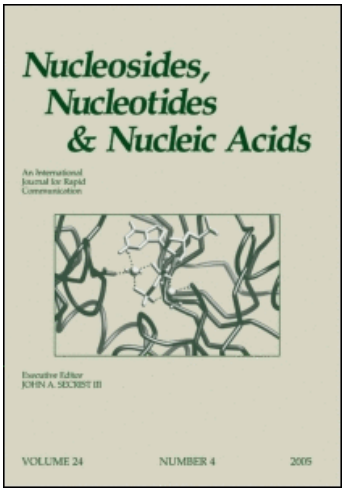

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Synthesis of a Novel C-Nucleoside, 2-Amino-7-(2-deoxy-β- D-*erythro*-pentofuranosyl)-3H,5H-pyrrolo-[3,2-d]pyrimidin-4-one (2'-Deoxy-9-deazaguanosine)

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SYNTHESIS OF A NOVEL *C*-NUCLEOSIDE, 2-AMINO-7-(2-DEOXY-β-D-*erythro*-PENTOFURANOSYL)-3H,5H-PYRROLO-[3,2-d]PYRIMIDIN-4-ONE (2'-DEOXY-9-DEAZAGUANOSINE)

Eric S. Gibson[a], Krystyna Lesiak[b], Kyoichi A. Watanabe[a,b], Lorraine J. Gudas[a], and Krzysztof W. Pankiewicz[b]*

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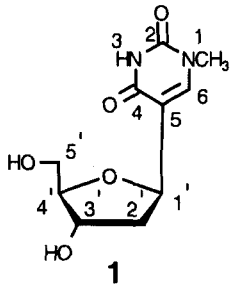
ABSTRACT: A synthesis of the *C*-nucleoside, 2-amino-7-(2-deoxy-β-D-*erythro*-pentofuranosyl)-3*H*,5*H*-pyrrolo[3,2-d]pyrimidin-4-one (9-deaza-2'-deoxyguanosine) was achieved starting from 2-amino-6-methyl-3*H*-pyrimidin-4-one (**5**) and methyl 2-deoxy-3,5-di-O-(*p*-nitrobenzoyl)-D-*erythro*-pento-furanoside (**11**). The anomeric configuration of the *C*-nucleoside was established by ^{1}H NMR, NOEDS and ROESY. This *C*-nucleoside did not inhibit the growth of T-cell lymphoma cells.

INTRODUCTION

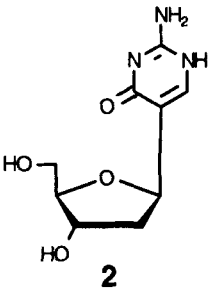
The chemical synthesis of *C*-nucleoside isosteres of the DNA constituents has been the subject of interest, and the 2'-deoxy-1-methyl-ψ-uridine (**1**, **FIG. 1**),[1-3] 2'-deoxy-ψ-isocytidine (**2**)[1-3] and 2'-deoxy-9-deazaadenosine (**3**)[4,5] have been synthesized as the *C*-nucleoside analogues of thymidine, 2'-deoxycytidine and 2'-deoxyadenosine, respectively. The corresponding 2'-deoxyguanosine analogue, *i.e.*, 2'-deoxy-9-deazaguanosine (**4**) has not been reported. The synthesis of the 2'-deoxy-9-deazaguanosine completes the set of *C*-nucleoside congeners of DNA constituents.

Certain immunodeficiency diseases are associated with deficiencies of adenosine deaminase (ADA) or purine nucleoside phosphorylase (PNPase)[6-12] which result in increased pools of deoxynucleoside triphosphate. In addition, 2'-deoxyguanosine 5'-triphosphate (dGTP) accumulates in the erythrocytes of patients who lack PNPase but not in the erythrocytes of normal controls or immunodeficient patients possessing normal PNPase activity.[8] Studies using a completely PNPase-deficient cell line from a mouse T



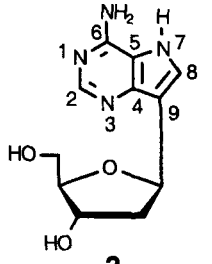
1

1-Methyl-2'-deoxy-ψ-uridine



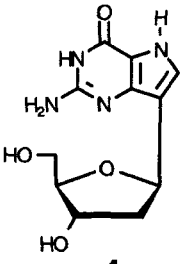
2

2'-Deoxy-ψ-isocytidine



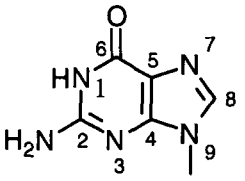
3

9-Deaza-2'-deoxyadenosine

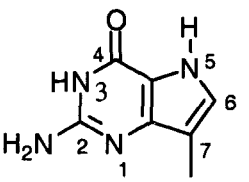


4

9-Deaza-2'-deoxyguanosine



Guanine



2-Amino-3H,5H-pyrrolo-
[3,2-d]pyrimidine
(9-Deazaguanine)

