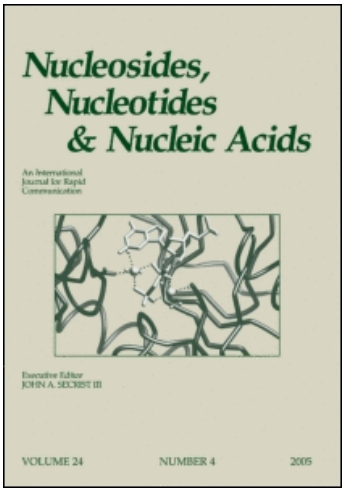

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A Convenient Route to 2'-Allenyl Nucleosides

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A CONVENIENT ROUTE TO 2'-ALLENYL NUCLEOSIDES#

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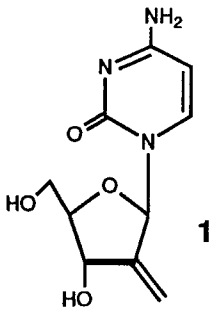
Abstract

The first synthesis of allenic nucleosides derived from natural ribonucleosides is reported. 2'-Deoxy-2'-(ethenylidene)cytidine (**8**) and 2'-deoxy-2'-(ethenylidine)adenosine (**21**) were prepared by a modification of the method developed by Tsuji and co-workers for the synthesis of allenes. The biological rationale for the synthesis of these compounds is discussed.

We have been interested in the synthesis and biological activity of 2',3'- and 4',5'-unsaturated nucleosides for a number of years.[1-4] Recently, we and others have reported methods for the synthesis of 2'-unsaturated nucleosides and the interesting biological activity that several of these compounds exhibit.[5-10,12] Two compounds of particular interest are 2'-deoxy-2'-(methylene)cytidine (**1**) and (*E*) 2'-deoxy-2'-(fluoromethylene)cytidine (**2**).



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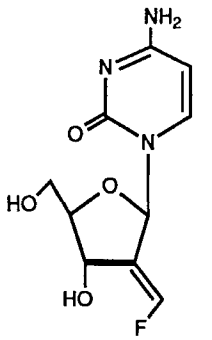
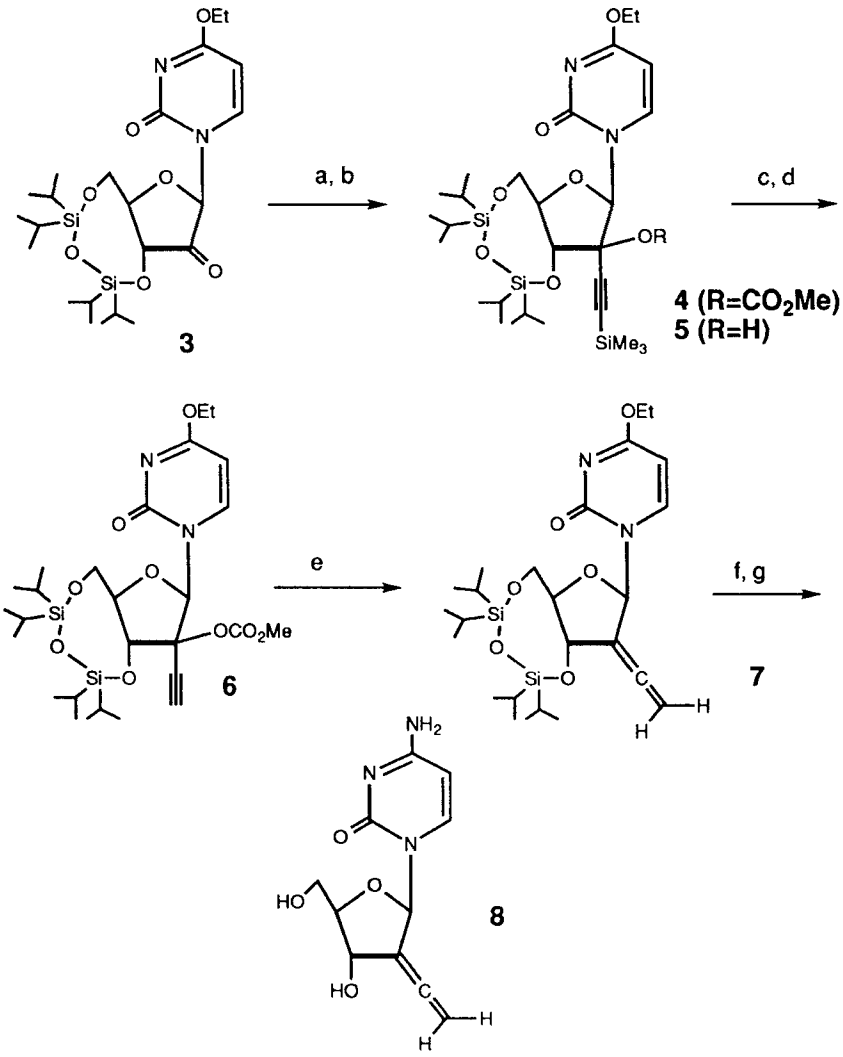


2

#This paper is dedicated in memory of Professor Roland K. Robins



Reagents: (a) $Me_3SiC{\equiv}CH$, MeMgCl (b) MeOCOCl (c) $AgNO_3$ (d) KCN (e) HCO_2NH_4, Bu_3P, $Pd_2(dba)_3$,DMF (f) CsF (g) NH_3,MeOH

