, t, $CH_3$), 1.88 (2H, m, C*H*$_2$CH$_3$), 2.25 (1H, m, H-2′a), 2.90 (2H, q, C*H*$_2$C$_2$H$_5$), 3.10 (1H, m, H-2′b), 3.74–4.00 (2H, m, H-5′ab), 4.20 (1H, brs, H-4′), 4.71 (1H, m, H-3′), 4.88 (1H, brs, 3′-OH), 6.25 (2H, brs, $NH_2$), 6.38 (1H, dd, H-1′), 6.62 (1H, brs, 5′-OH), 8.21 (1H, s, H-2). Anal. ($C_{13}H_{19}N_5O_3$) C, H, N.

**2′-Deoxy-8-pentyladenosine (3c):** yield 87%; mp 120–122 °C; $R_f$ (B) = 0.22 $[\alpha]^{22}_D$ = −8° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 212 (ε 16 084), 262 (ε 14 818); UV $\lambda_{min}$ (MeOH) 228 (ε 2814); IR (KBr) $\nu_{as}CH_2$ 2938 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.93 (3H, t, $CH_3$), 1.36–1.85 (6H, m, $(CH_2)_3$), 2.24 (1H, m, H-2′a), 2.90 (2H, q, C*H*$_2$C$_4$H$_9$), 3.13 (1H, m, H-2′b), 3.75–4.00 (2H, m, H-5′ab), 4.23 (1H, brs, H-4′), 4.80 (1H, m, H-3′), 5.80 (2H, brs, $NH_2$), 6.34 (1H, dd, H-1′), 8.26 (1H, s, H-2). Anal. ($C_{15}H_{23}N_5O_3$) C, H, N.

**2′-Deoxy-8-heptyladenosine (3d):** yield 85%; mp 124–126 °C; $R_f$ (B) = 0.23 $[\alpha]^{22}_D$ = −18° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 210 (ε 15 892), 262 (ε 12 463); UV $\lambda_{min}$ (MeOH) 228 (ε 3880); IR (KBr) $\nu_{as}CH_2$ 2948 cm$^{-1}$, $\nu_sCH_2$ 2850 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 0.90 (3H, t, $CH_3$), 1.25–1.85 (10H, m, $(CH_2)_5$), 2.22 (1H, m, H-2′a), 2.89 (2H, q, $CH_2C_6H_{13}$), 3.14 (1H, m, H-2′b), 3.75–4.02 (2H, m, H-5′ab), 4.23 (1H, brs, H-4′), 4.81 (1H, m, H-3′), 5.75 (2H, brs, $NH_2$), 6.33 (1H, dd, H-1′, $J^3_{1',2'a}$ = 5.5 Hz, $J^3_{1',2'b}$ = 9.5 Hz), 6.88 (1H, brs, 5′-OH), 8.26 (1H, s, H-2). Anal. ($C_{17}H_{27}N_5O_3$) C, H, N.

**General Method for the Synthesis of (*Z*)-8-(1-Alken-1-yl)-2′-deoxyadenosines (4b–d).** Compound **2c** or **2d** (0.5 mmol) was dissolved in MeOH while **2b** was dissolved in MeOH/$H_2O$ (2/1) (12 mL each) containing 2% quinoline. The solutions were added to the suspension of prehydrogenated Lindlar catalyst (300 mg) in MeOH (5 mL). The mixtures were shaken in a $H_2$ atmosphere at a slight positive pressure for 2.5–4 h. The catalyst was filtered through an asbestos pad and washed with the appropriate solvent (4 × 10 mL), and filtrates were evaporated to dryness. Since TLC indicated the presence of varying amounts of alkyl compounds, each residue was purified by DCFC using EtOAc/MeOH (1 → 7%) as eluant. The appropriate fractions were combined and evaporated to give the major products (**4b–d**) as white solids which were triturated with cold ether and then filtered and dried on air.

