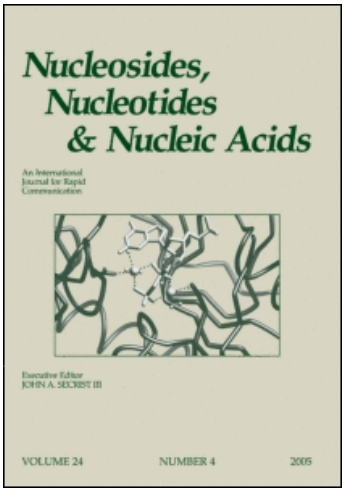

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

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Online publication date: 02 October 2004

To cite this Article Janeba, Zlatko , Lin, Xiaoyu and Robins, Morris J.(2004) 'Functionalization of Guanosine and 2'-Deoxyguanosine at C6: A Modified Appel Process and S_NAr Displacement of Imidazole ', Nucleosides, Nucleotides and Nucleic Acids, 23: 1, 137 — 147
To link to this Article: DOI: 10.1081/NCN-120027823
URL: http://dx.doi.org/10.1081/NCN-120027823

NUCLEOSIDES, NUCLEOTIDES & NUCLEIC ACIDS
Vol. 23, Nos. 1 & 2, pp. 137–147, 2004

Functionalization of Guanosine and 2′-Deoxyguanosine at C6: A Modified Appel Process and S_NAr Displacement of Imidazole[†,#]

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ABSTRACT

Treatment of sugar-protected 2-*N*-trityl derivatives of guanosine and 2′-deoxyguanosine with imidazole/triphenylphosphine/iodine/ethyldiisopropylamine gives the corresponding 6-(imidazol-1-yl)-2-(tritylamino)purine nucleosides. S_NAr displacement of the imidazole moiety with nucleophiles provides 2-amino-6-substituted-purine nucleosides and 2′-deoxynucleosides.

Key Words: 2-Amino-6-substituted-purine nucleosides and 2′-deoxynucleosides; 2′-Deoxyguanosine derivatives; Guanosine derivatives; Guanine nucleoside modifications.

[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

[#]This paper is: Nucleic Acid Related Compounds, 122. Paper 121 is Ref. [1].

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DOI: 10.1081/NCN-120027823 1525-7770 (Print); 1532-2335 (Online)

INTRODUCTION

Studies on the synthesis of nucleosides and nucleotides with modified bases have been pursued for many years, but the field remains very active. Significant new biological effects continue to be discovered with these compounds, including unnatural base pairing and medicinal activities, especially as antiviral and anticancer agents. Base-sugar coupling procedures provide access to varied bases on a given sugar analogue. However, such approaches often produce isomeric mixtures, and anomers usually are formed with sugar derivatives lacking an anchimeric C2 participating group. Modifications of naturally occurring nucleosides avoid these complications and can be employed to give good yields of regio- and stereochemically pure products.

Recently, several leaving groups at C6 of purines have been employed for modification of nucleosides and 2′-deoxynucleosides. These have included elaboration of an amino function into a (1,2,4-triazol-4-yl) leaving group[2] for direct transformation of 6-aminopurine compounds, halo-deoxygenation[3–6] for substitution of 6-oxopurine derivatives, and diazotization-halodediazoniation for indirect functionalization of aminopurine analogues.[7–11] Conversions of hypoxanthine and/or guanine compounds into 6-*O*-(pentafluorophenyl),[12] 6-pyridyl,[13] and 6-O-(2,4,6-triisopropylbenzenesulfonyl)[5] derivatives, and further activation of the hindered sulfonates by S_NAr displacements to provide quaternary amine salts,[14,15] have been used for transformations of 2′-deoxy- and/or inosine and guanosine derivatives. Enhanced interest in such nucleobase modifications has been stimulated by recent studies on palladium-promoted C–N bond formation at C6 of purine 2′-deoxy- and nucleoside derivatives, which has proven to be especially useful for S_NAr reactions with less nucleophilic aromatic amines.[16–19]

We developed a modified Appel[20,21] protocol [imidazole/Ph_3P/I_2/EtN(iPr)$_2$] for introduction of the 6-(imidazol-1-yl) group into inosine and 2′-deoxyinosine.[22] Véliz and Beal reported conversions of inosine and guanosine derivatives into the corresponding 6-bromo- and 2-amino-6-bromopurine compounds. However, their Appel reagent system (NBS/HMPT) was too acidic for the more sensitive 2′-deoxynucleoside derivatives, and glycosyl cleavage occurred.[6] In contrast, our combination [imidazole/Ph_3P/I_2/EtN(iPr)$_2$] provided a mild and highly efficient transformation of sugar-protected 2′-deoxyinosine, as well as inosine, into the 6-(imidazol-1-yl)purine compounds, which were converted into 6-substituted-purine 2′-deoxy- and nucleosides in high yields by S_NAr displacements with nitrogen, oxygen, and sulfur nucleophiles.[22] The serious limitation of our protocol was its failure to convert analogous 2′-deoxy- and guanosine derivatives into 2-amino-6-(imidazol-1-yl)purine compounds. We now report circumvention of this limitation with 2-*N*-trityl derivatives of sugar-protected guanosine and 2′-deoxyguanosine.

