Synthesis of 9-(4-Hydroxy-2-oxobutyl)guanine, 9-(2,4-Dihydroxybutyl)guanine, and Related Acyclic Nucleoside Analogues[1,2]

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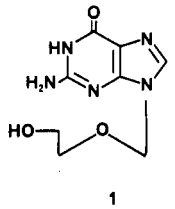
A series of acyclic nucleoside analogues **5a–d** and **7a–d** were synthesized for evaluation as antiviral agents. The key condensation reaction was the treatment of electrophile **12** with an excess of the bases guanine, adenine, uracil, or thymine and a catalytic amount of sodium hydride to give adducts **13a–d**. Hydrogenolysis of **13a–d** afforded the 2,4-dihydroxybutyl derivatives **7a–d**. Alternatively, **13c,d** were converted to ketones **14c,d** by the Moffatt oxidation and then hydrogenolyzed to give **5c,d**. In the purine series, **7a,b** were first tritylated and then oxidized to give **16e,b** which in turn were hydrolyzed to furnish **5a,b**. The N^2-trityl protecting group was found to greatly improve the yield of the Moffatt oxidation reaction of the guanosine derivative. Acyclic guanosine analogue **5a**, a potential suicide inhibitor for the herpes virus specified thymidine kinase, was a substrate for but did not irreversibly deactivate the enzyme.

Over the last several years, a number of acylic analogues of 2′-deoxyguanosine have been shown to possess antiherpes activity. The first of these was acycloguanosine (**1**),[3] which is similar in activity to the more recently described compounds **2**[4] and **3**.[5] We[6] and others[7] have reported the synthesis of DHPG (**4**), the most potent member of this



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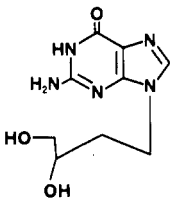

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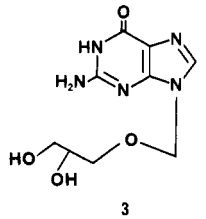

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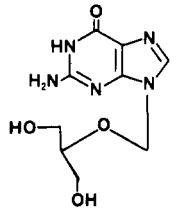

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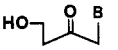
class of antiherpetic agents. These acyclic nucleoside derivatives exert an antiherpes effect by a mechanism similar to that of a number of other antiviral nucleosides.[8] The analogue is first phosphorylated by a virus-specified thymidine kinase[9] to the nucleoside monophosphate. Next, the monophosphate is converted by cellular kinases to the diphosphate and ultimately to the corresponding triphosphate. The nucleoside triphosphate prevents herpes virus replication by inhibition of the virus-specified DNA polymerase. The triphosphate also acts as an alternative substrate for the polymerase and once incorporated into the DNA leads to chain termination or inhibition of chain elongation.[10] In part, these nucleosides are selective in their antiviral action because the first phosphorylation to the monophosphate is effected by the virus-specified kinase present only in the infected cells. Additional selectivity is realized because the nucleoside triphosphate is a better inhibitor of the virus than the host DNA polymerases.[11]

We now report the synthesis of acyclic nucleoside analogues of general structure **5** which are similar to acycloguanosine (**1**) and potentially could exert an antiviral effect by the mechanism described above. This class of hydroxy ketones was also of interest to us because of the potential for the monophosphates of these analogues to undergo β-elimination at the catalytic site of the virus kinase to give enone **6**. This enone in turn could alkylate the active site of the enzyme resulting in the suicide destruction of the kinase.[12]



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Precedent exists for the β-elimination of phosphate derivatives. The mechanism of action of cyclophosphamide probably involves a β-elimination reaction to yield an alkylating phosphorodiamidic acid and acrolein.[13] Also it has been shown that ribonucleoside diphosphate reductase catalyzes the loss of inorganic pyrophosphate from 2′-chloro-2′-deoxyuridine 5′-diphosphate presumably via a β-elimination process of a 3′-keto intermediate.[14] Finally Moffatt oxidation of thymidine 5′-monophosphate leads to inorganic phosphate formation via the presumed 3′-keto

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(2) Presented in part at the 5th International Round Table: Nucleosides, Nucleotides and their Biological Applications, October 20, 1982, Research Triangle Park, NC; Abstract No. 9.

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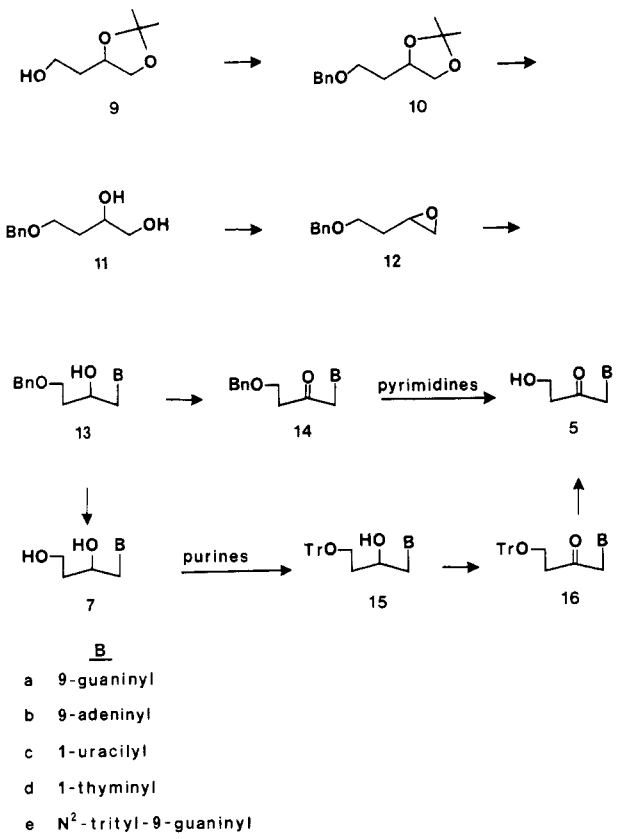
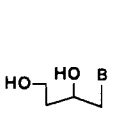
Scheme I



nucleotide.[15] Strains of herpes simplex virus exist which are deficient in the thymidine kinase, and these strains are less virulent and do not establish latency as effectively as the virus strains not deficient in the kinase.[16] A suicide inhibitor of this kinase could possibly provide information on what importance if any, this enzyme has in the establishment of latency.

