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Synthesis of oxygen-linked 8-phenoxy-deoxyguanosine nucleoside analogues

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Abstract

Nucleobase adducts, which form in vivo by the nucleophilic attack of nucleobases on exogenous electrophilic species, can impact conformation and biological influences of the adducted nucleoside. Contemporary studies aim to address the occurrence and relevance of *O*-linked 8-phenoxy-purine adducts; however, preparative techniques for synthesizing these nucleosides were not previously described. Reported herein is a relatively facile synthesis of *O*-linked 8-dG phenol adducts with a wide variety of electron-donating, electron-withdrawing, and sterically demanding phenols.

Keywords

Modified nucleoside synthesis; 8-Deoxyguanosine adduct; DNA adduct

Introduction

Nucleosides and nucleotides containing altered nucleobases have been utilized as therapeutics,^[1] as probes for detecting DNA damage,^[2] 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 exogenous electrophilic species, can exert a profound impact on the conformation and biological influences of the adducted nucleoside. If an adduct persists and escapes DNA repair processes, 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 molecular mechanisms underlying the chemical and biological influences of specific lesions, are enabled by an ability to synthesize adducted nucleosides.

Modifications at the 8-position of purines disrupt the natural *anti*-conformation depending on whether they are situated in a nucleoside, nucleotide, or oligonucleotide.^[7] Furthermore, the distortion to DNA may alter its replication properties. To illustrate, 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 around the

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

glycosidic bond, possess strikingly different mutational spectra.^[8] These and other 8-arylamine-purine adducts, such as those formed in vivo following 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-arylamine-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-e, 11]

Contemporary studies aim to address the occurrence and relevance of analogous *O*-linked 8-phenoxy-purine adducts, such as that 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, or whether the adducts even 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 further studying these adducts is that synthetic methods for preparing *O*-linked 8-phenoxy-purine adducts are considerably less developed than for their *N*-linked 8-arylamine-purine counterparts, although *O*-linked 8-alkoxy-purine and *S*-linked 8-thiophenoxy-purine adducts have been prepared through nucleophilic substitutions of 8-bromo-purines.^[14] A previously reported investigation of the formation of *O*-linked 8-phenoxy-purine adducts has involved peroxidase activation of chlorophenols to form phenoxy radicals that react with the 8-position of dG, the most easily oxidized nucleoside.^[12b, 15] A major drawback of extending this approach for preparative reactions is that many phenols are not competent substrates for the enzymatic reaction, over-oxidation of phenols leads to the generation of diverse side-products, and the method produced adducts on very small scale. Thus, reported herein is a relatively facile method for synthesizing *O*-linked 8-phenoxy-dG adducts with a variety of electron-donating, electron-withdrawing, and sterically demanding phenols; such adducts are expected to be useful as probes for further understanding the structural and toxicological impacts of DNA major groove-binding events.

Results and Discussion

The overall synthetic strategy for constructing *O*-linked 8-phenoxy-dG adducts **3a-g** involved addition of substituted phenols to a protected form of 8-bromo-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 promoted the reactions, while at 80 °C in DME no appreciable catalysis was observed, as monitored by ¹H NMR (Table 1, entries 1-9). However, at 135 °C in xylenes, both Pd-catalyzed and Pd-free variants proceeded to completion after only six hours (Table 1, entries 10-12). The ability to efficiently synthesize the adducts without Pd was beneficial, since Pd catalysts add expense and complicate reaction set-up.

