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Synthesis of 8-Phenoxy-2′-deoxyguanosine Nucleoside Analogues

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Nucleobase adducts, which form in vivo by nucleophilic attack of nucleobases on electrophilic chemical species, can impact on the conformation and biological influences of the adducted nucleoside. Contemporary studies aim to address the occurrence and relevance of 8-phenoxypurine adducts. However, preparative techniques for synthesizing these nucleosides have not previously been described. Reported herein is a relatively facile synthesis of 8-dG phenol adducts using a wide variety of electron-donating, electron-withdrawing, and sterically demanding phenols.

Introduction

Nucleosides and nucleotides containing altered nucleobases have been used as therapeutics,[1] as probes for detecting DNA damage,[2] in monitoring charge transfer in DNA,[3] signaling hybridization,[4] or sensing pH,[5] and as templates for mutagenesis research.[6] Studies with the latter have revealed that nucleobase adducts, which form in vivo by the nucleophilic attack of nucleobases on electrophilic species, can exert a profound impact on the conformation and biochemical processing of the adducted nucleoside. If an adduct persists and escapes DNA repair processes, the resulting mutations to cell-cycle regulatory genes may cause uncontrolled cell division leading to cancer. Structural determination studies and bioassays, which make it possible to elucidate the molecular mechanisms underlying the chemical and biological influences of specific lesions, are enabled by an ability to synthesize nucleoside adducts.

Modifications at the 8-position of purines disrupt the natural *anti* conformation depending on whether they are located in a nucleoside, nucleotide, or oligonucleotide.[7] Furthermore, the distortion to DNA may alter its replication properties. As an illustration, polymerase-mediated DNA synthesis with chemically modified templates revealed that the arylamine adduct 8-AF-dG, which equilibrates between *syn* and *anti* conformations, and 8-AAF-dG, which is in essence locked into the *syn* conformation by an acetyl group that hinders rotation of the nucleobase around the glycosidic bond, possess strikingly different mutational spectra.[8] These and other 8-(arylamino)purine adducts, such as those formed in vivo following the consumption of cooked meats and exposure to environmental toxins, have been chemically prepared either by biomimetic direct adduction of *N*-acetoxyamines[9] to DNA under neutral conditions or by Pd-catalyzed cross-coupling between arylamines and protected 8-bromopurines.[10] The latter method has become common for preparing 8-(arylamino)purine nucleosides for insertion into oligonucleotides, which are further used to study the chemical and biological impacts of specific arylamine lesions (particularly those linked to carcinogenesis) on DNA structure and replication.[10c–10e,11]

Contemporary studies aim to address the occurrence and relevance of analogous 8-phenoxypurines, such as those derived from Ochratoxin A (OTA), a food-borne mycotoxin derived from *Aspergillus*, and pentachlorophenol (PCP), a common environmental contaminant.[12] In the case of OTA, adducts have been shown to form in vitro, but the role of the adducts on cancer etiology, and whether the adducts exist in vivo, is debated.[12a,13] For PCP, DNA adducts have been identified in vivo, but their overall biological impact is unknown.[12b] An explicit limitation for the further study of these adducts is that synthetic methods for preparing 8-phenoxypurine adducts are considerably less developed than for preparing their *N*-linked 8-(arylamino)purine counterparts, although 8-alkoxy- and 8-(thiophenoxy)purines have been prepared by the nucleophilic substitution of 8-bromopurines.[14] A previously reported investigation of the formation of 8-phenoxypurine adducts involved the peroxidase activation of chlorophenols to form phenoxyl radicals that react at the 8-position of dG, the most easily oxidized nucleoside.[12b,15] A major drawback of extending this approach to preparative reactions is that many phenols are not suitable substrates for the enzymatic reaction, over-oxidation of phenols leads to the generation of diverse side-products, and the method produces adducts on a very small scale. Thus, reported herein is a relatively facile method for synthesizing 8-phenoxy-dG nucleoside analogues with a variety of electron-donating, electron-withdrawing, and sterically demanding phenols. Such adducts are expected to

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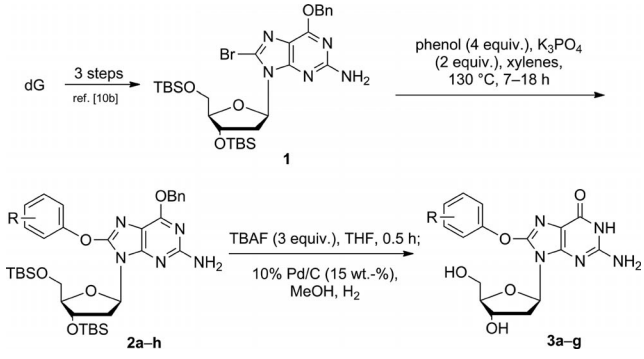
be useful as probes to gain a greater understanding of the structural and toxicological impacts of DNA major-groove-binding events.