From the intermediates for the synthesis of **5**, acyclic nucleosides **7** were also prepared. In that they closely resemble **2** and **3**, these analogues were potential inhibitors of herpes virus. Additionally, nucleoside **7b** is structurally related to (*S*)-9-(2,3-dihydroxypropyl)adenine (**8**) which has been reported to exhibit broad spectrum antiviral activity.[17]



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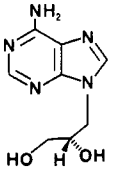

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Results and Discussion

We chose butanetriol acetonide **9**[18] as the starting point for this synthesis (Scheme I). Alcohol **9** is ideally functionalized to allow for the elaboration of the "acyclic sugar" side chain functionalities. Also if diols **7** had exhibited antiviral activity, the enantiomers of **9** being readily available could have been used to synthesize chiral **7** in order to probe the stereochemical effect on biological activity. For both guanine derivative **2**[4] and acyclic adenosine analogue **8**,[17] one stereisomer is significantly more active than the other. Benzylation of **9** (NaH then benzyl bromide) gave **10** in 92% yield. Hydrolysis of acetonide **10** with 80% aqueous acetic acid afforded **11** (88%). Diol **11** in turn was converted to epoxide **12** in 73% yield by successive treatments with methanesulfonyl chloride in pyridine and then NaOH in aqueous Me_2SO. Care needed to be taken in the distillation of **12** because the pot residue tended to decompose rapidly leading to contamination of the distilled product.

Epoxide **12** served as the key electrophile for the reaction with a variety of heterocyclic bases to give acyclic nucleoside derivatives. The best method found for carrying out this conversion was to treat the epoxide with an excess of the heterocycle as a buffer and a catalytic amount of sodium hydride.[19] Use of a stoichiometric amount of NaH led to more complex reaction mixtures as indicated by TLC. Yields of adducts **13b–d** ranged from 61% to 74% while guanosine derivative **13a** was isolated in only 27% yield. The sites of alkylation (N^1 for the pyrimidines and N^9 for the purines) were confirmed by spectroscopic comparisons (^1H NMR, ^{13}C NMR, UV) with the natural nucleosides. The chemical shifts in the ^{13}C NMR spectra of the heterocyclic moieties of **13a–d** are in very close agreement with those reported for the natural nucleosides.[20]

Benzyl ethers **13b–d** were deprotected catalytically (10% Pd/C H_2) to afford diols **7b–d** in 69–78% yield. Pyrimidine benzyl ethers **13c,d** were cleaved by reduction under 1 atm of H_2 while the reaction of **13b** was more sluggish and required 40 psi of H_2 to effect hydrogenolysis. Ether **13a** was exceptionally resistant to catalytic hydrogenolysis but was easily cleaved by sodium in ammonia[21] to furnish a 79% yield of **7a**. Because the sodium salts of guanosine derivatives have high water solubility, this latter reaction was quenched with excess ammonium chloride to adjust the pH so that the neutral product could be isolated directly by crystallization from water.

Alternatively **13a–d** were converted to ketones **14a–d** by the Moffatt oxidation[15] (dimethyl sulfoxide, dicyclohexylcarbodiimide, dichloroacetic, or methylphosphonic acid). Approximately 80–85% yields of **14c,d** were obtained, but **14a,b** were isolated in only 42% and 18% yields, respectively. Possibly because of the exocyclic amino group,[22] the oxidations of purines **13a,b** were not clean as indicated by TLC and also did not give consistent yields. Deprotection of **14c,d** by catalytic hydrogenation afforded the desired β-hydroxy ketones **5c** (59%) and **5d** (40%).

For the purine series, an alternative approach was investigated in order to avoid the troublesome final hydrogenolysis and to more suitably protect the guanosine derivative for the Moffatt oxidation. The diols **7a,b** were tritylated (trityl chloride, triethylamine, 4-(dimethylamino)pyridine in DMF) to give protected derivatives **15e,b** in 49% and 46% yields, respectively. Oxidation of **15b** gave only a 42% yield of **16b**. However, the N^2-trityl protection of the guanosine derivative **15e** greatly improved the oxidation step which was much cleaner than that of the unprotected **13a**. Also, the resulting product **16e** was nicely crystalline and was isolated in 86% yield without

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the need for chromatography. Both **16e,b** were deprotected (acetic acid/water) to give final analogues **5a** (75%) and **5b** (64%).

The only active compound in this series was **5a**, and its activity was marginal showing an ID_{50} of 400 μM vs. 0.2 μM for DHPG (**4**) against herpes simplex virus type 1 (F strain) in Vero cells. In spite of its low activity, **5a** was a substrate for the viral-specified thymidine kinase. The kinase assay[23] was carried out with enzyme purified by affinity chromatography (herpes simplex virus type 1, F strain),[24] and **5a** was found to be phosphorylated at 17% the rate of thymidine. The corresponding rates for acycloguanosine (**1**) and DHPG (**4**) were 23% and 116%, respectively. However, acyclic nucleoside **5a** is not a suicide inhibitor of the kinase since enzyme preincubated with **5a** did not show irreversible loss of thymidine phosphorylating activity. The lack of significant antiviral activity of **5a** is probably due to poor conversion of its monophosphate to the triphosphate by cellular kinases and/or an inability of the triphosphate to significantly inhibit the viral DNA polymerase.

Experimental Section

Nuclear magnetic resonance spectra were recorded on samples dissolved in deuteriodimethyl sulfoxide unless otherwise stated. For peak assignment, the carbons of the side chain are numbered 1′–4′ with C-1′ being attached to the heterocycle. All chromatographic purifications were carried out on silica gel. Melting points were determined on a hot-stage microscope and are corrected.