To test the scope of this reaction with respect to phenol chemical properties, the base-mediated substitution reaction was performed under nitrogen in xylenes, and adducts **2a-h** were obtained in 64-85% (Table 2). The phenol substrates ranged from highly electron-withdrawing pentachlorophenol (PCP) to modestly electron-donating 4-methylphenol, with methyl- and chloro-substitutions 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' hydroxyls 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 reverse-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 ¹H 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 purification challenges in obtaining extremely pure nucleosides. However, the yields for obtaining material of 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 phenol adduct **3a** and 4-chlorophenol adduct **3e**. Debenzylation of the halogen-substituted phenols was non-trivial; dehalogenated products were observed in NMR and mass spectra of the crude reaction mixtures following catalytic hydrogenation of trichlorophenol and 4-bromophenol-substituted adducts **2f** and **2h**. To avoid this drawback, substitution reactions were attempted with 3',5'-TBS silylated 8-Br-dG, under the same conditions used for the fully protected starting material **1**. While partial conversion to desired product could be observed by 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 H₂O, DMSO, or DMF.

Based on our observations of product decomposition during chromatography, we conclude that adducts **3a-g** are acid-labile. 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 the groups of Wetmore and Manderville suggest that under physiological conditions, homolytic cleavage during adduct formation rather than hydrolysis following adduct formation may be responsible for 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. Upon incorporation of adducts **3** into oligonucleotides, further studies will test this hypothesis.

Conclusions

We report a simple synthesis of *O*-linked 8-phenoxy-dG nucleosides that is complementary to known methods for preparing 8-alkoxy-purine and 8-thiophenoxy-purine nucleosides. Contrary to techniques for preparing 8-arylamine-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 purification. This work represents the scope of nucleophilic substitutions to produce *O*-linked 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 over POCl₃ 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. ¹H NMR spectra were acquired at 500 or 400 MHz, and ¹³C NMR at 125 or 100 MHz, on a 500 MHz Varian or 400 MHz Bruker NMR spectrometer. Chemical shifts are reported relative to the non-deuterated solvent signals (CHCl₃ was set to 7.26 and 77.23 ppm, and MeOD to 3.31 and 49.15 ppm, for ¹H and ¹³C NMR spectra, respectively). Flash chromatography (silica gel 60Å 200-400 mesh) was used for product purification. Normal phase thin-layer chromatography (TLC; plates obtained from Silicycle, QB, Canada) was used for reaction monitoring and the spots were visualized under UV light (254 nm). High-resolution ESI-MS (HRMS) was performed on a Bruker BioTOF II or Thermo Scientific Exactive mass spectrometer. Infrared (IR) spectra were acquired on an FT-IR instrument from thin-film samples prepared on NaCl plates, and reported in cm⁻¹. Reported yields represent an average of 2-3 trials.

8-Bromo-*O*⁶-benzyl-3',5'-*O*-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (1)

Prepared according to published procedure.^[10b]

General procedure for syntheses of compounds 2a-h: 8-(*O*-phenoxy)-*O*⁶-benzyl-3',5'-*O*-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2)

In a nitrogen-filled glovebox, to a vial containing 8-bromo-*O*⁶-benzyl-3',5'-*O*-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (~0.2 mmol) was added K₃PO₄ (2 equiv), phenol (4 equiv), and xylenes (0.25 M). The vial was sealed with a Teflon-lined cap, removed from the glovebox, and submerged in a 130 °C oil-bath. Alternatively, reactions were prepared in the air or nitrogen-flushed vials and sealed with Teflon-lined caps. After 12 hours, the reaction vial was allowed to cool to room temperature and then diluted in 1-2 ml ethyl acetate. 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 rotatory 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 ¹H NMR, and represent an average of 2-3 experiments.

8-(*O*-phenoxy)-*O*⁶-benzyl-3',5'-*O*-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2a)

IR: 35125w, 3348w, 2954m, 3215w, 2955m, 2930m, 2892m, 2857m, 1621s, 1601s, 1588s, 1554m, 1471s, 1417m, 1353m, 1253m, 1228m, 1206m, 1075m, 1030m, 836s, 777m

