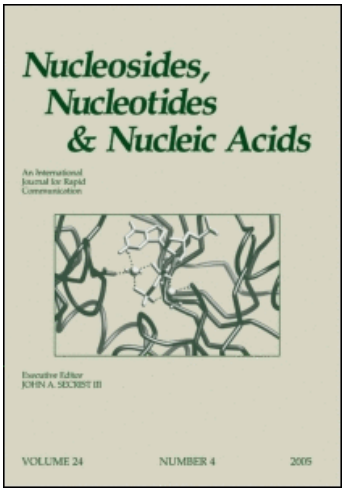

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Synthesis of 4'-(Hydroxymethyl)Guanosine and a Phosphonate Analogue of Guanylic Acid

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SYNTHESIS OF 4'-(HYDROXYMETHYL)GUANOSINE AND A PHOSPHONATE ANALOGUE OF GUANYLIC ACID[1]

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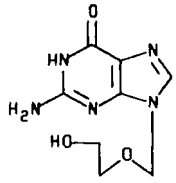
Abstract. The synthesis of 4'-(hydroxymethyl)guanosine (**7**) and the phosphonate analogue **8** of guanylic acid proceed from a common intermediate, 2',3'-O-isopropylidene-N^2-(monomethoxytrityl)-guanosine-5'-aldehyde (**13**).

INTRODUCTION

A number of guanosine nucleoside analogues[3] such as acyclovir (**1**)[4] and ganciclovir (**2**)[5] have been reported to be active against herpes simplex virus. For activity, these compounds are converted to their corresponding monophosphates by a viral thymidine kinase. Host kinases phosphorylate the monophosphates to triphosphates which in turn inhibit the viral DNA polymerase and thus virus replication. In as much as these analogues are not substrates for host kinases in the initial phosphorylation, selectivity is realized at this step.



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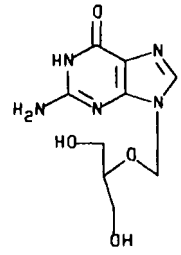

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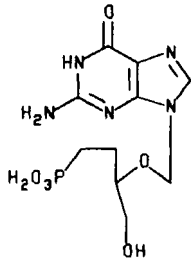
Additionally, nucleotide analogues which may bypass the activation step by the viral thymidine kinase can exert an antiviral effect against viruses which lack this enzyme.[6] An example of such a compound is ganciclovir phosphonate derivative **3** which is active in

vitro[7] and in vivo[8] against cytomegalovirus, a virus that does not encode a kinase. Even though phosphonate **3** bypasses the potential selectivity incurred by the kinase step, the compound showed very low toxicity in tissue culture indicating that such a nucleotide can be highly selective, presumably at the DNA polymerase level. Since the report of **3**, a PFA derivative of guanosine **4**[9] and HPMPA (**5**),[10] an especially broad-spectrum antiviral agent, have been described as antiviral nucleotide analogues.



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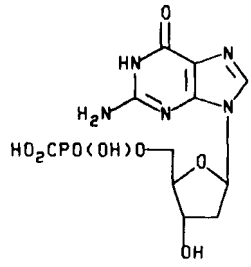

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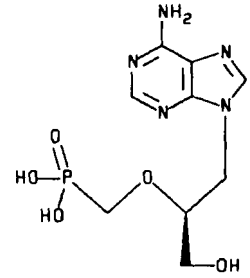

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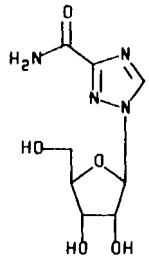
The activity of acyclic guanosine nucleoside and nucleotide analogues and the fact that the riboside derivative ribavirin (**6**) at least in part exerts its broad-spectrum activity as a guanosine analogue[11] prompted us to prepare guanosine derivatives 4'-(hydroxymethyl)guanosine (**7**) and the phosphonate analogue **8** of guanylic acid (**9**).



