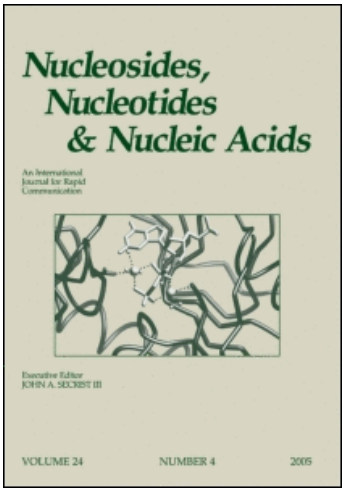

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Synthesis and Biological Evaluation of 2',3'-Didehydro-2',3'-Dideoxy-9-Deazaguanosine, a Monophosphate Prodrug and Two Analogues, 2',3'-Dideoxy-9-Deazaguanosine and 2',3'-Didehydro-2',3'-Dideoxy-9-Deazainosine

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SYNTHESIS AND BIOLOGICAL EVALUATION OF 2′,3′-DIDEHYDRO-2′, 3′-DIDEOXY-9-DEAZAGUANOSINE, A MONOPHOSPHATE PRODRUG AND TWO ANALOGUES, 2′,3′-DIDEOXY-9-DEAZAGUANOSINE AND 2′,3′-DIDEHYDRO-2′,3′-DIDEOXY-9-DEAZAINOSINE

Mao-Chin Liu, Mei-Zhen Luo, Diane E. Mozdziesz, Ginger E. Dutschman, Elizabeth A. Gullen, Yung-Chi Cheng, and Alan C. Sartorelli ▫ *Department of Pharmacology and Developmental Therapeutics Program, Cancer Center, Yale University School of Medicine, New Haven, Connecticut, USA*

▫ *2′,3′-Didehydro-2′,3′-dideoxy-9-deazaguanosine (**1**), its monophosphate prodrug (**2**), and two analogues, 2′,3′-dideoxy-9-deazaguanosine (**3**) and 2′,3′-didehydro-2′,3′-dideoxy-9-deazainosine (**4**), have been synthesized from benzoylated 9-deazaguanosine (**5**). Basic hydrolysis of **5**, selective protection of the 2-amino and 5′-hydroxy functions with isobutyryl and silyl groups, respectively, followed by reaction with thiocarbonyldiimidazole gave the cyclic thiocarbonate, which, upon reaction with triethyl phosphite, followed by deprotection, afforded **1**. Treatment of **1** with phenyl methoxyalaninyl phosphochloridate and N-methylimidazole gave **2**. Catalytic hydrogenation of **1** gave **3**. Hydrodediazoniation of **1** with tert-butyl nitrite and tris(trimethylsilyl)silane gave **4**. Compounds **1–4** were found to be inactive against the human immunodeficiency virus and exhibited minimal to no cytotoxic activity against the L1210 leukemia, CCRF-CEM lymphoblastic leukemia, and $B_{16}F_{10}$ melanoma in vitro.*

Keywords C-Nucleosides, Synthesis of Unsaturated 9-Deazanucleosides, Monophosphate Prodrug, Anti-HIV Activity, Cytotoxic Activity

INTRODUCTION

Numerous 2′,3′-dideoxy- and 2′,3′-didehydro-2′,3′-dideoxynucleosides have emerged as potent in vitro inhibitors of HIV. From this group, two purine nucleosides, ddI (didanosine, 2′,3′-dideoxyinosine) and Abacavir (1592U89) are approved for use in the treatment of AIDS in the United States. The glycosidic linkage between the purine base and the pentose moiety of these drugs is susceptible to the hydrolytic action of purine nucleoside phosphorylase, and ddI is also