¹H NMR: (400 MHz, CDCl₃) = 7.35 (m, 9H, Ar-H), 7.21 (app dt, *J*_{H,H} = 1.0, 7.5 Hz, 1H, Ar-H), 6.41 (app t, *J*_{H,H} = 7.0, Hz, 1H, 1'-H), 5.50 (d, *J*_{H,H} = 3 Hz, 2H, Bn-H₂), 4.69 (m, 3H, 3'-H, -NH₂), 3.93 (ddd, *J*_{H,H} = 3.0, 5.0, 7.0 Hz, 1H, 4'-H), 3.77 (dd, *J*_{H,H} = 7.0, 11.0 Hz, 1H, 5'-H), 3.67 (dd, *J*_{H,H} = 5.0, 11.0 Hz, 1H, 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, 1H, 2'-H), 0.92 (s, 9H, -SiCMe₃), 0.84 (s, 9H, -SiCMe₃), 0.12 (s, 6H, -SiMe₂), -0.01 (s, 3H, -SiMe), -0.03 (s, 3H, -SiMe) ppm.

¹³C NMR: (100 MHz, CDCl₃) = 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, -5.21ppm.

HRMS: (MH⁺) calc 678.3501, found 678.3628

TLC: 0.44 (15% ethyl acetate in hexanes)

Yield: 77%

8-(O-(2-methyl)phenoxy)-O⁶-benzyl-3',5'-O-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2b)

IR: 3494w, 3340w, 2954m, 2929m, 2857m, 1652w, 1634m, 1622vs, 1598vs, 1577m, 1471s, 1417m, 1352m, 1252m, 1225m, 1128w, 1109m, 1077m, 1031w, 956w, 834s, 776m, 747w, 694w, 663w

¹H NMR: (500 MHz, CDCl₃) = 7.41 (app d, $J_{H,H}$ = 7.0, 2H, Ar-H), 7.25 (m, 6H, Ar-H), 7.12 (app dt, $J_{H,H}$ = 1.5, 7.5, 7.5 Hz, 1H, Ar-H), 6.43 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.48 (d, $J_{H,H}$ = 2.5 Hz, 2H, Bn-H₂), 4.68 (m, 3H, 3'-H, -NH₂), 3.94 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.5 Hz, 1H, 4'-H), 3.75 (dd, $J_{H,H}$ = 7.5, 11.0 Hz, 1H, 5'-H), 3.67 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1H, 5'-H), 3.33 (ddd, $J_{H,H}$ = 5.5, 7.0, 13.0 Hz, 1H, 2'-H), 2.25 (s, 3H, Ar-Me), 2.19 (ddd, $J_{H,H}$ = 3.0, 7.0, 13.0 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.83 (s, 9H, -SiCMe₃), 0.12 (s, 6H, -SiMe₂), -0.01 (s, 3H, -SiMe), -0.03 (s, 3H, -SiMe) ppm.

¹³C NMR: (125 MHz, CDCl₃) = 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: (MH⁺) calc 692.3658, found 692.3785

TLC: 0.44 (15% ethyl acetate in hexanes)

Yield: 84%

8-(O-(4-methyl)phenoxy)-O⁶-benzyl-3',5'-O-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2c)

IR: 3504w, 3368w, 3207w, 2955m, 2930m, 2857m, 1622s, 1595s, 1577m, 1507m, 1472s, 1418m, 1351m, 1312w, 1253m, 1228m, 1205m, 1079m, 1031m, 953w, 836s, 778m, 732w, 696w, 668w

¹H NMR: (400 MHz, CDCl₃) = 7.43 (m, 2H, Ar-H), 7.30 (m, 3H, Ar-H), 7.18 (m, 4H, Ar-H), 6.40 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.50 (d, J = 3.0 Hz, 2H, Bn-H₂), 4.68 (m, 3H, 3'-H, -NH₂), 3.93 (m, 1H, 4'-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1H, 5'-H), 3.67 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1H, 5'-H), 3.30 (ddd, $J_{H,H}$ = 6.0, 7.0, 13.0 Hz, 2'-H), 2.34 (s, 3H, Ar-Me), 2.19 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.85 (s, 9H, -SiCMe₃), 0.13 (s, 6H, -SiMe₂), 0.01 (s, 3H, -SiMe), -0.01 (s, 3H, -SiMe) ppm.