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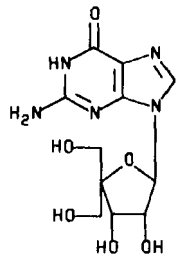

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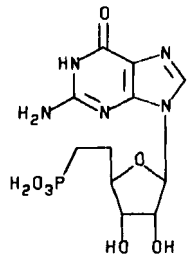

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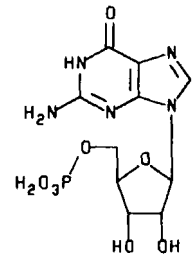

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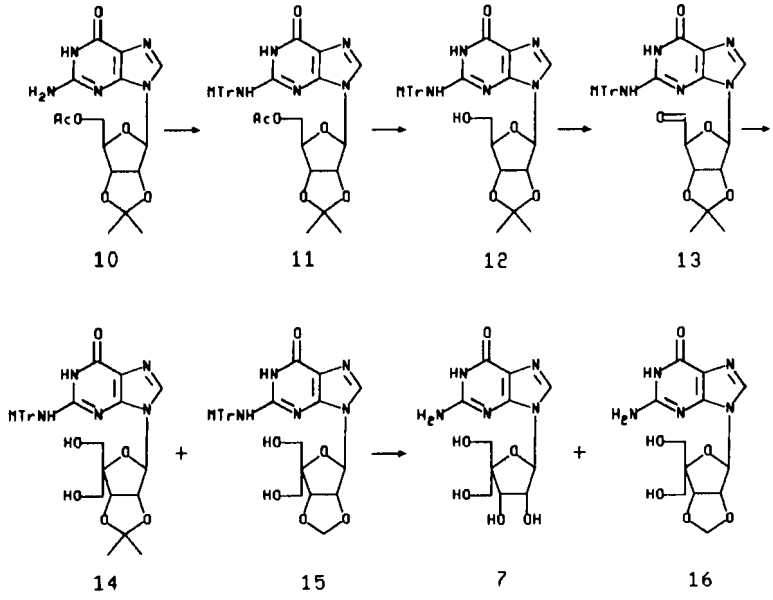
RESULTS AND DISCUSSION

The chemistry utilized for the synthesis of **7** and **8** is based on previous work at this Institute directed towards the preparations of 4'-substituted nucleosides[12] and nucleoside phosphonates.[13] Both classes of compounds were approached via nucleoside 5'-aldehyde intermediates. For this guanosine series, we utilized the monomethoxytrityl protecting group at the $\underline{N}^2$ position, which we have previously found protects and solubilizes guanosine derivatives.[7,14]

Thus, 5'-O-acetyl-2',3'-O-isopropylideneguanosine (**10**)[15] (Scheme 1) was monomethoxytritylated to give **11** which in turn was deacetylated (NH_4OH/MeOH) furnishing alcohol **12** (quantitative). Alcohol **12** was suitably protected so that Moffatt oxidation[16] afforded a quantitative yield of key intermediate aldehyde **13**.

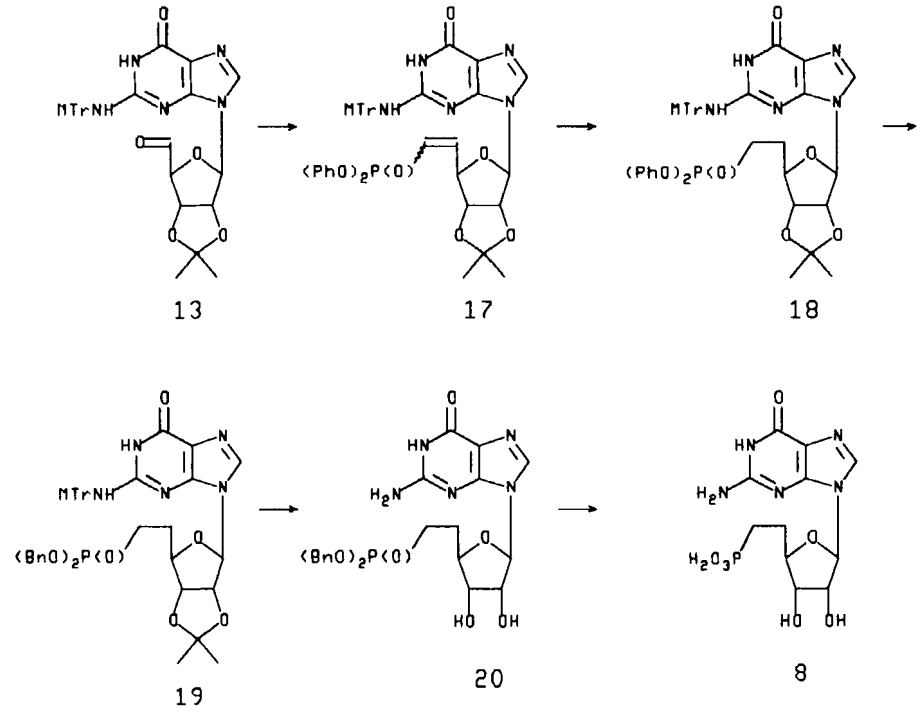
Reaction of the 5'-aldehyde **13** with paraformaldehyde in aqueous NaOH gave hydroxymethyl derivatives **14** and **15** in the low yields of 10% and 9%, respectively. The formation of methylene derivative **15** was