FIGURE 1. *C*-Nucleoside congeners of DNA components.

cell lymphoma (S49) showed that of the four substrates of PNPase, only 2'-deoxyguanosine is toxic to the PNPase-deficient (NSU-1) cells[13] at low concentrations. Later, it was reported that 9-β-D-arabinofuranosylguanine (ara-G), an analogue of 2'-deoxyguanosine, preferentially inhibited DNA synthesis in T- relative to B-lymphoblasts and was a selective inhibitor of T-lymphoblast growth.[14-18] The ability of these compounds to be phosphorylated by cellular kinases plays a role in their selective toxicity to T vs. B cells.[19]

Analogues of 2'-deoxyguanosine like ara-G, especially those that are resistant to PNPase, are attractive as chemotherapeutic agents for T-cell malignancies. Two such

candidates are considered. One of them is 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)-guanine (F-ara-G),[20,21] as the glycosyl bond of 2'-fluoro-arabino nucleosides is known to resist chemical and enzymic hydrolyses.[22-24] This compound was synthesized, and has indeed exhibited highly selective toxicity against T-cell lymphoma.[20,21] However, further development of this nucleoside has been hampered due to difficulty in the synthesis of F-ara-G. More recently, Pankiewicz *et al.* reported[25] a simpler method of synthesis of F-ara-G from the natural, commercially available guanosine.

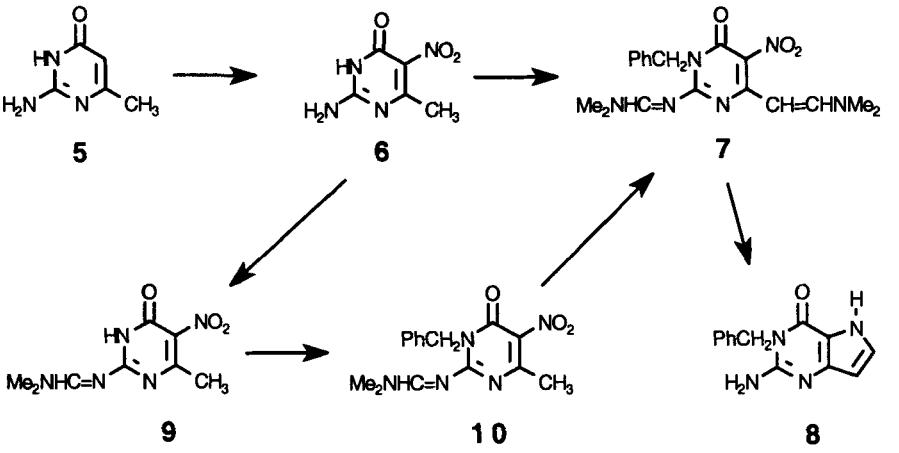
The other analogue is 2'-deoxy-9-deazaguanosine (**4**), a novel *C*-nucleoside,[26] in which the N9 of the guanine base is displaced by a methine carbon (-C=). Since the C-C glycosyl bond of **4** is stable to chemical and enzymatic cleavage, this *C*-nucleoside cannot be a substrate for PNPase and thus is expected to exibit some inhibitory activity.

RESULTS AND DISCUSSION

Although the synthesis of 9-deazaguanosine was first published[27] as early as 1981 and a more efficient preparation by Friedel-Crafts' condensation of 9-deazaguanine and 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose was reported later by Girgis *et al.*,[28] the synthesis of the corresponding 2'-deoxy derivative has not been described.

Recently, the synthesis of N^2-isobutyryl-2'-deoxy-9-deazaguanosine and its incorporation into oligodeoxynucleotides was reported.[29] This compound was prepared by conversion of the 9-deazaguanosine into the corresponding 2'-deoxy derivative in 6 steps with a 12% overall yield. However, the nucleoside, 2'-deoxy-9-deazaguanosine itself, was not described. This may be due to α,β epimerization, which is expected[26] to occur under basic conditions during removal of the N^2-isobutyryl protecting group. Consequently, the separation of anomers may have proven to be difficult. We found that such ribo to 2'-deoxyribo conversion without N^2-isobutyryl protection was quite troublesome. Treatment of the 9-deazaguanosine with 1,3-dichloro-1,1,3,3-tetraisopropyl-disiloxane resulted in the formation of intractable mixture.

