Novel, Stable Congeners of the Antiretroviral Compound 2′,3′-Dideoxyadenosine

Vasu Nair* and Greg S. Buenger

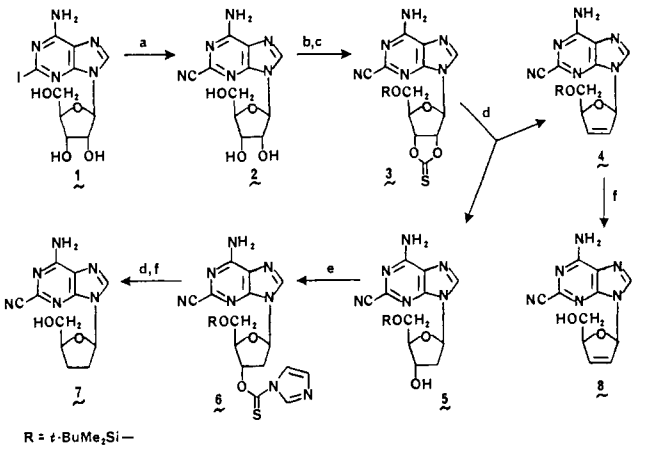
Contribution from the Department of Chemistry, The University of Iowa, Iowa City, Iowa 52242.
Received April 10, 1989

Abstract: Novel congeners of the antiretroviral compound 2′,3′-dideoxyadenosine (ddA) have been synthesized through metal-mediated and photochemical conversions as the key steps. These compounds are inherently more stable than ddA with respect to both glycosidic bond cleavage and deamination by adenosine deaminase.

2′,3′-Dideoxygenated analogues of the natural ribonucleosides have elicited considerable antiviral interest recently because of their ability to inhibit the cytopathic effect of the human immunodeficiency virus (HIV), the etiologic agent of acquired immunodeficiency syndrome (AIDS).[1-5] For example, 2′,3′-dideoxyadenosine (ddA), as its cellularly produced 5′-triphosphate (ddATP), is an inhibitor of HIV reverse transcriptase, an enzyme which plays a vital role in the life cycle of this virus.[5-8] However, ddA is rapidly deaminated by the ubiquitous enzyme adenosine deaminase to 2′,3′-dideoxyinosine (ddI),[7] which can return to the ddA nucleotide pool via ddIMP or be catabolized by purine-nucleoside phosphorylase.[9] In addition to this enzymatic instability, ddA is also unstable with respect to hydrolytic cleavage of the glycosidic bond.[10] Both of these factors limit the usefulness of ddA both as a biological probe and as an antiviral agent. The design of congeners of ddA that would be hydrolytically and enzymatically stable would be of considerable significance in this area. This paper reports on the synthesis and stability studies of such novel congeners of ddA. The rationale for the choice of functionalization at the 2-position was 2-fold. First, initial phosphorylation of ddA by mammalian deoxycytidine kinase[11] appears to be significant for its subsequent conversion to its triphosphate and its eventual biological activity.[5-9] Enzymatic data for 2′-deoxyadenosines suggest that judicious 2-substitution in general does not eliminate substrate activity by deoxycytidine kinase.[12] Second, greater stabilization of the glycosidic bond may also be possible with appropriate substitution at this position.

The syntheses are exemplified by the case of 2-cyano-2′,3′-dideoxyadenosine (**7**) where 2-iodoadenosine (**1**)[13] served as the key precursor (Scheme I). Palladium-catalyzed cross-coupling of *unprotected* 2-iodoadenosine with tri-*n*-butylcyanostannane in DMF resulted in regiospecific formation of 2-cyanoadenosine (**2**)[14]

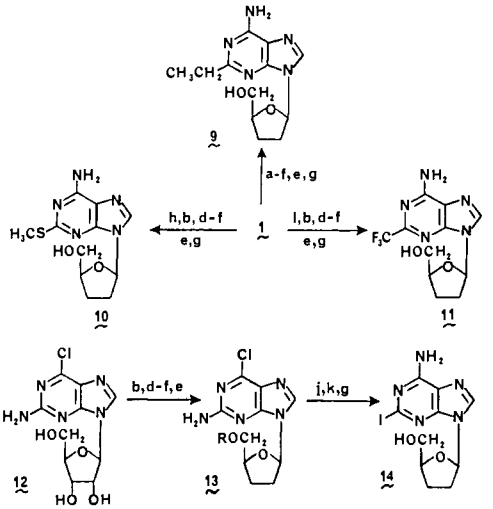
Scheme I[a]



