Synthesis and Antiviral Evaluation of 1,4-Dioxane Nucleoside Analogues Related to Nucleoside Dialdehydes[1]

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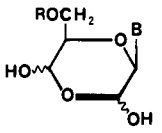
Since biologically active nucleoside 2',3'-dialdehydes exist as six-membered cyclic acetals (1) in solution, we have investigated the antiviral activity of some structurally similar 1,4-dioxane nucleoside analogues. By reacting 2',3'-seconucleoside tosylates with base, the guanine (10) and adenine (18) substituted (hydroxymethyl)dioxanes have been constructed. In addition, an unusual adenine-substituted divinyl ether (22) was synthesized via a base-catalyzed, double elimination of a 2',3'-di-*O*-tosyl-2',3'-secoadenosine. None of these compounds showed significant antiviral activity.

Many nucleoside dialdehydes are capable of disrupting a variety of enzymatic pathways, which often results in antiviral and/or antitumor activity. Some of the enzymes inhibited by these nucleoside analogues include ribonucleotide reductase,[2] dCMP deaminase,[3] *S*-adenosyl-L-homocysteine hydrolase,[4] TMP kinase,[5] and DNA-dependent RNA polymerase.[6] In addition, inosine dialdehyde has been shown to cross-link protein molecules.[7]

Conformational studies of the dialdehydes in solution have indicated that they exist as a complex mixture of several hydrated species having both acyclic and cyclic forms.[8] However, when the 5'-hydroxyl is removed from participation in cyclic acetal formation, as in the case of a 5'-phosphate, then the 1,4-dioxacyclohexane structure (1) predominates.[9] In this conformation, both the het-



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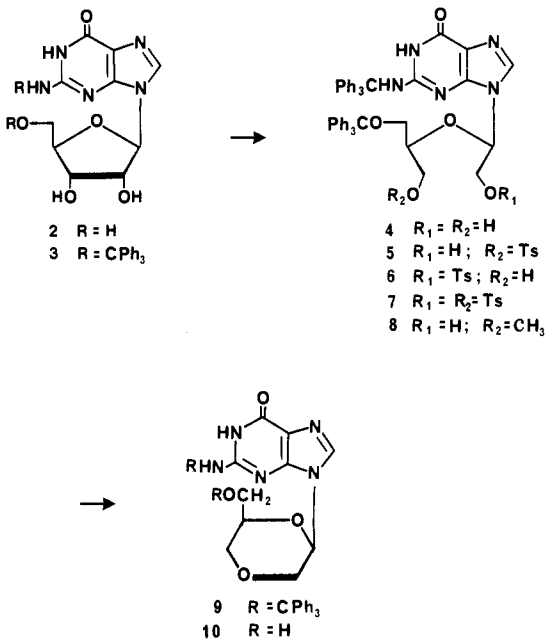
erocyclic base and the 5'-carbon occupy equatorial positions on the dioxane ring. We surmised that nucleoside analogues in which the ribose moiety is replaced with a similarly substituted 1,4-dioxane might mimic a nucleoside dialdehyde and exhibit useful antiviral properties. Furthermore, such an analogue may be more potent and/or selective, since its conformations would be limited and no aldehyde functions would be present that could bind proteins.

Scheme I



2 R = H
3 R = CPh$_3$

4 R$_1$ = R$_2$ = H
5 R$_1$ = H; R$_2$ = Ts
6 R$_1$ = Ts; R$_2$ = H
7 R$_1$ = R$_2$ = Ts
8 R$_1$ = H; R$_2$ = CH$_3$

9 R = CPh$_3$
10 R = H

Only a few examples of nucleoside analogues of 1,4-dioxane have been reported. Szarek and co-workers prepared 6-chloro-9-(1,4-dioxan-2-yl)-9*H*-purine by the acid-catalyzed fusion of 6-chloropurine and 2-(benzoyloxy)-1,4-dioxane,[10] then later converted it to the adenine and 6-mercaptopurine analogues.[11] Also, 1-(1,4-dioxan-2-yl)-5-fluorouracil has been prepared by coupling 2-(benzoyloxy)-1,4-dioxane with 2,4-bis(trimethylsilyl)-5-fluorouracil in the presence of stannic chloride[12] and by the Lewis acid catalyzed condensation of a [(trimethylsilyl)-oxy]alkanal diethyl acetal with 2,4-bis(trimethylsilyl)-5-fluorouracil.[13] Among these derivatives, only 6-chloro-9-(1,4-dioxan-2-yl)-9*H*-purine was reported as having biological activity: that being modest inhibition of murine leukemia L-1210 cell growth.[11]

The presence of a hydroxymethyl substituent on the dioxane ring mimicking the 5'-position of natural nucleosides may be requisite for activity, however, particularly if phosphorylation is necessary prior to the assumption of a metabolic role. We, therefore, chose to synthesize the

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(hydroxymethyl)dioxane analogues of adenosine and guanosine and evaluate their in vitro antiviral activity. In addition, an unusual divinyl ether substituted adenine was isolated and screened for biological activity.

Chemistry. The synthetic strategy was to prepare protected 2′,3′-secoguanosine and 2′,3′-secoadenosine, cyclize the diols to form 1,4-dioxanes, and then deprotect. The configuration of the purine and hydroxymethyl ring substituents would be expected to remain as in the starting nucleosides.

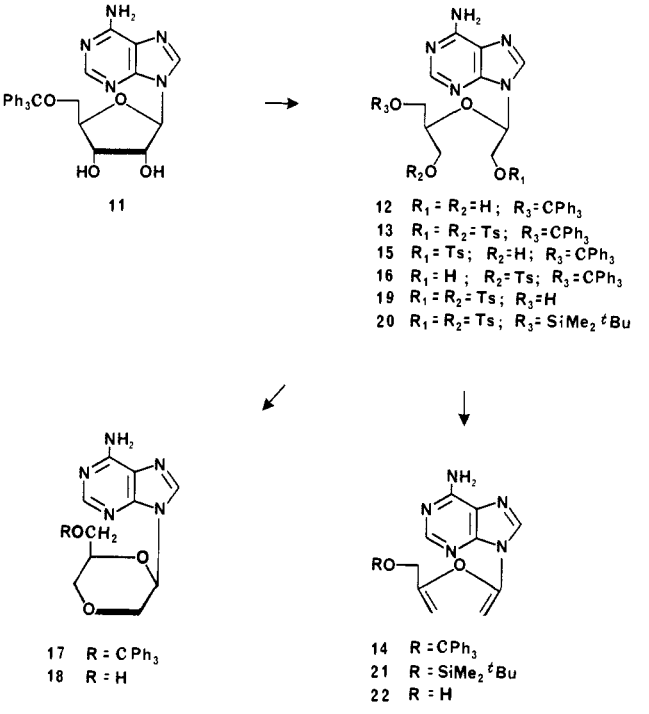
A solution of guanosine (**2**) and a catalytic amount of 4-(dimethylamino)pyridine in dimethylformamide was treated periodically with trityl chloride and triethylamine over several days to afford a 50% yield of N^2,$O^{5'}$-ditritylguanosine (**3**). Attempts to hasten this reaction by shortening the time between additions of trityl chloride resulted in lower yields. As seen in Scheme I, sodium periodate oxidation of the diol **3** followed by sodium borohydride reduction then gave N^2,$O^{5'}$-ditrityl-2′,3′-secoguanosine (**4**). A recent communication[14] describes a similar preparation of a number of 5′-*O*-monomethoxytrityl-2′,3′-seconucleosides.