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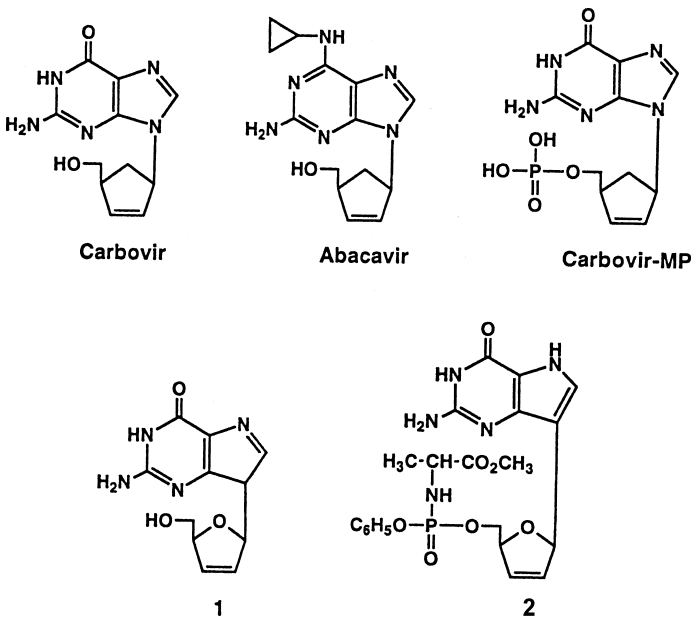
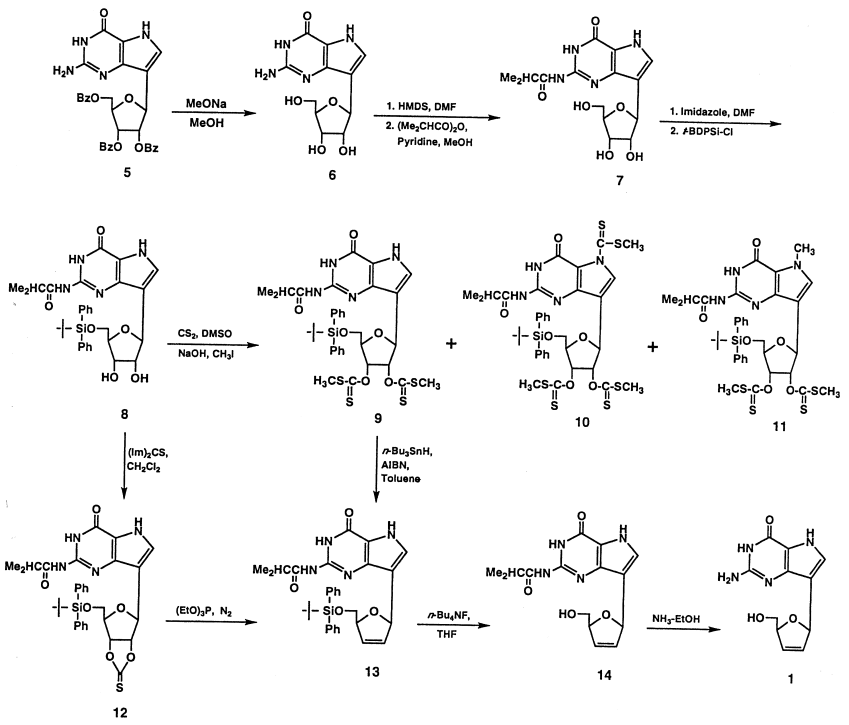


FIGURE 1 Nucleoside and nucleotide analogues of quanine.

particularly unstable under acidic conditions.[1,2] The carbon–carbon linked 9-deazapurine nucleoside analogues are resistant to purine nucleoside phosphorylase and acidic cleavage,[3] and several agents of this class exhibit anticancer,[4,5] antileishmanial,[6] and antitripanosomal activities.[7] We have synthesized 2′,3′-didehydro-2′,3′-dideoxy-9-deazaguanosine (**1**) and its monophosphate prodrug (**2**), which can be thought of as analogues of the carbocyclic nucleoside, Carbovir, and its monophosphate analogue, respectively (Figure 1) and the analogues, 2′,3′-dideoxy-9-deazaguanosine (**3**) and 2′,3′-didehydro-2′,3′-dideoxy-9-deazainosine (**4**). Carbovir is a carbocyclic analogue of 2′,3′-didehydro-2′,3′-dideoxyguanosine in which the oxygen of the carbohydrate moiety is substituted by a carbon atom. Carbovir exhibited similar anti-HIV activity to Abacavir and both of these agents were anabolized to carbovir monophosphate.[8–10] The newly synthesized agents were designed to hopefully retain the anti-HIV activity of drugs such as Abacavir and ddI and express complete resistance to purine nucleoside phosphorylase and acidic cleavage.