Scheme 1

not unexpected having been observed with a mechanism proposed previously for a similar reaction on $\underline{N}^6$-benzoyl-2',3'-$\underline{O}$-isopropylideneadenosine 5'-aldehyde.[12] Complete deprotection of **14** with aqueous trifluoroacetic acid afforded target compound **7** in 94% yield. Alternatively, the methylene derivative **16** was prepared by the treatment of **15** with aqueous acetic acid.

Aldehyde **13** was also utilized for the synthesis of guanylic acid phosphonate analogue **8** (Scheme 2). Condensation of **13** with diphenyl tributylphosphoranylidene methylphosphonate[17] in tetrahydrofuran gave unsaturated phosphonate **17** which was directly reduced with diimide furnishing **18** in 25% yield. Transesterification of **18** with sodium benzyl oxide gave dibenzyl ester **19** (61%). Acetic acid hydrolysis of **19** to **20** followed by transfer hydrogenation furnished nucleotide analogue **8** in 29% yield after recrystallization from water.



Scheme 2

Analogues **7** and **8** were found to be inactive when tested in vitro against herpes simplex virus types 1 and 2, parainfluenza 3, and respiratory syncytial virus.

EXPERIMENTAL

Nuclear magnetic resonance spectra were recorded on a Bruker WM-300 (^{1}H NMR, 300 MHz) and chemical shifts are reported in parts per million downfield from internal tetramethylsilane. Ultraviolet spectra were recorded on a Hewlett Packard 8450A spectrometer, and spectroscopic data and elemental analyses 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.

2',3'-O-Isopropylidene-N^2-(monomethoxytrityl)guanine (12). A solution of **10** (11.60 g, 31.8 mmol), monomethoxytritylchloride (13.3g, 48 mmol), triethylamine (8.9 mL, 64mmol), and 4-dimethylaminopyridine (0.19g, 1.5 mmol) in DMF (150 mL) was heated at 50 °C for 1.5 h, and then methanol (10 mL) was added. The solution was evaporated to dryness. The residue was dissolved in ethyl acetate, washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness. The residue was taken up in a mixture of methanol (100 mL) and conc. NH_4OH (40 mL), and the solution was stirred at room temperature for 20 h. Evaporation of the reagents left a syrup which was chromatographed (1:14 methanol/dichloromethane) to give 20 g (100%) of **12** as a foam; UV λ_{max} (methanol) 277 nm (ε 13500), 260 (15100); ^{1}H NMR (Me_2SO-d_6) δ 10.67 (s, broad, 1H, NH), 7.82 (s, 1H, H-8), 7.64 (s, broad, 1H, NH), 7.16-7.35 (m, 12H, aromatic), 6.86 (d, J = 9Hz, 2H aromatic), 5.36 (d, J = 4Hz, 1H, H-1'), 4.98 (t, J = 5 Hz, 1H, OH), 4.72 (dd, J = 4 and 6 Hz, 1H, H-2'), 4.37 (dd, J = 2.5 and 6 Hz, 1H, H-3'), 3.96 (m, 1H, H-4'), 3.71 (s, 3H, OCH_3), 3.30 (m, 2H, H-5'), 1.35 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). Anal. Calcd for $C_{33}H_{33}N_5O_6 \cdot 1.5H_2O$ (622.68): C, 63.65; H, 5.83; N, 11.25. Found: C, 63.56; H, 5.86; N, 11.28.