We therefore explored the synthesis of 2'-deoxy-9-deazaguanosine by direct condensation of a base with the known methyl 3,5-di-*O*-(*p*-nitrobenzoyl)-2-deoxy-D-ribofuranoside.[30] This synthesis requires preparation of 9-deazaguanine which was originally prepared by Imai[31] by a multi-step synthesis with overall yield of less than 1%. Later Klein *et al.* described[32] a more facile synthesis starting from 2-amino-6-methyl-3*H*-pyrimidin-4-one (**5**, **SCHEME 1**), which was converted into a pyridazine derivative.

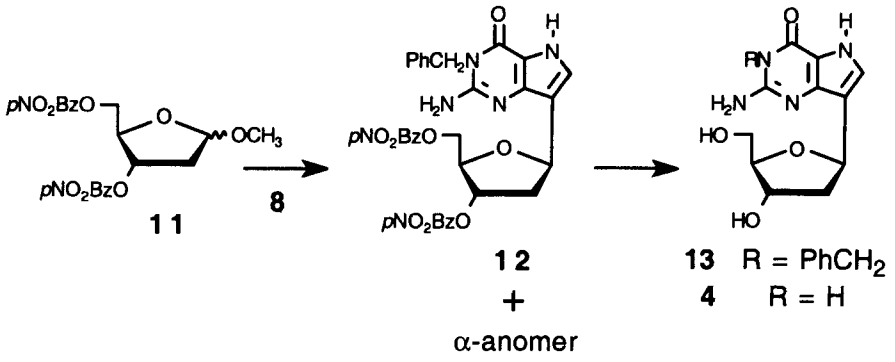


SCHEME 1. Synthesis of 1-benzyl-9-deazaguanine

Reductive nitrogen extrusion of the latter afforded the desired 9-deazaguanine. Unfortunately, we could not repeat this last conversion. All our attempts resulted either in over-reduction or recovery of the starting material. Taylor *et al*[33] also found this procedure to be nonreproducible, and reported[33] an alternative synthesis from 2-amino-6-methyl-5-nitro-3*H*-pyrimidin-4-one (**6**)[34] with a 21 % overall yield.

In our hand, however, nitration of **5** according to Mitchell and McKee[34] afforded **6** in a rather poor yield. We subsequently developed a repeatable, high yield (80%) synthesis of the nitro intermediate **6** from **5**. Treatment of **6** with DMF-dibenzylacetal at elevated temperatures afforded the corresponding 2,6-bis-dimethylamino-N^3-benzyl derivative **7** which upon reductive cyclization was converted to N^1-benzyl-9-deazaguanine (**8**) in a 66% overall yield. Alternatively, treatment of **6** with DMF-dimethylacetal at room temperature gave the 2-dimethylaminomethylene derivative **9**, which was then reacted with benzyl bromide in DMF containing 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give N^3-benzylated pyrimidine **10** in quantitative yield. Compound **10** was converted into the desired N^3-benzylated-2,6-bis-dimethylaminomethylene derivative **7**. The yield of **8** in this 5-step procedure was equally as good as the 3-step procedure and was found to be more economical, since DMF-dimethylacetal cost much less than DMF-dibenzyl-acetal.

Direct *C*-glycosylation of the N^1-benzyl-9-deazaguanine **8** with the 2-deoxy-ribofuranoside derivative **11** (**SCHEME 2**), was performed under Friedel-Crafts ($SnCl_4$) conditions in nitromethane in a similar manner as described for synthesis of



SCHEME 2. Synthesis of 2'-deoxy-9-deazaguanosine

9-deazaguanosine by Girgis *et al.*[28] As expected, condensation of **8** and **11** afforded a mixture of anomers **12** in about 30% yield. These compounds were separated on a silica gel column to give a faster (70%) and slower (30%) migrating anomer. Treatment of the major isomer of **12** with $MeOH/NH_3$ followed by catalytic hydrogenation on $Pd(OH)_2$ afforded the desired β–anomer of 2'-deoxy-9-deazaguanosine **4** in quantitative yield in pure crystalline form. No evidence for epimerization during deprotection was obtained. A small amount of the α-anomer was also prepared.

Assignment of the anomeric configuration of **4** was made on the basis of NMR spectroscopy. The ^1H NMR signal of the anomeric proton of the major product **4** appeared as a doublet of doublet whereas the corresponding signal of the minor product was an apparent triplet. Although there is a widely accepted empirical rule that the H-1' signal for β-nucleosides appears as an apparent triplet and a distinct double-doublet for α-nucleosides, it was also pointed out that this empirical rule is not applicable for C-nucleosides.[5, 35-37] Therefore, the anomeric configuration of these products was firmly established by ^1H NMR nuclear Overhauser effect difference spectroscopy (NOEDS), and rotating frame nuclear Overhauser and exchange spectroscopy (ROESY) experiments. Irradiation of the H1' proton of **4β** caused enhancement of signals of the H2" (6.3%) and H4' (3.1%) establishing that all these protons are located on the same side of the deoxyribose ring. In contrast, similar NOEDS experiments with **4α** resulted in enhancement of the H2' (8.6%) and H3' (1.7%) proving the α–configuration. Both α and β anomers, upon irradiation of H1', showed an increase (5% and 4.5%, respectively)