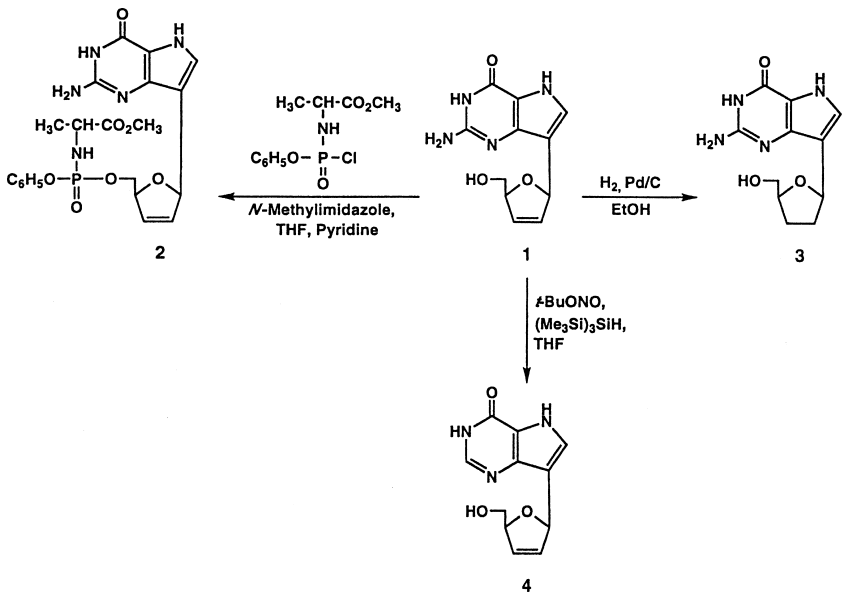
CHEMISTRY

Several methods have been reported in the literature for the conversion of ribonucleosides to the corresponding 2′,3′-unsaturated nucleosides.[11–15] Of these, simultaneous deoxygenation of 5′-*O*–protected ribonucleosides via their 2′,3′-bisxanthates or 2′,3′-cyclic thiocarbonates to form corresponding 2′,3′-unsaturated derivatives were some of the generally used synthetic routes.[11–13] Recently, we



SCHEME 1 Synthesis of 2′,3′-didehydro-2′,3′-dideoxy-9-deazaguanosine.

developed an efficient method for the synthesis of benzoylated 9-deazaguanosine (**5**).[16] Compound **5** was used in the present work as a precursor for the synthesis of compound **1** (Scheme 1). Deprotection of **5** with sodium methoxide in methanol gave crude 9-deazaguanosine (**6**) in almost quantitative yield, which was then treated with hexamethyldisilazane in anhydrous DMF, followed by pyridine and isobutyric anhydride to afford N^2-isobutyryl-9-deazaguanosine (**7**) in a total yield of 62%. The 5′-hydroxyl function of **7** was selectively protected by treatment with imidazole and *tert*-butylchlorodiphenylsilane in anhydrous DMF to give a 69% yield of the 5′-*O*-*tert*-butyldiphenylsilyl derivative **8**. Condensation of compound **8** with carbon disulfide in the presence of 50% aqueous sodium hydroxide solution, followed by iodomethane produced the bisxanthate **9** in 37% yield along with two side products **10** and **11**. Based on the ^{1}H NMR and mass spectra data, the structures of compounds **10** and **11** suggest they are derivatives of compound **9**. Compound **9** showed two methylthio groups at δ 2.55 and δ 2.61, compound **10** showed three methylthio groups at δ 2.51, δ 2.57, and δ 2.81, and compound **11** showed two methylthio groups at δ 2.50 and δ 2.55 and an *N*-methyl group at δ 3.90. The lack of N^1 substitution is likely due to the presence of the adjacent bulky N^2-isobutyryl group, which prevents the N^1 substitution of the corresponding guanosine derivative in a similar reaction.[11] The bisxanthate **9**, upon treatment with tri-*n*-butyltin hydride in the presence of azobisisobutyronitrile (AIBN) in



SCHEME 2 Synthesis of the mononucleotide prodrug of 2′,3′-didehydro-2′,3′-dideoxy-9-deazaguanosine, 2′,3′-dideoxy-9-deazaguanosine, and 2′3′-didehydro-2′,3′-dideoxy-9-deazainosine.

toluene, gave the 2′,3′-unsaturated nucleoside **13** in 75% yield. Because of the low yield of the bisxanthate **9**, we focused our attention on the synthesis of the corresponding 2′,3′-cyclic thionocarbonate **12**. Condensation of **8** with 1,1′-thiocarbonatediimidazole in anhydrous methylene chloride at room temperature gave compound **12** in 93% yield. Contrary to a report[11] that the similar protected 2′,3′-thionocarbonate derivative of guanosine only gave decomposition products in refluxing triethyl phosphite, treatment of compound **12** with triethyl phosphite at 170°C (oil bath temperature) for 3 h afforded a surprisingly high yield (88%) of compound **13** after silica gel chromatography. This result proved that the carbon–carbon linked bond in compound **8** was relatively stable under aggressive reaction conditions. Deprotection of compound **13** with tetra-*n*-butylammonium fluoride in THF produced compound **14**, which, upon reaction with ammonia saturated ethanol in a pressure vessel, furnished the target compound **1**.