4-*O*-Benzyl-1,2-*O*-isopropylidenebutane-1,2,4-triol (10). A solution of **9** (52.1 g, 0.36 mol) in DMF (100 mL) was added over 0.5 h to a stirred suspension of sodium hydride (20.4 g, 50%, 0.43 mol, prewashed with hexane) in DMF (800 mL) at room temperature. After an additional 0.5 h of stirring, benzyl bromide (45 mL, 0.43 mol) was added over 0.5 h as a solution in DMF (100 mL). Periodic cooling was necessary to keep the reaction temperature below 30 °C. After an additional 1.5 h, water (50 mL) was added, and the solvent was removed by evaporation at reduced pressure. The residue was dissolved in ethyl acetate, and the resulting solution was washed with water and then brine, dried over Na_2SO_4, and evaporated to dryness. The residue was distilled to give 77.4 g (92%) of **10**: bp 105–108 °C (1 torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.30 (s, 5 H, phenyl), 4.47 (s, 2 H, benzylic), 3.5–4.4 (m, 5 H, CHO) 1.87 (q, J = 6 Hz, 2 H, CH_2), 1.36 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3); MS 221 ($M^+ - CH_3$), 178, 160, 91 (base). Anal. Calcd for $C_{14}H_{20}O_3$ (236.31): C, 71.16; H, 8.53. Found: C, 71.05; H, 8.57.

4-*O*-Benzylbutane-1,2,4-triol (11). A solution of **10** (77.4 g, 0.33 mol) in 80% acetic acid (400 mL) was stirred at room temperature for 50 h then 50 °C for 1 h. The solution was evaporated to dryness and the residue distilled to give 56.5 g (88%) of **11**: bp 135–138 °C (1 torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.30 (s, 5 H, phenyl), 4.50 (s, 2 H, benzylic), 3.0–4.0 (m, 7 H, CHO and COH), 1.75 (q, J = 6 Hz, 2 H, CH_2); MS 196 (M^+), 178, 107, 91 (base). Anal. Calcd for $C_{11}H_{16}O_3$ (196.25): C, 67.32; H, 8.22. Found: C, 67.27; H, 8.22.

1,2-Anhydro-4-*O*-benzylbutane-1,2,4-triol (12). Methanesulfonyl chloride (4.8 mL, 62 mmol) was added over 10 min to a stirred solution of **11** (11.8 g, 60 mmol) in pyridine (75 mL) at 0 °C. After an additional 10 min, the resulting solution was added over 5 min to a stirred solution of NaOH (7.5 g, 190 mmol) in water (75 mL) plus Me_2SO (50 mL) at 0 °C. After an additional 10 min of stirring, the solution was poured into ice–water and the mixture extracted with ether. The ether phase was washed with water and then brine, dried over Na_2SO_4, and evaporated. The residue was distilled to give 7.82 g (73%) of **12**: bp 79–83 °C (1 torr); ^{1}H NMR (60 MHz, $CDCl_3$) δ 7.30 (s, 5 H, phenyl), 4.53 (s, 2 H, benzylic), 3.64 (t, J = 6 Hz, 2 H, CH_2O), 2.4–3.2 (m, 3 H, epoxide protons), 1.85 (m, 2 H, CH_2); MS 178 (M^+), 177, 160, 107, 91 (base). Anal. Calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.13; H, 7.92. Found: C, 73.91; H, 7.85.

9-[4-(Benzyloxy)-2-hydroxybutyl]guanine (13a). A suspension of guanine (15 g, 100 mmol) and sodium hydride (1.4 g, 50%, 29 mmol) in dry DMF (200 mL) was stirred at room temperature for 1 h. The epoxide **12** (10.4 g, 58 mmol) as a solution in dry DMF (50 mL) was added, and the resulting suspension was heated with stirring at 110 °C for 24 h. The DMF was removed by evaporation at reduced pressure and the residue chromatographed (gradient of 1:5 to 1:4 methanol/dichloromethane) to give 5.14 g (27%) of **13a** as a light yellow powder. An analytical sample was obtained by recrystallization from methanol: mp 211–213 °C; ^{1}H NMR (100 MHz) δ 10.65 (s, broad, 1 H, NH), 7.58 (s, 1 H, H-8), 7.28 (s, 5 H, phenyl), 6.43 (s, broad, 2 H, NH_2), 5.04 (s, br, 1 H, OH), 4.41 (s, 2 H, benzylic), 3.88 (m, 3 H, H-1′, H-2′), 3.51 (t, J = 6 Hz, 2 H, H-4′), 1.58 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 156.99 (C-6), 153.48 (C-2), 151.40 (C-4), 138.65 (C-8), 138.33, 128.25, 127.50 and 127.37 (phenyl), 116.83 (C-5), 71.98 (benzylic), 66.29 (C-2′), 65.83 (C-4′), 48.93 (C-1′), 34.49 (C-3′); UV λ_{max} (methanol) sh 270 nm (ϵ 9220), 253 (12 950); MS 329 (M^+), 238, 223, 194, 164, 152, 151, 91 (base). Anal. Calcd for $C_{16}H_{19}N_5O_3$ (329.36): C, 58.35; H, 5.81; N, 21.26. Found: C, 58.09; H, 5.89; N, 21.18.

9-(2,4-Dihydroxybutyl)guanine (7a). Sodium (1.5 g, 65 mmol) was carefully added to a stirred solution of **13a** (5.14 g, 15.6 mmol) in liquid ammonia (500 mL) at reflux. After 10 min, NH_4Cl (4 g) was added to the resulting blue solution. The ammonia was allowed to evaporate, and the residue was triturated two times with water to give 2.94 g (79%) of **7a** as a beige powder. An analytical sample was obtained by recrystallization from water/methanol: mp 250–252 °C; ^{1}H NMR (100 MHz) δ 10.68 (s, broad, 1 H, NH), 7.63 (s, 1 H, H-8), 6.47 (s, broad, 2 H, NH_2), 5.00 (s, broad, 1 H, OH), 4.43 (s, broad, 1 H, OH), 3.79 (m, 3 H, H-1′, H-2′), 3.50 (m, 2 H, H-4′), 1.50 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 156.89 (C-6) 153.31 (C-2), 151.33 (C-4), 138.26 (C-8), 116.29 (C-5), 65.93 (C-2′), 57.28 (C-4′), 48.93 (C-1′), 37.55 (C-3′); UV λ_{max} (methanol) sh 270 nm (ϵ 8260), 254 (11 850); MS 239 (M^+), 222, 208, 194, 164, 151 (base), 109, 43. Anal. Calcd for $C_9H_{13}N_5O_3$ (239.24): C, 45.19; H, 5.48; N, 29.27. Found: C, 44.99; H, 5.55; N, 29.10.