**(*Z*)-8-(Propen-1-yl)-2'-deoxyadenosine (4b)**: yield 75%; mp 208–210 °C; $R_f$ (B) = 0.17; $[\alpha]^{23}_D$ = −15° (*c* 0.5, MeOH); UV $\lambda_{max}$ (MeOH) 210 sh (ε 14 700), 228 (ε 22 366), 282 (ε 13 401); UV $\lambda_{min}$ (MeOH) 248 (ε 4600); IR (KBr) $\nu_{as}CH_3$ 2960 cm$^{-1}$, $\nu_sCH_3$ 2870 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$ + $CDCl_3$) δ 2.13 (1H, m, H-2'a), 2.17 (3H, dd, $CH_3$), 2.98 (1H, m, H-2'b), 3.55–3.76 (2H, m, H-5'ab), 3.96 (1H, brs, H-4'), 4.49 (1H, m, H-3'), 5.24 (1H, d, 3'-OH), 5.92 (1H, brs, 5'-OH), 6.26 (1H, m, C=C*H*CH$_3$), 6.35 (1H, dd, H-1', $J^3_{1',2'a}$ = 9.0 Hz, $J^3_{1',2'b}$ = 5.5 Hz), 6.56 (1H, d, *H*C=CHCH$_3$, $J^3_{cis}$ = 11.5 Hz), 7.10 (2H, brs, $NH_2$), 8.08 (1H, s, H-2). Anal. ($C_{13}H_{17}N_5O_3$) C, H, N.

**(*Z*)-8-(1-Penten-1-yl)-2'-deoxyadenosine (4c)**: yield 78%; mp 84–86 °C; $R_f$ (B) = 0.24, $[\alpha]^{23}_D$ = −29° (*c* 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 210 sh (ε 16 200), 228 (ε 22 354), 282 (ε 13 022); UV $\lambda_{min}$ (MeOH) 248 (ε 5800); IR (KBr) $\nu_{as}CH_2$ 2920 cm$^{-1}$, $\nu_sCH_2$ 2840 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$) δ 0.92 (3H, t, $CH_3$), 1.46–1.55 (2H, m, C*H*$_2$CH$_3$), 2.20 (1H, m, H-2'a), 2.58 (2H, q, C=CHC*H*$_2$), 3.72–3.97 (2H, m, H-5'ab), 4.16 (1H, brs, H-4'), 4.66 (1H, m, H-3'), 5.05 (1H, d, 3'-OH), 6.21 (1H, m, C=CHC$_3$H$_7$), 6.35–6.39 (3H, m, $NH_2$, 5'-OH), 6.40 (1H, dd, H-1'), 6.87 (1H, d, *H*C=CHC$_3$H$_7$, $J^3_{cis}$ = 11.5 Hz), 8.20 (1H, s, H-2). According to the spectrum the sample contained ~7% *E*-isomer (δ 6.52 and 7.00 ppm for the olefinic protons, $J^3_{trans}$ = 15.5 Hz). Anal. ($C_{15}H_{21}N_5O_3$) C, H, N.

**(*Z*)-8-(1-Hepten-1-yl)-2'-deoxyadenosine (4d)**: yield 86%; mp 112–114 °C; $R_f$ (B) = 0.27 $[\alpha]^{23}_D$ = −21° (c 1.0, MeOH); UV $\lambda_{max}$ (MeOH) 210 sh (ε 15 000), 228 (ε 22 328), 282 (ε 13 483); UV $\lambda_{min}$ (MeOH) 248 (ε 5800); IR (KBr) $\nu_{as}CH_2$ 2920 cm$^{-1}$, $\nu_sCH_2$ 2840 cm$^{-1}$; $^1$H NMR ($CDCl_3$ + DMSO-$d_6$) δ 0.90 (3H, t, $CH_3$), 1.15–1.55 (6H, m, $(CH_2)_3$), 2.20 (1H, m, H-2'a), 2.62 (2H, q, C=CC*H*$_2$), 3.00 (1H, m, H-2'b), 3.70–3.95 (2H, m, H-5'ab), 4.16 (1H, brs, H-4'), 4.64 (1H, m, H-3'), 5.11 (1H, d, 3'-OH), 6.20 (1H, m, C=CHC$_5$H$_{11}$), 6.37 (1H, dd, H-1', $J^3_{1',2'a}$ = 9.0 Hz, $J^3_{1',2'b}$ = 5.5 Hz), 6.41 (1H, brs, 5'-OH), 6.46 (2H, br, s, $NH_2$), 6.80 (1H, d, *H*C=CHC$_5$H$_{11}$, $J^3_{cis}$ = 11.0 Hz), 8.18 (1H, s, H-2). The spectrum indicated the presence of 3.7% of *E*-isomer in the sample (for the olefinic protons, δ 6.50 and 6.97 ppm, $J^3_{trans}$ = 15.5 Hz). Anal. ($C_{17}H_{25}N_5O_3$) C, H, N.

