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Strategies for Synthesis of Adducts of *o*-Quinone Metabolites of Carcinogenic Polycyclic Aromatic Hydrocarbons with 2′-Deoxyribonucleosides

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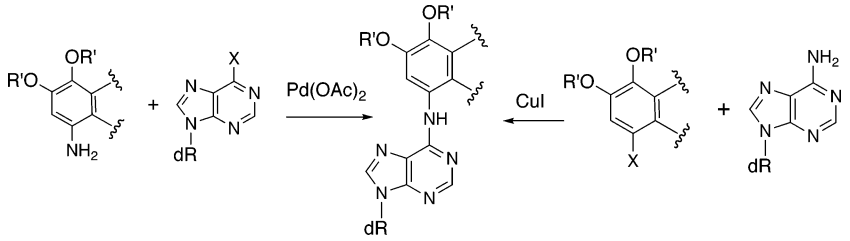

Polycyclic aromatic hydrocarbons (PAHs) are major environmental carcinogens produced in the combustion of fossil fuels, tobacco, and other organic matter. Current evidence indicates that PAHs are transformed enzymatically to active metabolites that react with DNA to form adducts that result in mutations. Three activation pathways have been proposed: the diol epoxide path, the radical-cation path, and the quinone path. The latter involves aldo-keto reductase mediated oxidation of PAH dihydrodiol metabolites to catechols that enter into redox cycles with quinones. This results in generation of reactive oxygen species (ROS) that attack DNA, and the PAH quinones also react with DNA to form adducts. Several strategies for synthesis of the stable adducts formed by the *o*-quinone metabolites of carcinogenic PAHs with 2′-deoxyribonucleosides were investigated and compared. The PAH quinones studied were benz[*a*]anthracene-3,4-dione and its 7-methyl- and 7,12-dimethyl- derivatives. The parent PAHs represent a range of carcinogenicity from inactive to highly potent. Two synthetic methods were devised that differ in the catalyst employed, $Pd(OAc)_2$ or CuI. The Pd-mediated method involved coupling a protected amino-catechol PAH derivative with a halo-2′-deoxyribonucleoside. The copper-mediated method entailed reaction of a halo-PAH catechol derivative with a 2′-deoxyribonucleoside. Adducts of benz[*a*]anthracene-3,4-dione (and its 7-methyl- and 7,12-dimethyl- derivatives) with 2′-deoxyadenosine and 2′-deoxyguanosine were prepared by these methods. Availability of adducts of these types through synthesis makes possible for the first time biological studies to determine the role of these adducts in tumorigenesis. The copper-mediated method offers advantages of economy, adaptability to large-scale preparation, utility for synthesis of ^{13}C- or ^{15}N-labeled analogues, and nonformation of bis-adducts as secondary products.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants produced in the combustion of fossil fuels, tobacco, and other organic matter.[1−3] They have recently been designated human carcinogens by the WHO.[4] The carcinogenic PAHs benzo[*a*]pyrene and dibenzo[*def,p*]chrysene[5] have been identified as components of tobacco smoke and vehicle exhaust condensate,[6,7] and current evidence suggests that they may be involved in initiation of lung cancer.[6,8,9]

[†] The University of Chicago.
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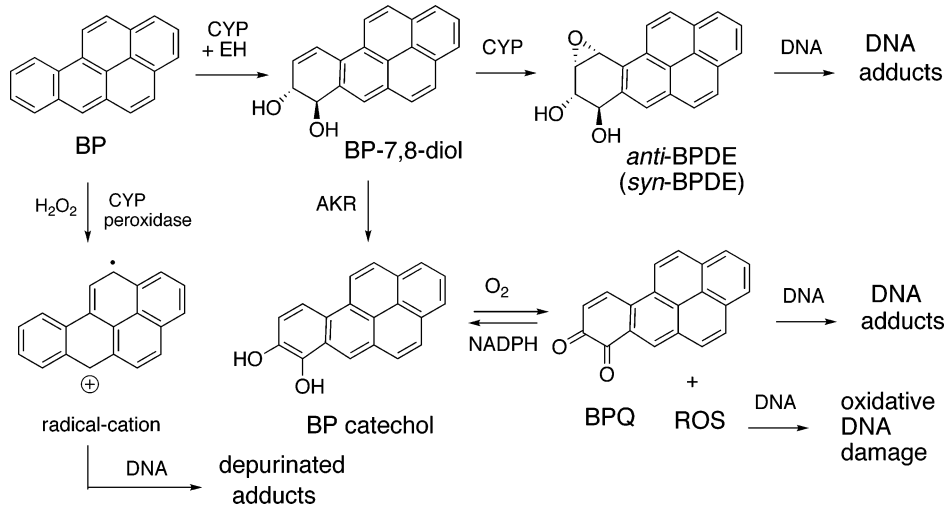

FIGURE 1. Pathways of metabolic activation of benzo[*a*]pyrene.

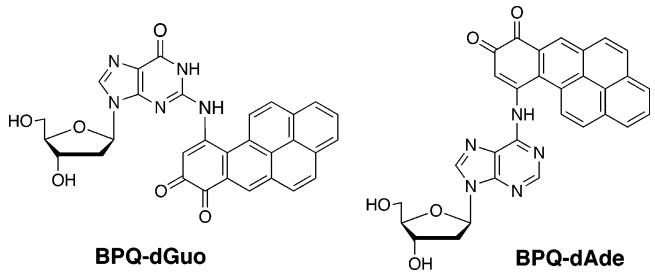

FIGURE 2. Structures of adducts formed by reaction of BPQ at dGuo and dAde sites in DNA.

For PAHs to exert their carcinogenic effects, metabolic activation is required. The most studied activation pathway involves cytochrome P-450 (CYP)-mediated oxidation of PAHs to diol epoxide metabolites, such as benzo[*a*]pyrene *anti*-diol epoxide (*anti*-BPDE) (Figure 1).[2,10] The PAH diol epoxides react with DNA to form adducts[11,12] that lead to mutations and induction of tumors.

Two additional activation pathways have been proposed (Figure 1). One of these entails aldo-keto reductase (AKR)-mediated oxidation of a dihydrodiol metabolite (e.g., BP-7,8-diol) to form a catechol that enters into a redox cycle with the corresponding quinone (BPQ).[13,14] In the process, O_2 is consumed and reactive oxygen species (ROS) are generated. The ROS attack DNA, and the quinone reacts with DNA to form stable and depurinated adducts.[15,16] The AKR pathway parallels AKR-mediated activation of estrogens.[17] The third activation pathway entails oxidation by CYP peroxidase to generate PAH radical-cations that react with DNA to form depurinated adducts.[18]

Determination of the relative importance of these pathways for human cancer requires synthetic access to the adducts formed by reactions of PAH metabolites with DNA. The structures of the adducts formed by PAH diol epoxides with 2′-deoxyguanosine (dGuo) and 2′-deoxyadenosine (dAde) are well-established,[11,12] and methods for their synthesis have been extensively investigated.[3,19] In contrast, very little is known concerning the synthesis or biological properties of the adducts arising from reactions of PAH quinones with DNA. The structures of the stable adducts of BPQ with dAde and dGuo (BPQ-dA and BPQ-dG) (Figure 2) are consistent with their origin via formal 1,4-Michael addition of the exocyclic amino groups of the purine bases to BPQ followed by auto-oxidation of the air-sensitive primary catechol intermediates.[15] However, attempts to synthesize these adducts by direct reaction of the components (Figure 3, Method A) were not successful, and their synthesis by Pd-catalyzed coupling of an amine derivative of a PAH quinone, e.g., 10-amino-BPQ, with a halopurine (Method