9-[4-(Benzyloxy)-2-oxobutyl]guanine (14a). To a stirred solution of **13a** (315 mg, 0.96 mmol) and dicyclohexylcarbodiimide (0.60 g, 3 mmol) in dry Me_2SO (6 mL) at 18 °C was added methylphosphonic acid (0.04 g, 0.5 mmol). The solution was allowed to warm to room temperature. After 20 h, the resulting suspension was cooled to 18 °C, and oxalic acid dihydrate (25 mg) in methanol (1.5 mL) was added. The suspension was stirred at room temperature for 16 h, filtered, and evaporated to dryness on a kugelrohr apparatus (80 °C (1 torr)). The residue was chromatographed (1:6 methanol/dichloromethane) and the product recrystallized from methanol to give 131 mg (42%) of **14a**: mp 200–202 °C; ^{1}H NMR (100 MHz) δ 7.53 (s, 1 H, H-8), 7.30 (s, 5 H, phenyl), 6.42 (s, broad, 2 H, NH_2), 4.95 (s, 2 H, H-1′), 4.46 (s, 2 H, benzylic), 3.67 (t, J = 6 Hz, 2 H, H-4′), 2.79 (t, J = 6 Hz, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 202.44 (C-2′), 156.86 (C-6), 153.67 (C-2), 151.49 (C-4), 138.26 (C-8), 137.94, 128.28 and 127.57 (phenyl), 116.12 (C-5), 72.04 (benzylic) 64.14 (C-4′), 51.49 (C-1′), 39.50 (C-3′); UV λ_{max} (methanol) sh 271 nm (ϵ 9130), 255 (12 500); MS 329 (M^+), 238, 223, 194, 164, 152, 91 (base). Anal. Calcd for $C_{16}H_{17}N_5O_3$ (327.34): C, 58.71; H, 5.23; N, 21.39. Found: C, 58.57; H, 5.21; N, 21.29.

9-[2-Hydroxy-4-(triphenylmethoxy)butyl]-N^2-(triphenylmethyl)guanine (15e). A stirred solution of **7a** (1.25 g, 5.2 mmol), triphenylmethyl chloride (3.3 g, 12 mmol), 4-(dimethylamino)pyridine (0.10 g), and triethylamine (3 mL, 22 mmol) in DMF (100 mL) was heated at 45 °C. After 24 h, additional triphenylmethyl chloride (1.0 g, 4 mmol) and triethylamine (2 mL, 14 mmol) were added. After an additional 24 h, methanol (1 mL) was added, and the solution was evaporated to dryness. The residue was chromatographed (1:12 methanol/dichloromethane) and the product crystallized from methanol/ethyl acetate to give 1.85 g (49%) of **15e**: mp 261–263 °C; ^{1}H NMR (300 MHz) δ 7.04–7.48 (m, 31 H, phenyl, H-8), 3.20–3.48 (m, 3 H, H-1′, H-2′), 2.80–3.04 (m, 2 H, H-4′), 1.27 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 156.66 (C-6), 150.45 (C-2), 149.64 (C-4), 144.70

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and 144.15 (phenyl), 138.49 (C-8), 128.57, 128.25, 127.89, 127.53, 126.98, 126.56, 126.10, and 125.84 (phenyl), 116.68 (C-5), 85.99 (Ph_3CO), 69.96 (Ph_3CN), 65.44 (C-2') 60.34 (C-4'), 48.99 (C-1'), 34.52 (C-3'); UV λ_{max} (methanol) sh 276 nm (ϵ 12100), 260 (14420); MS 243 (Tr^+), 57 (base). Anal. Calcd for $C_{47}H_{41}N_5O_3$ (723.88): C, 77.99; H, 5.71; N, 9.67. Found: C, 77.82; H, 5.73; N, 9.60.

9-[2-Oxo-4-(triphenylmethoxy)butyl]-N^2-(triphenylmethyl)guanine (16e). A solution of **15e** (3.20 g, 44.2 mmol), dicyclohexylcarbodiimide (2.50 g, 121 mmol), and methylphosphonic acid (0.19 g, 2.2 mmol) in dry Me_2SO (20 mL) was magnetically stirred at 18 °C for 2 h and then at room temperature for 16 h. The resulting suspension was cooled to 18 °C and oxalic acid dihydrate (90 mg) as a solution in methanol (3 mL) was added. The suspension was filtered then diluted with hot methanol (150 mL). The resulting solution was cooled to 0 °C to give 2.76 g (86%) of crystalline **16e**: mp 265–267 °C dec; ^1H NMR (90 MHz) δ 7.50 (s, 1 H, H-8), 7.03–7.42 (m, 30 H, phenyl), 4.35 (s, 2 H, H-1'), 3.11 (t, J = 6 Hz, 2 H, H-4'), 2.42 (t, J = 6 Hz, 2 H, H-3'); ^{13}C NMR (75.453 MHz) δ 201.11 (C-2'), 156.54 (C-6), 150.60 (C-2), 149.76 (C-4), 144.38 and 143.54 (phenyl), 138.09 (C-8), 128.33, 128.06, 127.84, 127.40, 127.04 and 126.49 (phenyl), 116.11 (C-5), 86.17 (Ph_3CO), 69.98 (Ph_3CN), 57.78 (C-4'), 50.91 (C-1'), 39.21 (C-3'); UV λ_{max} (methanol) sh 276 nm (ϵ 11200), 260 (13300); MS 260 (TrO^+), 243 (Tr^+), 183, 165, 105 (base). Anal. Calcd for $C_{47}H_{39}N_5O_3$ (721.86): C, 78.20; H, 5.45; N, 9.70. Found: C, 77.97; H, 5.51; N, 9.60.