of the H8 signal of guanine moiety. This is apparently due to the preferred *syn* conformation of these anomers. The same α,β-stereochemistry was concluded from two-dimensional ROESY spectra, which showed cross peaks between the H1' and both H2" and H4' signals for **4β**. Cross peaks between the H1' and H2', H3', H5', and H5" were observed as expected for the α-anomer.

2'-Deoxy-9-deazaguanosine (**4**, β-anomer) and previously synthesized 9-(2-deoxy-2-fluoro-β-D-arabinofuranosyl)guanine (F-ara-G)[25] were assayed for their antiproliferative activity against several cell lines. We found that F-ara-G was a potent inhibitor of cell growth (**FIG. 2**) with IC_{50}'s (shown in parenthesis) in the low micromolar level: L1210 (20 μM), WEHI (5 μM), S49WT (6 μM), BU-araC (more than 100 μM), NSU-1 (3 μM). As expected, PNP deficient cells such as NSU-1 were more sensitive to F-ara-G than S49 WT (wild type) since they would phosphorylate more F-ara-G and less of the compound would be cleaved to fluoroarabinose and guanine. The deoxycytidine kinase deficient line (BU-ara-C) was not very sensitive to growth inhibition by F-ara-G, suggesting that this nucleoside requires phosphorylation by deoxycytidine kinase for it to be cytotoxic.

In contrast to expectations, no cell toxicity was observed with 2'-deoxy-9-deaza-guanosine. In concentrations up to 100 μM, compound **4** (**FIG. 3**) was not growth inhibitory; its IC_{50} value was established as approximately 900 μM for all of the lines. Since no difference in the IC50 of 2'-deoxy-9-deazaguanosine between S49 WT and BU-araC was observed, 2'-deoxy-9-deazaguanosine: (a) is not a substrate for the deoxycytidine kinase, (b) is not phosphorylated to the triphosphate, or (c) does not inhibit ribonucleotide reductase. As expected, the α-anomer (**4α**) was devoid of biological activity up to100 μM. In order to gain more information about these possibilities, preparation of the 5'-phosphonate analogue of **4** is now under investigation.

EXPERIMENTAL SECTION

General Methods. HPLC was performed on a Dynamax-300A C18-83-243-C column with a flow rate of 20 mL/min of 0.1 M Et_3N-H_2CO_3 (TEAB) followed by a linear gradient of 0.1 M TEAB-aq.MeCN (70%). Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Nuclear magnetic resonance spectra was recorded on a JEOL Eclipse 270 Spectrometer. Chemical shifts are reported in ppm (δ) and signals

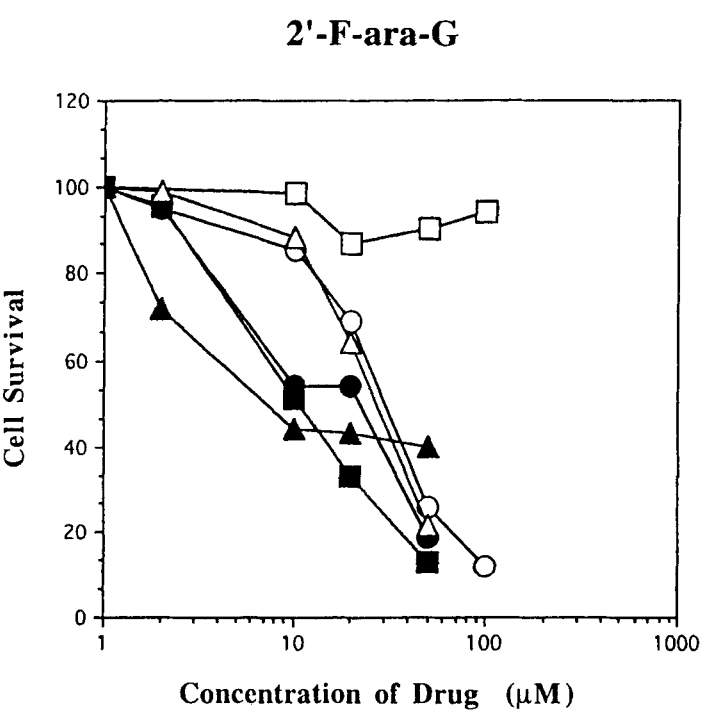


FIGURE 2.