It was hoped that under conditions of tosylation, the secoguanosine **4** would form a monotosyl intermediate that would immediately cyclize to form the dioxane ring via tosylate displacement by the remaining hydroxyl group. This procedure has precedent in the case of five-membered cyclic ether synthesis.[15] However, tosyl chloride in pyridine, tosyl chloride in dimethoxyethane containing triethylamine, and trifluoromethanesulfonic anhydride in pyridine all failed to effect this ring closure. In view of this, the monotosylates were isolated so that more vigorous cyclizing conditions could be employed. Treatment of N^2,$O^{5'}$-ditrityl-2′,3′-secoguanosine (**4**) with 2 equiv of tosyl chloride in pyridine resulted in the isolation of a 10% yield of the 3′-tosylate **5**, a 20% yield of the 2′-tosylate **6**, and a 37% yield of the 2′,3′-ditosylate **7**. The remaining material was unreacted diol **4**. The site of tosylation of compounds **5** and **6** was determined by decoupling the 1′-proton signal in their ^{1}H NMR spectra.

When the 3′-tosylate **5** was heated in a 1 N solution of sodium methoxide, a 94% yield of the desired cyclized derivative **9** was obtained. Examination of the ^{1}H NMR spectrum of **9** confirms that the guanine and (triphenylmethoxy)methyl substituents are in the desired, equatorial positions on the 1,4-dioxane ring. The NMR signal for the anomeric proton contains a 10-Hz coupling, which is typical of axial/axial interaction. Likewise, the 6′-proton[16] appears as a multiplet of 24-Hz width, which contains a 10.5-Hz axial/axial coupling.

In contrast to the reaction of the 3′-tosylate (**5**), the 2′-tosylate (**6**), when treated in an identical manner with sodium methoxide, afforded the same dioxane nucleoside **9** in 49% yield, but also gave a 44% yield of N^2,$O^{5'}$-ditrityl-2′,3′-secoguanosine (**4**). This facile hydrolysis of the 2′-tosylate led to the speculation that the 2′,3′-ditosylate (**7**), when treated with sodium methoxide, would undergo initial cleavage of the 2′-tosylate followed by rapid cyclization to form the desired dioxane ring. Before this hypothesis was tested, **7** was resynthesized, this time in 82% yield, by treating the diol **4** with excess tosyl chloride in pyridine. When the ditosylate **7** was then heated in a methanolic solution of sodium methoxide, the dioxane nucleoside **9** was obtained in 43% yield. Unpredicted was the isolation from this reaction of N^2,$O^{5'}$-ditrityl-3′-*O*-methyl-2′,3′-secoguanosine (**8**) in 30% yield. By substituting potassium *tert*-butoxide for sodium methoxide, and carrying out the reaction in *tert*-butyl alcohol, the yield of cyclized product rose to 82% with no appreciable generation of side products. Finally, removal of the trityl groups of **9** using 80% acetic acid afforded 9-[6(*R*)-(hydroxymethyl)-1,4-dioxacyclohexan-2(*R*)-yl]guanine (**10**).

Scheme II



As shown in Scheme II, a similar approach was applied to the synthesis of the adenosine analogue **18**. Oxidation of commercially available 5′-*O*-trityladenosine (**11**) with sodium periodate, followed by reduction of the resulting dialdehyde, furnished 5′-*O*-trityl-2′,3′-secoadenosine (**12**). The ditosylate (**13**) was then obtained by the treatment of **12** with excess *p*-toluenesulfonyl chloride. It was expected that subjecting **13** to strong base would lead to formation of the 1,4-dioxane ring as was the case of the guanosine analogue. However, when the ditosylate (**13**) was heated with potassium *tert*-butoxide in *tert*-butyl alcohol no cyclized product was detected, but instead a 91% yield of 2′,3′-dideoxy-5′-*O*-trityl-2′,3′-secoadenosine-1′,3′-diene (**14**) was isolated. Although such seconucleoside dienes are unprecedented, base-catalyzed double-elimination reactions of functionalized nucleosides to form furan derivatives are well-known.[17-20] As expected, the attempted removal of the 5′-*O*-trityl protecting group from **14** using mild acid resulted in rapid decomposition to free adenine.

In light of the failure of the ditosylate (**13**) to cyclize, the monotosylates were prepared. The slow addition of a limited amount of *p*-toluenesulfonyl chloride to the diol

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(16) In accordance with the dioxane numbering system, the oxygen adjacent to the anomeric position is now 1′; guanine resides at the 2′ position, and the protected hydroxymethyl group is at 6′.
(17) Horwitz, J. P.; Chua, J.; DaRooge, M. A.; Noel, M.; Klundt, I. L. *J. Org. Chem.* **1966**, *31*, 205.
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12 led to a 25% yield of the 2′-tosylate (15) and a 22% yield of the 3′-tosylate (16). Each tosylate was heated in a solution of 1 N sodium methoxide in methanol. The 2′-tosylate (15) formed the desired 1,4-dioxane (17) in 27% yield. The major side products were identified by ^{1}H NMR as the diol (12) and 2′-deoxy-5′-*O*-trityl-2′,3′-seco-adenosin-1′-ene. The 3′-tosylate 16, on the other hand, cyclized to 17 in 75% yield. As in the case of the guanosine analogue 9, the characteristic ^{1}H NMR axial/axial couplings evident for the anomeric proton (10 Hz) and H-6′ (11 Hz) are consistent with both the adenine and (triphenylmethoxy)methyl lying in equitorial positions on the dioxane ring. Finally, removal of the trityl protecting group with acetic acid gave the desired adenosine analogue 18.

Having completed the synthesis of the dioxane-ring analogues, we felt obligated to go back and attempt to make the deprotected secoadenosine diene. As the 5′-trityl derivative (14), the compound displays remarkable stability, and the free compound, if also stable, would represent a highly unusual, adenine-substituted divinyl ether.