SCHEME 1

Both compounds exhibit antitumor activity and inhibit the enzyme ribonucleotide reductase.[7,8] The rationale for the synthesis of fluoro olefin **2** was recently published.[9b] An elegant synthesis of the related 2'-spirocyclopropane nucleosides was reported by Samano and Robins as potential inhibitors of ribonucleotide reductase.[11]

As a result of investigating the structure activity relationship of fluoro olefin **2**, it was concluded that steric interactions at the 2'-position should be minimal to achieve antitumor activity and for inhibition of ribonucleotide reductase by the corresponding 5'-diphosphates. Thus, the 2'-allenic cytidine derivative **8** was targeted as an antitumor agent to further explore the scope and mechanism of inhibition of ribonucleotide reductase by 2'-unsaturated cytidine nucleosides.

In addition, the 2'-allenic adenosine analog **21** was proposed as a potential inhibitor of the enzyme *S*-adenosyl-L-homocysteine (SAH) hydrolase. Robins and co-workers reported the synthesis and inhibiton of SAH hydrolase by 2'-deoxy-2'-(methylene)adenosine.[12] The synthesis of a 2'-deoxy-2'-(fluoromethylene)adenosine has also been reported.[6]

Although acyclic allene-containing nucleosides are known,[13] we report the first examples of allenic nucleosides, **8** and **21**, derived from natural ribonucleosides. For the synthesis of the target allenes, the palladium-catalyzed method of Tsuji and co-workers was selected because of the mild reaction conditions.[14]

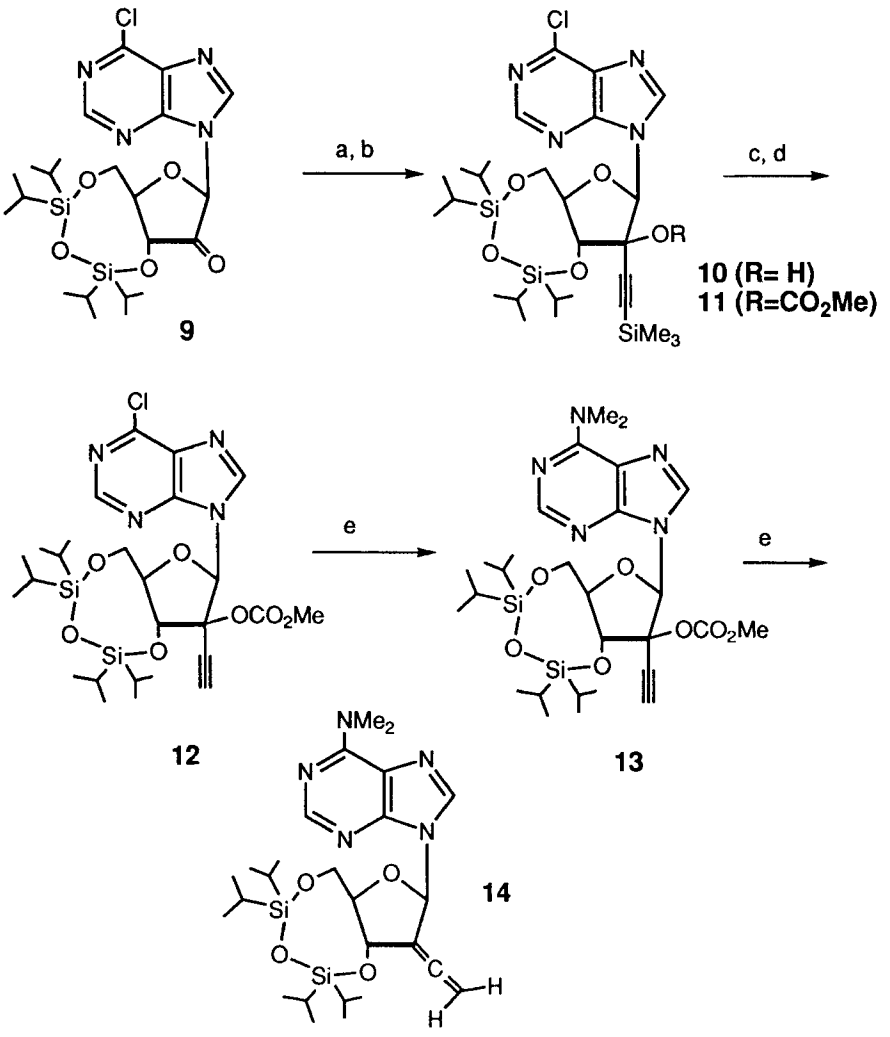
Trimethylsilylethynyl magnesium bromide was added to ketone **3**[15] and the resulting tertiary alkoxide was quenched with methyl chloroformate to form the acetylenic carbonate **4**, isolated in 55% yield as a white crystalline solid. The intermediate alkoxide also was quenched with aqueous ammonium chloride to provide alcohol **5**. Two dimensional NOE experiments with **5** showed a NOE between the 2'-OH and the 3'-hydrogen and no NOE was observed between the OH and the 1'-hydrogen. Thus, **4** and **5** were assigned the arabino configuration. After this work was initiated, other reports of the addition of acetylides to the a-face of ketonucleosides have appeared.[16] Selective removal of the trimethylsilyl protecting group from **4** was accomplished with silver nitrate and potassium cyanide[17] in 56% yield. Treatment of **6** with ammonium formate, a catalytic amount of tris(dibenzyldineacetone)dipalladium(0) ($Pd_2(dba)_3$), and tributylphosphine in DMF at 70°C under argon for 30 min., i.e., conditions similar to those of Tsuji and co-workers,[14] resulted in the formation of **7** in 45% yield with concomitant carbon dioxide evolution. Treatment of **7** with CsF in methanol removed the