Various cell lines were plated at 1 x 10^5/mL in DME medium plus 10% heat inactivated horse serum and then cultured in the presence of various concentrations of 9-(2-deoxy-2-fluoro-β-D-arabonofuranosyl)guanine (2'-F-ara-G). The drug was solubilized in water prior to addition to the cells. Cells were counted at 72 hr after plating, and the cell numbers were plotted as a percentage of the cells in control cultures. Triplicate counts were averaged, and this experiment was performed twice with very similar results. The cell lines are: ●, L1210; ○, WEHI; ■, S49-BU-araC-6-1; ❑, S49 WT; Δ, S49-dGuoL; and ▲, S49-NSU-1. L1210 is a murine B-cell line; S49 and WEHI are murine T-cell lymphomna and leukemia lines, respectively; and the S49 mutant cell lines include S49-BU-araC-6-1, a line which lacks deoxycytidine kinase; S49-dGuoL, which has a GTP feedback resistant ribonucleotide reductase; and S49-NSU-1, a purine nucleoside phosphorylase deficient line.

are described as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet), and dd (double doublet).

The cell lines were cultured in DME medium plus 10% heat inactivated horse serum, as described.[9,13] Growth curves were performed over a 72 hour period. Duplicate samples were counted in each experiment, and the entire growth experiment was performed at least two times with identical IC_{50}s.

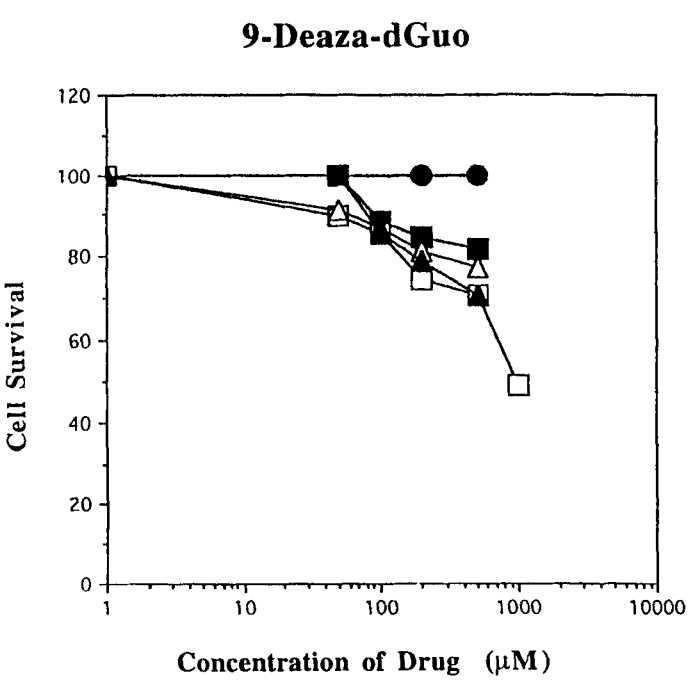


FIGURE 3.

Various cell lines were plated at 1 x 10^5/mL in DME medium plus 10% heat inactivated horse serum and then cultured in the presence of various concentrations of 9-(2-deoxy-β-D-*erythro*pentofuranosyl)-3*H*,5*H*-pyrroro[3,2-*d*]pyrimidin-4-one (9-Deaza-dGuo). The drug was solubilized in water prior to addition to the cells. Cells were counted at 72 hr after plating, and the cell numbers were plotted as a percentage of the cells in control cultures. Triplicate counts were averaged, and this experiment was performed twice with very similar results. The cell lines are: ●, L1210; ○, WEHI; ■, S49-BU-araC-6-1; □, S49 WT; Δ, S49-dGuoL; and ▲, S49-NSU-1. L1210 is a murine B-cell line; S49 and WEHI are murine T-cell lymphomna and leukemia lines, respectively; and the S49 mutant cell lines include S49-BU-araC-6-1, a line which lacks deoxycytidine kinase; S49-dGuoL, which has a GTP feedback resistant ribonucleotide reductase; and S49-NSU-1, a purine nucleoside phosphorylase deficient line.