The syntheses of the mononucleotide prodrug of 2′,3′-didehydro-2′,3′-dideoxy-9-deazaguanosine (**2**), 2′,3′-dideoxy-9-deazaguanosine (**3**), and 2′,3′-didehydro-2′,3′-dideoxy-9-deazainosine (**4**) are shown in Scheme 2. Treatment[17] of **1** with phenyl methoxyalaninyl phosphochloridate and *N*-methylimidazole in anhydrous pyridine afforded the target compound **2**. Catalytic hydrogenation of compound **1** with 10% palladium on carbon in ethanol at 35 psig gave **3** in an 83% yield. Hydrodediazoniation of **1** with *tert*-butyl nitrite and tris(trimethylsilyl)silane in anhydrous THF gave a number of complicated products along with compound **4**, which was isolated in 10–15% yield by silica gel column chromatography. The results were consistent with reports[18,19] that diazotization of electron-deficient heterocyclic

amines was problematic and multiple decomposition pathways were possible for transient purinediazonium species, which led to the various complicated products.

BIOLOGICAL EVALUATION

The synthesized compounds **1 4** were evaluated in vitro for their cytotoxicities against the L1210 leukemia, the CCRF-CEM lymphoblastic leukemia, and the $B_{16}F_{10}$ melanoma by previously reported methodologies.[20] 2′,3′-Didehydro-2′,3′-dideoxy-9-deazaguanosine (**1**) produced an IC_{50} value of 100 μM against $B_{16}F_{10}$ cells, and the monophosphate prodrug (**2**) produced IC_{50} values of 50, 55, and 44 μM against L1210, CCRF-CEM, and $B_{16}F_{10}$ cells, respectively. The remaining compounds had no activity up to 100 μM against these cell lines. Evaluation of the compounds for antiviral activity[20] demonstrated that compounds **1** and **2** were inactive against HIV-IIIB and also showed no cytotoxicity up to 100 μM against HIV-IIIB.

EXPERIMENTAL SECTION

Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 (90 MHz) or Gemini-300 (300 MHz) NMR spectrometer with Me_4Si as the internal reference. Mass spectra were recorded on a VG-ZAB-SE mass spectrometer in the fast bombardment (FAB) mode (glycerol matrix). Column chromatography was conducted with Merck silica gel 60, 230–400 mesh. The general ratio of silica gel to crude product used to run the columns was 20–25:1. When a compound was evaporated to dryness, a maximum bath temperature of 40°C was used. TLC was performed on EM precoated silica gel sheets containing a fluorescent indicator. Elemental analyses were carried out by the Baron Consulting Co., Orange, Connecticut, USA.

2-Isobutyrylamino-7-β-D-ribofuranosyl-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (7, N^2-Isobutyryl-9-deazaguanosine). To a suspension of compound **5** (10 g, 16.8 mmol) in methanol (100 mL) was added drop-wise enough sodium methoxide in methanol (1 g Na in 20 mL methanol) with stirring until the pH reached about 12. The reaction mixture formed a clear solution within a few minutes and was stirred at room temperature for 4 h, then cooled with an ice-water bath and neutralized with acetic acid. A white solid precipitated immediately with the addition of acetic acid and the resulting mixture was stirred at 0–5°C for 1 h, filtered, and washed with ethanol. The collected solid was refluxed with ethanol (50 mL), cooled, filtered, and washed with ethanol to give crude 9-deazaguanosine (**6**) as a white solid (4.7 g, 99%), which was then stirred with anhydrous DMF (21 mL), followed by hexamethyldisilazane (25 mL). The mixture