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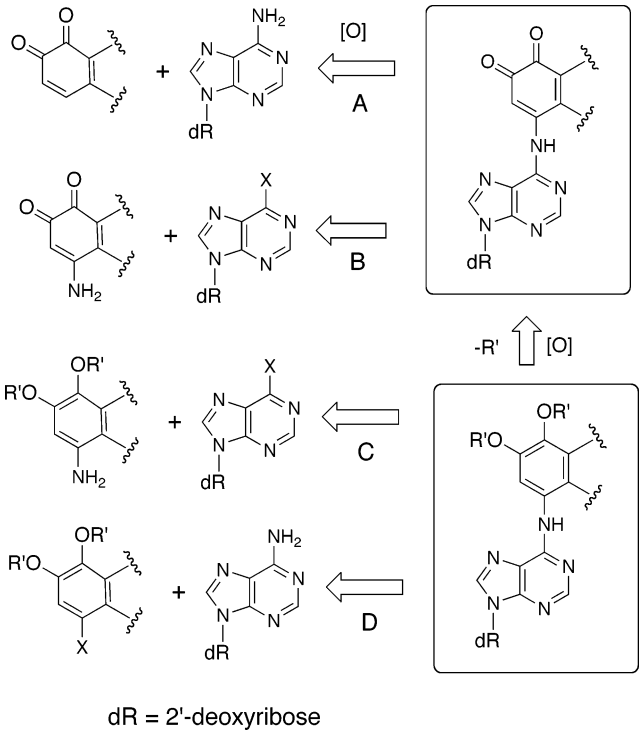

FIGURE 3. Strategies for synthesis of adducts of PAH *o*-quinones with 2′-deoxyribonucleosides: (A) Michael addition of 2′-deoxyribonucleoside to PAH quinone; (B) Pd-mediated coupling of amino derivative of PAH quinone with a halopurine; (C) Pd-mediated coupling of amino derivative of PAH catechol with a halopurine; (D) Cu-mediated coupling of halo derivative of PAH catechol with 2′-deoxyribonucleoside.

B) also failed. However, syntheses of BPQ-dAde and BPQ-dGuo were successfully accomplished by Pd-catalyzed coupling of a 10-amino-catechol derivative of BP (10-amino-7,8-dihydroxy-BP) with halopurine analogues of dAde and dGuo (Method C).[20]

The failure of 10-amino-BPQ to react despite the fact that the related amino-catechol derivative readily underwent coupling is attributed to the weak nucleophilic character of the amino group of the former due to the electron-withdrawing effect of the carbonyl groups. Reduction of the quinone to a catechol converted the carbonyl groups into electron-donating hydroxyl groups. However, Method C has the limitation that 1:2 adducts are formed as secondary products in the synthesis of the dAde adducts (but not the dGuo adducts).[20]

We now report synthesis of the stable adducts of the *o*-quinones of benz[*a*]anthracene (**1a**),[21] 7-methylbenz[*a*]anthracene (**1b**),[21] and 7,12-dimethylbenz[*a*]anthracene (**1c**)[21] with dAde (**2a**−**c**) and dGuo (**3a**−**c**) (Figure 4). These adducts are needed as standards for LC-MS-MS analysis of the adducts formed in human cells. The parent PAHs, BA, MBA, and DMBA, represent a range of carcinogenicity from inactive (BA) to intermediate (MBA) to highly potent (DMBA).[22]

Results

Michael Addition (Method A). The potentially most straightforward synthetic route to the stable adducts of **1a** with dAde (**2a**) and dGuo (**3a**) is via direct reaction of the components (Figure 3). However, it was shown previously[15b] that reactions of simple PAH quinones, such as naphthalene-1,2-dione and phenanthrene 3,4-dione, with dGuo in aqueous acetic acid take a different course, furnishing instead depurinated adducts arising from Michael addittion of the N^7-atom of dGuo to the PAH quinone. Attempts to react **1a** with Ade in the presence of various potential catalysts, such as $CuBr_2$, $PdCl_4$, $PdCl_2CN_2$, $CeCl_3 \cdot 7H_2O$, $AuCl_3$, and $InCl_3$, were not successful, providing neither **2a** nor the depurinated adduct arising from reaction on N^7 of dAde.

Palladium-Mediated Coupling of Aminoquinones and Aminocatechols with Halopurines (Methods B and C): Synthesis of dAde Adducts. 1-Aminobenz[*a*]anthracene 3,4-dione (**5a**) required as the starting compound for synthesis of the stable adducts of **1a** with dAde was prepared by addition of azidotrimethylsilane (Me_3SiN_3) to BAQ (Scheme 1). The unstable 1-azido-BA catechol product (**4a**) underwent loss of nitrogen and auto-oxidation to **5a** (92%).[20,23] 6-Bromo- and 6-chloro-9-(3,5-bis-*O*-acetyl-2-deoxy-*β*-D-*erythro*-pentofuranosyl)purine (**6a,b**) were synthesized by published procedures.[24a] Attempted coupling of **5a** with **6a** in the presence of $Pd(OAc)_2$/BINAP and Cs_2CO_3 failed to furnish adduct **2a**. This was consistent with the earlier finding that 10-aminobenzo[*a*]pyrene 7,8-dione did not couple with **6a**.[20] As in that case, the problem was solved by conversion of the amino-quinone into a protected amino-catechol derivative that readily underwent Pd-catalyzed coupling with **6a**. Pd-mediated coupling of arylamines with arylhalides,[25a] including the halopurine derivatives **6a,b**,[25b−f] is a well-known reaction.

Reduction of **5a** with hydrogen over a 5% Pd/C catalyst and protection of the air-sensitive hydroxyl groups of the catechol product by silylation with *N*-*tert*-butyldimethylsilyl-*N*-methyl-

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(16) The stable adducts are formed by covalent bonding of the PAH quinones to the exocylic amino groups of the purine bases; they are stable in the sense that they remain attached to the DNA helix. The depurinated adducts arise from reaction of the PAH quinones on the N^7 and N^9 atoms of dG and dA in DNA with consequent loss of 2′-deoxyribose.