Results and Discussion

The overall synthetic strategy for constructing 8-phenoxy-dG adducts **3a**–**g** involved the addition of substituted phenols to protected 8-Br-dG **1** (prepared according to previously described procedures[10b,16]) to form deoxyguanosine adducts **2a**–**h**, followed by purification and deprotection (Scheme 1). A variety of conditions were tested for both Pd-catalyzed and simple base-promoted reactions of phenol with precursor **1** (Table 1). At 110 °C in toluene, Pd catalysis in the presence of ligand **A** promoted the reactions (Table 1, entry 2), whereas at 80 °C in DME no appreciable catalysis was observed, as monitored by ^{1}H NMR (Table 1, entries 6–9). However, at 135 °C in xylenes, both Pd-catalyzed and Pd-free reactions proceeded to completion after only 6 h (Table 1, entries 10–12). The Pd-free reaction simplifies the reaction set-up and obviates the need for an expensive catalyst.

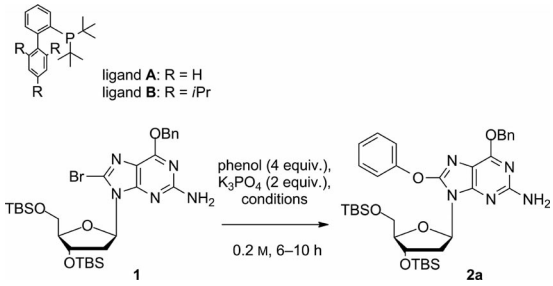


Scheme 1. Synthesis of the 8-phenoxy-dGs prepared in this study.

To test the scope of this reaction with respect to the chemical properties of the phenol, the base-mediated substitution reaction was performed in xylenes under nitrogen and adducts **2a**–**h** were obtained in yields of 64–85% (Table 2). The phenol substrates studied ranged from highly electron-withdrawing pentachlorophenol (PCP) to modestly electron-donating 4-methylphenol, with substituents at the *ortho* positions (**2b**,**f**,**g**) well tolerated. The reaction efficiency appears to have no dependence on the acid dissociation constants of the phenol substrates (pK_a values were between approximately 5 and 10). Aniline was also tested as a substrate, but no adduct formation was observed; this emphasizes the importance of previously described Pd-catalyzed cross-coupling methods for arylamine adduct formation.[10]

Free nucleosides were obtained by TBAF-mediated desilylation of the 3′- and 5′-hydroxys followed by catalytic hydrogenation to remove the O^6-benzyl protecting group. Adducts **3a**–**g** were sensitive to normal phase chromatography and to a lesser extent reversed-phase HPLC; significant hydrolysis of the nucleosides occurred during initial attempts at normal-phase chromatography. We found that minor amounts of triethylamine in the eluent could prevent hydrolysis but could also introduce further impurities in some cases. Therefore, the compounds were purified by trituration in acetone to provide analytically pure (>95% by ^{1}H NMR) material in isolated yields of 27–64% after both deprotection steps (Table 3). The low yields in part reflect the solubility of the nucleosides in the small volumes of acetone used during purification (the more soluble chlorinated adducts were obtained in lower yields) as well as common

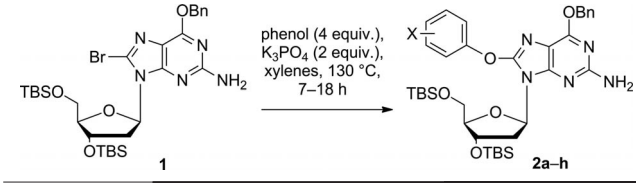
Table 1. Influence of conditions on the conversion of **1** to **2a**.



Entry	Solvent	Pd(OAc)$_2$ [%]	Ligand [%]	Temp. [°C]	Atm.[a]	**1/2a**[b]
1	toluene	0	0	110	air	53:47
2	toluene	6	**A** (5)	110	air	26:74
3	toluene	6	**B** (5)	110	air	45:55
4	toluene	8	**A** (11)	110	air	45:55
5	toluene	8	**A** (11)	110	N_2	53:47
6	DME	0	0	85	air	67:33
7	DME	0	0	85	N_2	56:44
8	DME	3	**A** (6)	85	air	63:37
9	DME	3	**A** (6)	85	N_2	59:41
10	xylenes	3	**A** (6)	135	N_2	0:100
11	xylenes	0	0	135	N_2	0:100
12	xylenes	0	0	135	air	0:100

[a] Atmosphere under which the reactions were conducted. [b] Percent ratio of starting material **1** to target compound **2a** as determined by ^{1}H NMR analysis of the crude reaction mixtures.

Table 2. Synthesis of protected adducts **2a**–**h**.

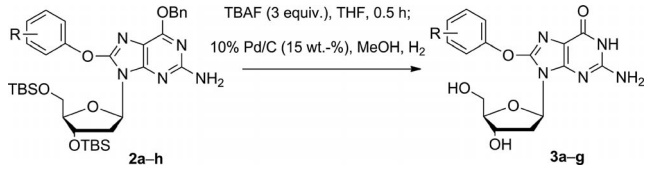


Product	Substrate	Yield [%][a]
2a	phenol	77
2b	2-methylphenol	84
2c	4-methylphenol	80
2d	4-methoxyphenol	80
2e	4-chlorophenol	82
2f	2,4,6-trichlorophenol	85
2g	2,3,4,5,6-pentachlorophenol	64
2h	4-bromophenol	85

[a] Isolated yield of analytically pure material.

purification challenges in obtaining extremely pure nucleosides. However, the yields of material obtained with 90–95% purity, which would not be suitable for biological study but which would be synthetically useful, were 90% after both deprotection steps for both the phenol (**3a**) and 4-chlorophenol adducts (**3e**). Debenzylation of the halogen-substituted phenols was nontrivial; dehalogenated products were observed in the NMR and mass spectra of the crude reaction mixtures following catalytic hydrogenation of trichlorophenol and 4-bromophenoxy compounds **2f** and **2h**. To avoid this drawback, substitution reactions were attempted with 3′,5′-bis(*tert*-butyldimethylsilyl)-substituted 8-Br-dG under the same conditions used for the fully protected starting material **1**. Although partial conversion to the desired product was observed in the NMR and mass spectra, the complex reaction mixtures were difficult to purify and the strategy was no longer pursued. No product formation was detected in analogous base-mediated reactions performed with unprotected 8-Br-dG in H_2O, DMSO, or DMF.