To begin, the 5′-*O*-trityl group had to be replaced by a protecting group that does not require acid cleavage and is stable to *tert*-butoxide. We hoped that the *tert*-butyldimethylsilyl group would fulfill these requirements. Thus, 2′,3′-di-*O*-*p*-toluenesulfonyl-5′-*O*-trityl-2′,3′-seco-adenosine (13) was detritylated with acetic acid and then reacted with *tert*-butyldimethylsilyl chloride in dimethylformamide in the presence of imidazole,[21] affording the 5′-O-silylated secoadenosine ditosylate (20). Since the completion of this work, Szarek and colleagues have reported the synthesis of 1-benzyl-5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-di-*O*-*p*-toluenesulfonyl-2′,3′-secoinosine via similar chemistry.[11] On heating 20 in *tert*-butyl alcohol containing potassium *tert*-butoxide, a 59% yield of the 5′-O-silylated diene 21 was recovered. Fluoride ion catalyzed cleavage of the silyl group[21] then provided 2′,3′-dideoxy-2′,3′-secoadenosine-1′,3′-diene (22) in 79% yield. The sharply melting product appears to be stable indefinitely at room temperature under air. The ^{1}H and ^{13}C NMR spectra, mass spectrum, combustion analysis, ultraviolet spectrum, and optical rotation were all consistent with the assigned structure.

Biological Results and Discussion

Both deprotected dioxane nucleoside analogues 10 and 18, as well as the divinyl ether adenine 22, were assayed for antiviral activity. Tests were carried out on herpes simplex virus-1 (HSV-1) (F strain), HSV-2 (G), HSV-2 (Lovelace), and parainfluenza-3 (C-243) infected HEP-2 cells. None of the compounds inhibited viral growth. Compounds 10 and 18 were nontoxic to monolayer cultures of HEP-2 cells, but compound 22 showed partial toxicity beginning at 3.2 μM and complete toxicity at 1000 μM concentrations.

Borchardt and co-workers have shown that many nucleoside dialdehydes are inhibitors of vaccinia virus replication.[4c,e] This effect correlates with the inhibition of *S*-adenosylhomocysteine (AdoHcy) hydrolase by the dialdehydes. Such inhibition leads to accumulation of AdoHcy, which is a feedback inhibitor of *S*-adenosylmethionine-dependent methylations. Vaccina virus appears to be critically reliant on these methylations and susceptible to their inhibition. To ascertain whether compounds 10, 18, and 22 are capable of acting in a similar manner, evaluations were carried out against vaccinia virus.

Table I. Inhibitory Effects of Nucleoside Analogues on Vaccinia Virus Replication and DNA Synthesis in Mouse L-Cells[a]

compound	ID_{50}, μM	% of control incorporation of [^{3}H]thymidine[b]
10	NA[c]	99
18	NA	95
22	30	104
adenosine dialdehyde	0.3	8.3

[a] See Experimental Section for details. [b] Compounds administered at 30 μM concentration. [c] NA, not active.

The results of these tests are summarized in Table I. Plaque reduction assays of vaccinia virus in monolayer cultures of mouse L-cells demonstrated no inhibition of virus plaque formation by compounds 10 and 18 at concentrations up to 30 μM. Compound 22 showed slight activity, having an ID_{50} of 30 μM. Adenosine dialdehyde was included as a control and produced an ID_{50} of 0.3 μM.

As a measure of cellular toxicity, the compounds were evaluated for their effect on [^{3}H]thymidine incorporation into DNA of uninfected mouse L-cells. At 30 μM concentrations, compounds 10, 18, and 22 showed no inhibition of thymidine uptake as measured 48 h after exposure to the compound. In contrast, adenosine dialdehyde reduced thymidine incorporation to 8.3% of control. It appears, therefore, that compounds 10, 18, and 22 are nontoxic to L-cells.

In order to preclude the possibility that the adenosine analogues 18 and 22 were being deactivated by deaminases, the ID_{50} and thymidine incorporation experiments were repeated in the presence of 10^{-8} M coformycin. No change in activity resulted.

The lack of conspicuous biological activity for the two dioxane derivatives (10 and 18) likely indicates that the 1,4-dioxane conformation (1) is not an important contributor to the activities of nucleoside dialdehydes. Other investigators[4e] have shown that the inhibition of AdoHcy hydrolase by a series of nucleoside dialdehyde derivatives is greatly diminished when the aldehydes are reduced to the corresponding diols, leading the authors to conclude that the aldehyde functionalities are crucial for this enzyme inhibition. Our data, too, suggest that although the hydrated forms of the dialdehydes predominate in solution, it is the free aldehyde functionality that is responsible for the biological activity.

The divinyl ether substituted adenine (22), on the other hand, warrants further investigation. Such a structure might act as a Michael-acceptor capable of forming covalent bonds with enzymes and possibly leading to irreversible inhibition. In any case, compound 22 presents a tempting substrate for additional synthetic manipulation.

Experimental Section

General Methods. Nuclear magnetic resonance spectra were recorded on Bruker WM-300 (^{1}H NMR, 300 MHz) and Bruker WH-90 (^{13}C NMR, 22.62 MHz) spectrometers, and chemical shfits are reported in parts per million downfield from internal tetramethylsilane. Mass spectra (MS) were recorded on a Finnigan MAT CH7 spectrometer operating in the direct inlet mode. UV spectra were recorded on a Hewlett-Packard 8450A spectrophotometer. Elemental analysis were obtained by Syntex Analytical Research. All chromatographic purifications were carried out on silica gel. Melting points were determined on a hot-stage microscope and are corrected.

***N*^{2},*O*$^{5'}$-Bis(triphenylmethyl)guanosine (3).**[22] A solution of guanosine (5.00 g, 17.7 mmol), triphenylmethyl chloride (10.0 g, 35.9 mmol), (dimethylamino)pyridine (0.05 g), and triethylamine

(21) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(22) This compound was first prepared and characterized in our laboratories by Dr. John C. Martin.

(6.0 mL, 43 mmol) in dimethylformamide (50 mL) was stirred at 50 °C. Additional triphenylmethyl chloride (4.0 g, 14 mmol) and triethylamine (4.0 mL, 29 mmol) were added after 2 days, 5 days, and 6 days. After 9 days the reaction was quenched by the addition of triethylamine (10 mL) and methanol (10 mL) and evaporated in vacuo. The residue was chromatographed on a silica gel column (600 g) using a stepwise gradient of 5%, 7%, and 11% methanol in dichloromethane. The product **3** was isolated as 6.80 g (50%) of tan solid, which was suitable for subsequent reactions. An analytical sample was prepared by precipitating **3** from hot ethanol: mp 194–196 °C; UV λ_{max} (methanol) sh 273 nm (ϵ 12400), 260 (15400); ^{1}H NMR (Me_2SO-d_6) δ 10.7 (br s, 1 H, NH), 7.73 (s, 1 H, H-8), 7.68 (s, 1 H, NH), 7.13–7.40 (m, 30 H, Ph), 5.20 (d, J = 3 Hz, 1 H, H-1′), 5.06 (d, J = 5 Hz, 1 H, OH), 4.81 (d, J = 7, 1 H, OH), 3.76–3.86 (m, 2 H, H-2′, H-3′), 3.42–3.51 (m, 1 H, H-4′), 3.05 (m, 2 H, H-5′). Anal. ($C_{48}H_{41}N_5O_5 \cdot H_2O$) C, H, N.