RESULTS AND DISCUSSION

Preliminary results with sugar-protected guanosine derivatives indicated that side reactions occurred with the 2-amino group and our Appel reagent combination.[23] Protection of the 2-amino function with common electron-withdrawing (acetyl,

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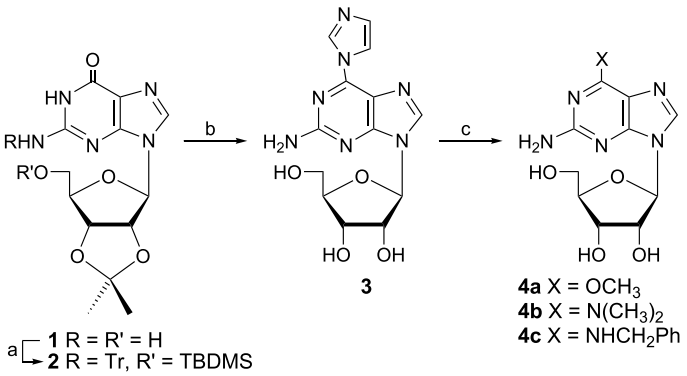
benzoyl, or pivaloyl) or electron-donating (*N,N*-dimethylaminomethylene) groups gave derivatives that did not undergo clean reactions to produce the 6-(imidazol-1-yl) compounds. However, treatment of 5′-*O*-(*tert*-butyldimethylsilyl)-2′,3′-*O*-isopropylidene-2-*N*-tritylguanosine (**2**) [prepared in 87% yield by protection of 2′,3′-*O*-isopropylideneguanosine (**1**) (Scheme 1) with TBDMSCl and then TrCl] with imidazole/Ph_3P/I_2/Et$N(iPr)_2$ in hot toluene gave 9-[5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-β-D-ribofuranosyl]-6-(imidazol-1-yl)-2-(tritylamino)purine (∼ 89%). The steric bulk of the trityl group might be a significant factor in the success of this amino-protection strategy. Deprotection of this material (TFA/H_2O) gave 2-amino-6-(imidazol-1-yl)-9-(β-D-ribofuranosyl)purine (**3**) (82% from **2**). S_NAr displacement reactions of **3** with nitrogen and oxygen nucleophiles proceeded more readily than with its protected derivative, but less readily than with the 6-(imidazol-1-yl)purine nucleosides without a 2-amino substituent.[22]

Treatment of **3** with Dowex 1 × 2 (OH^-) resin (pre-soaked in MeOH) in MeOH at ambient temperature gave 2-amino-6-methoxy-9-(β-D-ribofuranosyl)purine (**4a**) (93%), and Me_2NH/H_2O at ambient temperature converted **3** into 2-amino-6-(dimethylamino)-9-(β-D-ribofuranosyl)purine (**4b**) (88%). However, S_NAr displacement of imidazole from **3** with neat benzylamine was sluggish. This reaction was not complete after heating at 100°C for 48 h, and byproduct formation was problematic (TLC). Addition of DBU to the reaction mixture increased the rate, and 2-amino-6-(benzylamino)-9-(β-D-ribofuranosyl)purine (**4c**) (82%) was obtained after 39 h at 100°C. Such S_NAr displacements can be executed with 2-amino-6-chloro-[3–5] or the more reactive 2-amino-6-bromopurine[6] analogues, and the preparation of our 6-(imidazol-1-yl) derivatives requires tritylation and detritylation. However, these protection/deprotection steps are essentially quantitative, and the imidazol-1-yl substituent is stable under tin radical-mediated reaction conditions that are compromised by the presence of bromo or chloro groups.