Table 3. Deprotection of adducts **2a**–**h**.



Product	Substrate	Yield [%][a]
3a	phenol	44 (90)[b]
3b	2-methylphenol	64
3c	4-methylphenol	54
3d	4-methoxyphenol	61
3e	4-chlorophenol	24 (90)[c]
3f	2,4,6-trichlorophenol	29
3g	2,3,4,5,6-pentachlorophenol	27
	4-bromophenol	0[d]

[a] Isolated yields of analytically pure material following desilylation and debenzylation, unless otherwise indicated. [b] Isolated yield of 95% pure material. [c] Isolated yield of 90% pure material. [d] Product decomposed during debenzylation.

Based on our observations of product decomposition during chromatography, we conclude that adducts **3a**–**g** are acid-labile. The depurination of deoxyguanosines bearing bulky or electronegative adducts at the 8-position is well known and is proposed to lead to abasic site formation in DNA.[17] Recent studies by Wetmore and Manderville and co-workers suggest that under physiological conditions, homolytic cleavage during adduct formation rather than hydrolysis following adduct formation may be responsible for the depurination, particularly for purines substituted with small aryl adducts.[18] However, the C^8–O linkage for adducts **3a**–**g** differs significantly from the C^8–aryl linkage of the adducts studied by Wetmore and Manderville, which may render their lability relevant under physiological conditions. Incorporation of adducts **3** into oligonucleotides will enable the testing of this hypothesis in further studies.

Conclusions

We have reported herein a simple synthesis of 8-phenoxy-dG nucleosides that is complementary to known methods for preparing 8-alkoxy- and 8-(thiophenoxy)purine nucleosides. In contrast to techniques used to prepare 8-(arylamino)purine adducts, the method presented herein does not require the use of Pd catalysis. The substitution reactions are efficient and free of side-products, with overall yields after deprotection influenced by the rigor of the purification procedure. This work extends the scope of nucleophilic substitutions to produce 8-phenoxy-dG nucleosides.

Experimental Section

General: Chemicals were purchased from Sigma–Aldrich (Milwaukee, WI) or TCI (Tokyo, Japan) and used without further purification. Xylenes were dried with $POCl_3$ and vacuum distilled prior to use. Dry toluene for substitution reactions was obtained from an M-Braun solvent purification system in which the solvent is passed through a column of activated alumina before being dispensed under nitrogen. ^{1}H NMR spectra were acquired at 500 or 400 MHz, and ^{13}C NMR at 125 or 100 MHz, with a 500 MHz Varian or 400 MHz Bruker NMR spectrometer. Chemical shifts are reported relative to the non-deuteriated solvent signals ($CHCl_3$ was set to 7.26 and 77.23 ppm, and MeOD to 3.31 and 49.15 ppm for ^{1}H and ^{13}C NMR spectra, respectively). Flash chromatography (silica gel, 60 Å, 200–400 mesh) was used for product purification. Normal-phase thin-layer chromatography (plates obtained from Silicycle, QB, Canada) was used to monitor the reactions and the spots were visualized under UV light (254 nm). High-resolution ESI-MS was performed with a Bruker BioTOF II or Thermo Scientific Exactive mass spectrometer. Infrared spectra were acquired with an FT-IR instrument from thin-film samples prepared on NaCl plates and are reported in cm^{-1}. Reported yields represent an average of two to three trials.

6-*O*-Benzyl-8-bromo-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (1): Guanosine **1** was prepared according to a published procedure.[10b]

General Procedure for the Synthesis of 6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-phenoxy-2′-deoxyguanosines 2a–h: In a nitrogen-filled glove box, K_3PO_4 (2 equiv.), phenol (4 equiv.), and xylenes (0.25 M) were added to a vial containing 6-*O*-benzyl-8-bromo-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (ca. 0.2 mmol). The vial was sealed with a Teflon®-lined cap, removed from the glove box, and submerged in an oil bath at 130 °C. Alternatively, reactions were prepared in air or nitrogen-flushed vials and sealed with Teflon®-lined caps. After 12 h, the reaction vial was allowed to cool to room temperature and then diluted in ethyl acetate (1–2 mL). The resulting solution was loaded onto a Biotage Isolute PE-AX acid-scavenging column (500 mg, 3 mL capacity, pre-equilibrated with ethyl acetate) and eluted with ethyl acetate to remove excess phenol. The solution was then concentrated by rotary evaporation and purified by silica gel chromatography (3–30% gradient of ethyl acetate in hexanes). Yields are reported for material of 95% or greater purity as judged by ^{1}H NMR analysis and represent an average of two to three experiments.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-phenoxy-2′-deoxyguanosine (2a): Yield 77%. TLC: 0.44 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 35125 (w), 3348 (w), 2954 (m), 3215 (w), 2955 (m), 2930 (m), 2892 (m), 2857 (m), 1621 (s), 1601 (s), 1588 (s), 1554 (m),