9-(4-Hydroxy-2-oxobutyl)guanine (5a). A solution of **16e** (1.40 g, 1.9 mmol) in 80% aqueous acetic acid (300 mL) was heated at 50 °C for 40 h and then evaporated to dryness. The residue was triturated with hexane and then recrystallized from 1:1 water/methanol to give 0.35 g (75%) of **5a**: mp >300 °C; ^1H NMR (300 MHz) δ 10.60 (s, broad, 1 H, NH), 7.54 (s, 1 H, H-8), 6.43 (s, broad, 2 H, NH_2), 4.95 (s, 2 H, H-1'), 4.75 (t, J = 5 Hz, 1 H, OH), 3.68 (q, J = 6 Hz, 2 H, H-4'), 2.65 (t, J = 6 Hz, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 203.02 (C-2'), 156.81 (C-6), 153.52 (C-2), 151.42 (C-4), 138.03 (C-8), 115.96 (C-5), 55.86 (C-4'), 51.70 (C-1'), 42.75 (C-3'); UV λ_{max} (methanol) sh 272 nm (ϵ 9000), 254 (12800); MS 219 ($M^+ - H_2O$) 32 (base). Anal. Calcd for $C_9H_{11}N_5O_3$ (237.22): C, 45.57; H, 4.67; N, 29.52. Found: C, 45.67; H, 4.68; N, 28.99.

9-[4-(Benzyloxy)-2-hydroxybutyl]adenine (13b). A solution of adenine (3.0 g, 22 mmol), the sodium salt of adenine (0.65 g, 4 mmol), and **12** (3.65 g, 20.5 mmol) in DMF (100 mL) was stirred at 110 °C for 22 h. The DMF was evaporated to dryness at reduced pressure. The residue was chromatographed (1:9 methanol–dichloromethane) and the product recrystallized from methanol to give 3.91 g (61%) of **13b**: mp 135–137 °C; ^1H NMR (100 MHz) δ 8.15 (s, 1 H, H-8), 8.04 (s, 1 H, H-2), 7.30 (s, 5 H, phenyl), 7.19 (s, broad, 2 H, NH_2), 4.43 (s, 2 H, benzylic), 3.91–4.18 (m, 3 H, H-1', H-2'), 3.53 (t, J = 6 Hz, 2 H, H-4'), 3.37 (s, broad, 1 H, OH), 1.5–1.8 (m, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 155.75 (C-6), 152.27 (C-2), 149.67 (C-4), 141.68 (C-8), 138.59, 128.22 and 127.44 (phenyl) 118.30 (C-5), 71.91 (benzylic), 67.29 (C-2'), 66.25 (C-4'), 49.10 (C-1'), 34.39 (C-3'); UV λ_{max} (methanol) 261nm (ϵ 14740); MS 314 (MH^+), 222, 207, 178, 148, 135, 91 (base). Anal. Calcd for $C_{16}H_{19}N_5O_2$ (313.36): C, 61.33; H, 6.11; N, 22.35. Found: C, 61.06; H, 6.01; N, 22.66.

9-(2,4-Dihydroxybutyl)adenine (7b). A solution of **13b** (2.84 g, 9.1 mmol) in acetic acid (100 mL) was hydrogenated on a Parr hydrogenator (40 psi H_2) with shaking over 10% Pd/C (1 g) for 72 h at room temperature. The solution was filtered and evaporated to dryness, and the resulting white solid recrystallized from methanol to give 1.58 g (78%) of **7b**: mp 226–228 °C; ^1H NMR (100 MHz) δ 8.14 (s, 1 H, H-8), 8.04 (s, 1 H, H-2), 7.17 (s, broad, 2 H, NH_2), 5.02 (s, broad, 2 H, OH), 4.43 (s, broad, 1 H, OH), 3.87–4.17 (m, 3 H, H-1', H-2'), 3.53 (t, J = 6 Hz, 2 H, H-4'), 1.51 (m, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 155.85 (C-6), 152.31 (C-2), 149.71 (C-4), 141.71 (C-8) 118.46 (C-5), 65.93 (C-2'), 57.31 (C-4') 49.12 (C-1'), 37.52 (C-3'); UV λ_{max} (0.1 N HCl) 258 nm (ϵ 13800); (0.1 N NaOH) 261 (12000); MS 223 (M^+), 206, 178, 148 (base), 135. Anal. Calcd for $C_9H_{13}N_5O_2$ (223.24): C, 48.42; H, 5.87; N, 31.37. Found: C, 48.51; H, 5.85; N, 31.29.

9-[4-(Benzyloxy)-2-oxobutyl]adenine (14b). A solution of **13b** (0.30 g, 0.96 mmol), dicyclohexylcarbodiimide (0.60 g, 2.9 mmol), and dichloroacetic acid (40 μL, 0.48 mmol) in dry Me_2SO (3 mL) was stirred at 18 °C for 1 h and then at room temperature for 16 h. The resulting suspension was cooled to 18 °C and oxalic acid dihydrate (25 mg) as a solution in methanol (5 mL) was added. The suspension was then filtered, and the filtrate was evaporated to dryness. The residue was chromatographed (1:9 methanol/dichloromethane) and the product recrystallized from methanol to give 54 mg (18%) of **14b**: mp 175–176 °C; ^1H NMR (100 MHz) δ 8.12 (s, 1 H, H-8), 7.96 (s, 1 H, H-2), 7.31 (s, 5 H, phenyl), 7.22 (s, broad, 2 H, NH_2), 5.19 (s, 2 H, H-1'), 4.47 (s, 2 H, benzylic), 3.69 (t, J = 6 Hz, 2 H, H-4'), 2.84 (t, J = 6 Hz, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 202.47 (C-2'), 156.01 (C-6), 152.57 (C-2), 149.80 (C-4), 141.42 (C-8), 138.30, 128.90, 127.57; and 127.47 (phenyl), 118.27 (C-5), 72.04 (benzylic), 64.34 (C-4'), 51.59 (C-1'), 39.76 (C-3'); UV λ_{max} (methanol) 261 nm (ϵ 14850); MS 135 (base), 108. Anal. Calcd for $C_{16}H_{17}N_5O_2$ (311.35): C, 61.72; H, 5.50; N, 22.49. Found: C, 61.90; H, 5.64; N, 22.66.