was stirred at room temperature overnight, treated with anhydrous pyridine (25 mL) and isobutyric anhydride (40 mL) and stirred for an additional 24 h, cooled to 0–5°C, treated with methanol (45 mL), and stirred for another 4 h. The reaction mixture was evaporated with silica gel (20 g) to dryness and purified by silica gel column chromatography, using a gradient of 5–33% EtOH in CH_2Cl_2 to give 3.7 g (62%) of compound **7** as a white solid: mp 218–220°C (lit.[21] 222–224°C); TLC, R_f 0.34 (CH_2Cl_2/MeOH, 10:1, v/v); ^{1}H NMR (DMSO-d_6) δ 1.12 (2s, 6H, 2Me), 2.77 (m, 1H, CH), 3.48 (d, 1H, 5′-H_A), 3.55 (d, 1H, 5′-H_B), 3.71 (m, 1H, 4′-H), 3.93 (t, 1H, 3′-H), 4.07 (br s, 3H, 3OH, D_2O exchangeable), 4.09 (t, 1H, 2-H), 4.81 (d, 1H, 1′-H, J = 6.5 Hz), 7.39 (s, 1H, 6-H), 11.30 and 11.93 (2br s, 3H, 3NH, D_2O exchangeable).

2-Isobutyrylamino-7-(5-*tert*-butyldiphenylsilyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (8). To a stirred suspension of compound **7** (4.0 g, 11.4 mmol) in anhydrous DMF (160 mL) was added imidazole (4.0 g, 57 mmol). After the reaction mixture formed a clear solution in about 20 min, *tert*-butylchlorodiphenylsilane (3.6 mL, 13.8 mmol) was added and the mixture was stirred with the exclusion of moisture overnight. The mixture was then evaporated to dryness in vacuo and the residue was dissolved in methylene chloride (120 mL), washed with water (40 mL × 2) and brine (40 mL), dried ($MgSO_4$), and filtered. The filtrate and washings were evaporated to a small volume and purified by silica gel column chromatography (CH_2Cl_2/MeOH, 30:1, v/v) to give 4.7 g (69%) of product as an off-white foam: TLC, R_f 0.39 (CH_2Cl_2/MeOH, 30:1, v/v); MS *m/z* 591 $(M + H)^+$; ^{1}H NMR (DMSO-d_6) δ 0.99 (s, 9H, Me_3CSi), 1.12 (2s, 6H, Me_2C), 2.31 (m, 1H, CH), 3.77 and 3.80 (2 m, 2H, 5′-H), 3.86 (m, 1H, 4′-H), 4.08 (m, 1H, 3′-H), 4.14 (m, 1H, 2′-H), 4.78 and 4.82 (2 br s, 2H, 2OH, D_2O exchangeable), 4.89 (d, 1H, 1′-H, J = 6.0 Hz), 7.32 (d, 1H, 6-H, J = 3.5 Hz), 7.37–7.56 (m, 10H, ArH), 11.30 and 11.97 (2 br s, 3H, 3NH, D_2O exchangeable). Anal. Calcd. for $C_{31}H_{38}N_4O_6Si \cdot 0.7CH_3OH$: C, 62.09; H, 6.70; N, 9.14. Found: C, 61.79; H, 6.83; N, 9.49.

2-Isobutyrylamino-7-[5-*tert*-butyldiphenylsilyl-2,3-bis-*O*-(methylthio)thiocarbonyl-β-D-ribofuranosyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (9). To a solution of compound **8** (1.9 g, 3.2 mmol) in a mixture of CS_2 (3 mL) and DMSO (4.5 mL) an aqueous 50% sodium hydroxide solution (1.7 mL) at 15°C was added drop-wise with stirring. The red-colored suspension was stirred for 5 min, followed by addition of iodomethane (2 mL), which resulted in a yellow suspension that was stirred for 1 h at room temperature. The mixture was then evaporated to dryness in vacuo and the residue was dissolved in methylene chloride (100 mL), washed with water (30 mL × 2) and brine (30 mL), dried ($MgSO_4$), and filtered. The filtrate and washings were evaporated to a small volume and purified by silica gel column chromatography (CH_2Cl_2/EtOH, 40:1, v/v) to give compound **9** (0.92 g, 37%) along with the side products **10** (0.72 g, 26%) and **11** (0.4 g, 16%).

Compound **9** was isolated as an oil: TLC, R_f 0.36 (CH_2Cl_2/EtOH, 40:1, v/v); MS *m/z* 771 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.02 (s, 9H, Me_3CSi), 1.20 (2s, 6H, Me_2C), 2.48 (m, 1H, CH), 2.55 and 2.61 (2s, 6H, 2SMe), 3.92 (m, 2H, 5′-H), 4.37 (m, 1H, 4′-H), 5.14 (d, 1H, 1′-H, J = 7.2 Hz), 6.48 (m, 1H, 3′-H), 6.71 (m, 1H, 2′-H), 7.10–7.58 (m, 11H, ArH and 6-H), 10.82 (br s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{35}H_{42}N_4O_6S_4Si$: C, 54.51; H, 5.49; N, 7.27. Found: C, 54.43; H, 5.33; N, 7.01.