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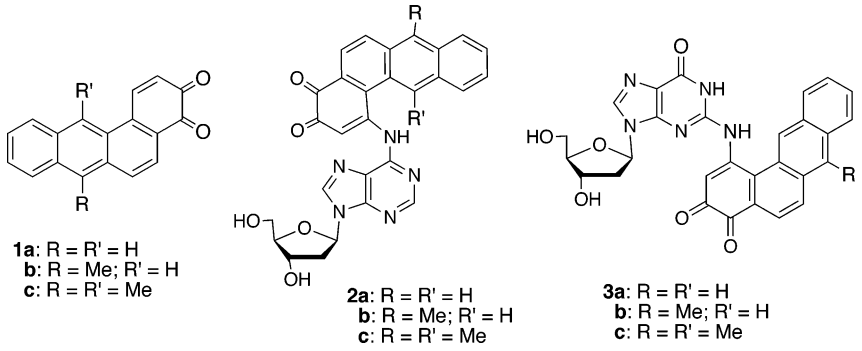
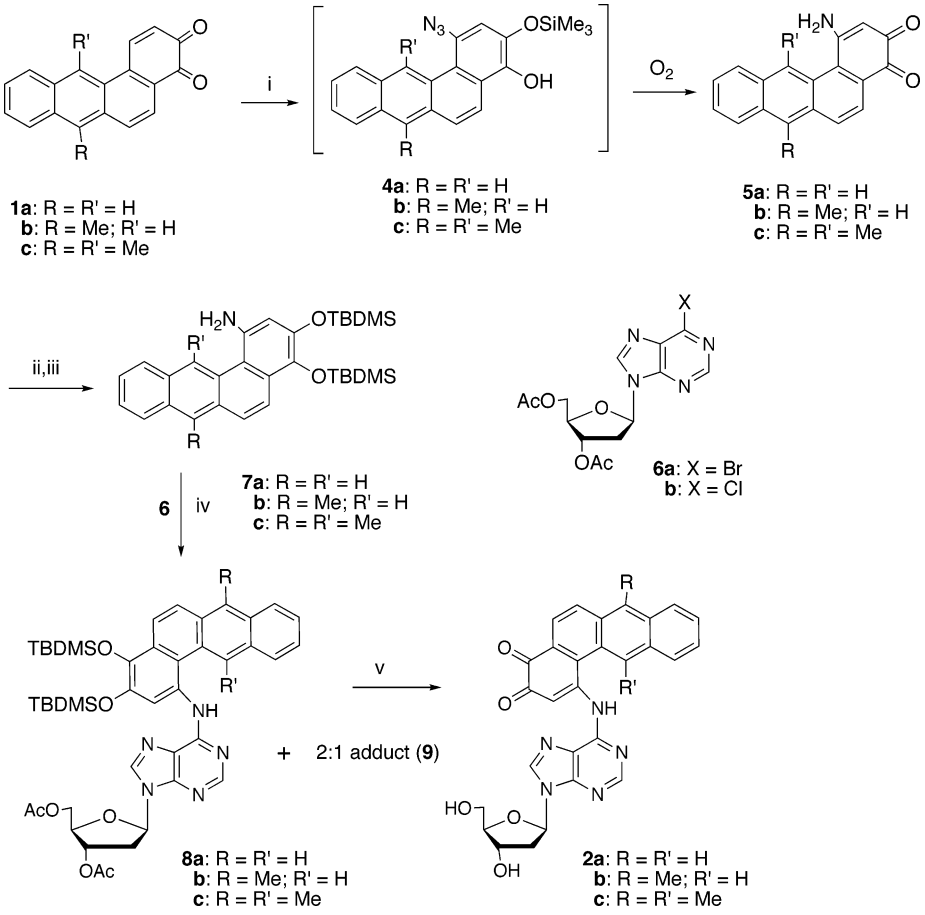


FIGURE 4. Structures of the quinone metabolites of BA, MBA, and DMBA (**1a**−**c**) and their adducts with dAde (**2a**−**c**) and dGua (**2a**−**c**).

SCHEME 1[a]



[a] Reagents and conditions: (i) Me_3SiN_3; (ii) H_2/Pd/C; (iii) *t*-$BuMe_2SiN(Me)COCF_3/K_2CO_3$; (iv) $Pd(OAc)_2$/BINAP, Cs_2CO_3; (v) TMG/KF/O_2.

trifluoroacetamide gave 1-amino-3,4-bis-*tert*-butyldimethylsilyloxy-BA (**7a**). This compound reacted with **6b** in the presence of $Pd(OAc)_2$/BINAP/Cs_2CO_3 in toluene at 80 °C to furnish the protected adduct (**8a**) (53%). It is worthy of note that the 6-bromo- and 6-chloro-2′-deoxyribonucleosides (**6a** and **6b**) exhibited essentially no difference in reactivity in these reactions. This was unexpected in view of reports that 6-chloro-nucleosides were more reactive than the 6-bromo- analogs in other related Pd-catalyzed coupling reactions of 6-halo-2′-deoxyribonucleosides with amines.[26] Coupling of **7a** with **6b** also furnished a 1:2 adduct (**9**) (33%) formed by reaction of a second molecule of **6b** on the amino group of **8a**. Formation of a 1:2 adduct was observed earlier in the analogous synthesis of the BPQ-dAde adduct by Pd-catalyzed coupling.[20] Deacetylation of **8a** with *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) followed by removal of the TBDMS groups with KF furnished a catechol derivative that underwent auto-oxidation to provide **2a**.

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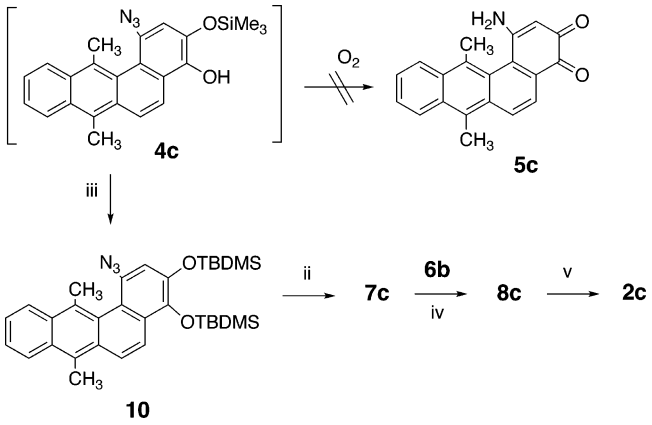
SCHEME 2[a]



[a] Reagents and conditions: (i) Me_3SiN_3; (ii) H_2/Pd/C; (iii) *t*-$BuMe_2$-SiN(Me)$COCF_3$/K_2CO_3; (iv) $Pd(OAc)_2$/BINAP, Cs_2CO_3; (v) TMG/KF/O_2.

Synthesis of the analogous adduct of MBA 3,4-dione with dAde (**2b**) was carried out by a similar reaction sequence (Scheme 1). Reaction of **1b** with Me_3SiN_3 and auto-oxidation of the primary catechol product furnished 1-amino-7-methylbenz[*a*]anthracene 3,4-dione (**5b**) (90%). This was converted into the catechol derivative **7b** (80%) via hydrogenation followed by silylation with *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide. Pd-catalyzed coupling of **7b** with **6b** gave adduct **8b** (40%) accompanied by an equal ratio of a 1:2 adduct. Deprotection of **8b** by deacetylation with TMG followed by treatment with KF and auto-oxidation gave 7-methylbenz[*a*]anthracene 3,4-dione-dAde (**2b**).

Extension of this approach to synthesis of the related adduct of DMBA 3,4-dione with dAde (**2c**) (Scheme 2) was complicated by steric crowding in the bay region of DMBA. DMBA has been shown to be distorted >23° from planarity as a result of the steric interaction in this region.[27] Although 1 equiv of Me_3SiN_3 failed to react with **1c** to give **5c**, reaction took place with a large excess of Me_3SiN_3 (10−20 equiv) to afford **4c** quantitatively.

Compound **4c**, unlike the related adducts **4a** and **4b**, failed to undergo spontaneous loss of nitrogen and auto-oxidation to the corresponding amino-quinone product (**5c**). Transformation of **4c** into a TBDMS-protected amino-catechol derivative (**7c**) was carried out by a procedure that did not involve **5c** (Scheme 2). Thus, treatment of **4c** with *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide and K_2CO_3 afforded a protected azido-catechol derivative (**10**). Reduction of **10** with hydrogen over a Pd/C catalyst furnished the amino-catechol derivative **8c** in good overall yield.