9-[2-Hydroxy-4-(triphenylmethoxy)butyl]adenine (15b). A stirred solution of **7b** (0.23 g, 1 mmol), triphenylmethyl chloride (0.55 g, 2 mmol), 4-(dimethylamino)pyridine (0.05 g), and triethylamine (0.55 mL, 4 mmol) in DMF (10 mL) was heated at 50 °C. After 24 h, additional triphenylmethyl chloride (0.30 g, 1 mmol) and triethylamine (0.55 mL, 4 mmol) were added. After an additional 48 h, methanol was added, and the solution was evaporated to dryness. The residue was chromatographed (1:14 methanol/dichloromethane) and the product recrystallized from ethyl acetate to give 0.23 g (46%) of **15b**: mp 177–179 °C; ^1H NMR (300 MHz) δ 8.13 (s, 1 H, H-8), 7.98 (s, 1 H, H-2), 7.19–7.41 (m, 15 H, phenyl), 7.12 (s, broad, 2 H, NH_2), 5.02 (d, J = 5 Hz, 1 H, OH), 4.02–4.21 (m, 3 H, H-1', H-2'), 3.13 (t, J = 6 Hz, 2 H, H-4'), 1.52–1.78 (m, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 155.98 (C-6), 152.34 (C-2), 149.74 (C-4), 144.08 (phenyl), 141.55 (C-8), 128.22, 127.89, and 126.92 (phenyl), 118.66 (C-5), 85.95 (Ph_3C), 65.86 (C-2'), 60.01 (C-4'), 49.35 (C-1'), 34.71 (C-3'); UV λ_{max} (methanol) 260nm (ϵ 14450); MS 466 (MH^+), 388, 310, 243 (base), 222, 206, 178, 165, 148, 135. Anal. Calcd $C_{28}H_{27}N_5O_2$ (461.52): C, 72.24; H, 5.85; N, 15.04. Found: C, 72.19; H, 5.88; N, 15.03.

9-[2-Oxo-4-(triphenylmethoxy)butyl]adenine (16b). A solution of **15b** (0.34 g, 0.75 mmol), dicyclohexylcarbodiimide (0.40 g, 2.0 mmol), and methylphosphonic acid (0.4 g, 0.5 mmol) in dry Me_2SO (20 mL) was stirred at 18 °C for 2 h and then at room temperature for 16 h. The resulting suspension was cooled to 18 °C and oxalic acid dihydrate (25 mg) as a solution in methanol (1 mL) was added. The solution was filtered, and the filtrate was evaporated to dryness on a kugelrohr apparatus (80 °C (1 torr)). The residue was chromatographed (1:15 methanol/dichloromethane) to give 145 mg (42%) of **16b** as a white solid and 189 mg (54%) of the starting alcohol 15b. An analytical sample was prepared by recrystallization from ethyl acetate/hexane: mp 174–176 °C; ^1H NMR (300 MHz) δ 8.11 (s, 1 H, H-8); 7.96 (s, 1 H, H-2), 7.30 (m, 17 H, phenyl, NH_2), 5.20 (s, 2 H, H-1'), 3.25 (t, J = 6 Hz, 2 H, H-4'), 2.91 (t, J = 6 Hz, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 202.53 (C-2'), 155.98 (C-6), 152.53 (C-2), 149.80 (C-4), 143.69 (phenyl), 141.35 (C-8), 128.28, 127.96 and 127.11 (phenyl), 118.20 (C-5), 86.22 (TrC) 58.39 (C-4'), 51.76 (C-1'), 39.45 (C-3'); UV λ_{max} (methanol) 259 nm (ϵ 15350); MS 260, 220, 183, 154, 105, 43 (base). Anal. Calcd for $C_{28}H_{25}N_2O_2$ (463.54): C, 72.55; H, 5.44; N, 15.11. Found: C, 72.28; H, 5.49; N, 15.01.

9-(4-Hydroxy-2-oxobutyl)adenine (5b). A solution of **16b** (148 mg, 0.32 mmol) in 80% aqueous acetic acid (10 mL) was heated at 50 °C for 18 h. The solution was evaporated to dryness and the residue recrystallized from methanol/ethyl acetate to give 45 mg (64%) of **5b**: mp 211–213 °C dec; ^1H NMR (100 MHz) δ 8.12 (s, 1 H, H-8), 8.01 (s, 1 H, H-2), 7.21 (s, broad, 2 H, NH_2), 5.21 (s, 2 H, H-1'), 4.80 (s, broad, 1 H, OH), 3.71 (t, J = 6 Hz, 2 H, H-4'), 2.71 (t, J = 6 Hz, 2 H, H-3'); ^{13}C NMR (22.62 MHz) δ 203.18 (C-2'), 155.95 (C-6), 152.53 (C-2), 149.71 (C-4), 141.42 (C-8), 118.24 (C-5), 56.01 (C-4'), 51.79 (C-1'), 42.88 (C-3'); UV λ_{max} (0.1 N HCl) 257 nm (ϵ 12200); (0.1 N NaOH) 260 (14800); MS 221 (M^+), 192, 148 (base), 135, 57, 43. Anal. Calcd for $C_9H_{11}N_5O_2$ (221.22): C, 48.87; H, 5.01; N, 31.66. Found: C, 48.77; H, 5.06; N, 31.59.

1-[4-(Benzyloxy)-2-hydroxybutyl]uracil (13c). A solution of uracil (0.67, 6 mmol) and sodium hydride (0.05 g, 50%, 1 mmol) in DMF (20 mL) was stirred at room temperature for 1 h. The epoxide **12** (0.90 g, 5 mmol) in DMF (3 mL) was added, and the resulting solution was heated at 110 °C for 16 h. The DMF was evaporated and the residue chromatographed (1:19 methanol/

dichloromethane) to give 1.09 g (74%) of **13c** as a white solid. An analytical sample was obtained by recrystallization from ethyl acetate: mp 124–125 °C; ^{1}H NMR (100 MHz) δ 7.48 (d, J = 8 Hz, 1 H-6), 7.30 (s, 5 H, phenyl), 5.48 (d, J = 8 Hz, 1 H, H-5), 5.00 (s, broad, 1 H, OH), 4.43 (s, 2 H, benzylic), 3.24–3.92 (m, 5 H, H-1′, H-2′, H-4′), 1.60 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 163.98 (C-4), 151.14 (C-2), 147.01 (C-6), 138.65, 128.25 and 127.44 (phenyl), 100.03 (C-5), 71.94 (benzylic), 66.29 (C-2′), 65.18 (C-4′), 53.67 (C-1′), 34.30 (C-3′); UV λ_{max} (methanol) 265 nm (ε 10130); MS 290 (M^+), 184, 126, 191 (base). Anal. Calcd for $C_{15}H_{18}N_2O_4$ (290.32): C, 62.06; H, 6.25; N, 9.65. Found: C, 62.17; H, 6.33; N, 9.56.