N^2,$O^{5'}$-Bis(triphenylmethyl)-2′,3′-secoguanosine (4). A solution of **3** (10.0 g, 13.0 mmol) and sodium metaperiodate (3.0 g, 14.0 mmol) in a mixture of methanol (1.0 L) and water (0.30 L) was stirred at room temperature for 16 h. After most of the methanol was removed by evaporation in vacuo, the remaining solution was diluted with ethyl acetate (0.5 L) and washed with water (3 × 250 mL). The dried ($MgSO_4$) organic phase was evaporated to give 9.48 g of nearly pure 2′,3′-dialdehyde. To a solution of this product in ethanol (1.0 L) was added sodium borohydride (20.0 g, 52.6 mmol). After stirring for 3 h at room temperature, the reaction was quenched by the careful addition of acetone (0.2 L), and then the solvent was removed by evaporation. The residue was coevaporated with methanol (3 × 0.2 L) and then dissolved in dichloromethane. This solution was washed with 3 N ammonium chloride (0.7 L) and water (0.5 L), dried ($MgSO_4$), and evaporated to a white foam. The foam was crystallized from ethyl acetate to give 7.93 g (83%) of **4**: mp 184–186 °C; UV λ_{max} (methanol) 261 nm (ϵ 14100); ^{1}H NMR (Me_2SO-d_6) δ 10.7 (br s, 1 H, NH), 7.81 (s, 1 H, H-8); 7.76 (s, 1 H, NH), 7.10–7.30 (m, 30 H, Ph), 5.09 (t, J = 5 Hz, 1 H, OH), 4.96 (t, J = 6 Hz, 1 H, H-1′), 4.42 (t, J = 5 Hz, 1 H, OH), 3.71 (ddd, J = 5, 6, 11 Hz, 1 H, H-2′$_a$), 3.49 (ddd, J = 5, 6, 11 Hz, 1 H, H-2′$_b$), 3.28 (br s, 1 H, H-4′), 3.14 (ddd, J = 5, 5, 12 Hz, 1 H, H-3′$_a$), 2.96 (ddd, J = 3, 5, 12 Hz, 1 H, H-3′$_b$), 2.78 (dd, J = 7, 9 Hz, 1 H, H-5′$_a$), 2.54 (dd, J = 3, 9 Hz, 1 H, H-5′$_b$). Anal. ($C_{48}H_{43}N_5O_5 \cdot H_2O$) C, H, N.

N^2,$O^{5'}$-Bis(triphenylmethyl)-3′-O-p-toluenesulfonyl-2′,3′-secoguanosine (5) and N^2,$O^{5'}$-Bis(triphenylmethyl)-2′-O-p-toluenesulfonyl-2′,3′-secoguanosine (6). A solution of **4** (3.85 g, 5.00 mmol) and p-toluenesulfonyl chloride (1.0 g, 5.0 mmol) in pyridine (100 mL) was kept at room temperature. After 5 h, then again after 24 h from the start of reaction, more p-toluenesulfonyl chloride was added (0.5 g, 2.5 mmol each addition). The reaction was quenched with methanol after a total of 48 h had elapsed, and then the solvent was removed by evaporation. A solution of the residue in ethyl acetate was washed with water, dried ($MgSO_4$), and reevaporated leaving a yellow foam. The foam was chromatographed on a silica gel column (500 g) eluting first with dichloromethane/acetone (9:1) containing 2% methanol, then with dichloromethane/acetone (9:1) containing 5% methanol. The first major component eluted was the ditosylate (**7**), which was obtained as a foam (2.01 g, 37%) identical in all respects to that isolated by its direct preparation. The second component was obtained as a foam and was identified as the 2′-monotosylate (**6**) (0.95 g, 20%): UV λ_{max} (ethanol) 262 nm (ϵ 14500), 211 (53600); ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 8 Hz, 2 H, TsAr), 6.97–7.29 (m, 33 H, H-8, TsAr, Ph), 5.24 (t, J = 4.5 Hz, 1 H, H-1′), 3.96 (dd, J = 6, 10 Hz, 1 H, H-2′$_a$), 3.82 (dd, J = 4.5, 10 Hz, 1 H, H-2′$_b$), 3.52 (dd, J = 3, 12 Hz, 1 H, H-3′$_a$), 3.41 (dd, J = 4.5, 12 Hz, 1 H H-3′$_b$), 3.19 (br s, 1 H, H-4′), 2.87 (dd, J = 4.5, 10 Hz, 1 H, H-5′$_a$), 2.74 (dd, J = 4.5, 10 Hz, 1 H, H-5′$_b$), 2.39 (s, 3 H, Me), 1.88 (br s, 1 H, OH). Anal. ($C_{55}H_{49}N_5O_7S \cdot H_2O$) C, H, N.

The most polar component was the 3′-monotosylate (**5**), which crystallized from ethyl acetate (0.45 g, 10%): mp 188–189 °C; UV λ_{max} (ethanol) 261 nm (ϵ 15000), 206 (88000); ^{1}H NMR ($CDCl_3$) δ 7.77, 7.36 (d's, J = 8 Hz, 4 H, TsAr), 6.96–7.29 (m, 31 H, H-8, Ph), 4.90 (t, J = 4.5 Hz, 1 H, H-1′), 3.86 (m, 2 H, 3′-CH_2), 3.53 (dd, J = 4.5, 12 Hz, 1 H, H-2′$_a$), 3.41 (dd, J = 4.5, 12 Hz, 1 H, H-2′$_b$), 3.26 (br s, 1 H, H-4′), 2.86 (dd, J = 6, 9 Hz, 1 H, H-5′$_a$), 2.71 (dd, J = 4.5, 9 Hz, 1 H, H-5′$_b$), 2.46 (s, 3 H, Me), 2.41 (br s, 1 H, OH). Anal. ($C_{55}H_{49}N_5O_7S$) C, H, N.

N^2,$O^{5'}$-Bis(triphenylmethyl)-2′,3′-di-O-p-toluenesulfonyl-2′,3′-secoguanosine (7). A solution of **4** (770 mg, 1.00 mmol) and p-toluenesulfonyl chloride (764 mg, 4.00 mmol) in pyridine (10 mL) was kept at room temperature for 18 h, before quenching with water and evaporating off the solvent. A solution of the syrupy residue in dichloromethane was washed first with saturated aqueous sodium bicarbonate then with water, dried ($MgSO_4$), and evaporated leaving a yellow foam, which was purified by column chromatography on silica gel (100 g, 4% methanol/dichloromethane). Pure **7** was isolated as 881 mg (82%) of white foam: UV λ_{max} (ethanol) 262 nm (ϵ 15000), 210 (62200); ^{1}H NMR ($CDCl_3$) δ 7.78, 7.52, 7.38, 7.27 (d's, J = 8 Hz, 8 H, TsAr), 6.99–7.28 (m, 31 H, Ph, H-8), 5.06 (br s, 1 H, H-1′), 3.77–3.99 (m, 4 H, 2′ and 3′ CH_2's), 3.14 (br s, 1 H, H-4′), 2.80 (dd, J = 4.5, 9 Hz, 1 H, H-5′$_a$), 2.68 (dd, J = 4.5, 9 Hz, 1 H, H-5′$_b$), 2.48 (s, 3 H, Me), 2.36 (s, 3 H, Me). Anal. ($C_{62}H_{55}N_5O_9S_2$) C, H, N.