Synthesis of the DMBA 3,4-dione-dAde adduct (**2c**) was carried out by the method used for synthesis of the related BA- and MBA-3,4-dione-dAde adducts (Scheme 2). Pd-catalyzed coupling of **7c** with **6b** took place readily to provide the protected DMBA catechol-dAde adduct (**8c**) (46%). In contrast to the analogous reactions of **7a** and **7b**, a 1:2 adduct was not obtained as a byproduct. Repression of secondary adduct formation is likely a consequence of increased steric crowding in the bay region of the BA ring system of **7c** due to the presence of a methyl group in the C^{12}-position that is lacking in **7a** and **7b**.

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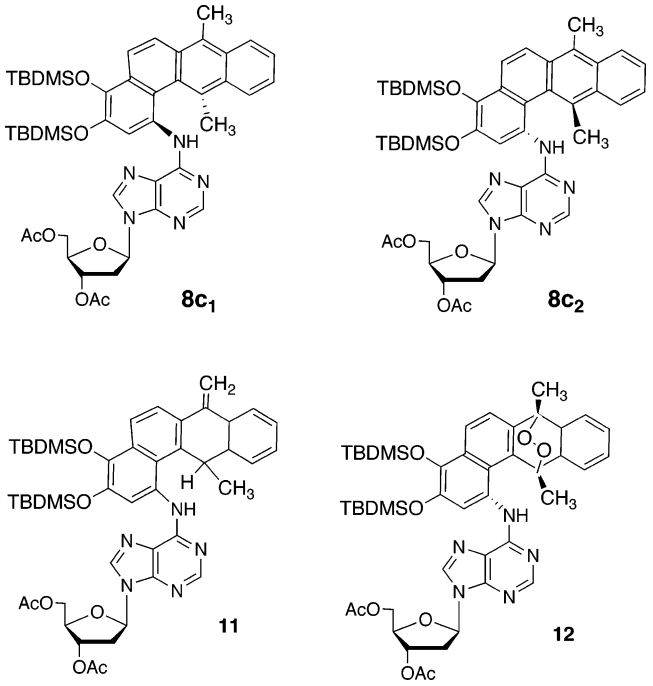

FIGURE 5. Structures of the isomers of the protected DMBA catechol-dA adduct (**8c$_1$** and **8c$_2$**). The tautomeric structure **11** is ruled out by the NMR data. Auto-oxidation of **8c** affords an unstable product tentatively assigned the 7,12-epidioxide structure (**12**).

Adduct **8c** exhibited a strong tendency to undergo decomposition. In spite of this difficulty, a pure sample of **8c** was obtained by flash chromatography on a silica gel column. HPLC analysis (CH_3CN/H_2O, 4:1) showed only a single peak. The mass spectrum of **8c** was consistent with its structure, and the ^1H NMR and ^{13}C NMR spectra were also in general agreement with this assignment, except that many of the signals appeared as slightly shifted duplicate peaks. This suggested the presence of conformationally restricted stereoisomers (**8c$_1$** and **8c$_2$**) (Figure 5) formed as a consequence of the severe steric interaction between the C^{12}-methyl group and dAde. It is likely that the bulky TBDMS protecting groups also contribute importantly to the steric crowding responsible for this effect. Formation of the methylene tautomer **11**[28,29] is ruled out by the ^1H NMR and ^{13}C NMR spectra, which exhibited none of the characteristic signals expected for this structure.

Compound **8c** also showed a strong tendency to undergo oxidative decomposition on exposure to air and light. DMBA itself is known to be highly susceptibile to photo-oxidation to form a transannular bridged 7,12-epidioxide,[30] and biological experiments with this PAH are routinely conducted in subdued light. It was not surprising, therefore, that a highly strained derivative of DMBA, such as **8c**, would also be susceptible to photo-decomposition. The primary photo-oxidation product is likely the DMBA 7,12-epidioxide (**12**); however, its characterization was prevented by its relative ease of decomposition.

Despite the facility of photo-oxidation of **8c**, its conversion to **2c** (Scheme 2) was successfully accomplished by conducting

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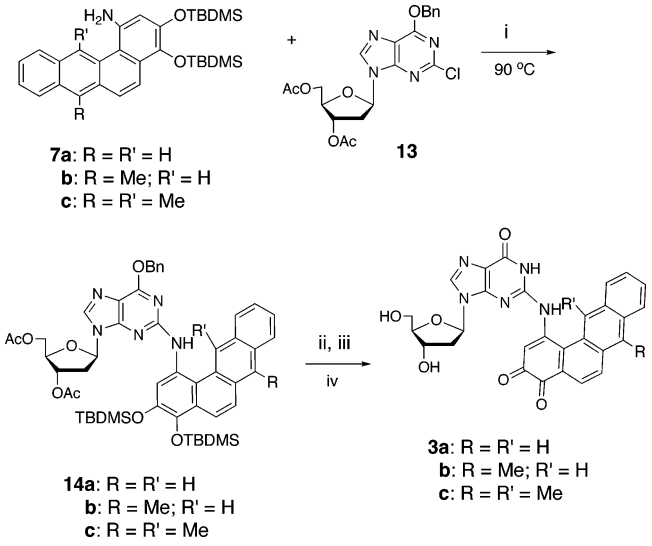
SCHEME 3[a]



[a] Reagents and conditions: (i) $Pd(OAc)_2$/BINAP, Cs_2CO_3; (ii) Pd/cyclohexadiene; (iii) TMG/MeOH; (iv) KF/O_2.

operations in the absence of air in yellow light. Deacetylation of **8c** with TMG and removal of the TBDMS groups with KF afforded a product that underwent auto-oxidation to yield adduct **2c** (19%). The ^{1}H NMR and ^{13}C NMR spectra of **2c** exhibited only a single set of peaks, in good agreement with the structural assignment. The loss of the multiplicity of the peaks evident in the spectra of **8c** is apparently indicative of the markedly diminished internal steric strain in **2c** as a consequence of removal of the bulky protecting groups, allowing it to exist as a single conformer.

Palladium-Mediated Coupling of Aminoquinones and Aminocatechols with Halopurines (Methods B and C): Synthesis of dGuo Adducts. Synthesis of the BA 3,4-dione-dGuo adduct (**3a**) was carried out by a modification of the method employed for synthesis of the corresponding dAde adduct (**2a**). This entailed in the key step Pd-catalyzed coupling of the protected 1-aminocatechol derivative of BA (**7a**) with 2-chloro-6-benzyloxy-9-[2′-deoxy-*β*-D-*erythro*-pentofuranosyl]-purine (**13**) (Scheme 3). Compound **13** was synthesized as previously described.[20] Reaction of **7a** with **13** took place in the presence of $Pd(OAc)_2$, BINAP, and Cs_2CO_3 to furnish the expected adduct (**14a**) (84%), unaccompanied by the corresponding 1:2 adduct. Debenzylation of **14a** by hydrogenation over a 5% Pd/C catalyst was complicated by partial hydrogenation of the 5,6-bond of the BA ring (evidenced by the ^{1}H NMR spectrum of the product). Secondary hydrogenation of the PAH ring system did not occur with the use of a Lindlar catalyst, but conversion was low (<50%). Debenzylation was most efficiently accomplished by transfer hydrogenation with 1,4-cyclohexadiene and Pd black.[31,32] Reaction took place at room temperature to provide the debenzylated product quantitatively. Deacetylation with TMG and removal of the TBDMS groups by treatment with KF furnished the BA catechol adduct, which underwent auto-oxidation to furnish BA-3,4-dione-dGuo (**3a**) (65%).