¹³C NMR: (100 MHz, CDCl₃) = 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: (MNa⁺) calc 714.3477, found 714.3422

TLC: 0.48 (15% ethyl acetate in hexanes)

Yield: 80%

8-(O-(4-methoxy)phenoxy)-O⁶-benzyl-3',5'-O-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2d)

IR: 3504w, 3376w, 2955m, 2930m, 2893w, 2837m, 1622s, 1595s, 1557m, 1505w, 1471s, 1418m, 1351m, 1310w, 1250w, 1228w, 1203w, 1077w, 1032w, 953w, 836s, 778m, 731w, 696w, 668w

¹H NMR: (500 MHz, CDCl₃) = 7.42 (m, 2H, Ar-H), 7.27 (m, 5H, Ar-H), 6.89 (app d, $J_{H,H}$ = 9.0 Hz, 2H, Ar-H), 6.40 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.49 (d, J = 3.0 Hz, 2H, Bn-H₂), 4.68 (m, 1H, 3'-H), 4.65 (s, 2H, -NH₂), 3.93 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.5 Hz, 1H, 4'-H), 3.80 (s, 3H, -OMe), 3.77 (m, 1H, 5'-H), 3.68 (dd, $J_{H,H}$ = 5.0, 10.5 Hz, 1H, 5'-H), 3.30 (ddd, $J_{H,H}$ = 6.0, 8.0, 12.5 Hz, 1H, 2'-H), 2.18 (ddd, $J_{H,H}$ = 4.0, 7.0, 12.5 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.84 (s, 9H, -SiCMe₃), 0.12 (s, 6H, -SiMe₂), 0.004 (s, 3H, -SiMe), -0.019 (s, 3H, -SiMe) ppm.

¹³C NMR: (125 MHz, CDCl₃) = 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: (MH⁺) calc 708.3607, found 708.3454

TLC: 0.34 (15% ethyl acetate in hexanes)

Yield: 80%

8-(O-(4-chloro)phenoxy)-O⁶-benzyl-3',5'-O-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2e)

IR: 3508w, 3356w, 3219w, 2956m, 2930m, 2884m, 2858m, 1622s, 1603s, 1589s, 1553s, 1495s, 1487s, 1471s, 1417m, 1353m, 1312w, 1253m, 1229m, 1090m, 1030w, 1014w, 958w, 836s, 778m, 697w

¹H NMR: (400 MHz, CDCl₃) = 7.73 (m, 2H, Ar-H), 7.31 (m, 7H, Ar-H), 6.37 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.50 (d, $J_{H,H}$ = 3.0 Hz, 2H, Bn-H₂), 4.69 (m, 3H, 3'-H, -NH₂), 3.92 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.0 Hz, 1H, 4'-H), 3.76 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1H, 5'-H), 3.65 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1H, 5'-H), 3.31 (ddd, $J_{H,H}$ = 6.0, 7.1, 13.2 Hz, 1H, 2'-H), 2.18 (ddd, $J_{H,H}$ = 3.6, 6.8, 13.2 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.84 (s, 9H, -SiCMe₃), 0.12 (s, 6H, -SiMe₂), 0.01 (s, 3H, -SiMe), -0.02 (s, 3H, -SiMe) ppm.