2-Isobutyrylamino-5-(methylthio)thiocarbonyl-7-[5-*tert*-butyldiphenylsilyl-2,3-bis-*O*-(methylthio)thiocarbonyl-β-D-ribofuranosyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (10). Compound **10** was isolated as an oil: TLC, R_f 0.76 (CH_2Cl_2/EtOH, 40:1, v/v); $C_{37}H_{44}N_4O_6S_6Si$: M = 861.22; MS *m/z* 862 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, Me_3CSi), 1.22 (2s, 6H, Me_2C), 2.49 (m, 1H, CH), 2.51, 2.57, and 2.81 (3 s, 9H, 3SMe), 3.95 (m, 2H, 5′-H), 4.42 (m, 1H, 4′-H), 5.40 (d, 1H, 1′-H, J = 7.2 Hz), 6.50 (m, 1H, 3′-H), 6.72(m, 1H, 2′-H), 7.20–7.72 (m, 11H, ArH and 6-H), 10.80 (br s, 1H, NH, D_2O exchangeable).

2-Isobutyrylamino-5-methyl-7-[5-*tert*-butyldiphenylsilyl-2,3-bis-*O*-(methylthio)thiocarbonyl-β-D-ribofuranosyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (11). Compound **11** was isolated as an oil: TLC, R_f 0.51 (CH_2Cl_2/EtOH, 40:1, v/v); $C_{36}H_{44}N_4O_6S_4Si$: M = 785.09; MS *m/z* 786 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H, Me_3CSi), 1.22 (2s, 6H, Me_2C), 2.48 (m, 1H, CH), 2.50 and 2.55 (2 s, 6H, 2SMe), 3.90 (m, 5H, 5′-H and NMe), 4.32 (m, 1H, 4′-H), 5.12 (d, 1H, 1′-H, J = 7.2 Hz), 6.42 (m, 1H, 3′-H), 6.63 (m, 1H, 2′-H), 7.10–7.61 (m, 11H, ArH and 6-H), 10.72 (br s, 1H, NH, D_2O exchangeable).

2-Isobutyrylamino-7-(5-*tert*-butyldiphenylsilyl-2,3-*O*-thiocarbonyl-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (12). A mixture of compound **8** (8.55 g, 14.5 mmol) and 1,1′-thiocarbonyldiimidazole (5.17 g, 29 mmol) in anhydrous methylene chloride (430 mL) was stirred overnight. The reaction mixture was then washed with water (2 × 100 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 30:1, v/v) to give 8.5 g (93%) as a foam. TLC, R_f 0.48 (CH_2Cl_2/EtOH, 20:1, v/v); MS *m/z* 633 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.04 (s, 9H, Me_3CSi), 1:24 (2s, 6H, Me_2C), 2.49 (m, 1H, CH), 3.79 and 3.85 (2 m, 2H, 5′-H), 4.31 (m, 1H, 4′-H), 5.23 (d, 1H, 1′-H, J = 6.0 Hz), 5.57 (m, 1H, 3′-H), 5.78 (m, 1H, 2′-H), 7.13–7.62 (m, 11H, ArH and 6-H), 8.14 and 10.64 (2 br s, 3H, 3NH, D_2O exchangeable). Anal. Calcd. for $C_{32}H_{36}N_4O_6SSi \cdot 0.1CH_2Cl_2$: C, 60.10; H, 5.69; N, 8.74. Found: C, 59.94; H, 5.62; N, 8.80.