2-Amino-6-methyl-5-nitro-3*H*-pyrimidin-4-one (6). To a mixture of 90 mL of nitric acid and 90 mL of conc. sulfuric acid was slowly added **5** (30 g, 0.24 mol). The nitration was very exothermic, and in order to avoid oxidation the temperature of the acid mixture was not allowed to rise above 50 °C. After the final addition of **5**, the mixture was heated at 50 °C for 1 h, to complete the reaction. The acid mixture was thoroughly cooled and poured into 500 mL of ice water. The clear yellow solution that resulted was then

made slightly alkaline with ammonium hydroxide. The neutralization was exothermic, therefore ice was added to rapidly cool the reaction. The residue was filtered and washed with ethanol to give crude **6**, which was treated with DMF (1.5 L); unsoluble material was collected by filtration and the solution was concentrated *in vacuo* to give **6** (32 g, 80%). ^{1}H NMR was identical with that reported previously. [34]

3-Benzyl-2-dimethylaminoethyleneimino-5-nitro-6-β-dimethylamino-vinyl-3*H*- pyrimidin-4-one (7). (a) To a suspension of compound **6** (17.0 g, 0.1 mol) in DMF (400 mL) heated at 80 °C was added slowly DMF-dibenzylacetal (92 mL). The mixture became a clear reddish-orange solution and a precipitate formed after 20-30 min. The mixture was stirred at 80 °C for 6-8 h until compound **6** disappeared (TLC, CH_2Cl_2-Me_2CO, 97:3, v/v) and then concentrated *in vacuo*. The residue was triturated with ethanol (50 mL), crystalline product was collected by filtration and washed with cold ethanol to give **7** (34g, 93%). ^{1}H NMR (DMSO-d_6) δ 3.05 (s, 3H, N-CH_3), 3.22 (s, 3H, N-CH_3), 3.30-3.40 (brs, 6H, two N-CH_3), 5.22 (s, 2H, CH_2-Ph), 5.40 (d, 1H, H_β-vinyl, $J_{H\alpha H\beta}$ = 12.1 Hz), 7.20-7.40 (m, 5H, Ph), 8.18 (d, 1H, H_α-vinyl), 8.88 (s, 1H, -CH=N-). Anal. Calcd for $C_{18}H_{22}N_6O_3$: C, 58.38; H, 5.94; N, 22.70. Found: C, 58.49; H, 6.06; N, 22.71.

(b) To a solution of **10** (31.5 g, 0.1 mol) in DMF (120 mL) at 65 °C DMF-dimethylacetal (14.3 g, 0.12 mol) was added and the mixture was stirred at this temperature for 2-3 h until TLC analysis (see above) showed disappearance of the substrate. Concentration and trituration of the residue with ethanol resulted in **7** , which had analytical data identical to those reported above.

1-Benzyl-9-deazaguanine (8). Compound **7** (37.0 g, 0.1 mol) was dissolved in a mixture of THF (260 mL) and aqueous saturated solution of $Na_2S_2O_4$ and stirred until the brown solution became orange (approximately 1 h). THF was then removed *in vacuo* and precipitate was collected by filtration to give the 2-dimethylaminomethyleneimino derivative of **8**[38] (29.5 g) in quantitative yield. This derivative was suspended in 3M NaOH (265 mL) and refluxed with addition of methanol (60 mL), which prevents formation of foam. After the reaction mixture became clear (4 - 4.5 h) it was cooled to 5 °C. White precipitate was collected by filtration and then placed in hot water and neutralized with HCl. The precipitate was collected by filtration and washed with water to give **8** (21.4g, 89%). ^{1}H NMR (DMSO-d_6) δ 5.27 (s, 2H, CH_2-Ph), 6.09 (s, 1H, H8), 7.23 (m, 6H, H9 and Ph),

11.99 (s, 1H, N7-H). *Anal.* Calcd for $C_{13}H_{12}N_4O$: C, 64.73; H, 5.40; N, 23.23. Found: C, 64.16; H, 5.56; N, 23.01.

2-[(Dimethylamino)methyleneimino]-5-nitro-6-methyl-3*H*-pyrimidin-4-one (9). To a suspension of **6** (17.0 g, 0.1 mol) in methylene chloride (300 mL) DMF-dimethylacetal (34 mL) was added and the mixture was stirred at room temperature for 1 h. The precipitated product was removed by filtration to give **9** (20.7 g, 92%). ^1H NMR (DMSO-d_6) δ 2.22 (s, 3H, 6-CH_3), 3.03 (s, 3H, N-CH_3), 3.17 (s, 3H, N-CH_3), 8.68 (s, 1H, CH=N). This compound did not give a correct elemental analysis and was used in the next step without further purification.