1471 (s), 1417 (m), 1353 (m), 1253 (m), 1228 (m), 1206 (m), 1075 (m), 1030 (m), 836 (s), 777 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (m, 9 H, Ar-H), 7.21 [app. dt, $J_{H,H}$ = 1.0, 7.5 Hz, 1 H, Ar-H], 6.41 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.50 (d, $J_{H,H}$ = 3 Hz, 2 H, Bn-H_2), 4.69 (m, 3 H, 3′-H, NH_2), 3.93 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.0 Hz, 1 H, 4′-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1 H, 5′-H), 3.67 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1 H, 5′-H), 3.30 (ddd, $J_{H,H}$ = 6.0, 7.5, 13.0 Hz, 2′-H), 2.19 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1 H, 2′-H), 0.92 (s, 9 H, $SiCMe_3$), 0.84 (s, 9 H, $SiCMe_3$), 0.12 (s, 6 H, $SiMe_2$), –0.01 (s, 3 H, SiMe), –0.03 (s, 3 H, SiMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 158.0, 153.70, 153.66, 152.4, 137.0, 129.9, 128.6, 128.5, 128.1, 125.6, 120.2, 111.1, 87.6, 82.9, 73.0, 68.0, 63.4, 36.9, 26.11, 26.05, 18.6, 18.3, –4.41, –4.45, –5.16, –5.21 ppm. HRMS: calcd. for $[MH]^+$ 678.3501; found 678.3628.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(2-methylphenoxy)-2′-deoxyguanosine (2b): Yield 84%. TLC: 0.44 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3494 (w), 3340 (w), 2954 (m), 2929 (m), 2857 (m), 1652 (w), 1634 (m), 1622 (vs), 1598 (vs), 1577 (m), 1471 (s), 1417 (m), 1352 (m), 1252 (m), 1225 (m), 1128 (w), 1109 (m), 1077 (m), 1031 (w), 956 (w), 834 (s), 776 (m), 747 (w), 694 (w), 663 (w) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 (app. d, $J_{H,H}$ = 7.0 Hz, 2 H, Ar-H), 7.25 (m, 6 H, Ar-H), 7.12 (app. dt, $J_{H,H}$ = 1.5, 7.5, 7.5 Hz, 1 H, Ar-H), 6.43 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.48 (d, $J_{H,H}$ = 2.5 Hz, 2 H, Bn-H_2), 4.68 (m, 3 H, 3′-H, NH_2), 3.94 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.5 Hz, 1 H, 4′-H), 3.75 (dd, $J_{H,H}$ = 7.5, 11.0 Hz, 1 H, 5′-H), 3.67 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1 H, 5′-H), 3.33 (ddd, $J_{H,H}$ = 5.5, 7.0, 13.0 Hz, 1 H, 2′-H), 2.25 (s, 3 H, Ar-Me), 2.19 (ddd, $J_{H,H}$ = 3.0, 7.0, 13.0 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.83 (s, 9 H, $SiCMe_3$), 0.12 (s, 6 H, $SiMe_2$), –0.01 (s, 3 H, SiMe), –0.03 (s, 3 H, SiMe) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 157.9, 153.8, 152.6, 151.9, 137.0, 131.7, 129.7, 128.6, 128.5, 128.0, 127.4, 125.9, 120.9, 111.2, 87.6, 82.9, 73.0, 67.9, 63.4, 36.8, 26.0, 26.0, 18.6, 18.3, 16.5, –4.45, –4.46, –5.21, –5.29 ppm. HRMS: calcd. for $[MH]^+$ 692.3658; found 692.3785.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(4-methylphenoxy)-2′-deoxyguanosine (2c): Yield 80%. TLC: 0.48 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3504 (w), 3368 (w), 3207 (w), 2955 (m), 2930 (m), 2857 (m), 1622 (s), 1595 (s), 1577 (m), 1507 (m), 1472 (s), 1418 (m), 1351 (m), 1312 (w), 1253 (m), 1228 (m), 1205 (m), 1079 (m), 1031 (m), 953 (w), 836 (s), 778 (m), 732 (w), 696 (w), 668 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (m, 2 H, Ar-H), 7.30 (m, 3 H, Ar-H), 7.18 (m, 4 H, Ar-H), 6.40 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.50 (d, J = 3.0 Hz, 2 H, Bn-H_2), 4.68 (m, 3 H, 3′-H, NH_2), 3.93 (m, 1 H, 4′-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1 H, 5′-H), 3.67 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1 H, 5′-H), 3.30 (ddd, $J_{H,H}$ = 6.0, 7.0, 13.0 Hz, 2′-H), 2.34 (s, 3 H, Ar-Me), 2.19 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.85 (s, 9 H, $SiCMe_3$), 0.13 (s, 6 H, $SiMe_2$), 0.01 (s, 3 H, SiMe), –0.01 (s, 3 H, SiMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.4, 158.0, 153.7, 152.8, 151.4, 137.0, 135.2, 130.3, 128.6, 128.5, 128.0, 120.0, 111.2, 87.6, 82.9, 73.0, 68.0, 63.5, 36.9, 26.1, 21.0, 18.6, 18.3, –4.43, –4.47, –5.17, –5.23 ppm. HRMS: calcd. for $[MNa]^+$ 714.3477; found 714.3422.