R = *t*-BuMe$_2$Si—

[a] (a) Bu_3SnCN, $[P(C_6H_5)_3]_4Pd$, DMF, Δ; (b) *t*-$Bu(CH_3)_2SiCl$, 4-(dimethylamino)pyridine, $(C_2H_5)_3N$, DMF, CH_2Cl_2; (c) 1,1′-thiocarbonyldiimidazole, DMF, 25 °C; (d) Bu_3SnH, AIBN, toluene, 110 °C; (e) 1,1′-thiocarbonyldiimidazole, DMF, 90 °C; (f) Et_4NF, CH_3CN.

Scheme II[a]



[a] (a) $Bu_3SnCH{=}CH_2$, $PdCl_2(CH_3CN)_2$, DMF, Δ; (b) *t*-$Bu(CH_3)_2SiCl$, 4-(dimethylamino)pyridine, $(C_2H_5)_3N$, DMF, CH_2Cl_2; (c) H_2, 10% Pd/C, C_2H_5OH; (d) 1,1′-thiocarbonyldiimidazole, DMF, 25 °C; (e) Bu_3SnH, AIBN, toluene, 110 °C; (f) 1,1′-thiocarbonyldiimidazole, DMF, 90 °C; (g) Et_4NF, CH_3CN; (h) $(CH_3S)_2$, CH_3CN, *hν*; (i) CF_3ZnBr, CuBr, DMF, HMPA; (j) *t*-BuONO, CH_2I_2, hexane, 70 °C; (k) NH_3, C_2H_5OH.

in 86% yield. This conversion represents another new type of application of the palladium-catalyzed methodology in nucleoside chemistry. Regiospecific 5′-silylation (70%) followed by treatment of the resulting silylated compound with 1,1′-thiocarbonyldiimidazole in DMF gave the cyclic thiocarbonate **3** (87%). Re-

(1) *AIDS*; Broder, S., Ed.; Dekker: New York, 1987; and references cited therein.
(2) AIDS. *Chem. Eng. News* **1987**, *Nov* 23, 12-70, and references cited therein.
(3) De Clercq, E. *J. Med. Chem.* **1986**, *29*, 1561.
(4) Fauci, A. S. *Science* **1988**, *239*, 617.
(5) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
(6) Balzarini, J.; Kang, G.; Dalal, M.; Herdewijn, P.; De Clereq, E.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1987**, *32*, 162.
(7) Cooney, D. A.; Ahluwalia, G.; Mitsuya, H.; Fridland, A.; Johnson, M.; Hao, Z.; Dalal, M.; Balzarini, J.; Broder, S.; Johns, D. G. *Biochem. Pharmacol.* **1987**, *36*, 1765.
(8) Mitsuya, H.; Jarrett, R. F.; Matsukura, M.; Veronese, F.; DeVico, A. L.; Sarngadharan, M. G.; Johns, D. G.; Reitz, M. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2033.
(9) Ahluwalia, G.; Cooney, D. A.; Mitsuya, H.; Fridland, A.; Flora, K. P.; Hao, Z.; Dalal, M.; Broder, S.; Johns, D. G. *Biochem. Pharmacol.* **1987**, *36*, 3797. Hao, Z.; Cooney, D. A.; Hartman, N. R.; Perno, C. F.; Fridland, A.; DeVico, A. L.; Sarngadharan, M. G.; Broder, S.; Johns, D. G. *Mol. Pharmacol.* **1988**, *34*, 431.
(10) York, J. L. *J. Org. Chem.* **1981**, *46*, 2171.
(11) Datta, N. S.; Shewach, D. S.; Hurley, M. C.; Mitchell, B. S.; Fox, I. H. *Biochemistry* **1989**, *28*, 114 and references cited therein.
(12) Krenitsky, T. A.; Tuttle, J. V.; Koszalka, G. W.; Chen, I. S.; Beacham, L. M., III; Rideout, J. L.; Elion, G. B. *J. Biol. Chem.* **1976**, *251*, 4055. Haertle, T.; Carrera, C. J.; Wasson, D. B.; Sowers, L. C.; Richman, D. D.; Carson, D. A. *J. Biol. Chem.* **1988**, *263*, 5870.
(13) Nair, V.; Young, D. A. *J. Org. Chem.* **1985**, *50*, 406.
(14) Murakami, T.; Otsuka, M.; Kobayashi, S.; Ohno, M. *Heterocycles* **1981**, *16*, 1315.