Preliminary experiments with 2-*N*-trityl derivatives of 2′-deoxyguanosine revealed that the glycosyl bond was too acid sensitive for efficient detritylation. Treatment of

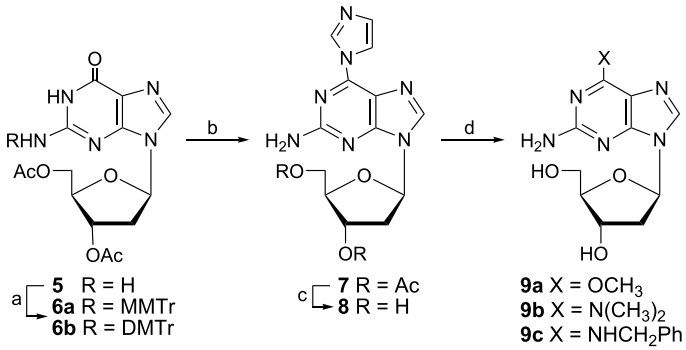


Scheme 1. Reagents: (a) (i) TBDMSCl/DMAP/Et_3N/pyridine; (ii) TrCl/Et_3N/pyridine. (b) (i) Imidazole/I_2/Ph_3P/Et$N(iPr)_2$/toluene; (ii) TFA/H_2O (9:1). (c) Dowex 1 × 2 (OH^-)/MeOH (for **4a**), Me_2NH/H_2O (for **4b**), and $PhCH_2NH_2$/DBU (for **4c**).

3′,5′-di-*O*-acetyl-2′-deoxyguanosine[24] (**5**) (Scheme 2) with mono- and dimethoxytrityl chloride gave the 3′,5′-di-*O*-acetyl-2-*N*-MMTr (**6a**) (97%) and 2-*N*-DMTr (**6b**) (95%) derivatives.[25] Treatment of **6a** and **6b** with imidazole/Ph_3P/I_2/EtN(*i*Pr)$_2$ followed by extraction of the reaction mixtures with EtOAc and detritylation with 80% AcOH/H_2O/dioxane[26] (55°C for MMTr; ambient temperature for DMTr) gave 2-amino-9-(3,5-di-*O*-acetyl-2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(imidazol-1-yl)purine (**7**) as a white foam. Purification of **7** was not straightforward, and S_NAr displacements with such protected derivatives had been found to proceed less readily. Deacetylation of **7** (NH_3/MeOH) was effected to give the crystalline 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(imidazol-1-yl)purine (**8**) (56% from **6a**; 58% from **6b**). Preparation of the 2-amino-6-chloropurine 2′-deoxy analogue by our modified deoxychlorination procedure[4,5] requires stringent conditions, and the convenient deoxybromination methodology of Véliz and Beal fails with 2′-deoxynucleosides.[6]

Treatment of **8** with Dowex 1 × 2 (OH^-) in MeOH at ambient temperature gave 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methoxypurine (**9a**) (61%), and Me_2NH/H_2O at 50°C gave 2-amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(dimethylamino)purine (**9b**) (59%). Benzylamine/DBU at 100°C gave 2-amino-6-(benzylamino)-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (**9c**) (76%).

In summary, the modified Appel combination of imidazole/Ph_3P/I_2/EtN(*i*Pr)$_2$ in hot toluene, which we developed for C6 functionalization of sugar-protected 2′-deoxyinosine and inosine derivatives, failed to give the corresponding 2-amino-6-(imidazol-1-yl) compounds with guanine nucleoside analogues. Protection of the guanine 2-amino group with trityl, MMTr, or DMTr gives derivatives that undergo near quantitative conversions into the 2-*N*-(trityl or substituted-trityl)-6-(imidazol-1-yl) analogues. Deprotection provides 2-amino-6-(imidazol-1-yl)purine compounds that undergo S_NAr reactions with nitrogen and oxygen nucleophiles to give 2-amino-6-substituted-purine nucleosides and 2′-deoxynucleosides in excellent to good yields. This provides a new approach for modification of the readily available guanosine and 2′-deoxyguanosine.



Scheme 2. Reagents: (a) RCl/EtN(*i*Pr)$_2$/pyridine. (b) (i) Imidazole/I_2/Ph_3P/EtN(*i*Pr)$_2$/toluene; (ii) 80% AcOH/(dioxane/H_2O, 4:1). (c) NH_3/MeOH. (d) Dowex 1 × 2 (OH^-)/MeOH (for **9a**), Me_2NH/H_2O (for **9b**), and $PhCH_2NH_2$/DBU (for **9c**).