TIPDS protecting group and catalyzed a partial displacement of the 4-ethoxy by a methoxy group. The resulting mixture was treated with methanolic ammonia, yielding allene **8** after flash chromatography. The chiral allenic protons appeared at δ 5.10 and 5.16 (DMSO-d_6) in the proton NMR as doublet of triplets with a characteristic geminal coupling constant of 12.0 Hz.[18]

The ketone **9** (Scheme 2) was selected as the starting material for the preparation of allene **21** and had previously been prepared in these laboratories.[6] Addition of trimethylsilylethynyl magnesium bromide to **9** yielded alcohol **10**. Alternatively, the alkoxide intermediate was quenched with methyl chloroformate to afford carbonate **11** in good yield. The arabino configuration for **11** was assigned based on the previous example and literature precedent.[16]

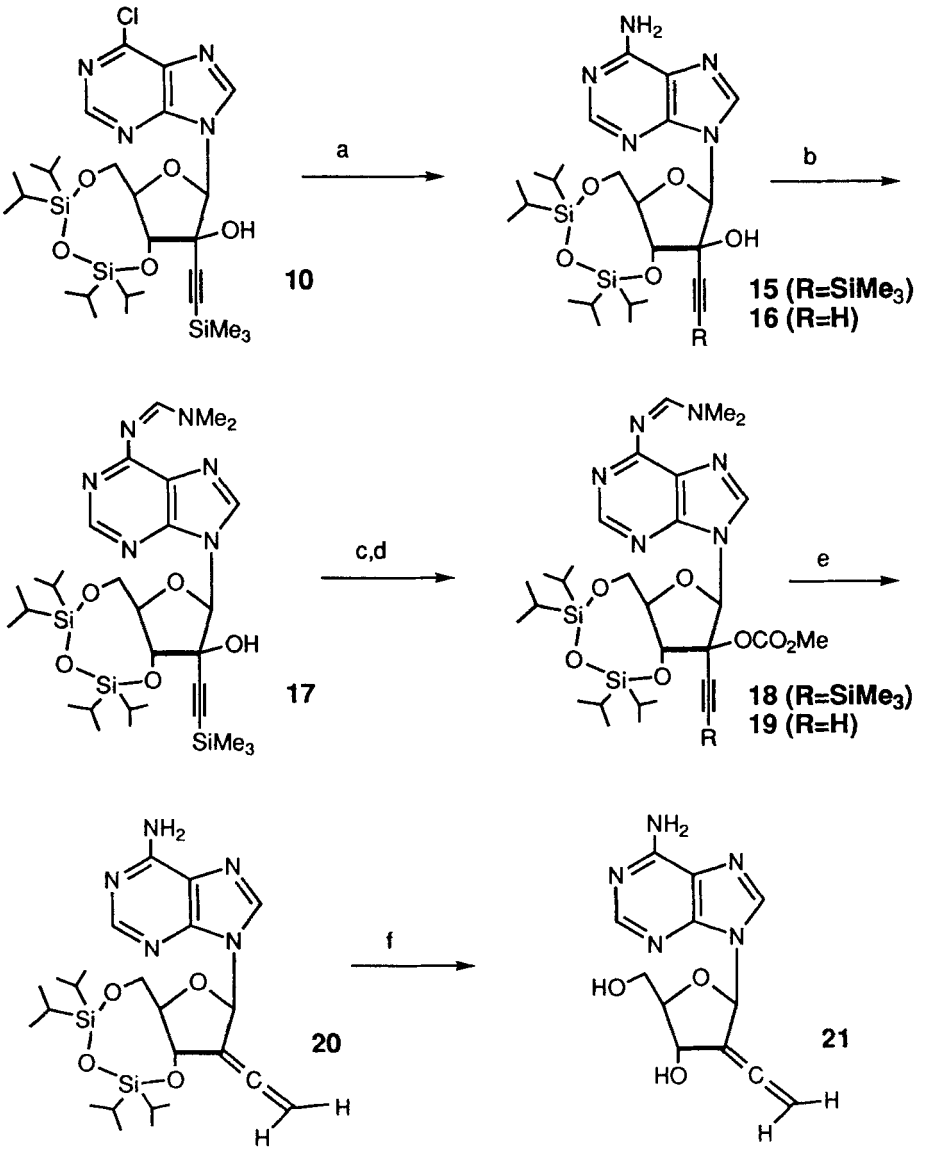
Selective deprotection of **11** with $AgNO_3$-KCN[17] yielded **12**. However, treatment of **12** under the conditions of Tsuji and co-workers for allene formation in DMF resulted in precipitation of the palladium catalyst and displacement of the 6-chloro group with a dimethylamino group, but no allene formation was observed. Apparently, the hydrogen chloride formed was detrimental to the palladium catalyzed reaction, since isolated **13** was readily converted to allene **14**. To avoid problems with the 6-chloro group, intermediate **10** was converted to the corresponding arabinosyl adenine analog **15** (Scheme 3) with ethanolic ammonia in 35% yield. Concomitant with the formation of **15**, desilylated acetylene **16** was formed. Attempts to avoid partial desilylation of the acetylene by running the reaction in other solvents were unsuccessful in our hands.