0002-7863/89/1511-8502$01.50/0

ductive cleavage of **3** with *n*-Bu_3SnH in the presence of AIBN[15] accomplished two things. First, 2'-deoxygenation occurred regiospecifically to give the deoxynucleoside **5** in 57% yield. This regiospecific cleavage at the 2'-position of nucleoside cyclic thiocarbonates has not been observed previously (cf. ref 15), but it is mechanistically consistent with the preferred mode of cleavage of the intermediate radical formed from **3** and *n*-Bu_3SnH and AIBN. Second, and interestingly, complete elimination of the thiocarbonate group produced the unsaturated nucleoside **4** in 30% yield. This is the first example of substantial amounts of such a product being produced from a purine nucleoside cyclic thiocarbonate under this radical deoxygenation procedure.[16]

The 2'-deoxygenated compound **5** was converted to the novel 2-cyano-2',3'-dideoxyadenosine (**7**) through its 3'-imidazolide by treatment with *n*-Bu_3SnH and AIBN,[17] followed by deprotection of the silyl group with tetraethylammonium fluoride. Alternatively, compound **7** may be synthesized more directly through the catalytic hydrogenation of **4** followed by deprotection. Compound **7** was characterized by UV data (λ_{max} 260, 266, 297 nm), FTIR (2200 cm^{-1}), FAB HRMS ($M^+ + H$ ion at 261.1069), and high-field ^1H and ^{13}C NMR data. Deprotection of **4** gave the novel didehydrodideoxynucleoside **8**. Thus, the deoxygenation reaction described can be used to synthesize both dideoxynucleosides and dideoxydidehydronucleosides through a single route.

The key precursor for the synthesis of 2-ethyl-2',3'-dideoxyadenosine was also 2-iodoadenosine (**1**) (Scheme II). Palladium-catalyzed cross-coupling of **1** with vinyltri-*n*-butylstannane,[18] resulted in regiospecific introduction of the vinyl group at the 2-position in almost quantitative yield. Subsequent selective 5'-silylation followed by catalytic hydrogenation of the 2-vinyl group and dideoxygenation and deprotection gave the target molecule **9**. 2-(Methylthio)-2',3'-dideoxyadenosine (**10**) was of interest because of the known contribution of the thiomethyl group to the biological activity of some related ribonucleosides.[19-21] The immediate precursor of **10** was 2-(methylthio)adenosine, which was prepared from 2-iodoadenosine (**1**) by photochemical alkylthiolation.[22] Application of the dideoxygenation procedure to this precursor gave **10**.

2-(Trifluoromethyl)adenosine was the immediate precursor for the synthesis of **11** through the previously described dideoxygenation sequence. This precursor was prepared directly from **1** in 70% yield by reaction with "CF_3Cu" (cf. ref 23). The copper reagent was generated in situ from CF_3ZnBr and CuBr.[24] Another 2-halogenated congener, 2-iodo-2',3'-dideoxyadenosine (**14**), was also prepared. 2-Amino-6-chloropurine ribonucleoside (**12**)[25] was dideoxygenated to provide the new dideoxy compound **13**. Halogen–amino group interchange followed by deprotection gave the novel dideoxynucleoside **14**.

The glycosidic bond stabilities of these dideoxynucleosides were investigated by differential UV spectroscopy at pH 3 where easily observable rates could be obtained.[26] The relative rate data can be summarized as follows: ddA (100), 2-cyano-ddA (47), 2-ethyl-ddA (75), 2-(methylthio)-ddA (64), 2-(trifluoromethyl)-ddA (81), and 2-iodo-ddA (55). It is immediately apparent that all of the dideoxynucleosides synthesized in this work are more stable with respect to glycosidic bond cleavage than 2',3'-dideoxyadenosine. Both electronic and conformational effects may be contributing to this increased stability. Additionally, all of the novel dideoxynucleosides synthesized were totally resistant to deamination by mammalian adenosine deaminase! Inhibition studies with this enzyme are currently being investigated.