¹³C NMR: (100 MHz, CDCl₃) = 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: (MH⁺) calc 712.3112, found 712.3089

TLC: 0.50 (15% ethyl acetate in hexanes)

Yield: 82%

8-(O-(2,4,6-trichloro)phenoxy)-O⁶-benzyl-3',5'-O-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (2f)

IR: 3512w, 3341w, 2954m, 2930m, 2886m, 2857m, 1652w, 1622s, 1599s, 1471s, 1413m, 1351m, 1312w, 1253m, 1228m, 1077m, 1031m, 954w, 836s, 777m, 732w, 695w, 668w

¹H NMR: (CDCl₃, 400 MHz) = 7.41 (m, 4H, Ar-H), 7.30 (m, 3H, Ar-H), 6.46 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.50 (s, 2H, Bn-H₂), 4.69 (m, 3H, 3'-H, -NH₂), 3.98 (ddd, $J_{H,H}$ = 3.0, 5.5, 7.0 Hz, 1H, 4'-H), 3.77 (dd, $J_{H,H}$ = 7.0, 10.5 Hz, 1H, 5'-H), 3.74 (dd, $J_{H,H}$ = 5.5, 10.5 Hz, 1H, 5'-H), 3.29 (ddd, $J_{H,H}$ = 6.0, 7.5, 13.0 Hz, 1H, 2'-H), 2.22 (ddd, $J_{H,H}$ = 3.5, 6.5, 13.0 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.84 (s, 9H, -SiCMe₃), 0.134 (s, 3H, -SiMe), 0.132 (s, 3H, -SiMe), 0.01 (s, 3H, -SiMe), -0.01 (s, 3H, -SiMe) ppm.

¹³C NMR: (100 MHz, CDCl₃) = 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: (MH⁺) calc 782.2308, found 782.2437

TLC: 0.53 (15% ethyl acetate in hexanes)

Yield: 85%

8-(O-(2,3,4,5,6-pentachloro)phenoxy)-O⁶-benzyl-3',5'-O-bis(tert-butylidimethylsilyl)-2'-deoxyguanosine (2g)

IR: 3519w, 3360w, 2956m, 2930m, 2888w, 2857m, 1622s, 1597vs, 154w, 1466s, 1415m, 1386s, 1363s, 1311w, 1258m, 1229m, 1107m, 1075m, 1029m, 953w, 836s, 774m, 717m, 663w

¹H NMR: (400 MHz, CDCl₃) = 7.41 (m, 2H, Ar-H), 7.30 (m, 3H, Ar-H), 6.44 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.49 (d, J = 3.0 Hz, 2H, Bn-H₂), 4.71 (m, 3H, 3'-H, -NH₂), 3.96 (ddd, $J_{H,H}$ = 3.0, 5.0, 7.0 Hz, 1H, 4'-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1H, 5'-H), 3.73 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1H, 5'-H), 3.31 (ddd, $J_{H,H}$ = 6.0, 7.0, 13.0 Hz, 1H, 2'-H), 2.23 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.83 (s, 9H, -SiCMe₃), 0.141 (s, 3H, -SiMe), 0.137 (s, 3H, -SiMe), 0.02 (s, 3H, -SiMe), -0.01 (s, 3H, -SiMe) ppm.

¹³C NMR: (125 MHz, CDCl₃) = 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: (MH⁺) calc 850.1529, found 850.1501

TLC: 0.57 (15% ethyl acetate in hexanes)

Yield: 64%

8-(O-(4-bromo)phenoxy)-O⁶-benzyl-3',5'-O-bis(tert-butylidimethylsilyl)-2'-deoxyguanosine (2h).

IR: 3515w, 3365w, 3207w, 2955m, 2930m, 2889w, 2857m, 1622s, 1599s, 1417m, 1351m, 1252m, 1228m, 1111m, 1069m, 1030m, 1011m, 953w, 836s, 778m, 692w, 667w