3-Benzyl-2-[(dimethylamino)methyleneimino]-5-nitro-6-methyl-3*H*-pyrimidin-4-one (10). To a suspension of compound **9** (22.5 g, 0.1 mol) in DMF (500 mL) DBU (16.7 g, 0.11 mol) was added and the reaction mixture became clear. To this solution was added benzyl bromide (20.5 g, 0.12 mol, over 1 h) and the mixture was stirred at room temperature for 1-2 h. The excess of DBU was neutralized with HCl, the mixture was concentrated *in vacuo*, the residue was dissolved in methylene chloride (700 mL), the solution was washed with water (3 x 200 mL), dried (Na_2SO_3) and concentrated. Trituration with ethanol afforded the crystalline product, which was washed with ethanol to give **10** (31.5 g, quantitative yield). ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H, 6-CH_3), 3.16 (s, 3H, N-CH_3), 3.23 (s, 3H, N-CH_3), 5.38 (s, 2H, CH_2-Ph), 7.23-7.26 and 7.38-7.39 (two m, 5H, Ph), 8.69 (s, 1H, -CH=N-). *Anal.* Calcd for $C_{15}H_{17}N_5O_3$: C, 57.14; H, 5.40; N, 22.22. Found: C, 57.20; H, 5.50; N, 22.06.

1-Benzyl-2'-deoxy-3',5'-di-*O*-(*p*-nitrobenzoyl)-9-deazaguanosine(12). To a suspension of **8** (6.26 g, 26.08 mmol) and methyl 2-deoxy-3,5-di-*O*-(*p*-nitrobenzoyl)-D-ribofuranoside (**11**, 13.96 g, 31.3 mmol) in nitromethane (270 mL) was added $SnCl_4$ (4.57 mL, 39.12 mmol), the reaction mixture was stirred at 60 °C for 1 h and diluted with ethyl acetate (350 mL). A saturated solution of $NaHCO_3$ (200 mL) was added, and then the organic layer was separated and concentrated *in vacuo*. The residue was chromatographed on a column of silica gel with toluene-ethyl acetate (6:4, v:v) to give the faster migrating β-anomer of **12** and a mixture of anomers. Repurification of **12**β and separation of the α,β mixture on a silica gel column with CH_2Cl_2-EtOH (99:1, v:v) as the

eluent afforded the ß anomer of **12** (3.5 g, 21%). ^{1}H NMR ($CDCl_3$) δ 2.49 (dd, 1H, H2", $J_{1',2"}$ = 5.2 Hz, $J_{2',2"}$ = 13.8 Hz), 2.71-2.82 (m, 1H, H2'), 4.51 (dd, 1H, H5', $J_{4',5'}$ = 1.0 Hz, $J_{5',5"}$ = 11.6 Hz), 4.60 (dd, 1H, H5", $J_{4',5"}$ = 4.9 Hz, $J_{5',5"}$ = 11.6 Hz), 4.75-4.81 (m, 3H, CH_2Ph, H4'), 5.33 and 5.35 (two s, 2H, NH_2), 5.46 (dd, 1H, H1', $J_{1',2'}$ = 10.8 Hz, $J_{1',2"}$ = 5.2 Hz), 5.66 (d, 1H, H3', $J_{2',3'}$ = 5.4 Hz), 7.24-7.30 (m. 6H, Ph, H8), 8.18-8.24 (m, 8H, two NO_2-Ph), 10.89 (d, 1H, NH, $J_{8,NH}$ = 2.5 Hz) along with α anomer **12** (1.5 g, 9 %) ^{1}H NMR ($CDCl_3$) δ 2.50 (dd, 1H, H2", $J_{1',2"}$ = 5.7 Hz, $J_{2',2"}$ = 13.9 Hz), 2.81 (ddd, 1H, H2', $J_{1',2'}$ = 10.8 Hz, $J_{2',3'}$ = 5.7 Hz, $J_{2',2"}$ = 13.9 Hz), 4.52-4.65 (m, 4H, H5', H5", CH_2Ph), 4.79-4.86 (m, 1H, H4'), 5.33 and 5.35 (two s, 2H, NH_2), 5.46 (dd, 1H, H1', $J_{1',2'}$ = 10.8 Hz, $J_{1',2"}$ = 5.4 Hz), 5.68 (d, 1H, H3', $J_{2',3'}$ = 5.7 Hz), 7.23-7.32 (m. 6H, Ph, H8), 8.20-8.43 (m, 8H, two NO_2-Ph), 10.05 (s, 1H, NH). These anomers, even after two to three purifications on a silica gel column, did not give a correct elemental analysis.

1-Benzyl-2'-deoxy-9-deazaguanosine (13β). Compound **12β** (0.15 g, 22.5 mmol) was suspended in saturated MeOH/NH_3, the mixture was kept overnight, and the clear solution was concentrated. The residue was chromatographed on a silica gel column with CH_2Cl_2-EtOH (9:1, v:v) to give **12β** (70 mg, 84%) as a foam. ^{1}H NMR (DMSO-d_6) δ 1.90 (dd, 1H, H2", $J_{1',2"}$ = 5.4 Hz, $J_{2',2"}$ = 12.6 Hz), 2.18 (dt, 1H, H2', $J_{1',2'}$ = 10.9 Hz, $J_{2',3'}$ = 5.4 Hz), 3.42-3.44 (m, 2H, H5', 5"), 3.71-3.72 (m, 1H, H4'), 4.17-4.19 (m, 1H, H3'), 5.11 (dd, 1H, H1'), 5.02 (d, 1H, OH-exchg) 5.24 (s, 2H, CH_2Ph), 5.26 (t, 1H, OH-exchg), 6.13 (s, 2H, NH_2-exchg), 7.15 - 7.30 (m, 6H, Ph, H8), 11.4 (s, 1H, NH-exchg). *Anal.* Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.40; N, 15.22. Found: C, 61.35; H, 5.86; N, 15.55.