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EXPERIMENTAL SECTION

Uncorrected melting points were determined with a capillary tube apparatus. UV spectra were determined with solutions in MeOH unless otherwise noted. NMR spectra were obtained with solutions in Me_2SO-d_6 (Me_4Si internal), ^1H at 300 MHz and ^{13}C at 75 MHz unless otherwise noted. High-resolution mass spectra (MS) were determined under FAB conditions (glycerol or thioglycerol matrix) unless otherwise noted. Reagent grade chemicals were used, and solvents were distilled before use. Toluene was dried over and distilled from CaH_2. TLC was performed with silica G plates with UV254 indicator (Sorbent Technologies), and MeOH/CH_2Cl_2 (1–15%) solvent systems. Merck Kieselgel 60 (230-400 mesh) and Dowex 1 × 2 (OH^-) were used for column chromatography. *Method 1* (nucleoside/Dowex 1 × 2 (OH^-)/MeOH) is described for **3** → **4a**, *method 2* (nucleoside/MMTrCl or DMTrCl/EtN(*i*Pr)$_2$/pyridine) is described for **5** → **6a**, and *method 3* [(i) nucleoside/imidazole/Ph_3P/I_2/EtN(iPr)$_2$; (ii) AcOH/H_2O/dioxane; (iii) NH_3/MeOH] is described for **6a** → **8**.

5′-*O*-(*tert*-Butyldimethylsilyl)-2′,3′-*O*-isopropylidene-2-*N*-tritylguanosine (2). TBDMSCl (7.54 g, 50.0 mmol), DMAP (40 mg, 0.32 mmol), and Et_3N (10.0 mL, 7.26 g, 0.072 mol) were added to a stirred suspension of 2′,3′-*O*-isopropylideneguanosine (10.4 g, 32.4 mmol) in pyridine (120 mL). Stirring was continued for 24 h, and volatiles were evaporated in vacuo. Pyridine (150 mL), trityl chloride (32 g, 0.11 mol), and Et_3N (16 mL, 11.6 g, 0.11 mol) were added to the residue, and the suspension was stirred for 24 h. Volatiles were evaporated and the residue was partitioned (H_2O/CH_2Cl_2). The aqueous phase was extracted (CH_2Cl_2, 5 × 15 mL), and the combined organic phase was washed (brine) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed (MeOH/CH_2Cl_2, 1 → 3%) to give a yellow solid foam. This material was recrystallized (toluene) to give **2** (19.13 g, 87%) as a white powder: mp 215–217°C; UV max 279 nm (sh, ε 12 600), 261 nm (ε 14 900), 255 (sh, ε 13 800); ^1H NMR ($CDCl_3$) δ 0.004, 0.017 (2 × s, 2 × 3H), 0.86 (s, 9H), 1.24, 1.47 (2 × s, 2 × 3H), 3.58 (d, *J* = 4.4 Hz, 2H), 4.17 (dt, *J* = 2.5, 4.4 Hz, 1H), 4.46 (dd, *J* = 2.4, 6.1 Hz, 1H), 4.69 (dd, *J* = 2.6, 6.1 Hz, 1H), 5.40 (d, *J* = 2.6 Hz, 1H), 7.06–7.25 (m, 9H), 7.33 (s, 1H), 7.35–7.48 (m, 6H), 7.65, 11.50 (2 × bs, 2 × 1H); ^{13}C NMR ($CDCl_3$) δ −5.17, −5.25, 18.5, 25.9, 26.1, 27.5, 63.6, 71.2, 81.2, 83.9, 86.6, 90.9, 113.7, 118.1, 126.8, 127.8, 129.2, 136.2, 144.7, 150.1, 151.4, 158.8; HRMS *m/z* 680.3271 [MH^+ ($C_{38}H_{46}N_5O_5Si$) = 680.3268].

2-Amino-6-(imidazol-1-yl)-9-(β-D-ribofuranosyl)purine (3). Imidazole (1.05 g, 0.015 mol) and **2** (2.05 g, 0.003 mol) were added to a stirred slurry of Ph_3P (3.86 g, 0.015 mol), I_2 (3.75 g, 0.015 mol), and EtN(*i*Pr)$_2$ (5.2 mL, 3.86 g, 0.030 mol) in freshly distilled toluene (80 mL). Stirring was continued at 95°C for 40 min. Volatiles were evaporated, and EtOAc (100 mL) was added. The solid was filtered, and volatiles were evaporated. The residue was chromatographed (EtOAc/hexanes, 10 → 30%) to give a white solid foam (1.94 g). A solution of this material in TFA/H_2O (9:1) was stirred at 0°C for 40 min. Volatiles were evaporated, and H_2O was added. Solids were filtered, and the filtrate was evaporated. The residue was chromatographed (MeOH/CH_2Cl_2, 1 → 6%) to give **3** (824 mg, 82%). Recrystallization (MeOH) gave **3** as a