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(4-methoxyphenoxy)-2′-deoxyguanosine (2d): Yield 80%. TLC: 0.34 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3504 (w), 3376 (w), 2955 (m), 2930 (m), 2893 (w), 2837 (m), 1622 (s), 1595 (s), 1557 (m), 1505 (w), 1471 (s), 1418 (m), 1351 (m), 1310 (w), 1250 (w), 1228 (w), 1203 (w), 1077 (w), 1032 (w), 953 (w), 836 (s), 778 (m), 731 (w), 696 (w), 668 (w) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.42 (m, 2 H, Ar-H), 7.27 (m, 5 H, Ar-H), 6.89 (app. d, $J_{H,H}$ = 9.0 Hz, 2 H, Ar-H), 6.40 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.49 (d, J = 3.0 Hz, 2 H, Bn-H_2), 4.68 (m, 1 H, 3′-H), 4.65 (s, 2 H, NH_2), 3.93 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.5 Hz, 1 H, 4′-H), 3.80 (s, 3 H, OMe), 3.77 (m, 1 H, 5′-H), 3.68 (dd, $J_{H,H}$ = 5.0, 10.5 Hz, 1 H, 5′-H), 3.30 (ddd, $J_{H,H}$ = 6.0, 8.0, 12.5 Hz, 1 H, 2′-H), 2.18 (ddd, $J_{H,H}$ = 4.0, 7.0, 12.5 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.84 (s, 9 H, $SiCMe_3$), 0.12 (s, 6 H, $SiMe_2$), 0.004 (s, 3 H, SiMe), –0.019 (s, 3 H, SiMe) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.3, 157.9, 157.2, 153.8, 153.1, 147.0, 137.0, 128.6, 128.4, 128.0, 121.4, 114.9, 111.1, 87.5, 82.8, 73.0, 67.9, 63.4, 55.9, 36.8, 26.1, 18.6, 18.3, –4.43, –4.48, –5.17, –5.23 ppm. HRMS: calcd. for $[MH]^+$ 708.3607; found 708.3454.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(4-chlorophenoxy)-2′-deoxyguanosine (2e): Yield 82%. TLC: 0.50 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3508 (w), 3356 (w), 3219 (w), 2956 (m), 2930 (m), 2884 (m), 2858 (m), 1622 (s), 1603 (s), 1589 (s), 1553 (s), 1495 (s), 1487 (s), 1471 (s), 1417 (m), 1353 (m), 1312 (w), 1253 (m), 1229 (m), 1090 (m), 1030 (w), 1014 (w), 958 (w), 836 (s), 778 (m), 697 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (m, 2 H, Ar-H), 7.31 (m, 7 H, Ar-H), 6.37 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.50 (d, $J_{H,H}$ = 3.0 Hz, 2 H, Bn-H_2), 4.69 (m, 3 H, 3′-H, NH_2), 3.92 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.0 Hz, 1 H, 4′-H), 3.76 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1 H, 5′-H), 3.65 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1 H, 5′-H), 3.31 (ddd, $J_{H,H}$ = 6.0, 7.1, 13.2 Hz, 1 H, 2′-H), 2.18 (ddd, $J_{H,H}$ = 3.6, 6.8, 13.2 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.84 (s, 9 H, $SiCMe_3$), 0.12 (s, 6 H, $SiMe_2$), 0.01 (s, 3 H, SiMe), –0.02 (s, 3 H, SiMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 158.1, 153.6, 152.11, 152.08, 136.9, 130.9, 129.9, 128.57, 128.52, 128.1, 121.7, 111.1, 87.6, 82.9, 72.9, 68.0, 63.3, 36.9, 26.1, 18.6, 18.3, –4.39, –4.44, –5.15, –5.21 ppm. HRMS: calcd. for $[MH]^+$ 712.3112; found 712.3089.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(2,4,6-trichlorophenoxy)-2′-deoxyguanosine (2f): Yield 85%. TLC: 0.53 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3512 (w), 3341 (w), 2954 (m), 2930 (m), 2886 (m), 2857 (m), 1652 (w), 1622 (s), 1599 (s), 1471 (s), 1413 (m), 1351 (m), 1312 (w), 1253 (m), 1228 (m), 1077 (m), 1031 (m), 954 (w), 836 (s), 777 (m), 732 (w), 695 (w), 668 (w) cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ = 7.41 (m, 4 H, Ar-H), 7.30 (m, 3 H, Ar-H), 6.46 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.50 (s, 2 H, Bn-H_2), 4.69 (m, 3 H, 3′-H, NH_2), 3.98 (ddd, $J_{H,H}$ = 3.0, 5.5, 7.0 Hz, 1 H, 4′-H), 3.77 (dd, $J_{H,H}$ = 7.0, 10.5 Hz, 1 H, 5′-H), 3.74 (dd, $J_{H,H}$ = 5.5, 10.5 Hz, 1 H, 5′-H), 3.29 (ddd, $J_{H,H}$ = 6.0, 7.5, 13.0 Hz, 1 H, 2′-H), 2.22 (ddd, $J_{H,H}$ = 3.5, 6.5, 13.0 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.84 (s, 9 H, $SiCMe_3$), 0.134 (s, 3 H, SiMe), 0.132 (s, 3 H, SiMe), 0.01 (s, 3 H, SiMe), –0.01 (s, 3 H, SiMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 158.1, 154.0, 150.6, 144.6, 137.0, 132.4, 129.9, 129.3, 128.51, 128.48, 128.0, 110.9, 87.8, 83.1, 73.1, 68.0, 63.6, 37.0, 26.10, 26.08, 21.0, 18.6, 18.3, –4.42, –4.44, –5.15, –5.25 ppm. HRMS: calcd. for $[MH]^+$ 782.2308; found 782.2437.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(2,3,4,5,6-pentachlorophenoxy)-2′-deoxyguanosine (2g): Yield 64%. TLC: 0.57 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3519 (w), 3360 (w), 2956 (m), 2930 (m), 2888 (w), 2857 (m), 1622 (s), 1597 (vs), 154 (w), 1466 (s), 1415 (m), 1386 (s), 1363 (s), 1311 (w), 1258 (m), 1229 (m), 1107 (m), 1075 (m), 1029 (m), 953 (w), 836 (s), 774 (m), 717 (m), 663 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (m, 2 H, Ar-H), 7.30 (m, 3 H, Ar-H), 6.44 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.49 (d, J = 3.0 Hz, 2 H, Bn-H_2), 4.71 (m, 3 H, 3′-H, NH_2), 3.96 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.0 Hz, 1 H, 4′-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1 H, 5′-H), 3.73 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1 H, 5′-H), 3.31 (ddd, $J_{H,H}$ = 6.0, 7.0, 13.0 Hz, 1 H, 2′-H), 2.23 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.83 (s, 9 H, $SiCMe_3$), 0.141 (s, 3 H, SiMe), 0.137 (s, 3 H, SiMe), 0.02 (s, 3 H, SiMe), –0.01 (s, 3 H, SiMe) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ

= 159.5, 158.2, 153.9, 150.1, 145.5, 136.9, 132.6, 132.1, 128.52, 128.50, 128.12, 128.10, 110.9, 87.7, 83.1, 72.7, 68.0, 63.4, 37.0, 26.1, 18.6, 18.3, –4.41, –4.44, –5.15, –5.25 ppm. HRMS: calcd. for $[MH]^+$ 850. 1529; found 850.1501.

6-*O*-Benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-(4-bromophenoxy)-2′-deoxyguanosine (2h): Yield 85%. TLC: 0.50 (15% ethyl acetate in hexanes). IR: $\tilde{\nu}$ = 3515 (w), 3365 (w), 3207 (w), 2955 (m), 2930 (m), 2889 (w), 2857 (m), 1622 (s), 1599 (s), 1417 (m), 1351 (m), 1252 (m), 1228 (m), 1111 (m), 1069 (m), 1030 (m), 1011 (m), 953 (w), 836 (s), 778 (m), 692 (w), 667 (w) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (m, 2 H, Ar-H), 7.44 (m, 2 H, Ar-H), 7.31 (m, 3 H, Ar-H), 7.23 (m, 2 H, Ar-H), 6.37 (app. t, $J_{H,H}$ = 7.0 Hz, 1 H, 1′-H), 5.51 (d, J = 3.0 Hz, 2 H, Bn-H_2), 4.70 (m, 3 H, 3′-H, NH_2), 3.92 (m, 1 H, 4′-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1 H, 5′-H), 3.66 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1 H, 5′-H), 3.31 (ddd, $J_{H,H}$ = 6.0, 7.5, 13.0 Hz, 1 H, 2′-H), 2.19 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1 H, 2′-H), 0.93 (s, 9 H, $SiCMe_3$), 0.84 (s, 9 H, $SiCMe_3$), 0.13 (s, 6 H, $SiMe_2$), 0.01 (s, 3 H, SiMe), –0.01 (s, 3 H, SiMe) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.6, 158.1, 153.6, 152.6, 152.0, 136.9, 132.9, 128.52, 128.50, 128.1, 122.1, 118.5, 111.1, 87.6, 82.9, 72.9, 68.0, 63.3, 36.9, 26.12, 26.07, 18.6, 18.3, –4.40, –4.44, –5.15, –5.21 ppm. HRMS: calcd. for $[MH]^+$ 758.2592; found 758.2610.

General Procedure for the Synthesis of 8-Phenoxy-2′-deoxyguanosines 3a–g: A solution of 0.5 M TBAF in THF (3 equiv.) was added to a vial containing 6-*O*-benzyl-3′,5′-*O*-bis(*tert*-butyldimethylsilyl)-8-phenoxy-2′-deoxyguanosine (**2**; ca. 0.15 mmol). The vial was capped and allowed to stand at room temperature. After monitoring the consumption of the starting material by thin-layer chromatography (reaction complete in about 30 min), the mixture was concentrated by rotary evaporation and purified by silica gel chromatography (0–10% gradient of methanol in dichloromethane) to yield a yellow oil that was analyzed by NMR and mass spectrometry and used in a debenzylation reaction without further characterization. The oil, 10% Pd/C (15% by weight), and anhydrous methanol (reaction concentration = 0.05 M) were combined in a 25 mL flask fitted with a three-way adapter. The flask was sequentially evacuated and then purged with hydrogen (from attached balloon) three times, then left open to the hydrogen balloon. When the starting material could no longer be observed by TLC (10% methanol in dichloromethane), the reaction mixture was filtered through a plug of Celite rinsed through with 1:1 MeOH/EtOAc and then concentrated by rotary evaporation. The solid product was purified by sequential trituration with 0.1–0.5 mL portions of acetone.