A similar treatment of **12α** afforded **13α** also as a foam. ^{1}H NMR (DMSO-d_6) δ 1.98-2.05 (m, 1H, H2"), 2.39-2.49 (m, 1H, H2'), 3.43-3.45 (m, 2H, H5', 5"), 3.75-3.76 (m, 1H, H4'), 4.11-4.13 (m, 1H, H3'), 4.65 (t, 1H, OH-exchg), 5.01-5.07 (m, 1H, H1'), 5.26 (s, 2H, CH_2Ph), 5.66 (d, 1H, OH-exchg), 6.25 (s, 2H, NH_2), 7.15 - 7.30 (m, 6H, Ph, H8), 11.4 (s, 1H, NH-exchg). *Anal.* Calcd for $C_{19}H_{20}N_4O_4$: C, 61.95; H, 5.40; N, 15.22. Found: C, 61.55; H, 5.77; N, 15.58.

2'-Deoxy-9-deazaguanosine (4). Compound **13β** (0.5 g, 1.40 mmol) was dissolved in methanol (300 mL), $Pd(OH)_2$ on charcoal (60 mg) was added, and the mixture was shaken in a Paar hydrogenation apparatus (40psi) for 5 h. The catalyst was removed by filtration, the filtrate was concentrated to a volume of 20-30 mL and a crystalline compound was collected by filtration. This compound was then repurified by HPLC to give an amorphous white foam of **4β** (357 mg, 98%) ^{1}H NMR (CD_3OD) δ 2.04 (dd, 1H, H2", $J_{1',2"}$ = 5.4 Hz, $J_{2',2"}$ = 13.0 Hz), 2.37-2.44 (ddd, 1H, H2', $J_{1',2'}$ = 11.06 Hz, $J_{2',2"}$ = 13.0 Hz, $J_{2',3'}$ = 5.1 Hz), 3.70 (dd, 1H, H5', $J_{4',5'}$ = 2.4 Hz, $J_{5',5"}$ = 12.0 Hz), 3.80 (dd, 1H, H5", $J_{4',5"}$ = 2.7 Hz, $J_{5',5"}$ = 12.0 Hz), 3.99-4.00 (m, 1H, H4'), 4.44 (d, 1H, H3', $J_{2',3'}$ = 5.1 Hz), 5.28 (dd, 1H, H1'), 7.21 (s, 1H, H8). *Anal.* Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.26; N, 21.05. Found: C, 49.60; H, 5.36; N, 21.0.

In a similar manner **4α** (290 mg, 97%) was obtained from **13α** (400 mg, 1.12 mmol). ^{1}H NMR (D_2O) δ 2.16 (ddd, 1H, H2", $J_{1',2"}$ = 7.6 Hz, $J_{2",3'}$ = 5.1 Hz, $J_{5',5"}$ = 13.2 Hz), 2.70 (ddd, 1H, H2', $J_{1',2'}$ = 7.2 Hz, $J_{2',3'}$ = 7.0 Hz, $J_{2',2"}$ = 13.2 Hz), 3.64 (dd, 1H, H5', $J_{4',5'}$ = 4.5 Hz, $J_{5',5"}$ = 11.2 Hz), 3.69 (dd, 1H, H5", $J_{4',5"}$ = 2.4 Hz, $J_{5',5"}$ = 11.2 Hz), 4.02-4.06 (m, 1H, H4'), 4.39-4.43 (m, 1H, H3'), 5.23 (pseudo t, 1H, H1', J = 7.3 Hz), 7.40 (s, 1H, H8). *Anal.* Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.26; N, 21.05. Found: C, 49.52; H, 5.32; N, 20.95.

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38. Analytical sample of this compound was obtained by purification of the small amount of the crude material on a silica gel column: ^{1}H NMR (DMSO-d_6): δ 2.95 (s, 3H, N-CH_3), 3.08 (s, 3H, N-CH_3), 5.40 (s, 2H, -CH_2Ph), 6.12 (d, 1H, H9, $J_{H8,H9}$ = 2.7Hz), 7.24-7.26 (m, 6H, H8 and Ph), 8.48 (-CH=N-).

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