4'-Hydroxymethyl-2',3'-O-isopropylidene-N^2-(monomethoxytrityl) guanosine (14) and 4'-hydroxymethyl-2',3'-O-methylene-N^2-(monomethoxytrityl)guanosine (15). A solution of **12** (6.23 g, 10 mmol), dicyclohexylcarbodiimide (8.25 g, 40 mmol) and methylphosphonic acid (0.86 g, 10 mmol) in DMSO (100 mL) was stirred at 18 °C for 4 h and then at room temperature for 18 h. The resulting suspension was cooled to 18 °C, and oxalic acid dihydrate (125 mg) as a solution in methanol (6 mL) was added. The suspension was filtered, and the filtrate was evaporated to dryness in a Kugelrohr apparatus (60 °C/1 mm) to give aldehyde **13**. A mixture of the residue in 37% aqueous paraformaldehyde (40 mL), 1 N sodium hydroxide (40 mL), THF (250 mL) and water (250 mL) was kept at room temperature for 48 h. Ammonium chloride (4 g) was then added and the solution evaporated to approximately 200 mL. The resulting mixture was extracted with dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed (1:14 methanol/dichloromethane) to give 0.621 g (10%) of **14** and 0.556 g (9%) of the more polar **15**. Both products were isolated as amorphous solids.

14: UV λ_{max} (methanol) 277 nm (ε 14200), 261 (15800); ^1H NMR (Me_2SO-d_6) δ 10.61 (s, broad, 1H, NH), 7.87 (s, 1H, H-8), 7.62 (s, broad, 1H, NH), 7.16-7.35 (m, 12H, aromatic), 6.84 (d, J = 9Hz, 2H, aromatic), 5.31 (d, J = 4.7 Hz, 1H, H-1), 4.96 (t, J = 5 Hz, 1H, OH), 4.80 (dd, J = 5 Hz, 1H, H-2'), 4.59 (t, J = 5 Hz, 1H, OH), 4.53 (d, J = 5 Hz, 1H, H-3'), 3.71 (s, 3H, OCH_3), 3.15-3.62 (m, 4H, CH_2OH), 1.26 (s, 3H, CH_3), 1.20 (s, 3H, CH_3)). Anal. Calcd for $C_{34}H_{35}N_5O_7 \cdot H_2O$ (643.71): C, 63.44; H, 5.79; N, 10.88. Found: C, 63.27; H, 5.77; N, 10.80.

15: UV λ_{max} (methanol) 277 nm (ε 14200), 260 (16000); ^1H NMR (Me_2SO-d_6) δ 10.66 (s, broad, 1H, NH), 7.82 (s, 1H, H-8), 7.63 (s, broad, 1H, NH), 7.17-7.35 (m, 12H, aromatic), 6.86 (d, J=9Hz, 2H, aromatic), 5.37 (d, J = 4.2 Hz, 1H, H-1'), 4.90 (t, J = 5 Hz, 1H, OH), 4.88 (s, 2H, OCH_2O), 4.79 (dd, J = 4 and 6 Hz, 1H, H-2'), 4.62 (t, J = 5 Hz, 1H, OH), 4.25 (d, J = 6Hz, 1H, H-3'), 3.72 (s, 3H, OCH_3), 3.10-3.60 (m, 4H, CH_2OH). Anal. Calcd for $C_{32}H_{31}N_5O_7 \cdot H_2O$ (615.65): C, 62.43; H, 5.40; N, 11.38. Found: C, 62.44; H, 5.40; N, 11.37.

4'-Hydroxymethylguanosine (7). A solution of **14** (0.621 g, 0.99 mmol) in 50% aq trifluoroacetic acid (7 mL) was kept at room temperature for 1 h and then evaporated to dryness. The residue was triturated with ethyl acetate and hexane to give 0.293 g (94%) of **7** as a beige powder. An analytical sample was obtained by recrystallization from water: mp >300 °C; UV λ_{max} (0.1 N HCl) sh 279 nm (ε 8500), 257 (12200), (0.1 N NaOH) 267 (11200); ^{1}H NMR (Me_2SO-d_6/D_2O) δ 7.96 (s, 1H, H-8), 5.73 (d, J = 7Hz, 1H, H-1'), 4.61 (dd, J = 5 and 7 Hz, 1H, H-2'), 4.15 (d, J = 5 Hz, 1H, H-3'), 3.50-3.80 (m, 4H, CH_2OH). Anal. Calcd for $C_{11}H_{15}N_5O_6 \cdot 0.5\ H_2O$ (322.28): C, 41.00; H, 5.00; N, 21.73. Found: C, 41.00; H, 5.01, N, 21.80.