8-Phenoxy-2′-deoxyguanosine (3a): Yield 44% (analytical purity), 90% (95% purity). TLC: 0.21 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 3312 (w), 3132 (w), 2945 (w), 1682 (s), 1597 (m), 1557 (s), 1487 (m), 1417 (m), 1372 (m), 1346 (w), 1278 (w), 1203 (m), 1098 (m), 1053 (m), 967 (w), 776 (w) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.43 (dd, $J_{H,H}$ = 7.5, 8.5 Hz, 2 H, Ar-H), 7.31 (app. d, $J_{H,H}$ = 8.0 Hz, 2 H, Ar-H), 7.26 (app. t, $J_{H,H}$ = 7.5 Hz, 1 H, Ar-H), 6.37 (dd, $J_{H,H}$ = 6.8, 7.7 Hz, 1 H, 1′-H), 4.56 (m, 1 H, 3′-H), 3.99 (m, 1 H, 4′-H), 3.80 (dd, $J_{H,H}$ = 4.0, 12.0 Hz, 1 H, 5′-H), 3.71 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1 H, 5′-H), 3.07 (ddd, $J_{H,H}$ = 6.2, 7.9, 13.7 Hz, 1 H, 2′-H), 2.27 (ddd, $J_{H,H}$ = 2.7, 6.6, 13.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 158.8, 155.5, 154.9, 151.7, 151.6, 131.0, 126.7, 120.8, 113.1, 89.4, 85.0, 73.4, 64.2, 39.2 ppm. HRMS: calcd. for $[MNa]^+$ 382.1122; found 382.1134.

8-(2-Methylphenoxy)-2′-deoxyguanosine (3b): Yield 64%. TLC: 0.20 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 2940 (w), 1672 (s), 1654 (s), 1588 (m), 1558 (s), 1419 (m), 1367 (m), 1345 (m), 1280 (w), 1225 (m), 1176 (m), 1105 (m), 1053 (w), 991 (w), 972 (w), 774 (w), 758 (w) cm^{-1}. ^1H NMR (500 MHz, MeOD): δ = 7.28 (d, $J_{H,H}$ = 7.6 Hz, 1 H, Ar-H), 7.20 (m, 3 H, Ar-H), 6.42 (dd, $J_{H,H}$ = 6.5, 8.0 Hz, 1 H, 1′-H), 4.56 (m, 1 H, 3′-H), 4.01 (m, 1 H, 4′-H), 3.81 (dd, $J_{H,H}$ = 4.0, 12.0 Hz, 1 H, 5′-H), 3.71 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1 H, 5′-H), 3.10 (ddd, $J_{H,H}$ = 6.0, 8.0, 13.5 Hz, 1 H, 2′-H), 2.34 (ddd, $J_{H,H}$ = 3.0, 6.5, 13.5 Hz, 1 H, 2′-H), 2.25 (s, 3 H, Ar-Me) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 158.7, 154.8, 153.4, 152.0, 151.8, 132.7, 131.0, 128.5, 127.3, 121.9, 113.0, 89.5, 85.0, 73.4, 64.2, 39.2, 16.4 ppm. HRMS: calcd. for $[MNa]^+$ 396.1278; found 396.1283.

8-(4-Methylphenoxy)-2′-deoxyguanosine (3c): Yield 54%. TLC: 0.21 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 3167 (s), 2935 (m), 1680 (s), 1559 (s), 1499 (m), 1410 (m), 1368 (w), 1342 (w), 1278 (w), 1203 (w), 1102 (w), 979 (w), 818 (w), 776 (w) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.18 (m, 4 H, Ar-H), 6.37 (dd, $J_{H,H}$ = 3.9, 7.7 Hz, 1 H, 1′-H), 4.56 (m, 1 H, 3′-H), 3.99 (m, 1 H, 4′-H), 3.80 (dd, $J_{H,H}$ = 3.9, 12.0 Hz, 1 H, 5′-H), 3.70 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1 H, 5′-H), 3.05 (ddd, $J_{H,H}$ = 6.2, 8.0, 13.5 Hz, 1 H, 2′-H), 2.34 (s, 3 H, Ar-Me), 2.26 (ddd, $^3J_{H,H}$ = 2.8, 6.6, 13.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 158.9, 154.9, 153.3, 151.9, 151.7, 136.6, 131.4, 120.6, 113.1, 89.5, 85.0, 73.4, 64.2, 39.2, 21.0 ppm. HRMS: calcd. for $[MNa]^+$ 396.1278; found 396.1275.