N^2,$O^{5'}$-Bis(triphenylmethyl)-3′-O-methyl-2′,3′-secoguanosine (8). A solution of **7** (1.10 g, 1.02 mmol) in 1 N sodium methoxide (50 mL) was heated at 60 °C for 40 h. After cooling to room temperature, an equal volume of dichloromethane was added and the solution was neturalized with Dowex 50 (H^+) cation exchange resin. The resin was removed by filtration, and the filtrate was washed with water, dried ($MgSO_4$), and evaporated to a foam. The foam was chromatographed on silica gel (100 g) eluting first with dichloromethane/acetone (9:1) + 3% methanol (1 L) then with dichloromethane/acetone (9:1) + 5% methanol (1 L). The first major reaction component to appear was the dioxane nucleoside **9**, which was crystallized from dichloromethane/ethanol to afford 326 mg (43%) identical in all respects to that obtained in the following preparations. Compound **8** then was eluted and crystallized from ethyl acetate to give 238 mg (30%): mp 182–183 °C; UV λ_{max} (ethanol) 261 nm (ϵ 14500), 212 (47800); ^{1}H NMR ($CDCl_3$) δ 9.83 (br s, 1 H, NH), 7.93 (br s, 1 H, NH), 6.98–7.34 (m, 31 H, H-8, Ph), 5.08 (dd, J = 4, 7 Hz, 1 H, H-1′), 3.52 (dd, J = 7, 11.5 Hz, 1 H, H-2′$_a$), 3.24–3.42 (m, 4 H, H-2′$_b$, H-3′, H-4′), 3.26 (s, 3 H, OMe), 2.89 (m, 2 H, H-5′), 2.85 (br s, 1 H, OH). Anal. ($C_{49}H_{45}N_5O_5$) C, H, N.

9-[6(S)-[(Triphenylmethoxy)methyl]-1,4-dioxacyclohexan-2(R)-yl]-N^2-triphenylmethylguanine (9). A. From Ditosylate 7. Potassium metal (0.8 g) was dissolved in *tert*-butyl alcohol (40 mL), and to this solution was added **7** (862 mg, 0.80 mmol). The mixture was heated at 60 °C for 20 h, diluted with dichloromethane (80 mL), clarified with water (1 mL), and neutralized with Dowex 50 (H^+) cation exchange resin. The resin was removed by filtration, and the filtrate was washed with saturated aqueous sodium bicarbonate then water. The dried ($MgSO_4$) organic phase was evaporated to a crystalline solid, which was recrystallized from dichloromethane/ethanol affording 491 mg (82%) of **9**: mp 268–269 °C dec; UV λ_{max} (ethanol) 260 nm (ϵ 15900), 206 (76000); ^{1}H NMR (Me_2-SO-d_6) δ 10.62 (br s, 1 H, NH), 7.67 (s, 1 H, H-8), 7.67 (s, 1 H, NH), 7.12–7.40 (m, 30 H, Ph), 5.12 (dd, J = 2.5, 10 Hz, 1 H, H-2′), 3.87 (m, 1 H, H-6′), 3.78 (dd, J = 2.5, 11 Hz, 1 H, H-5′$_{eq}$), 3.45 (dd, J = 10, 11 Hz, 1 H, H-3′$_{ax}$), 3.27 (dd, J = 3, 11 Hz, 1 H, H-3′$_{eq}$), 3.04 (dd, J = 5, 9.5 Hz, 1 H, H-7′$_a$) 2.84–2.92 (m, 2 H, H-5′$_{ax}$, H-7′$_b$). Anal. ($C_{48}H_{41}N_5O_4 \cdot 3H_2O$) C, H, N.

B. From 3′-Tosylate 5. A solution of **5** (265 mg, 0.287 mmol) in 1 N sodium methoxide (13 mL) was heated at 60 °C for 20 h, then cooled and diluted with dichloromethane (25 mL) and water (25 mL). The biphasic mixture was neutralized with Dowex 50 (H^+) cation exchange resin and filtered, and the organic phase was isolated and dried ($MgSO_4$). The solvent was removed by evaporation and the residue crystallized from dichloromethane/ethanol to give 204 mg (94%) of **9** identical to that obtained in method A above.

C. From 2′-Tosylate 6. In a manner identical to the 3′-tosylate (**5**), **6** (700 mg, 0.758 mmol) was treated with 1 N sodium methoxide (35 mL) to afford 255 mg of crystalline **9**. The mother liquors of crystallization were chromatographed on preparative silica gel plates (dichloromethane/acetone (9:1) + 5% methanol) to give 25 mg more **9** (49% total). This product was identical to that obtained in method A above.

Also isolated from the plates and crystallized from ethyl acetate was 255 mg (44%) of the more polar 2′,3′-diol (**4**), which was identical to that prepared above.

9-[6(*R*)-(Hydroxymethyl)-1,4-dioxacyclohexan-2(*R*)-yl]-guanine (10). A solution of **9** (565 mg, 0.75 mmol) in 80% acetic acid (15 mL) was heated at 65 °C for 6 h, diluted with water (150 mL), and extracted with dichloromethane (3 × 50 mL). The aqueous solution was evaporated to a solid, which was crystallized from water/ethanol leaving 181 mg (90%) of **10**: mp >300 °C dec; $[\alpha]_D$ −57.8° (*c* 1, 0.1 N NaOH); UV λ_{max} (0.1 N HCl) 256 nm (ϵ 12900); λ_{max} (0.1 N NaOH) 264 nm (ϵ 11600); ^{1}H NMR (Me_2SO-d_6) δ 7.83 (s, 1 H, H-8), 7.05 (br s, 2 H, NH_2), 5.58 (t, *J* = 6.5 Hz, 1 H, H-2′), 3.81–3.90 (m, 4 H, H-3′, H-5′), 3.32–3.56 (m, 3 H, H-6′, H-7′); ^{13}C NMR (Me_2SO_2-d_6) δ 156.6 (C-6), 153.8 (C-2), 150.7 (C-4), 134.9 (C-8), 116.2 (C-5), 77.35 (C-2′), 76.81 (C-6′), 66.92, 66.88 (C-3′, C-5′), 60.48 (C-7′); MS 267 (M^+, base). Anal. ($C_{10}H_{13}N_5O_4$·0.5H_2O) C, H, N.