The preferred glycosidic bond conformations of these dideoxypurine nucleosides in solution were qualitatively determined through correlation of their high-field ^{13}C NMR data.[27] Although such correlations for dideoxynucleosides have not been studied previously, it appears from the data of these and other dideoxynucleosides synthesized in our laboratory that in the preferred anti conformation Δ(C-2' minus C-3') is generally greater than 6 ppm and in the syn conformation this difference is less than 3 ppm.

In summary, novel congeners of the antiretroviral compound 2',3'-dideoxyadenosine, with high potential for antiretroviral activity, have been synthesized through photochemical and metal-mediated conversions as the key steps. These congeners are inherently more stable with respect to glycosidic bond cleavage than the parent ddA, and they are totally resistant to hydrolytic deamination by mammalian adenosine deaminase. High-field ^{13}C NMR data suggest that these functionalized congeners of ddA prefer the anti conformation in solution.

Experimental Section

The reported melting points are uncorrected and were determined on a Thomas-Hoover melting point apparatus fitted with a microscope. Nuclear magnetic resonance spectra were recorded on JEOL Model FX90Q and Bruker Model WM360 and MSL 300 pulse Fourier transform spectrometers. Mass spectra were determined on a Hewlett-Packard 5985 GC/MS system or a VG Analytical Model ZAB-HF instrument with high-resolution FAB capability. Ultraviolet spectra were recorded on a Varian Cary Model 219 or a Gilford Response spectrophotometer. Infrared spectra were recorded on a Mattson Cygnus 25 fourier transform instrument. Preparative layer chromatography plates were prepared by coating six 20 cm × 20 cm plates with a slurry made from 150 g of E. Merck PF_{254} silica gel in 400 mL of water. The silica gel plates were allowed to dry slowly and were then activated for 3 h at 135 °C. Flash chromatography was carried out in glass columns packed with 230–400-mesh silica gel.

General Synthetic Procedures (A–F). Procedure A: Preparation of 5'-*O*-(*tert*-Butyldimethylsilyl) Nucleosides. A mixture of the nucleoside (2 mmol), *tert*-butyldimethylsilyl chloride (2.2 mmol), triethylamine (2 mmol), and *N*,*N*-dimethylaminopyridine (0.3 mmol) in dimethylformamide (10 mL) and dichloromethane (5 mL) was stirred at room temperature under nitrogen for 20 h. The solvents were evaporated and the residue was chromatographed on silica gel with 5% methanol/chloroform.

Procedure B: Preparation of 2',3'-*O*-(Cyclic thiocarbonate). To a solution of the 5'-silylated nucleoside (3 mmol) in dry dimethylformamide (30 mL) was added 1,1'-thiocarbonyldiimidazole (5.25 mmol), and the resulting mixture was stirred at room temperature under nitrogen for 24 h. The solvent was evaporated, and the residue was dissolved in dichloromethane (50 mL) and extracted with water (3 × 20 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography on silica gel with chloroform.

Procedure C: Deoxygenation of 2',3'-*O*-(Cyclic thiocarbonate). A nitrogen-purged solution of tri-*n*-butyltin hydride (10.4 mmol) and azoisobutyronitrile (AIBN) (1.8 mmol) in anhydrous toluene (30 mL) was added dropwise to a refluxing solution of the cyclic thiocarbonate (2.6 mmol) in toluene (60 mL). The mixture was heated to 110 °C for 4 h, and the solvent was evaporated. The residue was purified on silica gel with chloroform followed by 5% methanol/chloroform.