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white solid: mp 179–182°C; UV max 321 nm (ε 9600), 251 nm (sh, ε 9200), 227 nm (ε 30 200); ^{1}H NMR δ 3.56 (dd, *J* = 4.0, 11.8 Hz, 1H), 3.67 (dd, *J* = 4.0, 11.8 Hz, 1H), 3.93 (''dd'', *J* = 3.9, 7.5 Hz, 1H), 4.15 (''dd'', *J* = 4.0, 4.4 Hz, 1H), 4.52 (dd, *J* = 5.1, 5.5 Hz, 1H), 4.89–5.71 (m, 3H), 5.88 (d, *J* = 5.5 Hz, 1H), 7.17–7.31 (m, 1H), 8.20–8.33 (m, 1H), 8.47 (s, 1H), 8.90–9.08 (m, 1H); ^{13}C NMR δ 61.3, 70.3, 73.6, 85.4, 86.6, 115.2, 117.3, 129.6, 136.6, 141.1, 145.1, 155.9, 160.0; HRMS *m/z* 334.1258 [MH^+ ($C_{13}H_{16}N_7O_4$) = 334.1264]. Anal. Calcd for $C_{13}H_{15}N_7O_4$: C, 45.61; H, 4.71; N, 28.64. Found: C, 45.63; H, 4.83; N, 28.44.

2-Amino-6-methoxy-9-(β-D-ribofuranosyl)purine (4a).[3] *Method 1.* A suspension of **3** (72.2 mg, 0.217 mmol) and Dowex 1 × 2 (OH^-) resin (4 ml, pre-soaked in MeOH) in MeOH (5 ml) was stirred at ambient temperature for 27 h. The mixture was filtered, and volatiles were evaporated from the filtrate. The residue was dissolved (H_2O) and chromatographed [Dowex 1 × 2 (OH^-); MeOH/H_2O, increasing gradient] to give **4a** (60 mg, 93%) as a white powder. Recrystallization (MeOH/Et_2O) gave an analytical sample (recovery 75%): mp 120°C (softening); UV (H_2O) max 280 nm (ε 8500), 248 nm (ε 8900); ^{1}H NMR δ 3.53 (ddd, *J* = 4.1, 5.9, 12.0 Hz, 1H), 3.63 (ddd, *J* = 4.3, 5.0, 12.0 Hz, 1H), 3.89 (''dd'', *J* = 3.9, 7.6 Hz, 1H), 3.96 (s, 3H), 4.07–4.13 (m, 1H), 4.46 (''dd'', *J* = 6.0, 11.1 Hz, 1H), 5.10 (dd, *J* = 5.4, 5.8 Hz, 1H), 5.14 (d, *J* = 4.6 Hz, 1H), 5.41 (d , *J* = 6.1 Hz, 1H), 5.78 (d, *J* = 6.0 Hz, 1H), 6.46 (bs, 2H), 8.17 (s, 1H); ^{13}C NMR δ 53.2, 61.4, 70.4, 73.5, 85.2, 86.5, 114.0, 138.0, 154.1, 159.8, 160.7; HRMS *m/z* 320.0964 [MNa^+ ($C_{11}H_{15}N_5O_5Na$) = 320.0971]. Anal. Calcd for $C_{11}H_{15}N_5O_5$: C, 44.44; H, 5.09; N, 23.56. Found: C, 44.19; H, 5.32; N, 23.45.

2-Amino-6-(dimethylamino)-9-(β-D-ribofuranosyl)purine (4b).[3,27] A solution of **3** (49 mg, 0.15 mmol) in 40% Me_2NH/H_2O (2 ml) was stirred at ambient temperature for 48 h. The solution was concentrated and chromatographed [Dowex 1 × 2 (OH^-), H_2O/MeOH]. The residue was recrystallized (MeOH) to give **4b** (40 mg, 88%) as white pellets: mp 200–202°C; UV (H_2O) max 284 nm (ε 15 000), 229 nm (ε 18 200); ^{1}H NMR δ 3.36 (bs, 6H), 3.47–3.69 (m, 2H), 3.89 (''dd'', *J* = 3.4, 6.7 Hz, 1H), 4.09 (''dd'', *J* = 4.5, 7.8 Hz, 1H), 4.47 (''dd'', *J* = 6.0, 11.1 Hz, 1H), 5.12 (d, *J* = 4.6 Hz, 1H), 5.34–5.39 (m, 2H), 5.75 (d, *J* = 6.1 Hz, 1H), 5.80 (bs, 2H), 7.94 (s, 1H); ^{13}C NMR δ 37.7, 61.6, 70.6, 73.3, 85.3, 86.8, 113.9, 135.0, 152.5, 154.7, 159.3; HRMS *m/z* 311.1474 [MH^+ ($C_{12}H_{19}N_6O_4$) = 311.1468].