Synthesis of the related adduct of MBA-3,4-dione with dGuo (**3b**) was carried out by an analogous sequence involving Pd-mediated coupling of **7b** with **13** (Scheme 3). The coupled adduct **14b** was obtained in good yield (82%) unaccompanied by a 1:2 adduct. Debenzylation of **14b** by transfer hydrogenation, followed by deacetylation of the product with TMG, removal of the TBDMS groups with KF, and auto-oxidation furnished **3b** in good overall yield (64%).

Extension of this approach to synthesis of the analogous DMBA-3,4-dione-dGuo adduct (**3c**) was only partially successful. Pd-catalyzed coupling of the protected 1-amino-catechol derivative of DMBA (**7c**) with **13** took place smoothly under the conditions employed in preceding examples to yield the adduct of the protected DMBA catechol with dGuo (**14c**). Again, a 1:2 adduct was not detected. However, **14c** was highly sensitive to oxidative decomposition. Its ^{1}H NMR and ^{13}C NMR spectra, like those of the dAde adduct **8c**, exhibited duplicate peaks. Despite the instability of **14c**, it was possible to investigate its conversion to the target molecule by taking appropriate precautions for exclusion of air and light. Under these conditions, debenzylation of **14c** and deacetylation of the product proceeded normally. However, attempts to remove the TBDMS protecting groups with KF led to rapid decomposition and formation of complex product mixtures. It appears that the DMBA-3,4-catechol-dGuo adduct and/or the DMBA-3,4-dione-dGuo adduct (**3c**) formed by its auto-oxidation may be too unstable to isolate and characterize.

Synthesis of dAde Adducts via Copper-Mediated Coupling of Halo Derivatives of PAH Catechols with 2′-Deoxyribonucleosides (Method D). A longer-range goal of these studies was to develop methods for synthesis of ^{13}C- and/or ^{15}N-labeled analogues of these adducts. Isotopically labeled analogues are required as standards for isotope dilution liquid chromatography/tandem mass spectrometric analysis of the adducts formed by metabolites of carcinogenic PAHs in human cells. Progress in the development of these new methodologies has recently been reported.[33−35]

Copper-mediated coupling of halo-substituted PAH catechols with nucleosides (Method D) offers significant potential advantages for synthesis of isotopically labeled analogues. Copper-mediated coupling[36] is tolerant of most substituents, and protection of hydroxyl groups is not required. Methods for copper-mediated regioselective N^1- and N^6-arylation of 2′-deoxyribonucleosides have been reported.[37,38]

Synthesis of BA-3,4-dione-dAde (**2a**) via Method D (Scheme 4) requires a halo-substituted catechol, such as 1-bromo-3,4-diacetoxy-BA (**17a**). Attempts to synthesize **17a** from 4-bromo-BA-3,4-dione (**15**) via addition of Me_3SiBr to **1a** were blocked by failure of the inital step to take place. Although addition of Me_3SiBr appeared to occur, as evidenced by temporary loss of

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(35) Ruan, Q.; Kim, H. Y. H.; Jiang, H.; Penning, T. M.; Harvey, R.; G.; Blair, I. A. *Rapid Commun. Mass Spectrom.* **2006**, *20*, 1369−1380.
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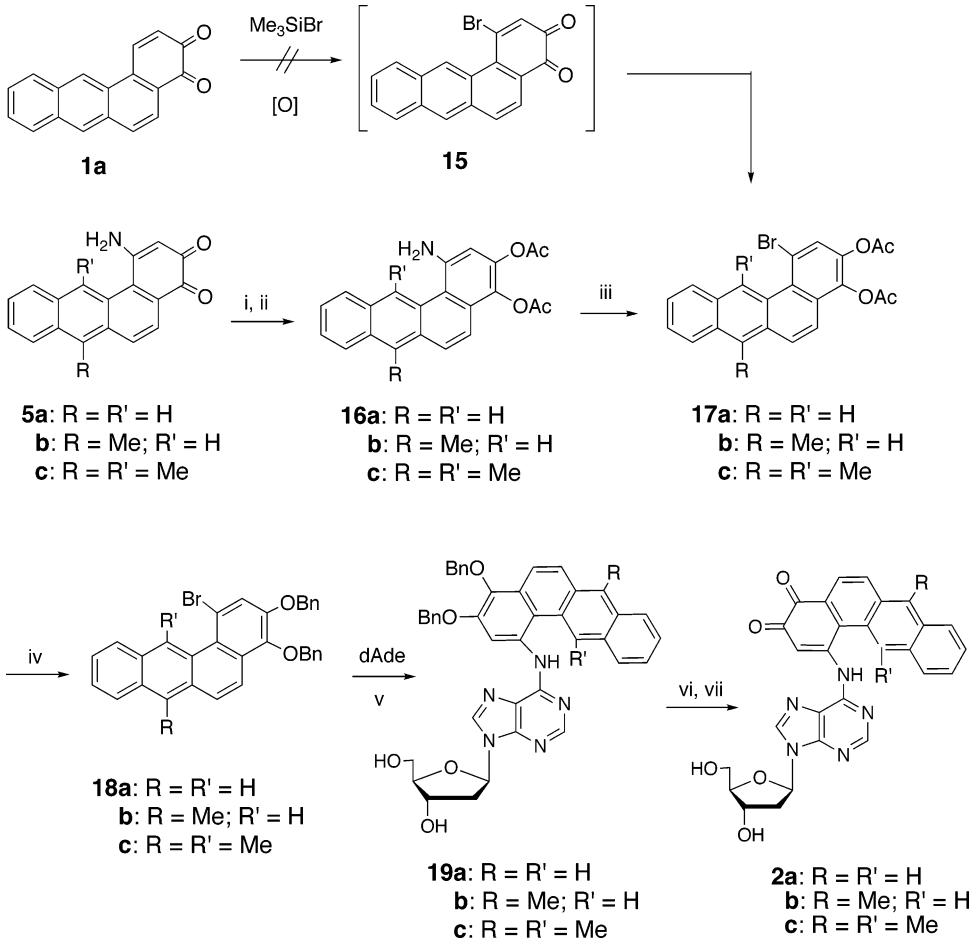
(37) Ran, C.; Dai, C.; Harvey, R. G. *J. Org. Chem.* **2005**, *70*, 3724−3726.
(38) Dai, C.; Ran, C.; Harvey, R. G. *Tetrahedron* **2005**, *62*, 1764−1771.

SCHEME 4[a]



[a] Reagents and conditions: (i) H_2/Pd/C/DM; (ii) Ac_2O/K_2CO_3; (iii) *t*-BuONO; TMSBr, Bu_4N/Br^-; (iv) KOH/18-crown/BnBr/DMF; (v) CuI/DMEDA/DMSO; (vi) Pd/cyclohexadiene; (vii) KF/DMF.

the intense purple color of the quinone, the bromocatechol intermediate reverted rapidly to the unsubstituted quinone. Attempted trapping of the bromocatechol intermediate by trimethylsilylation was also unsuccessful. Similar behavior was previously observed in the analogous reaction of Me_3SiBr with BPQ.[20] Evidently, introduction of a Br atom into the bay regions of PAH quinones is strongly disfavored by steric crowding.