Procedure D: Preparation of 2'-Deoxy-3'-*O*-(1-imidazolylthiocarbonyl)-5'-*O*-(*tert*-butyldimethylsilyl) Nucleosides. To a solution of the 2'-deoxynucleoside (3 mmol) in dry dimethylformamide (25 mL) was added 1,1'-thiocarbonyldiimidazole (4.5 mmol), and the mixture was

(15) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

(16) Although Barton and Subramanian (ref 15) did not report the formation of alkenyl products in their original deoxygenation work, such unsaturated compounds have been produced as minor products during this type of deoxygenation in pyrimidine C-nucleoside chemistry (see Matsuda, A.; Chu, C. K.; Reichman, U.; Pankiewicz, K.; Watanabe, K. A.; Fox, J. J. *J. Org. Chem.* **1981**, *46*, 3603 and Doboszewski, B.; Chu, C. K.; Van Halbeek, H. *J. Org. Chem.* **1988**, *53*, 2777).

(17) Prisbe, E. J.; Martin, J. C. *Synth. Commun.* **1985**, *15*, 401. Webb, R. R., II; Wos, J. A.; Martin, J. C.; Brodfuehrer, P. R. *Nucleosides Nucleotides* **1988**, *7*, 147.

(18) Nair, V.; Turner, G. A.; Chamberlain, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 7223.

(19) Henderson, J. F.; Paterson, A. R. P.; Caldwell, I. C.; Paul, B.; Chan, M. C.; Lau, K. F. *Cancer Chemother. Rep., Part 2* **1972**, *3*, 71.

(20) Miller, R. L.; Adamczyk, D. L.; Miller, W. H.; Koszalka, G. W.; Rideout, J. L.; Beacham, L. M., III; Chao, E. Y.; Haggerty, J. J.; Krenitsky, T. A.; Elion, G. B. *J. Biol. Chem.* **1979**, *254*, 2346.

(21) Sartorelli, A. C.; Shansky, C. W.; Rosman, M. *Cancer* **1975**, *36*, 2445.

(22) Nair, V.; Young, D. A. *Synthesis* **1986**, 450.

(23) Gough, G.; Maguire, M. H. *J. Med. Chem.* **1965**, *8*, 866.

(24) Burton, D. J.; Wiemers, D. M. *J. Am. Chem. Soc.* **1986**, *108*, 832.

(25) Gerster, J. F.; Jones, J. W.; Robins, R. K. *J. Org. Chem.* **1963**, *28*, 945.

(26) Garrett, E. R.; Mehta, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 8532.

(27) Nair, V.; Young, D. A. *Magn. Reson. Chem.* **1987**, *25*, 937.

stirred at 90 °C for 4 h with protection from moisture. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 5% methanol/chloroform.

Procedure E: Deoxygenation of 3′-*O*-(1-Imidazolylthiocarbonyl) Nucleosides. To a refluxing solution of the 3′-*O*-(imidazolylthiocarbonyl) nucleoside (1 mmol) in dry toluene (25 mL) was added a solution of tri-*n*-butyltin hydride (3.5 mmol) and AIBN (0.8 mmol) in toluene (25 mL). The mixture was refluxed for 2 h, the solvent was evaporated, and the residue was purified by preparative TLC with 10% methanol/chloroform as the eluting solvent.

Procedure F: Desilylation. The 5′-silylated 2′,3′-dideoxynucleoside (1.5 mmol) was dissolved in acetonitrile (40 mL). Tetraethylammonium fluoride (4.5 mmol) was added, and the mixture was stirred at room temperature for 2 h. Water (10 mL) was added and stirring continued for 20 min. The solvents were evaporated and the residue was purified by preparative TLC (10% methanol/chloroform) to provide the dideoxynucleoside.