**Antiviral Activity Assays.** The antiviral assays were based on inhibition of virus-induced cytopathicity in either ESM, HEL, HeLa, or MDCK cell cultures, following previously established procedures.[24-26]

**Inhibition of AdoHcy Hydrolase Activity.** Inhibition of murine L929 AdoHcy hydrolase activity was measured as described previously.[27]

**Acknowledgment.** These investigations were supported by grants from the Belgian Fonds voor Geneeskundig Wetenschappelijk Onderzoek (project no 3,0026,91), the Belgian Geconcerteerde Onderzoeksacties (project no 90/94-2), and the Hungarian Scientific Research Fund (OTKA, project no. 1752). We thank Anita Van Lierde, Frieda De Meyer, Anita Camps, Ria Van Berwaer, and Márta Hanzély, for excellent technical assistance, and Christiane Callebaut, for dedicated editorial help.

## References

(1) Robins, M. J.; Barr, P. J. Nucleic Acid Related Compounds. 39. Efficient Conversion of 5-Iodo to 5-Alkynyl and Derived 5-Substituted Uracil Bases and Nucleosides. *J. Org. Chem.* **1983**, *48*, 1854–1862.

(2) Tanaka, H.; Haraguchi, K.; Koizumi, Y.; Fukui, M.; Miyasaka, T. Synthesis of 6-alkynylated Uridines. *Can. J. Chem.* **1986**, *64*, 1560–1563.

(3) De Clercq, E.; Descamps, J.; De Somer, P.; Barr, P. J.; Jones, A. S.; Walker, R. T. (E)-5-(2-bromovinyl)-2'-deoxyuridine: A potent and selective anti-herpes agent. *Proc. Natl. Acad. Sci. U.S.A.* **1979**, *76*, 2947–2951.

(4) (a) Nógrádi M. Hevizos. *Drugs Today* **1989**, *25*, 7–9. (b) Sági, J.; Stokrova, J.; Vorlickova, M.; Spanova, A.; Kypr, J.; Ruff, É.; Ötvös, L. Structures of Poly(dA-dT, ip$^5$dU) Containing Various Small Amounts of the Antiherpetic 5-Isopropyl-2'-deoxyuridine *Biochem. Biophys. Res. Commun.* **1992**, *185*, 96–102.

(5) De Clercq, E.; Descamps, J.; Balzarini, J.; Giziewicz, J.; Barr, P. J.; Robins, M. J. Nucleic Acid Related Compounds. 40. Synthesis and Biological Activities of 5-Alkynyluracil Nucleosides. *J. Med. Chem.* **1983**, *26*, 661–666.

(6) Matsuda, A.; Shinozaki, M.; Yamaguchi, T.; Homma, H.; Nomoto, R.; Miyasaka, T.; Watanabe, Y.; Abiru, T. Nucleosides and Nucleotides. 103. 2-Alkynyladenosines: A Novel Class of Selective Adenosine $A_2$ Receptor Agonists with Potent Antihypertensive Effects. *J. Med. Chem.* **1992**, *35*, 241–252.

(7) Abiru, T.; Yamaguchi, T.; Watanabe, Y.; Kogi, K.; Aihara, K.; Matsuda, A. The antihypertensive effect of 2-alkynyladenosines and their selective affinity for adenosine $A_2$ receptors. *Eur. J. Pharmacol.* **1991**, *196*, 69–76.

(8) Koyama, S.; Kumazawa, Z.; Kashimura, N. Synthesis of 6- and 8-alkylylated purines and their ribonucleosides by the coupling of halopurines with alkynes. *Nucleic Acids Res. Symp. Ser.* **1982**, *11*, 41–44.

(9) Cong-Danh, N.; Beaucourt, J. P.; Pichat, L. Modification of Purine Nucleosides and Adenosine-3',5'-Cyclic Monophosphate. Catalytic Coupling Reactions of Grignard Reagents with Silyl-protected 8-Bromo-Purine Ribofuranosides and -Adenosine-3',5'-Cyclic Monophosphate in the Presence of Bis-Triphenylphosphine-palladium-(II)-chloride. *Tetrahedron Lett.* **1979**, *34*, 3159–3162.

(10) Tanaka, H.; Uchida, Y.; Shinozaki, M.; Hayakawa, H.; Matsuda, A.; Miyasaka, T. A Simplified Synthesis of 8-Substituted Purine Nucleosides via Lithiation of 6-Chloro-9-(2,3-O-isopropylidene-β-D-ribofuranosyl)-purine. *Chem. Pharm. Bull.* **1983**, *31*, 787–790.