Synthesis of **17a** was successfully accomplished by an alternative approach based on 1-amino-BA-3,4-dione (**5a**) (Scheme 4). Thus, Pd-catalyzed reduction of **5a** with hydrogen over Pd/charcoal followed by acetylation of the catechol product furnished the 1-amino-catechol diacetate **16a**. Diazotization of **16a** with *t*-BuONO and Me_3SiBr in CH_2Br_2 at 0 to −35 °C furnished **17a**. This compound was unstable at higher temperatures, tending to undergo deacetylation. For this reason, **17a** was converted to the more stable dibenzyl derivative, 1-bromo-3,4-dibenzyloxybenz[*a*]anthracene (**18a**), by treatment with benzyl bromide, 18-crown-6 ether, and KOH. Attempts to abbreviate this sequence by converting **16a** to the dibenzyl derivative prior to diazotization gave less satisfactory results.

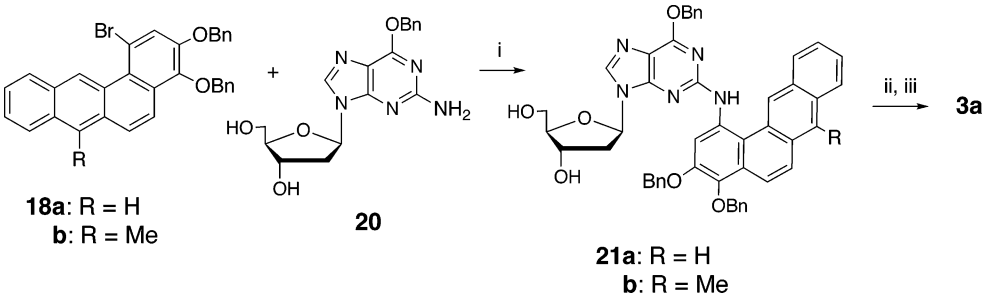
Coupling of **18a** with dAde took place smoothly in the presence of CuI and *N*,*N*′-dimethylethylenediamine in DMSO to furnish adduct **19a** (60%). In contrast to the Pd-mediated coupling, a 1:2 adduct was not obtained as a secondary product. The yield of **19a** was dependent on the concentrations of the reactants. At low concentrations of dAde and **18a** (10^{-5} M) only low yields of adducts (<5%) were obtained, but at higher concentrations (0.5 M) yields of **19a** in the range of 60% were attainable.

Adduct **19a** was converted to the BA-3,4-dione-dAde adduct (**2a**) via reductive debenzylation with Pd black and 1,4-cyclohexadiene. The catechol adduct obtained underwent autooxidation in the presence of KF/DMF to furnish **2a** in excellent yield (91%).

Synthesis of the MBA-3,4-dione-dAde adduct (**2b**) was carried out by a similar reaction sequence (Scheme 4). 3,4-Diacetoxy-1-amino-MBA (**16b**) was prepared from the corresponding amino-quinone (**5b**) by reduction with H_2 over Pd/C followed by acetylation. Compound **16b** was converted into the bromocatechol derivative (**17b**) by diazotization with *tert*-butylnitrite followed by reaction with Me_3SiBr and *n*-Bu_4NBr at 0 °C. This was transformed into the more stable dibenzyl derivative (**18b**) by treatment with benzyl bromide, 18-crown-6 ether, and KOH. Copper-mediated coupling of **18b** by the procedure employed for **18a** furnished the coupled adduct **2b** in good yield (79%).

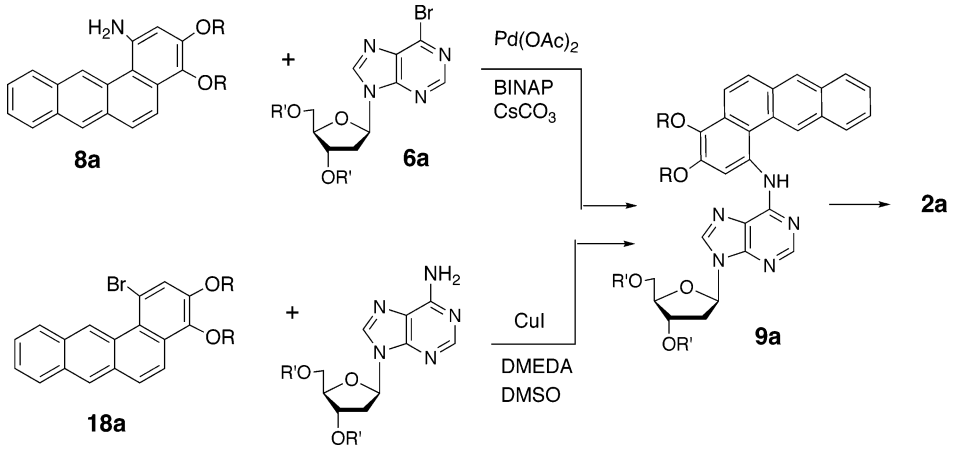
In the case of the DMBA-3,4-dione-dAde adduct, synthesis of the bromocatechol diacetate derivative (**17c**) from **5c** was accomplished by a similar reaction sequence, but all attempts to convert **17c** to the dibenzyl derivative **18c** provided intractable mixtures. As a consequence, synthesis of the DMBA-3,4-dione-dAde adduct could not be achieved.

SCHEME 5[a]



[a] Reagents and conditions: (i) NaI/CuI/DMEDA/DMSO; (ii) Pd/cyclohexadiene/MeOH; (iii) KF/DMF.

SCHEME 6



Synthesis of dGua Adducts via Copper-Mediated Coupling of Halo Derivatives of PAH Catechols with 2′-Deoxyribonucleosides (Method D). Synthesis of the BA-3,4-dione-dGua adduct (**3a**) via copper-mediated coupling of **18a** with derivatives of 2′-deoxyguanosine was also explored (Scheme 5). Attempts to couple dGua with **18a** in the absence of a catalyst were unsuccessful, and analogous reaction of 2′-deoxy-(6-benzyloxy)-guanosine (**20**) with **18a** gave only a low yield of adduct **21a**. However, **20** coupled readily with **18a** in the presence of NaI/CuI and DMEDA in DMSO to yield **21a** (50%). It is likely that **18a** is transformed to its more reactive iodocatechol analogue under these conditions. Complete debenzylation of **21a** was accomplished by treatment with 1,4-cyclohexadiene and Pd black in MeOH. The primary catechol product underwent auto-oxidation in the presence of KF in DMF to provide **3a** (88%).

Synthesis of the MBA-3,4-dione-dGua adduct (**3b**) via analogous copper-mediated coupling of **18b** with **20** was also investigated, but the coupled adduct could not be obtained. It appears the failure of coupling to occur is due to the relative slow rate of coupling relative to the fast rate of decomposition of the unstable bromocatechol (or iodocatechol) precursor. This was confirmed by TLC monitoring, which showed relatively rapid disappearance of the halobromocatechol under the conditions employed.