¹H NMR: (400 MHz, CDCl₃) = 7.49 (m, 2H, Ar-H), 7.44 (m, 2H, Ar-H), 7.31 (m, 3H, Ar-H), 7.23 (m, 2H, Ar-H), 6.37 (app t, $J_{H,H}$ = 7.0 Hz, 1H, 1'-H), 5.51 (d, J = 3.0 Hz, 2H, Bn-H₂), 4.70 (m, 3H, 3'-H, -NH₂), 3.92 (m, 1H, 4'-H), 3.77 (dd, $J_{H,H}$ = 7.0, 11.0 Hz, 1H, 5'-H), 3.66 (dd, $J_{H,H}$ = 5.0, 11.0 Hz, 1H, 5'-H), 3.31 (ddd, $J_{H,H}$ = 6.0, 7.5, 13.0 Hz, 1H, 2'-H), 2.19 (ddd, $J_{H,H}$ = 3.5, 7.0, 13.0 Hz, 1H, 2'-H), 0.93 (s, 9H, -SiCMe₃), 0.84 (s, 9H, -SiCMe₃), 0.13 (s, 6H, -SiMe₂), 0.01 (s, 3H, -SiMe), -0.01 (s, 3H, -SiMe) ppm.

¹³C NMR: (100 MHz, CDCl₃) = 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: (MH⁺) calc 758.2592, found 758.2610

TLC: 0.50 (15% ethyl acetate in hexanes)

Yield: 85%

General procedure for syntheses of compounds 3a-g: 8-(*O*-phenoxy)-2'-deoxyguanosine (3)

To a vial containing 8-(*O*-phenoxy)-*O*⁶-benzyl-3',5'-*O*-bis(*tert*-butyldimethylsilyl)-2'-deoxyguanosine (**2**) (~0.15 mmol) was added a solution of 0.5 M TBAF in THF (3 equiv). The vial was capped allowed to stand at room temperature. After monitoring the consumption of starting material by thin-layer chromatography (reaction complete in about 30 min), the mixture was concentrated by rotatory 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 carried forward to debenzylation 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 which was fitted with a three-way adapter. The flask was sequentially evacuated then purged with hydrogen (from attached balloon) three times, then left open to the hydrogen balloon. When starting material was no longer observable by TLC (10% methanol in dichloromethane), the reaction mixture was filtered through a plug of Celite rinsed through with 1:1 MeOH:EtOAc, then concentrated by rotatory evaporation. The solid product was purified by sequential triturations of the with 0.1-0.5 mL portions of acetone.

8-(*O*-phenoxy)-2'-deoxyguanosine (3a)

IR: 3312w, 3132w, 2945w, 1682s, 1597m, 1557s, 1487m, 1417m, 1372m, 1346w, 1278w, 1203m, 1098m, 1053m, 967w, 776w

¹H NMR: (400 MHz, MeOD) = 7.43 (dd, $J_{H,H}$ = 7.5, 8.5 Hz, 2H, Ar-H), 7.31 (app d, $J_{H,H}$ = 8.0 Hz, 2H, Ar-H), 7.26 (app t, $J_{H,H}$ = 7.5 Hz, 1H, Ar-H), 6.37 (dd, $J_{H,H}$ = 6.8, 7.7 Hz, 1H, 1'-H), 4.56 (m, 1H, 3'-H), 3.99 (m, 1H, 4'-H), 3.80 (dd, $J_{H,H}$ = 4.0, 12.0 Hz, 1H, 5'-H), 3.71 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1H, 5'-H), 3.07 (ddd, $J_{H,H}$ = 6.2, 7.9, 13.7 Hz, 1H, 2'-H), 2.27 (ddd, $J_{H,H}$ = 2.7, 6.6, 13.4 Hz, 1H, 2'-H) ppm.

¹³C NMR: (100 MHz, MeOD) = 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: (MNa⁺) calc 382.1122, found 382.1134

TLC: 0.21 (10% methanol in dichloromethane)

Yield: 44% (analytical purity), 90% (95% purity)

8-(*O*-(2-methyl)phenoxy)-2'-deoxyguanosine (3b)

IR: 2940w, 1672s, 1654s, 1588m, 1558s, 1419m, 1367m, 1345m, 1280w, 1225m, 1176m, 1105m, 1053w, 991w, 972w, 774w, 758w