The 6-amino group on **15** was protected as the dimethyl amidine by treatment with dimethylformamide diethyl acetal in THF to give **17** in 77% yield. This protection step was first attempted in ethanol, but partial loss of the trimethylsilyl group was observed as in the methanolic ammonia reaction described above. The tertiary alcohol **17** was converted to the carbonate **18** via the alkoxide anion and the acetylenic trimethylsilyl group was removed with $AgNO_3$-KCN to provide **19** in 73% yield. This intermediate was converted to allene **20** and the N-6-amino protecting group was removed during this conversion. Deprotection of **20** with CsF and methanol gave the target molecule **21** and a small amount of an unidentified side product, which was removed by preparative HPLC. The ^1H NMR showed the characteristic chiral allenic protons at δ 5.09 and 5.19 as doublet of triplets with coupling constants of 12 Hz and 3.7 Hz. Only preliminary biological data is available on **21** and **8**.[19]



Reagents: (a) $Me_3SiC{\equiv}CH$, MeMgCl (b) MeOCOCl (c) $AgNO_3$ (d) KCN (e) HCO_2NH_4 Bu_3P, $Pd_2(dba)_3$, DMF

SCHEME 2



Reagents: (a) NH_3, EtOH (b) $HC(OEt)_2NMe_2$, THF (c) $(Me_3Si)_2NLi$, MeOCOCl (d)$AgNO_3$, then KCN (e) HCO_2NH_4, Bu_3P, $Pd_2(dba)_3$, DMF (f) CsF, MeOH

SCHEME 3

In summary, the first allenic nucleosides **8** and **21** containing a sugar modified at the 2'-position were prepared under mild conditions by the procedure developed by Tsuji for the synthesis of allenes. This method should be amenable to the preparation of other allenic nucleosides.

EXPERIMENTAL

General: All melting points are uncorrected. ^{1}H-NMR spectra were determined with a Varian VXR-300 spectrometer. Mass spectra were obtained with a Finnigan MAT Model 4600 spectrometer. Exact mass determinations were obtained on a ZAB2-SE high resolution mass spectrometer with perfluoro kerosene as reference. Reactions were carried out under nitrogen unless otherwise indicated. The silica gel used in flash chromatography was 40-63 mm size. Commercially available (Aldrich, Sure Seal) dry solvents were used except for aqueous reactions. Tris(dibenzylidineacetone)dipalladium(0), $Pd_2(dba)_3$, was used as received from the supplier (Johnson & Mathey).

TIPDS is used as an abbreviation for tetraisopropyldisiloxyl.

4-Ethoxy-1-[2-0-methoxycarbonyl-2-(trimethylsilylethynyl)-3,5-0-TIPDS-1,3-diyl-β-D-arabinofuranosyl]-2(1H)-pyrimidone (**4**) and alcohol (**5**). To 5.6 mL (39.6 mmol) of trimethylsilylacetylene in 50 mL dry THF, cooled in an ice-bath, was added 14 mL of 2.0 M EtMgBr in THF (Aldrich) over 3 min. After 40 min. at this temperature, 4.77 g (9.34 mmol) of 4-methoxy-1-(3,5-0-TIPDS-1,3-diyl-β-D-erythropentofuran-2-ulosyl)-2(1H)-pyrimidinone **15** in 18 mL THF was added. After 2 h, 3.6 mL (46 mmol) of methyl chloroformate was added. The mixture was allowed to come to ambient temperature and stirred overnight. Quenching with water and extractive workup with brine and EtOAc (600 ml) yielded an oil after concentration *in vacuo*. Part of the oil crystallized on standing and was stirred with 20 mL of cyclohexane and filtered yielding 1.83 g of **4**, mp 151-152°C. The filtrate was concentrated. Flash chromatography (10% EtOAc-90% cyclohexane) yielded another 1.57 g (combined yield 55%) of solid **4** after seed crystals were added. ^{1}H NMR ($CDCl_3$) δ 0.16 (5, 9H), 1.0-1.15 (m, 28 H) 1.33 (t, 3H, *J*=7.1 Hz), 3.71 (s, 3H), 3.95-4.10 (m, 3H), 4.42 (q, 2H, *J*=7.1 Hz), 4.61 (m, 1H), 5.21 (d, 1H, *J*=7.7 Hz), 7.62 (d, 1H, *J*=7.4 Hz). Anal. Calcd for $C_{30}H_{52}O_9N_8Si_2$: C, 53.86, H, 7.83, N, 4.19. Found: C, 53.52; H, 7.61; N, 4.27.

If the methylchloroformate is omitted and the reaction is quenched with aqueous ammonium chloride, extractive workup yields alcohol **5** as an oil in 53% yield.

^{1}H NMR (DMSO-d_6, 500 MHz): δ 0.13 (s, 9H), 0.92-0.97 (m, 28H), 1.26 (t, 3H, *J*=7.1 Hz, CH_3), 3.78 (m, 1H, H'-4'), 3.95 (dd, 1H, *J*=12.7 Hz, 2.8, H-5'), 3.99

(dd, 1H, *J*=12.7 Hz, 4.4, H-5'), 4.06 (d, 1H, *J*= 7.8 Hz, H-5'), 4.27 (q, 2H, *J*=6.8 Hz, CH_2), 5.91 (d, 1H, *J*=7.6 Hz), 6.12 (s, 1H, H-1'), 6.39 (s, 1H, 2'-OH), 7.2 (d, 1H, *J*=7.3 Hz).