(11) Ueda, T.; Nomoto, Y.; Matsuda, A. Synthesis of 8-Alkyladenosines, 8,2'-Anhydro-8-hydroxymethyl-9-(β-D-arabinofuranosyl)adenine and Related Compounds. *Chem. Pharm. Bull.* **1985**, *33*, 3263–3270.

(12) Mamos, P.; Van Aerschot, A. A.; Weyns, N. J.; Herdewijn, P. A. Straightforward C-8 alkylation of adenosine analogues with tetraalkyltin reagents. *Tetrahedron Lett.* **1992**, *33*, 2413–2416.

(13) Moriarty, R. M.; Epa, W. R.; Awasthi, A. K. Palladium Catalysed C-8 Allylation and Vinylation of Adenosine, 2'-Deoxyadenosine and 2',3'-Dideoxyadenosine Nucleosides. *Tetrahedron Lett.* **1990**, *31*, 5877–5880.

(14) Hirota, K.; Kitade, Y.; Kanbe, Y.; Maki, Y. Convenient Method for the Synthesis of C-Alkylated Purine Nucleosides: Palladium-Catalyzed Cross-Coupling Reaction of Halogenopurine Nucleosides with Trialkylaluminums. *J. Org. Chem.* **1992**, *57*, 5268–5270.

(15) Mitsuya, H.; Broder, S. Inhibition of the in vitro infectivity and cytopathic effect of human T-lymphotrophic virus type II/lymphadenopathy-associated virus (HTLV-III/LAV) by 2',3'-dideoxynucleosides. *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 1911–1915.

(16) Robins, M. J.; Hatfield, P. W.; Balzarini, J.; De Clercq, E. Nucleic Acid Related Compounds. 47. Synthesis and Biological Activities of Pyrimidine and Purine "Acyclic" Nucleoside Analogues. *J. Med. Chem.* **1984**, *27*, 1486–1492.

(17) Hobbs, F. W. Jr. Palladium-Catalyzed Synthesis of Alkynylamino Nucleosides. A Universal Linker for Nucleic Acids. *J. Org. Chem.* **1989**, *54*, 3420–3422.

(18) Robins, M. J.; Vinayak, R. S.; Wood, S. G. Solvent not Palladium Oxidation State is the Primary Determinant for Successful Coupling of Terminal Alkynes with Iodo-Nucleosides. *Tetrahedron Lett.* **1990**, *31*, 3731–3734.

(19) Ikehara, M.; Uesugi, S.; Kaneko, M. 8-Bromoadenosine and its 5'-Phosphate. Direct Bromination of Adenine Nucleosides and Nucleotides. In *Nucleic Acid Chemistry*; Townsend, L. B., Tipson, R. S., Eds.; John Wiley and Sons: New York, 1978; Vol II, pp 837–841.

(20) Harwood, L. M. "Dry Column" Flash Chromatography. *Aldrichimica Acta* **1985**, *18*, 25.

(21) Holly, S. unpublished results.

(22) Burmeister, J. L.; Basolo, F. Inorganic Linkage Isomerism for the Thiocyanate Ion. *Inorg. Chem.* **1964**. *3*, 1587–1593.

(23) Hurd, C. D.; Meinert, R. N.; Spence, L. U. Allene and Methylacetylene Tetrabromides. *J. Am. Chem. Soc.* **1930**, *52*, 1138–1146.

(24) De Clercq, E.; Descamps, J.; Verheist, G.; Walker, R. T.; Jones, A. S.; Torrence, P. F.; Shugar, D. Comparative efficacy of different antiherpes drugs against different strains of herpes simplex virus. *J. Infect. Dis.* **1980**, *141*, 563–574.

(25) De Clercq, E. Antiviral and antimetabolic activities of neplanocins. *Antimicrob. Agents Chemother.* **1985**, *28*, 84–89.

(26) De Clercq, E.; Holy, A.; Rosenberg, I.; Sakuma, T.; Balzarini, J.; Maudgal, P. C. A novel selective broad-spectrum anti-DNA virus agent. *Nature* **1986**, *323*, 464–467.

(27) Cools, M.; Balzarini, J.; De Clercq, E. Mechanism of antiviral and cytotoxic action of (±)-6'β-fluoroaristeromycin, a potent inhibitor of *S*-adenoxylhomocysteine hydrolase. *Mol. Pharmacol.* **1991**, *39*, 718–724.