2-Amino-6-(benzylamino)-9-(β-D-ribofuranosyl)purine (4c).[28] A solution of **3** (65 mg, 0.195 mmol) and DBU (0.30 mL, 305 mg, 2 mmol) in benzylamine (2.5 mL) was stirred at 100°C for 40 h. Volatiles were evaporated in vacuo, and AcOH/H_2O was added. The neutralized mixture was filtered, and the filtrate was concentrated and chromatographed [Dowex 1 × 2 (OH^-), H_2O/MeOH] to give **4c** (63 mg, 82%) as a glass. Recrystallization (MeOH/Et_2O) gave material: mp ∼120°C (softening); UV max 284 nm (ε 14 800), 261 nm (ε 10 200), 252 nm (sh, ε 9100); ^{1}H NMR δ 3.52 (ddd, *J* = 3.7, 6.9, 12.0 Hz, 1H), 3.63 (ddd, *J* = 3.8, 4.5, 12.0 Hz, 1H), 3.90 (''dd'', *J* = 3.3, 6.5 Hz, 1H), 4.05–4.13 (m, 1H), 4.51 (''dd'', *J* = 6.0, 11.1 Hz, 1H), 4.64 (bs, 2H), 5.12 (d, *J* = 4.4 Hz, 1H), 5.33–5.47 (m, 2H), 5.73 (d, *J* = 6.1 Hz, 1H), 5.82 (bs, 2H), 7.16–7.36 (m, 5H), 7.88 (bs, 1H), 7.93 (s, 1H); ^{13}C NMR δ 42.5, 61.7, 70.7, 73.2, 85.5, 86.9,

113.6, 126.5, 127.2, 128.1, 136.1, 140.5, 150.9, 154.9, 160.0; HRMS *m/z* 395.1493 [MNa^+ ($C_{17}H_{20}N_6O_4Na$) = 395.1443].

3′,5′-Di-*O*-acetyl-2′-deoxy-2-*N*-(mono-*p*-methoxytrityl)guanosine (6a). *Method 2*. A solution of **5** (1.76 g, 5.0 mmol) in pyridine (75 mL) was treated with MMTrCl (4.63 g, 15.0 mmol) and $EtN(iPr)_2$ (2.6 mL, 1.94 g, 15.0 mmol) under Ar at room temperature for 15 h. MeOH (2.5 mL) was added, and the mixture was stirred for 30 min. Volatiles were evaporated in vacuo, and toluene was added and evaporated (3 × 30 mL) from the residue. The oil was dissolved in CH_2Cl_2 (100 mL), and washed (H_2O, 2 × 30 mL). The organic phase was dried (Na_2SO_4), and volatiles were evaporated. The residue was chromatographed ($MeOH/CH_2Cl_2$, 0 → 5%) to give **6a** (3.02 g, 97%) as a white solid: mp 212–216°C; UV max 278 nm (ε 18 400), 261 nm (ε 20 600), 234 nm (sh, ε 21 500); ^1H NMR δ 1.87–1.89 (m, 1H), 2.02 (s, 3H), 2.11 (s, 3H), 2.15–2.17 (m, 1H), 3.72 (s, 3H), 4.02–4.03 (m, 2H), 4.09–4.10 (m, 1H), 5.06–5.07 (m, 1H), 5.61–5.63 (m, 1H), 6.72–6.74 (m, 2H), 7.11–7.33 (m, 13H), 7.58 (bs, 1H), 11.33 (bs, 1H); ^{13}C NMR δ 21.0, 21.2, 36.7, 55.3, 63.7, 70.7, 74.8, 82.2, 84.9, 113.3, 118.4, 126.9, 128.0, 129.0, 130.4, 135.7, 136.8, 144.9, 150.2, 151.4, 158.5, 158.8, 170.3, 170.6; HRMS (EI) *m/z* 623.2384 [M^+ ($C_{34}H_{33}N_5O_7$) = 623.2380].