The arabino configuration for **5** was assigned based on two dimensional NOE experiments: A NOE was observed between the 2'-OH and 3'-H and between H-1' and H-4', but no NOE between the 2'-OH and H-1'.

4-Ethoxy-1-(2-0-methoxycarbonyl-2-ethynyl-3,5-0-TIPDS-1,3-diyl-β-D-arabinofuranosyl)-2(1H)-pyrimidone (6). To trimethylsilylacetylene **4** (691 mg, 1.0 mmol) in 4 mL ethanol was added 700 mg $AgNO_3$ (4.12 mmol, dissolved in 1.5 mL H_2O, then diluted with 9 mL ethanol). After stirring for 40 min., a solution of 860 mg (13.2 mmol) KCN in 2.6 mL H_2O was added. After 3 min., EtOAc and brine were added. The EtOAc layer was separated and evaporated *in vacuo*. The residue was partitioned between EtOAc and water and the EtOAc layer yielded an oil on evaporation. Flash chromatography (30% EtOAc-70% cyclohexane) yielded 346 mg (56%; yields varied from 55-68% in other runs) of **6**, mp 65-70°C. ^1H NMR ($CDCl_3$) δ 1.0-1.1 (m, 28H), 1.35 (t, 3H, *J*=7.0 Hz), 2.81 (s, 1H, C≡C-H), 3.74 (s, 3H), 3.95-4.10 (m, 3H), 4.44 (q, 2H, *J*=7.1 Hz), 4.64 (m, 1H), 5.84 (d, 1H, *J*=7.7 Hz), 6.65 (m, 1H, H-1'), 7.65 (d, 1H, *J*=7.5 Hz); MS (CI/CH_4) m/z 5.97 (MH^+). Anal. Calcd for $C_{27}H_{44}O_9N_2Si_2$: C, 54.34; H, 7.43; N, 4.69. Found: C, 54.27; H, 7.29; N, 4.75.

4-Ethoxy-1-(2-deoxy-2-ethenylidene-3,5-O-TIPDS-1,3-diyl-β-D-erythro-pentofuranosyl)-2(1H)-pyridimidone (7). To a mixture of 28 mL DMF, 613 mg of ammonium formate (9.6 mmol) and 303 mg (0.33 mmol) of $Pd_2(dba)_3$ (Johnson and Mathey), stirred under argon, was added 318 ml Bu_3P. After 20 min., 1.92 g (3.2 mmol) of **6** in 15 mL DMF was added and the mixture placed in a 70°C oil bath. Gas evolution (CO_2) was over in 10 min. and Pd catalyst precipitated as a dark solid. After 30 min., at 70°C, the reaction mixture was partitioned between 700 mL EtOAc and H_2O (several extractions). The EtOAc yielded 2.15 g of greenish oil. Flash chromatography (20-30% EtOAc and cyclohexane) yielded 752 mg of **7** as an oil (R_f=0.67 with 1:1 EtOAc-cyclohexane on silica gel TLC), 45% yield. ^1H NMR ($CDCl_3$) δ 1.0-1.15 (m, 28H), 1.35 (t, 3H, *J*=7.1 Hz), 3.87 (m, 1H), 4.07 (m, 2H), 4.35 (q, 2H, *J*=7.1 Hz), 5.0-5.12 (m, 2H, C=C=CH_2), 5.24 (m, 1H), 5.87 (d, 1H, *J*=7.4 Hz), 6.80 (m, 1H, H-1'), 7.56 (d, 1H, *J*=7.4 Hz); MS (CI/CH_4) m/z 523 (MH^+). Exact mass calcd for $C_{25}H_{42}O_6N_2Si_2$: 522.2581 (M^+). Found: 522.2570.

2'-Deoxy-2'-(ethenylidene)cytidine (8). A mixture of 226 mg (0.43 mmol) of **7** and 170 mg (1.1 mmol) of CsF in 2 mL MeOH was stirred overnight. TLC

(5% MeOH-95% $CHCl_3$) indicated an intermediate (R_f=0.38) and completely desilylated product (R_f=0.1) An additional 30 mg of CsF was added and the mixture was heated at 60°C for 3 h. TLC indicated only the R_f=0.1 product. The cooled reaction mixture was placed on a 30 mm x 22 cm flash column and eluted with $CHCl_3$, then 10% MeOH-90% $CHCl_3$. The desired product, 104 mg, was isolated upon evaporation of the fractions containing UV-active material.

The ^1H NMR ($CDCl_3$) of this oil revealed loss of the TIPDS-protecting group but also partial conversion of OEt to OMe.