1-(2,4-Dihydroxybutyl)uracil (7c). A slurry of 0.10 g of 20% $Pd(OH)_2$/C in water (1.5 mL) was added to a solution of **13c** (364 mg, 1.25 mmol) in methanol (15 mL), and the resulting mixture was stirred vigorously under H_2 (1 atm) at room temperature for 14 h. The solution was then filtered through Celite and evaporated to dryness. The residue was recrystallized from methanol/ethyl acetate to give 191 mg (76%) of **7c**: mp 153–154 °C; ^{1}H NMR (100 MHz) δ 7.49 (d, J = 8 Hz, 1 H, H-6), 5.47 (d, J = 8 Hz, 1 H, H-5), 4.90 (d, J = 5 Hz, 1 H, OH), 4.39 (t, J = 5 Hz, 1 H, OH), 3.15–3.92 (m, 5 H, H-1′, H-2′, H-4′), 1.49 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 163.95 (C-4), 151.10 (C-2), 146.98 (C-6), 99.97 (C-5), 65.28 (C-2′), 57.28 (C-4′), 52.96 (C-1′), 37.26 (C-3′); UV λ_{max} (0.1 N HCl) 266 nm (ε 10100); (0.1 N NaOH) 265 (7230); MS 201 (MH^+), 200, 183, 155, 126 (base), 113, 83, 55. Anal. Calcd for $C_8H_{12}N_2O_4$ (200.20): C, 48.00; H, 6.04; N, 13.99. Found: C, 48.00; H, 6.06; N, 13.96.

1-[4-(Benzyloxy)-2-oxobutyl]uracil (14c). To a solution of **13c** (266 mg, 0.92 mmol) and dicyclohexylcarbodiimide (0.50 g, 2.4 mmol) in Me_2SO (8 mL) at 18 °C was added methylphosphonic acid (35 mg, 0.41 mmol). The solution was then allowed to warm to room temperature. After 27 h, the resulting suspension was cooled to 18 °C, and oxalic acid dihydrate (25 mg) in methanol (2 mL) was added. After an additional 0.5 h, the suspension was filtered and the filtrate evaporated to dryness on a kugelrohr apparatus (80 °C (1 torr)). The residue was chromatographed (1:19 methanol/dichloromethane) to give 224 mg (85%) of **14c** as a white solid. An analytical sample was prepared by recrystallization from ethyl acetate: mp 117–118 °C; ^{1}H NMR (100 MHz) δ 7.42 (d, J = 8 Hz, 1 H, H-6), 7.30 (s, 5 H, phenyl), 5.56 (d, J = 8 Hz, 1 H, H-5), 4.64 (s, 2 H, H-1′), 4.45 (s, 2 H, benzylic), 3.65 (t, J = 6 Hz, 2 H, H-4′), 2.75 (t, J = 6 Hz, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 202.76 (C-2′), 163.82 (C-4), 150.94 (C-2), 146.00 (C-6), 138.26, 128.25 and 127.53 (phenyl), 100.75 (C-5), 72.01 (benzylic), 64.27 (C-4′), 55.82 (C-1′), 39.66 (C-3′); UV λ_{max} (methanol) 262 nm (ε 10210); MS 289 (MH^+), 270, 182, 126, 113, 108, 91 (base). Anal. Calcd for $C_{15}H_{16}N_2O_4$ (288.31): C, 62.49; H, 5.59; N, 9.72. Found: C, 62.44; H, 5.65; N, 9.72.

1-(4-Hydroxy-2-oxobutyl)uracil (5c). A slurry of 0.07 g of 20% $Pd(OH)_2$/C in water (3 mL) was added to a solution of **14c** (140 mg, 0.48 mmol) in methanol (10 mL), and the resulting mixture was stirred vigorously under 1 atm of H_2 at room temperature for 16 h. The solution was then filtered through Celite and evaporated to dryness. The residue was recrystallized from methanol/ethyl acetate to give 57 mg (59%) of **5c**: mp 137–139 °C; ^{1}H NMR (100 MHz) δ 7.46 (d, J = 8 Hz, 1 H, H-6), 5.57 (d, J = 8 Hz, 1 H, H-5), 4.76 (s, broad, 1 H, OH), 4.66 (s, 2 H, H-1′), 3.69 (q, J = 6 Hz, 2 H, H-4′), 2.64 (t, J = 6 Hz, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 203.54 (C-2′), 163.85 (C-4), 150.88 (C-2), 146.16 (C-6), 100.75 (C-5), 56.01 (C-1′, C-4′), 42.68 (C-3′); UV λ_{max} (methanol) 263 (ε 9090); MS 198 (M^+), 180, 168, 152, 126 (base), 82, 73, 55, 43. Anal. Calcd for $C_8H_{10}N_2O_4$ (198.18): C, 48.49; H, 5.09; N, 14.14. Found: C, 48.61; H, 5.19; H, 14.05.

1-[4-(Benzyloxy)-2-hydroxybutyl]thymine (13d). A solution of thymine (1.51 g, 12 mmol) and sodium hydride (0.10 g, 50%, 2 mmol) in DMF (15 mL) was stirred at room temperature for 2 h. The epoxide **12** (1.80 g, 10 mmol) in DMF (5 mL) was added, and the resulting solution was heated at 110 °C for 16 h. The DMF was evaporated and the residue chromatographed (1:19 methanol/dichloromethane) to give 2.02 g (66%) of **13d** as a white solid. An analytical sample was obtained by recrystallization from ethyl acetate/hexane: mp 113–114 °C; ^{1}H NMR (100 MHz) δ 7.36 (d, J = 2 Hz, 1 H, H-6), 7.30 (s, 5 H, phenyl), 4.92 (s, broad, 1 H, OH), 4.44 (s, 2 H, benzylic), 3.22–3.90 (m, 5 H, H-1′, H-2′, H-4′), 1.72 (s, 3 H, CH_3), 1.60 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 164.47 (C-4), 151.10 (C-2), 142.75 (C-6), 138.65, 128.25 and 127.44 (phenyl), 107.51 (C-5), 71.98 (benzylic), 66.35 (C-2′), 65.34 (C-4′), 53.48 (C-1′), 34.36 (C-3′), 11.83 (CH_3); UV (methanol) λ_{max} 271 nm (ε 9810); MS 304 (M^+), 198, 140, 91 (base). Anal. Calcd for $C_{16}H_{20}N_2O_4$ (304.35): C, 63.14; H, 6.62; N, 9.20. Found: C, 63.08; H, 6.66; N, 9.14.