3′,5′-Di-*O*-acetyl-2′-deoxy-2-*N*-(di-*p*-methoxytrityl)guanosine (6b).[25] Treatment of **5** (1.76 g, 5.0 mmol) with DMTrCl (5.1 g, 15.0 mmol) by method 2 gave **6b** (3.12 g, 95%) as a slightly yellow solid foam: mp 134–137°C; UV max 278 nm (ε 17 100), 261 nm (ε 18 100), 234 nm (ε 25 600); ^1H NMR δ 1.92–1.94 (m, 1H), 2.03 (s, 3H), 2.11 (s, 3H), 2.21–2.24 (m, 1H), 3.72 (s, 6H), 4.02–4.07 (m, 2H), 4.10–4.12 (m, 1H), 5.08–5.09 (m, 1H), 5.66–5.67 (m, 1H), 6.72–6.75 (m, 4H), 7.12–7.30 (m, 10H), 7.46 (bs, 1H), 11.14 (bs, 1H); ^{13}C NMR δ 20.9, 21.1, 36.7, 55.3, 63.7, 70.4, 74.8, 82.2, 84.9, 113.3, 118.3, 126.9, 128.0, 128.8, 130.2, 135.7, 136.9, 145.1, 150.3, 151.4, 158.4, 170.3, 170.6; HRMS (EI) *m/z* 653.2491 [M^+ ($C_{35}H_{35}N_5O_8$) = 653.2486].

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(imidazol-1-yl)purine (8). *Method 3*. (i) Imidazole (782 mg, 11.5 mmol) and **6a** (1.43 g, 2.3 mmol) were added to a stirred slurry of Ph_3P (2.99 g, 11.5 mmol), I_2 (2.92 g, 11.5 mmol), and $EtN(iPr)_2$ (3 mL, 2.2 g, 17 mmol) in freshly distilled toluene (70 mL). Stirring under Ar was continued at 80°C for 2 h. Volatiles were evaporated, and EtOAc (100 mL) was added. The solid was filtered, and volatiles were evaporated from the filtrate. Chromatography of the residue ($MeOH/CH_2Cl_2$, 0 → 5%) gave a white solid foam. (ii) This material was dissolved in 80% AcOH/(dioxane/H_2O, 4:1) (50 mL), and the solution was stirred at 55°C for 3 h. Volatiles were evaporated, and the residue was dissolved in CH_2Cl_2 (100 mL). The solution was washed ($NaHCO_3/H_2O$, H_2O) and dried (Na_2SO_4). Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$, 0 → 8%) to give **7** (813 mg) as a white foam: ^1H NMR (500 MHz) δ 2.02 (s, 3H), 2.10 (s, 3H), 2.50–2.56 (m, 1H), 3.05–3.08 (m, 1H), 4.21–4.31 (m, 3H), 5.34–5.36 (m, 1H), 6.30–6.33 (m, 1H), 6.92 (bs, 2H), 7.20 (s, 1H), 8.23 (s, 1H), 8.42 (s, 1H), 8.91 (s, 1H); HRMS *m/z* 402.1542 [MH^+ ($C_{17}H_{20}N_7O_5$) = 402.1526]. (iii) NH_3/MeOH (10 mL, saturated at 0°C) was added to a solution of crude **7** (813 mg) in MeOH (10 mL) in a pressure tube, and the sealed vessel was heated at 70°C for 3 h. Volatiles were evaporated, and the residue was chromatographed ($MeOH/CH_2Cl_2$,

5 → 15%) and recrystallized (MeOH/EtOAc) to give **8** (407 mg, 56% from **6a**) as white crystals: mp 202°C; UV max 321 nm (ε 10 200), 251 nm (sh, ε 10 700), 226 nm (ε 33 600); ^{1}H NMR (500 MHz) δ 2.27–2.31 (m, 1H), 2.62–2.67 (m, 1H), 3.52–3.61 (m, 2H), 3.84–3.87 (m, 1H), 4.397–4.403 (m, 1H), 4.98 (''t'', *J* = 5.6 Hz, 1H), 5.32–5.33 (m, 1H), 6.29 (t, *J* = 6.8, 1H), 6.86 (bs, 2H), 7.19 (s, 1H), 8.23 (s, 1H), 8.43 (s, 1H), 8.92 (s, 1H); ^{13}C NMR δ (125 MHz) δ 39.4, 61.6, 70.6, 82.8, 87.8, 115.2, 117.1, 130.0, 136.6, 140.8, 145.1, 155.5, 159.9; HRMS (EI) *m/z* 317.1239 [M^+ ($C_{13}H_{15}N_7O_3$) = 317.1236]. Anal. Calcd for $C_{13}H_{15}N_7O_3$: C, 49.21; H, 4.76; N, 30.90. Found: C, 49.14; H, 4.84; N, 30.90.

Treatment of **6b** (1.53 g, 2.34 mmol) by method 3 [(ii) AcOH/(dioxane/H_2O, 4:1) (50 mL) at ambient temperature] gave **8** (430 mg, 58%) as white crystals: mp 200–201°C; UV and ^{1}H and ^{13}C NMR spectra were identical to those of **8** prepared from **6a**.