2-Isobutyrylamino-7-(5-*tert*-butyldiphenylsilyl-2,3-didehydro-2,3-dideoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (13). A solution of compound **12** (3.3 g, 5.2 mmol) in 50 mL of triethyl phosphite was heated at 170°C (oil bath temperature) with stirring under nitrogen

for 3 h until TLC showed the reaction was complete. After cooling, the reaction mixture was evaporated in vacuo to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 30:1, v/v) to give 2.6 g (88%) as a foam. TLC, R_f 0.37 (CH_2Cl_2/EtOH, 20:1, v/v); MS *m/z* 557 $(M + H)^+$; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9H, Me_3CSi), 1.18 (2s, 6H, Me_2C), 2.36 (m, 1H, CH), 3.91 and 3.98 (2 m, 2H, 5′-H), 4.38 (m, 1H, 4′-H), 5.42 (d, 1H, 1′-H, J = 6.0 Hz), 6.55 (m, 1H, 2′-H), 6.78 (m, 1H, 3′-H), 7.18–7.65 (m, 11H, ArH and 6-H), 7.98, 10.21, and 11.91 (3 br s, 3H, 3NH, D_2O exchangeable). Anal. Calcd. for $C_{31}H_{36}N_4O_4Si \cdot 0.8CH_2Cl_2$: C, 61.15; H, 6.07; N, 8.97. Found: C, 61.44; H, 5.95; N, 8.60.

Method B, from Bisxanthate 9. To a solution of compound **9** (0.83 g, 1.1 mmol) in 15 mL of dry toluene was added azobisisobutyronitrile (AIBN, 80 mg) and tri-*n*-butyltin hydride (1.1 mL, 4 mmol) with stirring. The reaction mixture was stirred further at 65–70°C for 2 h and evaporated in vacuo to dryness. The residue was purified by silica gel column chromatography, eluting first with (CH_2Cl_2/EtOAc, 4:1, v/v), then with (CH_2Cl_2/EtOH, 20:1, v/v) to give 0.45 g (75%) of compound **13**.

2-Isobutyrylamino-7-(2,3-didehydro-2,3-dideoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (14). To a stirred solution of compound **13** (2.8 g, 5 mmol) in THF (100 mL), 1.0 M tetra-*n*-butylammonium fluoride in THF (20 mL, 20 mmol) was added at ambient temperature. The reaction mixture was stirred for 1 h and evaporated in vacuo to dryness. The residue was purified by silica gel column chromatography (CH_2Cl_2/EtOH, 30:1, v/v) to give 2.6 g (88%) of product as a white solid: mp 118°C (dec.); TLC, R_f 0.27 (CH_2Cl_2/EtOH, 20:1, v/v); MS *m/z* 318 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 1.12 (2s, 6H, Me_2C), 2.75 (m, 1H, CH), 3.44 (m, 2H, 5′-H), 4.70 (t, 1H, 5′-OH, D_2O exchangeable), 4.74 (d, 1H, 4′-H, J = 1.5 Hz), 5.93 (d, 1H, 1′-H, J = 6.0 Hz), 6.00 (d, 1H, 2′-H, J = 6.0 Hz), 6.05 (d, 1H, 3′-H, J = 6.0 Hz), 7.22 (d, 1H, 6-H, J = 3.5 Hz), 11.33 and 11.96 (2 br s, 3H, 3NH, D_2O exchangeable). Anal. Calcd. for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.40; H, 5.92; N, 17.34.

2-Amino-7-(2,3-didehydro-2,3-dideoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (1, 2′,3′-Didehydro-2′,3′-dideoxy-9-deazaguanosine). A suspension of compound **14** (0.63 g, 0.96 mmol) in 50 mL of saturated ethanol-ammonia solution was stirred in a steel bomb at 82°C for 20 h. The cooled reaction mixture was evaporated to dryness with 4.5 g of silica gel and the residue was purified by silica gel column chromatography, eluting with a gradient of 10–30% EtOH in CH_2Cl_2 to obtain 0.75 g (64%) of product as a white solid: mp 245–247°C; TLC, R_f 0.35 (CH_2Cl_2/EtOH, 3:1, v/v); MS *m/z* 249 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 3.51 (m, 2H, 5′-H), 4.75 (m, 1H, 4′-H), 5.41 (br s, 1H, 5′-OH, D_2O exchangeable), 5.66 (br s, 2H, NH_2, D_2O exchangeable),

5.81 (d, 1H, 2′-H, J = 5.0 Hz), 5.94 (m, 2H, 1′-H and 3′-H), 7.04 (d, 1H, 6-H, J = 5.0 Hz), 10.42 and 11.39 (2 br s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{12}N_4O_3 \cdot 0.5H_2O$: C, 51.35; H, 5.09; N, 21.78. Found: C, 51.41; H, 5.08; N, 21.49.