4'-Hydroxymethyl-2',3'-O-methyleneguanosine (16). A solution of **15** (556 mg, 0.93 mmol) in 80% aqueous acetic acid was heated at 80 °C for 2 h and then evaporated to dryness. The residue was triturated with ethyl acetate and then recrystallized from methanol to give 78 mg (26%) of **16** mp >300 °C; UV λ_{max} (methanol) sh 270mm (ε 10100), 254 (14200); ^{1}H NMR (Me_2SO-d_6) δ 10.40 (s, broad, 1H, NH), 8.00 (s, 1H, H-8), 6.52 (s, broad, 2H, NH_2), 5.90 (d, J = 4 Hz, 1H, H-1'), 5.27 (dd, J = 4 and 6 Hz, 1H, H-2'), 5.22 (t, J = 5 Hz, 1H, OH), 5.19 and 5.06 (s, 1H, OCH_2O) 4.77 (t, J = 5 Hz, 1H, OH), 4.72 (d, J = 6 Hz, 1H, H-3'), 3.45-3.72 (m, 4H, CH_2OH). Anal. Calcd for $C_{12}H_{15}N_5O_6 \cdot 0.33\ H_2O$ (331.29); C, 43.51; H, 4.77; N, 21.14. Found: C, 43.64; H, 4.77; N, 21.19.

9-[5,6-dideoxy-6-Diphenoxyphosphinyl-2,3-O-isopropylidene-β-D-ribo-hex-5-enofuranosyl]-N^2-monomethoxytritylguanine (17). A solution of **13** (10 mmol, prepared as described above), diphenyl tributylphosphoranylidenemethylphosphonate (7.28 g, 15 mmol), and triethylamine (2.8 mL, 20 mmol) in THF (200 mL) was kept at room temperature for 72 h. After evaporation to dryness, the residue was dissolved in dichloromethane, washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed three times (1:24 methanol/dichloromethane) to give 2.75 g of **17** still contaminated with a small amount of tributylphosphine oxide. ^{1}H NMR (Me_2SO-d_6) δ 10.76 (s, broad, 1H, NH), 7.77 (s, 1H, H-8), 7.69 (s, broad, 1H, NH), 7.10-7.45 (m, 22H, aromatic), 6.87 (d, J = 9 Hz, 2H,

aromatic), 6.80 (d, J = 2 Hz, 1H, H-1'), 6.71 (ddd, $J_{5'6'}$ = 17.4, $J_{5'P}$ = 24.2, $J_{5'4'}$ = 4.7Hz, 1H, H-5'), 4.98 (dd, J = 2 and 6 Hz, 1H, H-2'), 5.61 (ddd, $J_{6'5'}$ = 17.4, $J_{6',P}$ = 22.5, $J_{6',4'}$ = 1.7 Hz, 1H, H-6'), 4.67 (m, 1H, H-4'), 3.99 (dd, J = 3 and 6 Hz, 1H, H-3'), 3.70 (s, 3H, OCH_3), 1.34 (s, 3H, CH_3), 1.23 (s, 3H, CH_3).

9-[5,6-Dideoxy-6-diphenoxyphosphinyl-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl]-N^2-monomethoxytritylguanine (18). A solution of impure **17** from above (2.10 g, 2.5 mmol), potassium azidodicarboxylate (5.5 g, 2.8 mmol), and acetic acid (3.2 mL) in pyridine (70 mL) was kept at room temperature for 4 days and then evaporated to dryness. The residue was dissolved in dichloromethane, washed with water, dried over Na_2SO_4, and then evaporated to dryness. The residue was chromatographed (1:24 methanol/dichloromethane) and the product recrystallized from ethanol to give 0.514g (25%) of **18**: mp 163-165 °C; UV λ_{max} (methanol) 277 nm (ε 14000), 261 (16600); ^{1}H NMR (Me_2SO-d_6) δ 10.70 (s, broad, 1H, NH), 7.80 (s, 1H, H-8), 7.63 (s, broad, 1H, NH), 7.10-7.45 (m, 22H, aromatic), 6.85 (d, J = 9 Hz, 2H, aromatic), 5.51 (d, J = 3 Hz, 1H, H-1'), 4.94 (dd, J = 3 and 6 Hz, 1H, H-2'), 4.00 (m, 2H, H-3', H-4'), 3.70 (s, 3H, OCH_3), 1.60-2.15 (m, 4H, H-5', H-6'), 1.38 (s, 3H, CH_3), 1.20 (s, 3H, CH_3). Anal. Calcd for $C_{46}H_{44}N_5O_8P$ (825.86): C, 66.90; H, 5.37; N, 8.48; P, 3.75. Found: C, 66.93; H, 5.51; N, 8.54; P, 3.93.