5′-*O*-(Triphenylmethyl)-2′,3′-secoadenosine (12). A suspension of 5′-*O*-(triphenylmethyl)adenosine (Waldhof) (10 g, 20 mmol) in methanol (1.0 L) and water (0.3 L) containing sodium periodate (4.5 g, 21 mmol) was stirred at room temperature for 20 h. The mixture was concentrated by evaporation to approximately 0.2 L, diluted with ethyl acetate (1 L), and extracted with water (2 × 500 mL). The organic phase was dried ($MgSO_4$) and evaporated to 9.9 g of dialdehyde. Sodium borohydride (2.0 g, 53 mmol) was slowly added to a stirred solution of the dialdehyde (9.9 g) in ethanol (1 L). After stirring for 2 h at room temperature, the excess borohydride was quenched with acetone and the mixture evaporated to dryness in vacuo. The residue was coevaporated with methanol (3 × 0.4 L) finally leaving a white foam. A solution of the foam in a mixture of 1-butanol/dichloromethane (1:9, 1.5 L) was washed with water (2 × 500 mL) then reevaporated to another foam. Taking the foam up in hot water produced a milky oil, which quickly crystallized affording 8.4 g (87%) of **12**. A portion was recrystallized from methanol to furnish an analytical sample: mp 169–170 °C; UV λ_{max} (ethanol) 260 nm (ϵ 13700), 212 (32500); ^{1}H NMR (Me_2SO-d_6) δ 8.34 (s, 1 H, H-8), 8.30 (s, 2 H, NH_2), 8.19 (s, 1 H, H-2), 7.09–7.29 (m, 15 H, Ph), 5.91 (t, *J* = 6 Hz, 1 H, H-1′), 5.26 (br s, 1 H, OH), 4.82 (br s, 1 H, OH), 4.03 (d, *J* = 6 Hz, 2 H, H-2′), 3.85 (m, 1 H, H-4′), 3.47 (d, *J* = 5 Hz, 2 H, H-3′), 2.88 (dd, *J* = 7, 10 Hz, 1 H, H-5′$_a$) 2.75 (dd, *J* = 3.5, 10 Hz, 1 H, H-5′$_b$). Anal. ($C_{29}H_{29}N_5O_4$) C, H, N.

2′,3′-Di-*O*-*p*-toluenesulfonyl-5′-*O*-(triphenylmethyl)-2′,3′-secoadenosine (13). A solution of **12** (1.02 g, 2 mmol) and *p*-toluenesulfonyl chloride (1.53 g, 8 mmol) in dry pyridine (20 mL) was kept at room temperature for 24 h before evaporating to a foam. A solution of the foam in dichloromethane was washed first with saturated aqueous sodium bicarbonate then with water. The organic phase was dried ($MgSO_4$) and evaporated to a foam, which crystallized from acetone affording 0.99 g of **13** in one crop. The mother liquors were chromatographed on a silica gel column (gradient, 1–5% methanol in dichloromethane) to furnish another 0.24 g of **13** after crystallization from acetone (total 77%): mp 102–104 °C; UV λ_{max} (ethanol) 260 nm (ϵ 13600), 222 (34500), 215 (39200); ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1 H, H-8), 7.80, 7.56, 7.35 (d's, *J* = 8, 6 H, TsAr), 7.74 (s, 1 H, H-2), 7.10–7.19 (m, 17 H, TsAr, Ph), 6.02 (br s, 2 H, NH_2), 5.91 (dd, *J* = 4, 6 Hz, 1 H, H-1′), 4.49 (dd, *J* = 6, 11 Hz, H-2′$_a$), 4.30 (dd, *J* = 4, 11 Hz, 1 H, H-2′$_b$), 4.24 (dd, *J* = 3, 11 Hz, 1 H, H-3′$_a$), 4.05 (dd, *J* = 7, 11 Hz, 1 H, H-3′$_b$), 3.56 (m, 1 H, H-4′), 2.89–3.00 (m, 2 H, H-5′), 2.45 (s, 3 H, Me), 2.38 (s, 3 H, Me). Anal. ($C_{48}H_{41}N_5O_8S_2$) C, H, N.

5′-*O*-(Triphenylmethyl)-2′,3′-dideoxy-2′,3′-secoadenosine-1′,3′-diene (14). Potassium metal (0.25 g, 6.4 mmol) was dissolved in *tert*-butyl alcohol (12 mL), and to this solution was added **13** (205 mg, 0.25 mmol). A precipitate appeared almost immediately as heating was begun at 60 °C. After 1.5 h the mixture was cooled to room temperature, clarified by the addition of dichloromethane (15 mL), and neutralized by stirring vigorously with Dowex 50 (H^+) cation exchange resin and a little water. After filtering off the resin, the solution was washed with saturated aqueous sodium bicarbonate then water. The organic phase was dried ($MgSO_4$) and evaporated to a white foam (130 mg). The product was purified by preparative thin-layer chromatography (5% methanol in dichloromethane/acetone, 9:1) affording 108 mg (91%) of **14** as a slightly hygroscopic, white foam: UV λ_{max} (ethanol) 259 nm (ϵ 12800); ^{1}H NMR ($CDCl_3$) δ 8.41 (s, 1 H, H-8), 8.11 (s, 1 H, H-2), 7.24–7.48 (m, 15 H, Ph), 6.06 (br s, 2 H, NH_2), 5.71 (d, *J* = 3 Hz, 1 H, H-2′$_a$), 4.83 (d, *J* = 2 Hz, 1 H, H-3′$_a$), 4.78 (d, *J* = 3 Hz, 1 H, H-2′$_b$), 4.74 (d, *J* = 2 Hz, 1 H, H-3′$_b$), 3.77 (s, 2 H, H-5′); ^{13}C NMR ($CDCl_3$) δ 156.3 (C-6), 155.7 (C-4), 153.7 (C-2), 149.4 (C-1′), 144.1 (C-4′), 143.5 (Ph), 138.0 (C-8), 127.0–129.1 (Ph), 120.3 (C-5), 95.13 (C-3′), 88.74 (C-2′), 87.54 (*C*Ph_3), 62.78 (C-5′). Anal. ($C_{29}H_{25}N_5O_2$) C, H, N.