2-Cyano-2′,3′-dideoxyadenosine (7). To a solution of 2-iodoadenosine (**1**) (0.500 g, 1.27 mmol) in DMF (70 mL) were added tetrakis(triphenylphosphine)palladium(0) (0.220 g, 0.19 mmol) and tri-*n*-butyltin cyanide (0.442 g, 1.39 mmol). The mixture was stirred at 120 °C for 20 h under nitrogen. The solvent was then evaporated, and the residue was purified on silica gel to give 2-cyanoadenosine (**2**)[14] in 86% yield. 2-Cyanoadenosine (**2**) was converted to **3** by procedure A (60% yield) and procedure B (89% yield). Deoxygenation of the cyclic thiocarbonate with procedure C gave the 2′-deoxy and the 2′,3′-dideoxy-2′,3′-didehydro compounds **5** and **4** in 57% and 30% yields, respectively. Compound **5**: ^{1}H NMR (Me_2SO-d_6) δ 0.00 (s, 6 H), 0.83 (s, 9 H), 2.67 (m, 2 H), 3.77 (m, 3 H), 4.42 (m, 1 H), 5.37 (m, 1 H), 6.33 (m, 1 H), 7.95 (br s, 2 H), 8.49 (s, 1 H); UV (EtOH) λ_{max} 296, 266, 260 nm. Compound **4**: ^{1}H NMR (Me_2SO-d_6) δ −0.04 (s, 6 H), 0.81 (s, 9 H), 3.81 (m, 2 H), 4.95 (m, 1 H), 6.20 (m, 1 H), 6.50 (m, 1 H), 6.94 (s, 1 H), 7.96 (br s, 2 H), 8.33 (s, 1 H); UV (EtOH) λ_{max} 296, 266, 260 nm.

Desilylation of **4** with procedure F provided 2-cyano-2′,3′-didehydro-2′,3′-dideoxyadenosine (**8**) in 45% yield: mp >250 °C dec ^{1}H NMR (Me_2SO-d_6) δ 3.51 (m, 2 H), 4.90 (m, 2 H), 6.16 (m, 1 H), 6.51 (m, 1 H), 6.94 (m, 1 H), 7.94 (br s, 2 H), 8.39 (s, 1 H); UV (H_2O) λ_{max} 296 (ε 6770), 265.5 (ε 10710), 260 nm (ε 10050); FAB HRMS obsd (M^+ + H) 259.0970, calcd for $C_{11}H_{10}N_6O_2$ 259.0943.

Compound **5** was converted to 2-cyano-2′,3′-dideoxyadenosine (**7**) by in sequence procedure D (63% yield), procedure E (70% yield), and procedure F (70% yield): mp 195–197 °C; ^{13}C NMR (Me_2SO-d_6) δ 25.4, 32.0, 62.6, 82.3, 84.7, 117.0, 120.7, 136.6, 141.5, 147.9, 156.2; ^{1}H NMR (Me_2SO-d_6) δ 2.06 (m, 2 H), 2.39 (m, 2 H), 3.56 (m, 2 H), 4.13 (m, 1 H), 4.92 (m, 1 H), 6.24 (m, 1 H), 7.90 (br s, 2 H), 8.59 (s, 1 H); UV (H_2O) λ_{max} 297 (ε 6470), 266 (ε 9980), 260 nm (ε 9270); FAB HRMS obsd (M^+ + H) 261.1069, calcd for $C_{11}H_{12}N_6O_2$ 261.1099.

2′,3′-Dideoxy-2-ethyladenosine (9). To a solution of 2-iodoadenosine (**1**) (1.585 g, 4.03 mmol) and bis(acetonitrile)palladium chloride (0.053 g, 0.20 mmol) in DMF (20 mL) was added vinyltributyltin (1.24 mL, 4.23 mmol), and the mixture was stirred at 100 °C for 1 h. The reaction mixture was cooled and filtered. The solvent was evaporated, and the residue was purified on silica gel with chloroform and 10% methanol/chloroform to give 1.099 g (92%) of 2-vinyladenosine: ^{1}H NMR (Me_2SO-d_6) δ 3.66 (m, 2 H), 3.98 (m, 1 H), 4.16 (m, 1 H), 4.65 (m, 1 H), 5.18 (d, 1 H), 5.38–5.62 (m, 3 H), 5.89 (d, 1 H), 6.41 (dd, 1 H), 6.59 (dd, 1 H), 7.27 (br s, 2 H), 8.32 (s, 1 H); UV (EtOH) λ_{max} 293, 271, 265 nm.