The above 104 mg was dissolved in 4 mL MeOH and placed in a pressure tube (Ace Glass). Ammonia was bubbled through the ice-cooled mixture and the capped tube was kept 8 h at 60°C and left for 3 days at ambient temperature. Solvent was evaporated and the residue was chromatographed on a 22 mm x 23 cm flash column with 10% MeOH -90% $CHCl_3$ followed by 25% MeOH. The fractions containing the new product (R_f=0.6, 1:1 MeOH-$CHCl_3$) yielded 68 mg of **8** as a foam (62%). Evaporation from EtOAc yielded a solid which retained some solvent. ^1H NMR (DMSO-d_6) δ 3.47-3.67 (m, 2H, H-5'), 3.67-3.77 (m, 1H, H-4'), 4.66 (m, 1H, H-3'), 4.91 (t, 1H, *J*=5.6 Hz, 5'-OH), 5.10 (dt 1H, *J*=12.0 Hz, 3.9 allene), 5.16 (dt, 1H, *J*=12.0 Hz, 3.9, allene), 5.72 (d, 1H, *J*=6.9 Hz, OH), 5.73 (d, 1H, *J*=7.3 Hz, H-5), 6.72 (td, 1H, *J*=4.0 Hz, 1.2, H-1'); MS (CI/CH_4): m/z 252 (MH^+). Exact mass calcd for $C_{11}H_{13}N_3O4$: 251.0906 (M^+). Found: 251.0909.

9-[2-(Trimethylsilylethynyl)-3,5-0-TIPDS-1,3-diyl-β-D-arabinofuranosyl]-6-chloropurine (**10**). The ketone **9** (6.10 g, 11.5 mmol) was refluxed for 1 h in 100 mL benzene with a Dean-Stark setup. Evaporation yielded a foam, which turned to an oil/glass on gentle heating while kept *in vacuo* (1 mm). The oil was dissolved in 30 mL of THF. To 4.7 mL (33.2 mmol) of trimethylsilylacetylene in 20 mL dry THF, cooled in an ice bath and under nitrogen, was added 22 mL of 1.0 M MeMgCl in THF. After 20 min., ketone **9** (predried as above) was added. After 15 min., the cooling bath was removed and the mixture was stirred for 2 h. Quenching with 10 mL saturated aq. NH_4Cl followed by extractive (EtOAc) workup yielded 6.82 g of **10** as an oil/foam (94%). ^1H NMR ($CDCl_3$) δ 0.18 (s, 9H), 1.0-1.15 (m, 28H), 4.05-4.15 (m, 4H), 4.46 (d, 1H, *J*=7.3 Hz), 6.35 (s, 1H), 8.54 (s, 1H), 8.74 (s, 1H).

9-[2-0-methoxycarbonyl-2-(trimethylsilylethynyl)-3,5-0-TIPDS-1,3-diyl-β-D-arabinofuranosyl]-6-chloropurine (**11**). Under conditions similar to those described above, 2.80 mL (19.8 mmol) of trimethylsilylacetylene in 20 mL THF and 14.8 mL of 1.0 M EtMgBr were allowed to react, followed by addition of

2.61 g of ketone **9** (4.95 mmol). After 1 h, the mixture was cooled in an ice bath and 2.0 mL (25.8 mmol) of methyl chloroformate was added. The mixture was allowed to come to ambient temperature, stirred overnight, quenched with 10 mL of saturated NH_4Cl solution and extracted with EtOAc to yield 4.27 g of an oil on evaporation of the solvent. Flash chromatography (40 mm x 22 cm column) with 10% EtOAc-90% cyclohexane yielded 2.98 g (88%) of **11** as oil/foam, R_f=0.26 (silica gel, 20% EtOAc-80% cyclohexane). ^1H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.05-1.20 (m, 28H), 3.57 (s, 3H), 4.05-4.20 (m, 3H), 5.27 (d, 1H, *J*=6.6 Hz), 6.63 (s, 1H), 8.28 (s, 1H), 8.74 (s, 1H).

9-(2-O-methoxycarbonyl-2-ethynyl-3,5-O-TIPDS-1,3-diyl-β-D-arabinofuranosyl)-6-chloropurine (**12**). A solution of $AgNO_3$ (1.7 g, 10 mmol) was prepared by dissolving in 3.5 mL water and diluting with 23 mL ethanol. This was added to 1.67 g (2.44 mmol) of **11** in 10 mL ethanol. The mixture was stirred 1 h and then 2.6 g (40 mmol) of KCN in 8 mL water was added. The mixture was stirred 5 min and extracted with 400 mL EtOAc. The EtOAc was separated and concentrated *in vacuo*. The residue was partitioned between saturated NaCl and EtOAc. KCN (5 g) was added until all solids dissolved. The EtOAc layer was dried ($MgSO_4$) and evaporated. Flash chromatography (20% EtOAc-cyclohexane) of the residue yielded 1.28 g (86%) of **12** as a foam. ^1H NMR ($CDCl_3$) δ 1.05-1.20 (m, 22H), 2.83 (s, 1H, acetylenic), 3.56 (s, 3H), 4.05-4.20 (m, 3H), 5.30 (d, 1H, *J*=7.2 Hz, H-3'), 6.67 (s, 1H, H-1') 8.25 (s, 1H), 8.76 (s, 1H); MS (CI/CH_4): Exact mass calcd for (MH^+), $C_{26}H_{40}ClN_4O_7Si_2$: 611.2124. Found: 611.2106.