2′-*O*-*p*-Toluenesulfonyl-5′-*O*-(triphenylmethyl)-2′,3′-secoadenosine (15) and 3′-*O*-*p*-Toluenesulfonyl-5′-*O*-(triphenylmethyl)-2′,3′-secoadenosine (16). To a solution of **12** (5.12 g, 10.0 mmol) in pyridine (100 mL) was added *p*-toluenesulfonyl chloride (4.0 g, 20 mmol) in two equal portions, 4 h apart. Six hours from the time of the first addition, the reaction was quenched with water and the solvent was removed in vacuo. A solution of the residue in dichloromethane was washed with saturated sodium bicarbonate solution and water. The dried ($MgSO_4$) organic phase was chromatographed on a column of silica gel eluted with a gradient consisting of 2–7% methanol in a 1:9 mixture of acetone/dichloromethane. The less polar of the two major reaction products was the 2′-monotosylate **15**, which crystallized from ethanol to afford 1.67 g (25%): mp 159–160 °C; UV λ_{max} (ethanol) 261 nm (ϵ 12500), 213 (34300); ^{1}H NMR (Me_2SO-d_6) δ 8.29 (s, 1 H, H-8), 8.04 (s, 1 H, H-2), 7.62, 7.31 (d's, *J* = 8, 4 H, Ar), 7.33 (s, 2 H, NH_2), 7.10–7.25 (m, 15 H, Ph), 6.12 (dd, *J* = 5, 7 Hz, 1 H, H-1′), 4.85 (dd, *J* = 7, 10.5 Hz, 1 H, H-2′$_a$), 4.84 (t, *J* = 3.5 Hz, 1 H, OH), 4.69 (dd, *J* = 5, 10.5 Hz, 1 H, H-2′$_b$), 3.76 (m, 1 H, H-4′), 3.33–3.41 (m, 2 H, H-3′), 2.85 (dd, *J* = 7, 10 Hz, 1 H, H-5′$_a$), 2.70 (dd, *J* = 3, 10 Hz, 1 H, H-5′$_b$), 2.38 (s, 3 H, Me). Anal. ($C_{36}H_{35}N_5O_6S$) C, H, N.

The more polar 3′-monotosylate **16** was crystallized from ethanol to give 1.48 g (22%): mp 160–162 °C; UV λ_{max} (ethanol) 260 nm (ϵ 13900), 212 (39900); ^{1}H NMR (Me_2SO-d_6) δ 8.24 (s, 1 H, H-8), 8.13 (s, 1 H, H-2), 7.74, 7.43 (d's, *J* = 8, 4 H, Ar), 7.30 (s, 2 H, NH_2), 7.00–7.24 (m, 15 H, Ph), 5.77 (t, *J* = 6.5, 1 H, H-1′), 5.21 (t, *J* = 6, 1 H, OH), 4.20 (dd, *J* = 3.5, 11 Hz, 1 H, H-3′$_a$), 4.09 (dd, *J* = 4.5, 11 Hz, 1 H, H-3′$_b$), 3.80–4.02 (m, 2 H, H-2′), 2.40 (s, 3 H, Me). Anal. ($C_{36}H_{35}N_5O_6S$) C, H, N.

9-[6(*S*)-[(Triphenylmethoxy)methyl]-1,4-dioxacyclohexan-2(*R*)-yl]adenine (17). A. From 3′-Monotosylate 16. A suspension of **16** (1.00 g, 1.50 mmol) in 1 N sodium methoxide in methanol (20 mL) was heated at 60 °C for 2.5 h during which time dissolution occurred. The mixture was diluted with dichloromethane (80 mL) and neutralized with Dowex 50 (H^+) cation exchange resin. The filtered mixture was washed with water, dried ($MgSO_4$), and evaporated to a crystalline solid, which was recrystallized from ethanol leaving 0.55 g (75%) of **17**: mp 133–135 °C; UV λ_{max} (ethanol) 259 nm (ϵ 14100), 213 (31300); ^{1}H NMR ($CDCl_3$) δ 8.36 (s, 1 H, H-8), 7.98 (s, 1 H, H-2), 7.21–7.44 (m, 15 H, Ph), 6.00 (dd, *J* = 3, 10 Hz, 1 H, H-2′), 6.01 (s, 1 H, NH), 4.22 (br s, 1 H, H-6′), 4.11 (dd, *J* = 3, 11 Hz, 1 H, H-3′$_{eq}$), 4.01 (dd, *J* = 2.5, 11.5 Hz, 1 H, H-5′$_{eq}$), 3.68 (dd, *J* = 10, 11 Hz, 1 H, H-3′$_{ax}$), 3.53 (dd, *J* = 11, 11.5 Hz, 1 H, H-5′$_{ax}$), 3.31 (dd, *J* = 4.5, 9.5 Hz, 1 H, H-7′$_a$), 3.15 (dd, *J* = 5.5, 9.5 Hz, 1 H, H-7′$_b$). Anal. ($C_{29}H_{27}N_5O_3$) C, H, N.

B. From 2′-Monotosylate 15. A suspension of **15** (100 mg, 0.15 mmol) in 1 N sodium methoxide in methanol (2.0 mL) was heated at 65 °C for 4 h during which time dissolution occurred. The reaction was worked up as in A, and the least polar product was isolated by preparative thin-layer chromatography (dichloromethane/acetone, 9:1, + 5% methanol—two elutions). Crystallization from ethanol gave 20 mg (27%) of **17** identical in all respects to the product of method A.

9-[6(*R*)-(Hydroxymethyl)-1,4-dioxacyclohexan-2(*R*)-yl]-adenine (18). A solution of **17** (400 mg, 0.81 mmol) in 80% acetic acid (5 mL) was heated at 60 °C for 4 h. The solvent was removed in vacuo and the residue partitioned between water/methanol (9:1) and toluene. The aqueous phase was evaporated and the residue crystallized from ethanol to give 184 mg (91%) of **18**: mp 262–263 °C; $[\alpha]_D$ −12.0° (*c* 1, Me_2SO); UV λ_{max} (0.1 N HCl) 257 nm (ϵ 14500); λ_{max} (0.1 N NaOH) 259 nm (ϵ 14600); ^{1}H NMR (Me_2SO-d_6) δ 8.32 (s, 1 H, H-8), 8.17 (s, 1 H, H-2), 7.32 (br s, 2 H, NH_2), 5.85 (dd, *J* = 3, 10 Hz, 1 H, H-2′), 4.85 (t, *J* = 6 Hz, 1 H, OH), 3.85–4.06 (m, 5 H, H-3′, H-5′, H-6′), 3.42–3.45 (m, 2 H, H-7′); ^{13}C NMR (Me_2SO-d_6) δ 156.1 (C-6), 152.8 (C-2), 149.1 (C-4), 139.0 (C-8), 118.5 (C-5), 77.91 (C-2′), 76.80 (C-6′), 67.02, 66.86 (C-3′, C-5′), 60.52 (C-7′), MS 251 (M^+), 135 (base). Anal. ($C_{10}H_{13}N_5O_3$) C, H, N.