8-(4-Methoxyphenoxy)-2′-deoxyguanosine (3d): Yield 61%. TLC: 0.20 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 3126 (s), 1667 (s), 1552 (s), 1500 (s), 1410 (m), 1361 (m), 1350 (m), 1248 (w), 1200 (w), 1099 (w), 1050 (w), 825 (w), 776 (w) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.23 (d, $J_{H,H}$ = 9.0 Hz, 2 H, Ar-H), 6.95 (d, $J_{H,H}$ = 9.0 Hz, 2 H, Ar-H), 6.38 (app. t, $J_{H,H}$ = 7.3 Hz, 1 H, 1′-H), 4.56 (m, 1 H, 3′-H), 4.00 (m, 1 H, 4′-H), 3.81 (dd, $J_{H,H}$ = 4.0, 12.0 Hz, 1 H, 5′-H), 3.80 (s, 3 H, OMe), 3.71 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1 H, 5′-H), 3.07 (ddd, $J_{H,H}$ = 6.5, 8.0, 13.8 Hz, 1 H, 2′-H), 2.27 (ddd, $J_{H,H}$ = 2.8, 6.5, 13.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 158.9, 158.7, 154.8, 152.4, 151.8, 148.7, 122.2, 115.9, 113.0, 89.4, 84.9, 73.4, 64.2, 56.3, 39.2 ppm. HRMS: calcd. for $[MNa]^+$ 412.1228; found 412.1226.

8-(4-Chlorophenoxy)-2′-deoxyguanosine (3e): Yield 24% (analytical purity), 90% (90% purity). TLC: 0.13 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 3297 (m), 2927 (m), 1683 (s), 1642 (m), 1594 (m), 1559 (s), 1485 (m), 1414 (w), 1373 (w), 1212 (m), 1088 (m), 1056 (w), 1013 (w), 970 (w), 822 (w), 776 (w) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.42 (d, $J_{H,H}$ = 9.0 Hz, 2 H, Ar-H), 7.35 (d, $J_{H,H}$ = 9.0 Hz, 2 H, Ar-H), 6.45 (app. t, $J_{H,H}$ = 7.3 Hz, 1 H, 1′-H), 4.55 (m, 1 H, 3′-H), 3.98 (m, 1 H, 4′-H), 3.80 (dd, $J_{H,H}$ = 3.9, 12.0 Hz, 1 H, 5′-H), 3.69 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1 H, 5′-H), 3.07 (ddd, $J_{H,H}$ = 6.4, 8.0, 13.4 Hz, 1 H, 2′-H), 2.26 (ddd, $J_{H,H}$ = 2.9, 6.6, 13.4 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 158.9, 155.1, 154.0, 151.8, 151.3, 131.9, 131.0, 122.6, 113.1, 89.4, 85.0, 73.3, 64.1, 39.2 ppm. HRMS: calcd. for $[MNa]^+$ 416.0738; found 416.0731.

8-(2,4,6-Trichlorophenoxy)-2′-deoxyguanosine (3f): Yield 29%. TLC: 0.26 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 3351 (s), 2933 (m), 1686 (s), 1587 (s), 1561 (s), 1443 (m), 1416 (m), 1340 (w), 1241 (w), 1101 (w), 1051 (w), 968 (w), 819 (w), 774 (w) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 7.63 (s, 2 H, Ar-H), 6.45 (app. t, $J_{H,H}$ = 7.2 Hz, 1 H, 1′-H), 4.56 (m, 1 H, 3′-H), 4.03 (m, 1 H, 4′-H), 3.82 (dd, $J_{H,H}$ = 4.0, 12.0 Hz, 1 H, 5′-H), 3.76 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1 H, 5′-H), 3.09 (ddd, $J_{H,H}$ = 6.2, 8.0, 13.6 Hz, 1 H, 2′-H), 2.33 (ddd, $J_{H,H}$ = 2.8, 6.4, 13.6 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (125 MHz, MeOD): δ = 158.8, 155.1, 152.1, 150.1, 145.9, 134.0, 131.1, 130.5, 112.9, 89.6, 85.1, 73.4, 64.3, 39.4 ppm. HRMS: calcd. for $[MNa]^+$ 483.9958; found 483.9950.

8-(2,3,4,5,6-Pentachlorophenoxy)-2′-deoxyguanosine (3g): Yield 27%. TLC: 0.30 (10% methanol in dichloromethane). IR: $\tilde{\nu}$ = 3327 (m), 2922 (m), 1680 (s), 1631 (m), 1586 (m), 1563 (m), 1420 (w), 1381 (m), 1098 (m), 775 (w), 713 (m) cm^{-1}. ^1H NMR (400 MHz, MeOD): δ = 6.45 (dd, $J_{H,H}$ = 6.9, 7.6 Hz, 1 H, 1′-H), 4.56 (m, 1 H, 3′-H), 4.03 (m, 1 H, 4′-H), 3.82 (dd, $J_{H,H}$ = 4.2, 12.0 Hz, 1 H, 5′-H), 3.76 (dd, $J_{H,H}$ = 4.8, 12.0 Hz, 1 H, 5′-H), 3.11 (ddd, $J_{H,H}$ = 6.2, 7.8, 13.5 Hz, 1 H, 2′-H), 2.34 (ddd, $J_{H,H}$ = 2.9, 6.6, 13.5 Hz, 1 H, 2′-H) ppm. ^{13}C NMR (100 MHz, MeOD): δ = 155.2, 152.2, 149.7, 147.1, 133.6, 133.1, 129.4, 112.8, 89.6, 85.1, 73.3, 64.2, 39.3 ppm. HRMS: calcd. for $[MNa]^+$ 551.9149; found 551.9153.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of compounds **2a**–**h** and **3a**–**g**.

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