¹H NMR: (500 MHz, MeOD) = 7.28 (d, $J_{H,H}$ = 7.6 Hz, 1H, Ar-H), 7.20 (m, 3H, Ar-H), 6.42 (dd, $J_{H,H}$ = 6.5, 8.0 Hz, 1H, 1'-H), 4.56 (m, 1H, 3'-H), 4.01 (m, 1H, 4'-H), 3.81 (dd,

$J_{H,H} = 4.0, 12.0$ Hz, 1H, 5'-H), 3.71 (dd, $J_{H,H} = 4.5, 12.0$ Hz, 1H, 5'-H), 3.10 (ddd, $J_{H,H} = 6.0, 8.0, 13.5$ Hz, 1H, 2'-H), 2.34 (ddd, $J_{H,H} = 3.0, 6.5, 13.5$ Hz, 1H, 2'-H), 2.25 (s, 3H, Ar-Me) ppm.

^{13}C NMR: (100 MHz, MeOD) = 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: (MNa⁺) 396.1278, found 396.1283

TLC: 0.20 (10% methanol in dichloromethane)

Yield: 64%

8-(O-(4-methyl)phenoxy)-2'-deoxyguanosine (3c)

IR: 3167s, 2935m, 1680s, 1559s, 1499m, 1410m, 1368w, 1342w, 1278w, 1203w, 1102w, 979w, 818w, 776w

^1H NMR: (400 MHz, MeOD) = 7.18 (m, 4H, Ar-H), 6.37 (dd, $J_{H,H} = 3.9, 7.7$ Hz, 1H, 1'-H), 4.56 (m, 1H, 3'-H), 3.99 (m, 1H, 4'-H), 3.80 (dd, $J_{H,H} = 3.9, 12.0$ Hz, 1H, 5'-H), 3.70 (dd, $J_{H,H} = 4.5, 12.0$ Hz, 1H, 5'-H), 3.05 (ddd, $J_{H,H} = 6.2, 8.0, 13.5$ Hz, 1H, 2'-H), 2.34 (s, 3H, Ar-Me), 2.26 (ddd, $^3J_{H,H} = 2.8, 6.6, 13.5$ Hz, 1H, 2'-H) ppm.

^{13}C NMR: (100 MHz, MeOD) = 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: (MNa⁺) 396.1278, found 396.1275

TLC: 0.21 (10% methanol in dichloromethane)

Yield: 54%

8-(O-(4-methoxy)phenoxy)-2'-deoxyguanosine (3d)

IR: 3126s, 1667s, 1552s, 1500s, 1410m, 1361m, 1350m, 1248w, 1200w, 1099w, 1050w, 825w, 776w

^1H NMR: (400 MHz, MeOD) = 7.23 (d, $J_{H,H} = 9.0$ Hz, 2H, Ar-H), 6.95 (d, $J_{H,H} = 9.0$ Hz, 2H, Ar-H), 6.38 (app t, $J_{H,H} = 7.3$ Hz, 1H, 1'-H), 4.56 (m, 1H, 3'-H), 4.00 (m, 1H, 4'-H), 3.81 (dd, $J_{H,H} = 4.0, 12.0$ Hz, 1H, 5'-H), 3.80 (s, 3H, -OMe), 3.71 (dd, $J_{H,H} = 4.5, 12.0$ Hz, 1H, 5'-H), 3.07 (ddd, $J_{H,H} = 6.5, 8.0, 13.8$ Hz, 1H, 2'-H), 2.27 (ddd, $J_{H,H} = 2.8, 6.5, 13.4$ Hz, 1H, 2'-H) ppm.