N^6-Dimethyl-9-(2-O-methoxycarbonyl-2-ethynyl-3,5-O-TIPDS-1,3)-diyl-β-D-arabinofuranosyl)adenine (**13**). When 340 mg of **12** was treated with palladium catalyst under the same conditions as described for **7** no gas evolution was observed [340 mg of **12**, 105 mg HCO_2NH_4, 53 mg $Pd_2(dba)_3$, 54 ml Bu_3P and 8 mL DMF]. The mixture was heated starting at 55°C and warming to 80°C over 50 min., cooled, and worked up with EtOAc and water. The EtOAc layer was dried ($MgSO_4$), evaporated to an oil and purified by flash chromatography (20% EtOAc-80% cyclohexane) to provide 98 mg (28%) of **13** as the only major product. Other solvents were tried (THF and 1-methyl-2-pyrrolidone) but did not afford any detectable allene products. ^1H NMR ($CDCl_3$) δ 1.0-1.2 (m, 28H), 2.79 (s, 1H, acetylenic), 3.52 (broad, 6H, NMe_2), 3.59 (s, 3H), 4.03-4.13 (m, 2H), 4.22 (m 1H), 5.40 (d, 1H, *J*=6.8 Hz), 6.58 (s, 1H), 7.87 (s, 1H), 8.34 (s, 1H); MS (CI/CH_4): m/z 620 (MH^+).

N^6-Dimethyl-2'-deoxy-2'-(ethynylidene)adenosine (**14**) A mixture of 3 mL DMF, 105 mg (1.7 mmol) of HCO_2NH_4 and $Pd_2(dba)_3$ (51 mg, 0.05 mmol) was stirred under argon. Bu_3P (51 ml) was added and after 20 min., 271 mg of **13** in 2 mL of DMF was added. The flask was placed in a 65-75°C oil bath for 1 h (gas evolution for 10-20 min.). The mixture was partitioned between EtOAc and water. Evaporation of the EtOAc layer gave 301 mg of an oil. Flash chromatography (10% EtOAc-90% cyclohexane, then 15% EtOAc) yielded 88 mg of **14** (36%) as an oil. ^1H NMR ($CDCl_3$) δ 1.0-1.2 (m, 28H), 3.52 (m, 6H), 3.95-4.10 (m, 3H), 5.04 (ddd, 1H, *J*=11.8 Hz, 5.1, 3.4, allenic), 5.25 (ddd, 1H, *J*=11.8 Hz, 5.0, 3.3, allenic), 5.44 (m, 1H), 6.77 (td, 1H, *J*=3.4 Hz, 1.5, H-1'), 7.82 (s, 1H), 8.33 (s, 1H); MS (CI/CH_4): m/z 546 (MH^+). Exact mass calcd. for $C_{26}H_{44}N_5O_4Si_2$: 546.2931 (MH^+). Found: 546.2949.

9-[2-(Trimethylsilylethynyl)-3,5-O-TIPDS-1,3-diyl-β-D-arabinofuranosyl]adenine (**15**) and 9-(2-ethynyl-3,5-O-TIPDS-1,3-diyl-β-D-arabinofuranosyl)adenine (**16**). A 6.3 g (10 mmol) sample of **10** was dissolved in ethanol and concentrated *in vacuo* two times. The residue was dissolved in 100 mL of dry ethanol and placed into a pressure tube. The tube was cooled in an ice bath and anhydrous ammonia was bubbled through the solution for 20 min. The tube was capped and placed in a 50°C oil bath for 5 h and allowed to stand overnight at ambient temperature. TLC (50% EtOAc-50% cyclohexane) indicated incomplete reaction; the solution was resaturated with ammonia (ice bath), capped and kept at 60°C for 24 h. The tube was cooled, opened and the solution concentrated. The residue was chromatographed on a 44 mm x 10 cm flash column with 1:1 EtOAc-cyclohexane. The first component eluted was **15** which was obtained as an oil/foam (2.04 g, 33%) after concentration of the appropriate fractions *in vacuo*. The second component collected was **16** (2.31 g, 43%). In other runs that were monitored by TLC, **16** was always present by the time starting material was nearly consumed. **15**:^1H NMR ($CDCl_3$) δ 0.13 (s, 9H), 1.0-1.2 (m, 28H), 4.0-4.18 (m, 3H), 4.48 (d, 1H, *J*=7.0 Hz), 5.92 (broad, 2H, NH_2), 6.24 (s, 1H, H-1'), 8.14 (s, 1H), 8.20 (d, 1H, *J*=2.3 Hz); MS (CI/CH_4): m/z 606 (MH^+); **16**:^1H NMR ($CDCl_3$) δ 1.0-1.2 (m, 28H), 2.72 (s, 1H, acetylenic), 4.0-4.2 (m, 3H), 4.47 (d, 1H, *J*=7.4 Hz), 6.15 (broad 2H, NH_2), 6.29 (s, 1H, H-1'), 8.16 (m, 1H), 8.16 (s, 1H).

N-[Dimethylamino)methylene]-9-[2-(trimethylsilylethynyl)-3,5-O-TIPDS-1,3-diyl-β-D-arabinofuranosyl]adenine (**17**). To a mixture of 303 mg (0.5 mmol) of **15** in 1 mL THF was added 0.26 mL (1.5 mmol) of dimethylformamide diethyl acetal. The mixture was stirred 2 h and then placed on a 30 mm x 14 cm flash

column. Elution with 5% MeOH - 95% $HCCl_3$ yielded 254 mg (77%) of **17** as an oil. ^1H NMR ($CDCl_3$) δ 0.15 (s, 9H), 3.20 (s, 3H), 3.26 (s, 3H), 4.0-4.15 (m, 3H), 4.50 (d, 1H, *J*=6.3 Hz), 6.21 (s, 1H, H-1'), 8.17 (s, 1H), 8.48 (s, 1H), 8.90 (s, 1H, amidine).