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-methoxypurine (9a).[13,29] Treatment of **8** (80 mg, 0.252 mmol) by method 1 gave **9a** (34 mg, 61%) as a glass, which was recrystallized (EtOH/EtOAc) to give white crystals (29 mg, 52%): mp 142°C; UV (H_2O) max 280 nm (ε 10 100), 248 nm (ε 10 500); ^{1}H NMR (500 MHz) δ 2.21 (ddd, *J* = 2.9, 5.9, 13.2 Hz, 1H), 2.56–2.59 (m, 1H), 3.47–3.52 (m, 1H), 3.54–3.58 (m, 1H), 3.816–3.821 (m, 1H), 3.95 (s, 3H), 4.347–4.352 (m, 1H), 5.00 (''t'', *J* = 5.5 MHz, 1H), 5.27–5.28 (m, 1H), 6.21 (t, *J* = 6.8 Hz, 1H), 6.46 (bs, 2H), 8.08 (s, 1H); ^{13}C NMR (125 MHz) δ 39.5, 53.2, 61.7, 70.8, 82.7, 87.6, 113.9, 137.7, 153.8, 159.8, 160.7; HRMS *m/z* 304.1006 [MNa^+ ($C_{11}H_{15}N_5O_4Na$) = 304.1022].

2-Amino-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)-6-(dimethylamino)purine (9b).[30] A solution of **8** (90 mg, 0.284 mmol) in 40% Me_2NH/H_2O (3 mL) was stirred at 50°C for 16 h. Volatiles were evaporated, and the residue was chromatographed (preparative silica gel TLC plate; MeOH/CH_2Cl_2, 1:9) to give **9b** (49 mg, 59%) as a glass: UV (H_2O) max 284 nm (ε 15 000), 229 nm (ε 18 600); ^{1}H NMR (500 MHz) δ 2.17 (ddd, *J* = 2.7, 6.1, 12.9 Hz, 1H), 2.52–2.57 (m, 1H), 3.36 (bs, 6H), 3.48–3.52 (m, 1H), 3.55–3.59 (m, 1H), 3.81–3.83 (m, 1H), 4.345–4.350 (m, 1H), 5.21 (''t'', *J* = 5.4 Hz, 1H), 5.27–5.28 (m, 1H), 5.81 (bs, 2H), 6.18–6.21 (m, 1H), 7.93 (s, 1H); ^{13}C NMR (125 MHz) δ 37.6, 39.4, 61.9, 70.9, 82.8, 87.6, 113.9, 134.6, 152.3, 154.7, 159.3; HRMS (EI) *m/z* 294.1433 [M^+ ($C_{12}H_{18}N_6O_3$) = 294.1440].

2-Amino-6-(benzylamino)-9-(2-deoxy-β-D-*erythro*-pentofuranosyl)purine (9c). A solution of **8** (57 mg, 0.180 mmol) and DBU (0.3 mL, 305 mg, 2 mmol) in benzylamine (2.5 mL) was stirred at 100°C for 48 h. Volatiles were evaporated in vacuo, and AcOH/H_2O was added. Volatiles were evaporated from the neutrallized solution, and EtOH was added and evaporated (2 × 5 mL). The residue was chromatographed (preparative silica gel TLC plate; MeOH/CH_2Cl_2, 1:9) to give **9c** (49 mg, 76%) as a glass: UV max 284 nm (ε 14 700), 261 nm (ε 9900); ^{1}H NMR (500 MHz) δ 2.18 (ddd, *J* = 2.4, 5.9, 12.7 Hz, 1H), 2.58–2.63 (m, 1H), 3.51–3.53 (m, 1H), 3.58–3.60 (m, 1H), 3.84–3.85 (m, 1H), 4.358–4.362 (m, 1H), 4.64 (s, 2H), 5.28 (s, 2H), 5.85 (bs, 2H), 6.19 (t, *J* = 6.8 Hz, 1H), 7.18–7.21 (m, 1H), 7.26–7.34 (m, 4H), 7.88 (bs, 1H), 7.94 (s, 1H); ^{13}C NMR (125 MHz) δ 39.4, 42.5, 62.0, 71.1, 83.1, 87.7, 113.6, 126.5, 127.2, 128.1, 135.7, 140.5, 150.7, 154.9, 160.1; HRMS *m/z* 379.1486 [MNa^+ ($C_{17}H_{20}N_6O_3Na$) = 379.1495].

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ACKNOWLEDGMENTS

We are grateful for Graduate Research Fellowships from Brigham Young University (X.L.) and pharmaceutical company gift funds (M.J.R.) for financial support.

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Received August 7, 2003
Accepted October 6, 2003

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