^{13}C NMR: (100 MHz, MeOD) = 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: (MNa⁺) 412.1228, found 412.1226

TLC: 0.20 (10% methanol in dichloromethane)

Yield: 61%

8-(O-(4-chloro)phenoxy)-2'-deoxyguanosine (3e)

IR: 3297m, 2927m, 1683s, 1642m, 1594m, 1559s, 1485m, 1414w, 1373w, 1212m, 1088m, 1056w, 1013w, 970w, 822w, 776w

¹H NMR: (400 MHz, MeOD) = 7.42 (d, $J_{H,H}$ = 9.0 Hz, 2H, Ar-H), 7.35 (d, $J_{H,H}$ = 9.0 Hz, 2H, Ar-H), 6.45 (app t, $J_{H,H}$ = 7.3 Hz, 1H, 1'-H), 4.55 (m, 1H, 3'-H), 3.98 (m, 1H, 4'-H), 3.80 (dd, $J_{H,H}$ = 3.9, 12.0 Hz, 1H, 5'-H), 3.69 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1H, 5'-H), 3.07 (ddd, $J_{H,H}$ = 6.4, 8.0, 13.4 Hz, 1H, 2'-H), 2.26 (ddd, $J_{H,H}$ = 2.9, 6.6, 13.4 Hz, 1H, 2'-H) ppm.

¹³C NMR: (100 MHz, MeOD) = 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: (MNa⁺) 416.0738, found 416.0731

TLC: 0.13 (10% methanol in dichloromethane)

Yield: 24% (analytical purity), 90% (90% purity)

8-(O-(2,4,6-trichloro)phenoxy)-2'-deoxyguanosine (3f)

IR: 3351s, 2933m, 1686s, 1587s, 1561s, 1443m, 1416m, 1340w, 1241w, 1101w, 1051w, 968w, 819w, 774w

¹H NMR: (400 MHz, MeOD) = 7.63 (s, 2H, Ar-H), 6.45 (app t, $J_{H,H}$ = 7.2 Hz, 1H, 1'-H), 4.56 (m, 1H, 3'-H), 4.03 (m, 1H, 4'-H), 3.82 (dd, $J_{H,H}$ = 4.0, 12.0 Hz, 1H, 5'-H), 3.76 (dd, $J_{H,H}$ = 4.5, 12.0 Hz, 1H, 5'-H), 3.09 (ddd, $J_{H,H}$ = 6.2, 8.0, 13.6 Hz, 1H, 2'-H), 2.33 (ddd, $J_{H,H}$ = 2.8, 6.4, 13.6 Hz, 1H, 2'-H) ppm.

¹³C NMR: (125 MHz, MeOD) = 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: (MNa⁺) 483.9958, found 483.9950

TLC: 0.26 (10% methanol in dichloromethane)

Yield: 29%

8-(O-(2,3,4,5,6-pentachloro)phenoxy)-2'-deoxyguanosine (3g)

IR: 3327m, 2922m, 1680s, 1631m, 1586m, 1563m, 1420w, 1381m, 1098m, 775w, 713m

¹H NMR: (400 MHz, MeOD) = 6.45 (dd, $J_{H,H}$ = 6.9, 7.6 Hz, 1H, 1'-H), 4.56 (m, 1H, 3'-H), 4.03 (m, 1H, 4'-H), 3.82 (dd, $J_{H,H}$ = 4.2, 12.0 Hz, 1H, 5'-H), 3.76 (dd, $J_{H,H}$ = 4.8, 12.0 Hz, 1H, 5'-H), 3.11 (ddd, $J_{H,H}$ = 6.2, 7.8, 13.5 Hz, 1H, 2'-H), 2.34 (ddd, $J_{H,H}$ = 2.9, 6.6, 13.5 Hz, 1H, 2'-H) ppm.

¹³C NMR: (100 MHz, MeOD) = 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: (MNa⁺) 551.9149 found 551.9153

TLC: 0.30 (10% methanol in dichloromethane)

Yield: 27%

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Synthesis of 8-phenoxy-dG adducts prepared in this study.

Table 1

Influence of conditions on 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	B (11)	110	Air	45 : 55
5	toluene	8	B (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 ¹H NMR of the crude reaction mixtures.

Table 2Synthesis 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.

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.