Discussion

Two complementary methods were developed for synthesis of the adducts formed by the quinone metabolites of carcinogenic PAHs with 2′-deoxyribonucleosides, a Pd-catalyzed method and a Cu-catalyzed method (Scheme 6). The former involves in the key step coupling a protected aminocatechol, such as **8a**, with a halonucleoside (**6a** or **6b**), and the latter entails coupling a protected bromocatechol, such as **18a**, with dA or dG. These are the first methods for the synthesis of these types of adducts to be reported.

The Pd-mediated method was employed successfully for synthesis of the dAde adducts (**2a**,**b**,**c**) of all three quinones (**1a**,**b**,**c**) as well as the dGua adducts (**3ab**,**3b**) of **1a** and **1b**. This approach was shown previously to also provide convenient synthetic access to the related adducts of BPQ with dAde and dGua.[20] However, attempted synthesis of the dGua adduct of **1c** (**3c**) by this approach was not successful because of the facility of decomposition of **3c** and related compounds.

Cu-mediated coupling was explored because of its potential advantages over the Pd-mediated method for synthesis of ^{13}C- and/or ^{15}N-labeled adducts needed as standards for LC-MS-MS analysis of PAH adduct formed in human cells.[33,34] Synthesis of the dAde adducts **2a** and **2b** by the Cu-mediated method required protected derivatives of the 1-bromo-BA- and 1-bromo-MBA-3,4-catechols (**18a** or **18b**) as the starting compounds. However, preliminary experiments strongly indicated that PAH quinones or catechols containing a Br atom in a bay region, such as **18a** or **18b**, would be unstable, if they could be synthesized at all. Despite this, syntheses of **18a** and **18b** were successfully accomplished by diazotization of aminocatechols **16a** and **16b** with *tert*-butylnitrite followed by reaction with Me_3SiBr and *n*-Bu_4NBr and conversion of the catechol products to dibenzyl ethers. Compounds **18a** and **18b** were used directly as starting compounds for synthesis of adducts **2a** and **2b**. The adducts were obtained in good yields, and bis-adducts were not produced as byproducts.

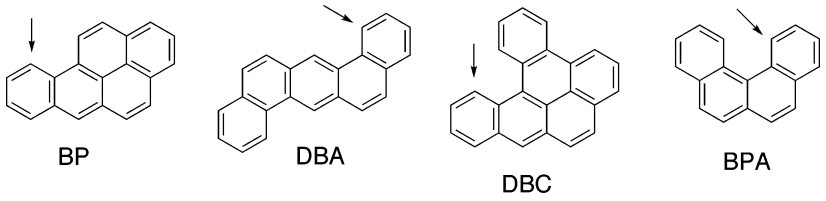


FIGURE 6. Examples of PAH carcinogens. The sites of attachment of diol epoxide or quinone metabolites to DNA bases are indicated by arrows.

Attempts to extend the Cu-mediated method to synthesis of the dAde and dGua adducts of DMBA-3,4-dione (**2c** and **3c**) were not successful due to decomposition of the products. The instability of the DMBA-derived compounds is most likely due to the severe steric crowding in the bay molecular regions of the adducts.

Both the Pd- and Cu-mediated methods appear to be general in scope. The Pd method has the disadvantage that bis-adducts (with two purines per PAH) are secondary products in the synthesis of the dAde adducts (but not the dGua adducts). The Cu-mediated method has the advantages that relatively inexpensive copper catalysts are used, protection and deprotection of the sugar hydroxyl groups is not required, bis-adducts are not obtained as secondary products, and 2′-deoxyribonucleosides may be used directly in the coupling step (without conversion to halides). The latter feature is important for synthesis of $^{15}N_5$-labeled adducts, because it allows retention of all five ^{15}N-atoms of the purine in the labeled adducts.

The utility of these methods for synthesis of analogous adducts of quinone metabolites of other PAH carcinogens merits comment. Not all PAHs are carcinogens. Some examples of relatively potent PAH carcinogens are benzo[*a*]pyrene (BP),[39] dibenzo[*def*,*p*]chrysene (DBC),[40] dibenzo[*a*,*h*]anthracene (DBA),[42] and benzo[*c*]phenanthrene (BPA)[43] (Figure 6). Carcinogenic PAHs are distinguished by possession of a *bay* or *fjord* region. It is at these sites (indicated by an arrow) that adduct formation takes place. Our findings indicate that adducts of PAH quinones at unsubstituted *bay* region positions (BA, MBA, BP) are stable and synthetically accessible by the methods reported, but analogous adducts at a sterically restricted position (DMBA) are unstable. We tentatively predict that adducts of the quinone metabolites of DBA and other PAHs at unsubstituted bay region positions are likely to be stable and synthetically accessible by these methods, whereas the adducts of DBC, BPA, and other PAHs with a crowded *fjord* region are likely to be significantly less stable.

(39) Benzo[*a*]pyrene is commonly employed as a standard for PAHs in the environment. It is also implicated as a cancer-causative agents in tobacco smoke.[6−9]

(40) Dibenzo[*def*,*p*]chrysene is the most potent PAH carcinogen currently known based on rodent bioassays.[5,37] Significant levels are present in cigarette smoke, vehicle exhaust condensate, in the particulate matter formed in combustion of smoky coal, and in soil and sediment samples: (a) Reference 7. (b) Mumford, J. L.; Harris, D. B.; Williams, K.; Chuang, J. C.; Cooke, M. *Environ. Sci. Technol.* **1987**, *21*, 308−311. (c) Kozin, I. S.; Gooijer, C.; Velthorst, N. H. *Justus Liebigs Ann. Chem.* **1995**, *67*, 1623−1626.

(41) (a) Masuda, Y.; Kagawa, R. *Chem. Pharm. Bull.* **1972**, *20*, 2736−2737. (b) Lacassagne, A.; Buu-Hoi, F.; Zajdela, F. A. *Naturwissenschaften* **1968**, *55*, 43.

(42) Dibenzo[*a*,*h*]anthracene was the first PAH shown to be carcinogenic. It is moderately active, ranking between BA and BP in activity.[3]

(43) Although benzo[*c*]phenanthrene exhibits weak activity as a tumor initiator in mouse skin, its bay region *anti*-diol epoxide shows exceptionally high activity in rodent bioassays. This difference is apparently due to the low efficiency of metabolic activation of BPA in mouse skin. Subsequently, it was shown that the human mammary carcinoma cell line MCF-7 can activate BPA to an *anti*-diol epoxide: (a) Levin, W.; Wood, A. W.; Chang, R. L.; Ittah, Y.; Croisy-Delcey, M.; Yagi, H.; Conney, A. H.; Jerina, D. M. *Cancer Res.* **1980**, 3910−3914. (b) Einholf, H. J.; Amin, S.; Yagi, H.; Jerina, D. M.; Baird, W. M. *Carcinogenesis* **1996**, 2237−2244.

Experimental Section

Caution: 7-Methylbenz[*a*]anthracene (MBA) and 7,12-dimethylbenz[*a*]anthracene (DMBA) are carcinogens and should be handled with appropriate caution following the procedures recommended in the publication *NIH Guidelines for the Laboratory Use of Chemical Carcinogens*.