2′,3′-Di-*O*-*p*-toluenesulfonyl-2′,3′-secoadenosine (19). A solution of **13** (540 mg, 0.66 mmol) in 80% acetic acid (10 mL)

was heated for 6 h at 65 °C. The solvent was removed in vacuo, and the residue was coevaporated with toluene before chromatographing on a column of silica gel (dichloromethane/acetone (9:1) + 5% methanol). After crystallization from ethyl acetate/hexane, 297 mg (73%) of compound **19** was obtained: mp 128–129 °C; UV λ_{max} (ethanol) 261 nm (ϵ 14 100); ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1 H, H-8), 7.83 (s, 1 H, H-2), 7.82, 7.59, 7.39, 7.21 (d's, J = 8 Hz, 8 H, Ar), 6.00 (dd, J = 4, 7 Hz, 1 H, H-1'), 5.79 (br s, 2 H, NH_2), 4.54 (dd, J = 7, 11 Hz, 1 H, H-2'$_a$), 4.42 (dd, J = 4, 11 Hz, 1 H, H-2'$_b$), 4.16 (dd, J = 3.5, 11 Hz, 1 H, H-3'$_a$), 4.07 (dd, J = 6, 11 Hz, 1 H, H-3'$_b$), 3.83 (m, 1 H, H-4'), 3.44 (d, J = 5, 2 H, 5'-CH_2), 2.48 (s, 3 H, Me), 2.41 (s, 3 H, Me). Anal. ($C_{24}H_{27}N_5O_8S_2$) C, H, N.

5'-*O*-(*tert*-Butyldimethylsilyl)-2',3'-di-*O*-*p*-toluenesulfonyl-2',3'-secoadenosine (20). A solution of **19** (167 mg, 0.29 mmol), *tert*-butyldimethylsilyl chloride (72 mg, 0.48 mmol), and imidazole (68 mg, 1.0 mmol) in dimethylformamide (1.0 mL) was kept at room temperature for 3.5 h, before evaporation of the solvent in vacuo. Preparative thin-layer chromatography of the resulting syrup using dichloromethane/acetone (9:1) containing 3% methanol as eluent afforded 186 mg (93%) of **20** after crystallization from methanol: mp 141–142 °C; UV λ_{max} (ethanol) 262 nm (ϵ 14 100), 226 (24 400), 215 (25 000); ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1 H, H-8), 7.86 (s, 1 H, H-2), 7.82, 7.59, 7.39, 7.22 (d's, J = 8 Hz, 8 H, Ar), 5.98 (dd, J = 4, 6 Hz, 1 H, H-1'), 5.91 (br s, 2 H, NH_2), 4.53 (dd, J = 6, 11 Hz, 1 H, H-2'$_a$), 4.35 (dd, J = 4, 11 Hz, 1 H, H-2'$_b$), 4.25 (dd, J = 3, 11 Hz, 1 H, H-3'$_a$), 4.07 (dd, J = 6, 11 Hz, 1 H, H-3'$_b$), 3.68 (m, 1 H, H-4'), 3.31 (m, 2 H, H-5'), 2.47 (s, 3 H, Me), 2.41 (s, 3 H, Me), 0.70 (s, 9 H, *t*-Bu), −0.17 (s, 3 H, SiMe), −0.19 (s, 3 H, SiMe). Anal. ($C_{30}H_{41}N_5O_8S_2Si$) C, H, N.

5'-*O*-(*tert*-Bu ldimethylsilyl)-2',3'-dideoxy-2',3'-secoadenosine-1',3'-d ae (21). To a solution of potassium metal (5.0 g, 0.13 mmol) issolved in *tert*-butyl alcohol (250 mL) was added **20** (5.00 g, 7.23 mmol). The mixture was heated at 60 °C for 2.5 h, diluted with dichloromethane (350 mL), and neutralized with Dowex 50 (H^+) cation exchange resin. After filtering off the resin, the solution was washed with brine, dried ($MgSO_4$), and evaporated to a solid, which crystallized from methanol/water (9:1) giving 1.47 g (59%) of **21**: mp 128–130 °C; UV λ_{max} (ethanol) 259 nm (ϵ 12 500); ^{1}H NMR (Me_2SO-d_6) δ 8.44 (s, 1 H, H-8), 8.15 (s, 1 H, H-2), 6.08 (br s, 2 H, NH_2), 5.77 (d, J = 3 Hz, 1 H, H-2'$_a$), 4.85 (d, J = 3 Hz, 1 H, H-2'$_b$), 4.69 (dd, J = 1, 2.5 Hz, 1 H, H-3'$_a$), 4.67 (d, J = 2.5 Hz, 1 H, H-3'$_b$), 4.25 (s, 2 H, H-5'), 0.93 (s, 9 H, *t*-Bu), 0.11 (s, 6 H, $SiMe_2$). Anal. ($C_{16}H_{26}N_5O_2Si$) C, H, N.

2',3'-Dideoxy-2',3'-secoadenosine-1',3'-diene (22). A solution of **21** (350 mg, 1.0 mmol) in 1 M tetrabutylammonium fluoride in tetrahydrofuran (5 mL) was kept at room temperature for 20 min then stirred briefly with Dowex 50 (H^+) cation exchange resin (~10 mL). The filtered solution was evaporated to an oil, which was crystallized twice from ethanol affording 186 mg (79%) of **22**: mp 180–181 °C; $[\alpha]_D$ 0° (*c* 1, Me_2SO); UV λ_{max} (H_2O) 259 nm (ϵ 10 000), 206 (17 000), λ_{max} (0.1 N NaOH) 259 nm (ϵ 7460), 217 (8810); ^{1}H NMR (Me_2SO-d_6) δ 8.30 (s, 1 H, H-8), 8.25 (s, 1 H, H-2), 7.45 (br s, 2 H, NH_2), 5.65 (d, J = 3 Hz, 1 H, H-2'$_a$), 5.40 (t, J = 6 Hz, 1 H, OH), 4.84 (d, J = 3 Hz, 1 H, H-2'$_b$), 4.62 (d, J = 2 Hz, 1 H, H-3'$_a$), 4.50 (d, J = 2 Hz, 1 H, H-3'$_b$), 4.07 (d, J = 6 Hz, 2 H, H-5'); ^{13}C NMR (Me_2SO-d_6) δ 159.7 (C-6), 156.3 (C-4), 153.5 (C-2), 148.7 (C-1'), 143.8 (C-4'), 137.8 (C-8), 119.2 (C-5), 91.64 (=CH_2), 89.60 (=CH_2), 59.60 (C-5'); MS 234 (MH^+), 202 (base). Anal. ($C_{10}H_{11}N_5O_2$) C, H, N.

Biological Methods. Compounds were tested for inhibition of cytopathogenic effects produced by HSV-1 (F strain), HSV-2 (G), HSV-2 (Lovelace), and parainfluenza-3 (C-243) in HEP-2 cells and evaluated for toxic effects on replicating, uninfected HEP-2 cells using the methods of Sidwell and Huffman.[23]

To determine ID_{50} concentrations for vaccina virus, infected mouse L-cells were overlayed with the compound (0.3, 3.0, and 30 μM) in agarose. After incubation for 3 days, the cells were stained and the number of plaques read on day four.[24]

[^{3}H]Thymidine incorporation was measured by adding the compound (0.3, 3.0, and 30 μM) to replicating mouse L-cells and incubating for 2 days. After pulse labeling with [^{3}H]thymidine for 1 h, the trichloroacetic acid precipitable radioactivity was determined and the counts compared to that of the untreated control.[25]

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