N-[(Dimethylamino)methylene]-9-[2-O-methoxycarbonyl-2 (trimethylsilylethynyl)-3,5-O-TIPDS-1,3-diyl-β-D-arabinofuranosyl]adenine (**18**) and N-[(Dimethylamino)methylene]-9-[2-O-methoxycarbonyl-2-ethynyl-3,5-O-TIPDS-1,3-diyl-β-D-arabinofuranosyl]adenine (**19**). To 840 (1.27 mmol) **17** in 3 mL THF cooled in ice was added 1.90 mL (1.5 eq) of 1.0 M $LiN(SiMe_3)_2$ in THF. After 20 min., 0.16 mL (2.0 mmol) of methyl chloroformate was added. Quenching after 6 h with saturated aq. NH_4Cl and EtOAc extraction provided 978 mg (100%) of **18** as an oil. ^1H NMR ($CDCl_3$) δ 0.17 (s, 9H), 1.0-1.2 (m, 28H), 3.21 (s, 3H, NMe), 3.26 (s, 3H, NMe), 3.53 (s, 3H, OMe), 4.0-4.3 (m, 3H), 5.45 (d, 1H, *J*=6.9 Hz), 6.59 (s, 1H, H-1'), 8.01 (s, 1H), 8.53 (s, 1H), 8.93 (s, 1H).

To the 978 mg of **18** in 5 mL ethanol was added 856 mg of $AgNO_3$ in 1.8 mL of water and 11 mL ethanol. After 1 h, 3.94 g KCN in 12 mL H_20 was added. The mixture was extracted with 600 mL EtOAc. The EtOAc layer was dried ($MgSO_4$) and concentrated *in vacuo* and the residue was partitioned between water and EtOAc. The EtOAc layer yielded 925 mg oil. This oil was placed on a 30 mm x 14 cm flash column and eluted with 5% MeOH-95% EtOAc to afford 606 mg (73%) of **19** as an oil. NMR samples of **19** in $CDCl_3$ showed loss of amidine on standing. ^1H NMR ($CDCl_3$) δ 1.00-1.20 (m, 28H), 2.81 (s, 1H), 3.21 (s, 3H, NMe), 3.27 (s, 3H, NMe), 3.53 (s, 3H, OMe), 4.03-4.15 (m, 3H), 4.27 (m, 1H), 5.48 (d, 1H, *J*=7.4 Hz), 6.62 (s, 1H), 8.01 (s, 1H), 8.54 (s, 1H), 8.94 (s, 1H).

3',5'-O-TIPDS-1,3-diyl-2'-deoxy-2'-(ethenylidene)adenosine (**20**). The reagents were added in the order mentioned under **14** and **8** and a mixture of 236 mg (0.36 mmol) of **19**, 87 mg HCO_2NH_4, 42 mg $Pd(dba)_3$, 45 ml Bu_3P and 4.5 mL DMF was placed into a 68°C oil bath for 30 min. EtOAc extraction yielded 203 mg crude products. Flash chromatography (1:1 EtOAc cyclohexane, then EtOAc) yielded 61 mg of **20** as an oil (Rf=0.28, silica gel and EtOAc TLC). ^1H NMR ($CDCl_3$) δ 1.0-1.2 (m, 28H), 3.95-4.15 (m, 3H), 5.05 (ddd, 1H, *J*=11.8 Hz, 5.1, 3.3), 5.28 (ddd, 1H, *J*=3.3, 4.9, 11.9), 6.1 (broad, 2H, NH_2), 6.75 (m, 1H, H-1'), 7.92 (s, 1H), 8.33 (s, 1H); MS (CI/CH_4): m/z 518 (MH^+). Exact mass calcd for $C_{24}H_{39}N_5O_4Si_2$: 517.2541 (M^+). Found: 517.2542.

2'-Deoxy-2'-(ethynylidene)adenosine (**21**). To 128 mg of **20** (0.25 mmol) in 1 mL of MeOH was added 130 mg (0.85 mmol) CsF. The mixture was stirred

overnight and placed on a 20 mm x 19 cm flash column. Elution with 10% MeOH-90% EtOAc yielded 73 mg of **18**. (R_f=0.21, 10% MeOH-90% EtOAc, silica gel) as a solid. HPLC indicated an impurity, eluting earlier than **21** (up to 30% of the HPLC sample). Preparative HPLC with a 19 mm x 30 cm Deltapak column with 5-10% CH_3CN in water yielded 25 mg (37%) of pure **21**, mp 195-200°C (decomp) after freeze drying of the appropriate fractions. ^1H NMR (DMSO-d_6): δ 3.53-3.73 (m, 2H), 3.90 (m, 1H, H-4'), 4.93 (m, 1H, H-3'), 5.0-5.2 (broad, 1H, 5'-OH), 5.09 (dt, 1H, *J*=12, 3.7 Hz, allenic), 5.19 (dt, 1H, *J*=12 Hz, 3.7, allenic), 5.83 (br s, 1H, 3'-OH), 6.78 (m, 1H, H-1'), 7.30 (s, 2H, NH_2), 8.13 (s, 1H, H-2), 8.26 (s, 1H, H-8); MS (CI/CH_4): Exact mass calcd for $C_{12}H_{13}N_5O_3$ 275.1018 (M^+). Found: 275.1002.

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19. Nucleoside **21** inhibited HeLa cell proliferation and HSV-1 with IC_{50} values in the 5-10 mg/mL range. It was also deaminated by calf spleen adenosine deaminase (Sigma). Nucleoside **8** had similar modest activity in these screens.

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