2-Amino-7-[2,3-didehydro-2,3-dideoxy-5-(phenylmethoxyalaninyl)-β-D-ribofuranosyl]-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (2). To a stirred solution of compound **1** (100 mg, 0.40 mmol) in anhydrous pyridine (15 mL) a solution of phenyl methoxyalaninyl phosphochloridate (0.56 g, 2 mmol) in anhydrous THF (15 mL) was added drop-wise over 5 min at room temperature. The reaction mixture was stirred for an additional 5 min, followed by the addition of *N*-methylimidazole (0.4 mL, 4 mmol) with vigorous stirring. The mixture was stirred for 22 h and evaporated in vacuo to dryness with 1 g of silica gel and the residue was purified by silica gel column chromatography, eluting with a gradient of 10–30% EtOH in CH_2Cl_2 to yield 48 mg (24%) of product as a white solid: mp 148–150°C; TLC, R_f 0.57(CH_2Cl_2/EtOH, 2:1, v/v); MS *m/z* 490 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 1.15–1.25 (d, 3H, ala-Me), 3.56 (s, 3H, ala-OMe), 3.75–3.95 (m, 3H, ala-CH and 5′-H), 4.93 (m, 1H, 4′-H), 5.84–5.96 (m, 5H, 2′-H, 3′-H, 2-NH_2, and ala-NH), 6.09 (d, 1H, 1′-H, J = 5.0 Hz), 7.02 (s, 1H, 6-H, J = 5.0 Hz), 7.15–7.37 (m, 5H, ArH), 10.60 and 11.51 (2 br s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{21}H_{24}N_5O_7P$: C, 51.53; H, 4.94; N, 14.31. Found: C, 51.31; H, 5.20; N, 14.03.

2-Amino-7-(2,3-dideoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (3, 2′,3′-Dideoxy-9-deazaguanosine). A mixture of compound **1** (120 mg, 0.48 mmol) and 10% Pd/C (50 mg) in 100 mL of ethanol was hydrogenated at 35 psig for 6 h. The catalyst was removed by filtration and carefully washed with ethanol. The combined filtrate and washings were evaporated in vacuo to give 100 mg (83%) as a white solid: mp 164–166°C; TLC, R_f 0.58 (CH_2Cl_2/EtOH, 2:1, v/v); MS *m/z* 251 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 1.82–2.03 (m, 4H, 2′-H and 3′-H), 3.40 (m, 1H, 5′-H_A), 3.48 (m, 1H, 5′-H_B), 3.92 (m, 1H, 4′-H), 4.86 (t, 1H, 1′-H, J = 12.0 Hz), 5.25 (br s, 1H, 5′-OH, D_2O exchangeable), 5.73 (br s, 2H, NH_2, D_2O exchangeable), 7.11 (d, 1H, 6-H, J = 5.0 Hz), 10.41 and 11.30 (2 br s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{14}N_4O_3$: C, 52.79; H, 5.64; N, 22.39. Found: C, 53.07; H, 5.42; N, 22.32.

7-(2,3-Dideoxy-β-D-ribofuranosyl)-5*H*-pyrrolo[3,2-*d*]pyrimidin-4-one (4, 2′,3′-Didehydro-2′,3′,-dideoxy-9-deazainosine). To a stirred suspension of compound **1** (200 mg, 0.81 mmol) in anhydrous THF (50 mL) was added tris(trimethylsilyl)silane (1 mL, 3.2 mmol) and *tert*-butyl nitrite (2 mL, 16.8 mmol). The reaction mixture was stirred under nitrogen at room temperature for 40 h, after which time the mixture became homogenous and TLC showed that just a trace of starting material remained. The reaction mixture was evaporated with 1 g of silica gel to dryness and the residue was purified by silica gel

column chromatography, eluting with a gradient of 1–10% EtOH in CH_2Cl_2 to obtain 25 mg (13%) of product as a white solid: mp 182–184°C; TLC, R_f 0.26 (CH_2Cl_2/EtOH, 10:1, v/v); MS *m/z* 233 $(M + H)^+$; ^1H NMR (DMSO-d_6) δ 3.52 (m, 2H, 5′-H), 4.80 (m, 1H, 4′-H), 5.12 (t, 1H, 5′-OH, D_2O exchangeable), 5.94–6.00 (m, 1H, 3H, 1′-H, 2′-H and 3′-H), 7.29 (d, 1H, 6-H, J = 5.0 Hz), 7.78 (d, 1H, 2-H, J = 5.0 Hz), 11.89 and 13.02 (2 br s, 2H, 2NH, D_2O exchangeable). Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.76; N, 18.02. Found: C, 56.47; H, 5.01; N, 17.82.

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