2-Vinyladenosine was silylated with procedure A (54% yield). To a solution of 5′-silylated 2-vinyladenosine (0.925 g, 2.27 mmol) in absolute ethanol (110 mL) was added 5% palladium/charcoal (0.220 g). This mixture was shaken under 33 psi of hydrogen for 2 h and was filtered through cotton. The solvent was evaporated, and the residue was purified on silica gel (5% methanol/chloroform) to give 0.670 g (72%) of 2-ethyl-5′-*O*-(*tert*-butyldimethylsilyl)adenosine: ^{1}H NMR (Me_2SO-d_6) δ 0.04 (s, 6 H), 0.87 (s, 9 H), 1.23 (t, 3 H, J = 7.3 Hz), 2.67 (q, 2 H, J = 7.3 Hz), 3.80 (m, 3 H), 4.17 (m, 1 H), 4.60 (m, 1 H), 5.40 (br s, 2 H), 5.88 (d, 1 H, J = 5.4 Hz), 7.11 (br s, 2 H), 8.18 (s, 1 H); UV (EtOH) λ_{max} 262 nm.

2-Ethyl-5′-*O*-(*tert*-butyldimethylsilyl)adenosine was dideoxygenated with in sequence procedure B (82% yield), procedure C (53% yield), procedure D (76%), and procedure E (80%) to give 2′,3′-dideoxy-2-ethyl-5′-*O*-(*tert*-butyldimethylsilyl)adenosine. Deprotection of the latter compound by procedure F provided **9** in 79% yield: mp 205–207 °C; ^{13}C NMR (Me_2SO-d_6) δ 13.2, 26.0, 31.6, 31.9, 63.3, 81.5, 84.5, 117.5, 138.8, 149.6, 155.8, 165.4; ^{1}H NMR (Me_2SO-d_6) δ 1.23 (t, 3 H, J = 7.3 Hz), 2.11 (m, 2 H), 2.38 (m, 2 H), 2.66 (q, 2 H, J = 7.3 Hz), 3.51 (m, 2 H), 4.11 (m, 1 H), 5.11 (m, 1 H), 6.19 (t, 1 H, J = 5.41 Hz), 7.08 (br s, 2 H), 8.33 (s, 1 H); UV (H_2O) λ_{max} 262.5 nm (12630); FAB HRMS obsd (M^+ + H) 264.1482, calcd for $C_{12}H_{17}N_5O_2$ 264.1461.

2′,3′-Dideoxy-2-(methylthio)adenosine (10). 2-(Methylthio)-adenosine[22] was converted to **10** by in sequence procedures A (70% yield), B (75% yield), C (59% yield), and D, E, and F (49% overall yield): mp 200–203 °C; ^{13}C NMR (Me_2SO-d_6) δ 13.7, 26.0, 31.5, 63.1, 81.7, 84.2, 116.8, 138.2, 149.7, 155.4, 164.0; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (m, 2 H), 2.48 (m, 5 H), 3.55 (m, 2 H), 4.17 (m, 1 H), 4.88 (t, 1 H, J = 5.4 Hz), 6.18 (m, 1 H), 7.28 (br s, 2 H), 8.21 (s, 1 H); UV (H_2O) λ_{max} 274.5 nm (ε 13150); FAB HRMS obsd (M^+ + H) 282.1003, calcd for $C_{11}H_{15}N_5O_2S$ 282.1025.

2′,3′-Dideoxy-2-(trifluoromethyl)adenosine (11). A solution of (trifluoromethyl)zinc bromide (1.308 g, 6.10 mmol) in DMF (25 mL) and HMPA (10 mL) was added to copper bromide (0.438 g, 3.05 mmol), and the resulting mixture was stirred for 30 min.[24] 2-Iodoadenosine (0.800 g, 2.03 mmol) was added, and the solution was warmed at 70 °C for 4 h. The solvents were evaporated and the residue was purified on silica gel with 10% methanol/chloroform to give 2-(trifluoromethyl)adenosine[23] in 63% yield. 2-(Trifluoromethyl)adenosine was converted to **11** by in sequence procedure A (58% yield), procedure B (84% yield), procedure C (51% yield), procedure D (73% yield), procedure E (75% yield), and procedure F (53% yield): mp 173–175 °C; ^{13}C NMR (Me_2SO-d_6) δ 25.7, 31.8, 62.8, 82.1, 84.5, 119.8, 141.1, 148.3, 156.2; ^{1}H NMR (Me_2SO-d_6) δ 2.10 (m, 2 H), 2.40 (m, 2 H), 3.51 (m, 2 H), 4.13 (m, 1 H), 4.88 (m, 1 H), 6.25 (m, 1 H), 7.85 (br s, 2 H), 8.54 (s, 1 H); UV (H_2O) λ_{max} 259.5 nm (ε 11300); FAB HRMS obsd (M^+ + H) 304.0996, calcd for $C_{11}H_{12}F_3N_5O_2$ 304.1021.