9-[6-Dibenzyloxyphosphinyl-5,6-dideoxy-2,3-O-isopropylidene-b-D-ribo-hexofuranosyl]-N^2-monomethoxytritylguanine (19). To a suspension of NaH (0.25 g, 50%, 5.2 mmol; prewashed with hexane) and benzyl alcohol (1.1 mL, 10.7 mmol) in dry DMSO (15 mL) was added a solution of **18** (1.04 g, 1.13 mmol) in DMSO (10 mL). After 3 min, the resulting solution was diluted with ethyl acetate, washed twice with 1% aqueous NH_4Cl, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed (1:19 methanol/dichloromethane) to give 0.656 g (61%) of **19** as an amorphous solid: UV (methanol) λ_{max} 277 nm (ε 14000), 263 (15600); ^{1}H NMR (Me_2SO-d_6) δ 10.68 (s, broad, 1H, NH), 7.75 (s, 1H, H-8), 7.61 (s, broad, 1H, NH), 7.12-7.41 (m, 22H, aromatic), 6.84 (d, J = 9 Hz, 2H, aromatic), 5.44 (d, J = 3Hz, 1H, H-1'), 4.85-5.03 (m, 5H, H-2', benzylic), 3.87 (m, 2H, H-3', H-4'),

3.69 (s, 3H, OCH_3), 1.40-1.80 (m, 4H, H-5', H-6'), 1.35 (s, 3H, CH_3), 1.19 (s, 3H, CH_3). Anal. Calcd for $C_{48}H_{48}N_5O_8P$ (853.92): C, 67.52; H, 5.67, N, 8.20. Found: C, 67.33; H, 5.67; N, 8.03.

9-[6-Dibenzyloxyphosphinyl]-5,6-dideoxy-2,3-O-isopropylidene-β-D-ribo-hexofuranosyl]guanine (20). A solution of **19** (446 mg, 0.52 mmol) in 80% acetic acid was heated at 80 °C for 10 h and then evaporated to dryness. The residue was chromatographed (1:5 methanol/dichloromethane) to give 160 mg (57%) of **20** as a white solid: ^1H NMR (Me_2SO-d_6) δ 10.72 (s, broad, 1H, NH), 7.84 (s, 1H, H-8), 7.35 (s, 10H, phenyl), 6.54 (s, broad, 2H, NH_2), 5.65 (d, J = 2.7 Hz, 1H, H-1'), 5.44 (d, J = 5.8 Hz, 1H, OH), 5.15 (d, J = 5.2 Hz, 1H, OH), 5.00 (m, 4H, benzylic), 4.44 (m, 1H, H-2'), 3.8-3.9 (m, 2H, H-3', H-4'), 1.90 (m, 4H, H-5', H-6').

9-[5,6-Dideoxy-6-dihydroxyphosphinyl-β-D-ribo-hexofuranosyl] guanine (8). A suspension of **20** (61.0 mg, 0.11 mmol) and 20% $Pd(OH)_2/C$ (30 mg) in cyclohexene (1 mL), ethanol (2 mL) and water (2 mL) was heated at reflux for 4h and then filtered through Celite. The filtrate was evaporated to dryness. The residue was crystallized from water to give 20 mg (50%) of **8**: mp browns gradually at 200 °C, UV λ_{max} (0.1N HCl) sh 280 nm (ε 7890), 256 (11600), (0.1N NaOH) 267 (7890); ^1H NMR (D_2O) δ 8.33 (s, 1H, H-8), 5.91 (d, J = 5 Hz, 1H, H-1'), 5.80 (m, buried under HOD, 1H, H-2'), 4.28 (dd, J = 5 Hz, 1H, H-3'), 4.17 (m, 1H, H-4'), 1.60-2.10 (m, 4H, H-5', H-6'). Anal. Calcd for $C_{11}H_{16}N_5O_7P \cdot 1.5\ H_2O$ (388.28): C, 34.03; H, 4.93; N, 18.04. Found: C, 33.85; H, 4.75; N, 17.97.

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