1-(2,4-Dihydroxybutyl)thymine (7d). A slurry of 0.2 g of 10% Pd/C in water (2 mL) was added to a solution of **13d** (195 mg, 0.64 mmol) in methanol (10 mL), and the resulting mixture was stirred vigorously under H_2 (1 atm) at room temperature for 21 h. The solution was the filtered through Celite and evaporated to dryness. The residue was recrystallized from methanol/ethyl acetate to give 94.3 mg (69%) of **7d**: mp 161–162 °C; ^{1}H NMR (100 MHz) δ 7.36 (d, J = 2 Hz, 1 H, H-6), 3.20–3.88 (m, 5 H, H-1′, H-2′, H-4′), 1.71 (s, 3 H, CH_3), 1.45 (m, 2 H, H-3′); ^{13}C NMR (22.62 MHz) δ 164.47 (C-4), 151.10 (C-2), 142.81 (C-6), 107.41 (C-5), 65.41 (C-2′), 57.38 (C-4′), 53.51 (C-1′), 37.32 (C-3′) 11.87 (CH_3); UV λ_{max} (0.1 N HCl) 272 nm (ε 9500); (0.1 N NaOH) 270 (7070); MS 215 (MH^+), 214, 197, 169, 140 (base), 127. Anal. Calcd for $C_9H_{14}N_2O_4$ (214.22): C, 50.46; H, 6.59; N, 13.08. Found: C, 50.42; H, 6.52; N, 12.97.

1-[4-(Benzyloxy)-2-oxobutyl]thymine (14d). To a solution of **13d** (0.50 g, 1.6 mmol) and dicyclohexylcarbodiimide (0.83 g, 4.0 mmol) in Me_2SO (12 mL) at 18 °C was added methylphosphonic acid (0.06 g, 0.7 mmol). The solution was then allowed to warm to room temperature. After 20 h, the resulting suspension was cooled to 18 °C, and oxalic acid dihydrate (0.05 g) in methanol (3 mL) was added. After an additional 0.5 h, the suspension was filtered and the filtrate evaporated to dryness on a kugelrohr apparatus (80 °C (1 torr)). The residue was chromatographed (1:19 methanol/dichloromethane) to give 407 mg (81%) of **14d** as a white solid. An analytical sample was prepared by recrystallization from ethyl acetate: mp 133–135 °C; ^{1}H NMR (100 MHz) δ 7.30 (s, 6 H, H-6, phenyl), 4.59 (s, 2 H, H-1′), 4.44 (s, 2 H, benzylic), 3.64 (t, J = 6 Hz, 2 H, H-4′), 2.74 (t, J = 6 Hz, 2 H, H-3′), 1.71 (s, 3 H, CH_3); ^{13}C NMR (22.62 MHz) δ 202.92 (C-2′), 164.37 (C-4), 150.97 (C-2), 141.74 (C-6), 138.36, 128.28 and 127.57 (phenyl), 108.32 (C-5), 72.04 (benzylic), 64.37 (C-4′), 55.72 (C-1′), 39.73 (C-3′), 11.77 (CH_3); UV λ_{max} (methanol) 268 nm (ε 8820); MS 303 (MH^+), 225, 212, 195 (base). Anal. Calcd for $C_{16}H_{18}N_2O_4$ (302.33): C, 63.57; H, 6.00; N, 9.27. Found: C, 63.72; H, 6.17; N, 9.36.

1-(4-Hydroxy-2-oxobutyl)thymine (5d). A slurry of 0.09 g of 20% $Pd(OH)_2$/C in water (2 mL) was added to a solution of **14d** (182 mg, 0.60 mmol) in methanol (10 mL), and the resulting mixture was stirred vigorously under H_2 (1 atm) at room temperature for 22 h. The solution was then filtered through Celite and evaporated to dryness. The residue was recrystallized from methanol/ethyl acetate to give 51 mg (40%) of **5d**: mp 184–185 °C; ^{1}H NMR (100 MHz) δ 7.29 (d, J = 2 Hz, 1 H, H-6), 4.68 (s, broad, 1 H, OH), 4.57 (s, 2 H, H-1′), 3.66 (m, 2 H, H-4′), 2.60 (t, J = 6 Hz, 2 H, H-3′), 1.73 (s, 3 H, CH_3); ^{13}C NMR (22.62 MHz) δ 203.67 (C-2′), 164.34 (C-4), 150.88 (C-2), 141.84 (C-6), 108.29 (C-5), 55.85 (C-1′, C-4′), 42.72 (C-3′), 11.74 (CH_3); UV λ_{max} (methanol) 268 nm (ε 10000); MS 212 (M^+), 194, 182, 140, 96 (base), 73, 55, 43. Anal. Calcd for $C_9H_{12}N_2O_4$ (212.21): C, 50.94; H, 5.70; N, 13.20. Found: C, 50.86; H, 5.77; N, 13.07.

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Registry No. 5a, 90493-91-7; **5b**, 94426-67-2; **5c**, 94426-68-3; **5d**, 94426-69-4; **7a**, 83470-65-9; **7b**, 94426-70-7; **7c**, 87009-05-0; **7d**, 71709-64-3; **9**, 5754-34-7; **10**, 94426-71-8; **11**, 71998-69-1; **12**, 94426-72-9; **13a**, 94426-73-0; **13b**, 94426-74-1; **13c**, 94426-75-2; **13d**, 94426-76-3; **14a**, 94426-77-4; **14b**, 94426-78-5; **14c**, 94426-79-6; **14d**, 94426-80-9; **15b**, 94426-81-0; **15e**, 94426-82-1; **16b**, 94426-83-2; **16e**, 94458-42-1; guanine, 73-40-5; adenine, 73-24-5; adenine sodium salt, 40428-86-2; uracil, 66-22-8; thymine, 65-71-4; thymidine kinase, 9002-06-6.