2′,3′-Dideoxy-2-iodoadenosine (14). 2-Amino-6-chloronebularine (**12**) was converted to 2-amino-6-chloro-2′,3′-dideoxy-5′-*O*-(*tert*-butyldimethylsilyl)nebularine by in sequence procedures A (82%), B (73%), C (62%), D (75%), and E (83%): ^{1}H NMR (Me_2SO-d_6) δ 0.00 (s, 6 H), 0.84 (s, 9 H), 2.07 (m, 2 H), 2.35 (m, 2 H), 3.74 (m, 2 H), 4.13 (m, 1 H), 6.11 (m, 1 H), 6.88 (br s, 2 H) , 8.27 (s, 1 H); UV (EtOH) λ_{max} 310, 247, 222 nm.

Desilylation of 2-amino-6-chloro-2′,3′-dideoxy-5′-*O*-(*tert*-butyldimethylsilyl)nebularine by procedure F gave 2-amino-6-chloro-2′,3′-dideoxynebularine in 69% yield: mp 139–141 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.05 (m, 2 H), 2.38 (m, 2 H), 3.55 (m, 2 H), 4.10 (m, 1 H), 4.91 (m, 1 H), 6.10 (t, 1 H, J = 4.9 Hz), 6.88 (br s, 2 H), 8.36 (s, 1 H); UV (H_2O) λ_{max} 307, 248 nm.

To a nitrogen-purged solution of 2-amino-6-chloro-2′,3′-dideoxy-5′-*O*-(*tert*-butyldimethylsilyl)nebularine (0.232 g, 0.604 mmol) and diiodomethane (0.20 mL, 2.483 mmol) in hexane (50 mL) was added *tert*-butyl nitrite (0.32 mL, 2.690 mmol). The reaction mixture was stirred at 70 °C for 3 h under N_2. The solvents were evaporated, and the residue was purified on silica gel with 5% methanol/chloroform to provide 0.087 g (29%) of 6-chloro-2-iodo-2′,3′-dideoxy-5′-*O*-(*tert*-butyldimethylsilyl)nebularine: ^{1}H NMR (Me_2SO-d_6) δ −0.03 (s, 6 H), 0.81 (s, 9 H), 2.10 (m, 2 H), 2.40 (m, 2 H), 3.75 (m, 2 H), 4.13 (m, 1 H), 6.30 (m, 1 H), 8.74 (s, 1 H); UV (EtOH) λ_{max} 281, 255, 220 nm. This 6-chloro-2-iodo compound (0.087 g, 0.175 mmol) was dissolved in 50 mL of absolute ethanol saturated with ammonia. This solution was allowed to stand at room temperature for 7 h. The solvent was evaporated and the residue purified on silica gel with 5% methanol/chloroform to give 0.043 g (52%) of 2-iodo-2′,3′-dideoxy-5′-*O*-(*tert*-butyldimethylsilyl)-adenosine, which was desilylated with procedure F to give 2-iodo-2′,3′-dideoxyadenosine (**14**) in 83% yield: mp >220 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.07 (m, 2 H), 2.36 (m, 2 H), 3.55 (m, 2 H), 4.10 (m, 1 h), 4.89 (m, 1 H), 6.14 (m, 1 H), 7.63 (br s, 2 H), 8.28 (s, 1 H); UV (H_2O) λ_{max} 266.5 nm (ε 13250); FAB HRMS obsd (M^+ + H) 362.0088, calcd for $C_{10}H_{12}IN_5O_2$ 362.0114.

Acknowledgment. We thank the U.S. Army Medical Research and Development Command, the Burroughs Wellcome Co., and The University of Iowa for support of this research. The high-field NMR spectrometers used in this work were purchased in part from funds provided by the National Science Foundation and the National Institutes of Health. We thank Mr. Todd Sells and Mr. David Purdy for technical assistance.