1-Aminobenz[*a*]anthracene-3,4-dione (5a). To a solution of benz[*a*]anthracene-3,4-dione (**1a**) (0.30 g, 1.16 mmol) in DMF (1.0 mL) was added Me_3SiN_3 (0.20 g, 1.75 mmol). *Caution*: exothermic reaction takes place vigorously with emission of nitrogen gas. The mixture was stirred at room temperature for 1.5 h, then the solution was cooled to room temperature and filtered, and the resulting dark purple solid was washed with EtOAc to yield **5a** (0.29 g, 92.0%), mp >260 °C: ^{1}H NMR (DMSO-d_6) δ 5.83 (s, 1H), 7.65 (dd, 2H, J = 7.2, 7.2 Hz), 7.92 (d, 1H, J = 8.4 Hz), 8.15 (d, 1H, J = 8.0 Hz), 8.24 (d, 1H, J = 8.0 Hz), 8.34 (d, 1H, J = 8.4 Hz), 8.75 (s, 1H), 8.98 (br, 2H, NH_2), 9.17 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 99.44(C-2), 121.02 (C-1), 125.40, 127.08, 127.65, 128.01, 128.12, 128.52, 129.87, 129.97, 131.60, 132.21, 132.55, 132.66, 133.58, 161.39 (C-12), 174.76 (C═O), 183.09 (C═O); HRMS (M + Na^+) calcd for $C_{18}H_{11}NO_2Na$ 296.0687, found 296.0684.

1-Amino-7-methylbenz[*a*]anthracene-3,4-dione (5b). Yield = 91%; ^{1}H NMR (DMSO-d_6) δ 3.02 (s, 3H), 5.82 (s, 1H), 7.57 - 7.67 (m, 2H), 7.85 (d, 1H, J = 9.0 Hz), 8.04 (br, NH_2, 2H), 8.14 (d, 1H, J = 8.0 Hz), 8.31 (d, 1H, J = 8.6 Hz), 8.49 (d, 1H, J = 9.1 Hz), 8.93 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 99.5 (C-2), 120.6, 124.9, 125.3, 126.5, 127.0, 127.9, 128.8, 129.2, 130.8, 131.2, 131.7, 131.9, 161.4 (C-12), 174.7 (C═O), 183.1 (C═O); HRMS (M^+ + 1) calcd for $C_{19}H_{13}NO_2$ 288.1025, found 288.0998.

1-Amino-3,4-bis-*O*-TBDMS-benz[*a*]anthracene (7a). To a solution of **5a** (81.0 mg, 0.3 mmol) in DMSO (3.0 mL) was added 5% Pd/C (8.0 mg). Hydrogen gas was bubbled through the suspension, and it was stirred at room temperature for 30 min. The color changed from black to slightly yellow. The Pd/C catalyst was filtered off and washed with DMSO (1.0 mL). To the filtrate was added *N*-*tert*-butyldimethylsilyl-*N*-methyltrifluoramide (1.0 mL), and the resulting mixture was stirred for 1.0 h. Then it was poured into ice−water, extracted with EtOAc, dried over $NaSO_4$, and purified by chromatography on silica gel. Elution with hexanes/EtOAc (30/1) gave **7a** as a yellow solid (125.0 mg, 82.8%): ^{1}H NMR ($CDCl_3$/D_2O) δ 0.15 (s, 6H), 0.30 (s, 6H), 1.04 (s, 9H), 1.13 (s, 9H), 6.64 (s, 1H), 7.54 (dd, 2H, J = 3.0, 6.5 Hz), 7.65 (d, 1H, J = 9.0 Hz), 7.93 (d, 1H, J = 9.0 Hz), 8.01 (dd, 1H, J = 3.5, 6.0 Hz), 8.30 (s, 1H), 9.60 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.5, 18.6, 26.2, 110.5, 114.1, 124.2, 125.3, 125.4, 126.2, 126.3, 126.4, 127.3, 128.1, 128.5, 129.8, 130.7, 131.0, 131.8, 135.4, 139.7, 145.1; HRMS (M + H^+) calcd for $C_{30}H_{42}NO_2Si_2$ 504.2793, found 504.2784.

1-Amino-3,4-bis-*O*-TBDMS-7-methylbenz[*a*]anthracene (7b). Yield = 80%; ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 6H), 0.32 (s, 6H), 1.06 (s, 9H), 1.16 (s, 9H), 3.08 (s, 3H), 4.26 (br, NH_2, 2H), 6.63 (s, 1H), 7.51 - 7.58 (m, 2H), (dd, 2H, J = 8.5, 8.5 Hz), 8.04 (d, 1H, J = 7.5 Hz), 8.27 (d, J = 7.5 Hz), 9.52 (s, 1H); ^{13}C NMR ($CDCl_3$)

δ −3.5, −3.6, 14.2, 14.4, 18.6, 18.7, 26.2, 26.3, 110.2, 114.4, 122.4, 122.9, 124.1, 124.9, 125.3, 127.6, 128.8, 129.2, 129.5, 129.6, 129.7, 131.2, 135.1, 139.7, 144.9; HRMS (M^+) calcd for $C_{31}H_{43}NO_2Si_2$ 517.2832, found 517.2822.

1-Amino-3,4-bis-*O*-TBDMS-7,12-dimethylbenz[*a*]anthracene (7c). To a solution of **1c** (0.29 g, 1.0 mmol) in DMF (3 mL) was added Me_3SiN_3 (3.2 g, 10.0 mmol). The reaction mixture was stirred at room temperature until the solution became clear, and then excess Me_3SiN_3 was removed by high vacuum to give a red residue. This was redissolved in DMF (3 mL), and *N*-*tert*-butyldimethylsilyl-N-methyl-trifluoric amide (1.0 mL) was added. The mixture was stirred at room temperature for 3.0 h and worked up by evaporation of the solvent and flash chromatography on a silica gel column eluted with hexane/EtOAc (30:1) to give a yellow solid product (0.45 g). This was dissolved in CH_2Cl_2 (10 mL), 5% Pd/C (∼50 mg) was added, and hydrogen gas was bubbled through the suspension for 1.5 h. The Pd/C was removed by filtration, and the solvent was evaporated off to give a yellow residue that was purified by flash chromatography to afford **7c** (0.40 g, 80%): ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 3H), 0.25 (s, 3H), 0.35 (s, 3H), 0.46 (s, 3H), 1.07 (s, 6H), 1.17 (s, 6H), 2.90 (s, 3H), 3.08 (s, 3H), 7.57 − 7.67 (m, 4H), 7.76 (s, 2H), 8.36 (d, 1H, J = 5.5 Hz), 8.39 (d, 1H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ −3.9, −3.7, −3.5, −3.3, 14.1, 18.6, 18.7, 20.6, 22.7, 26.2, 26.3, 31.6, 106.9, 113.3, 122.0, 122.2, 124.8, 124.9, 125.1, 125.4, 126.4, 127.4, 127.5, 128.0, 128.9, 130.4, 131.8, 133.4, 139.7, 146.2; HRMS ($M + H^+$) calcd for $C_{32}H_{46}NO_2Si_2$ 532.3062, found 532.3057.

***N*^{6}-(3,4-bis-*O*-TBDMS-benz[*a*]anthracenyl)-3′,5′-bis-*O*-acetyl-2′-deoxyadenosine (8a).** To a Telfon sealing tube were added a solution of (**7a**) (81.0 mg, 0.16 mmol) and **7a** (47.2 mg, 0.13 mmol) in anhydrous toluene (5 mL), $Pd(OAc)_2$ (2.9 mg, 10%), BINAP (24.2 mg, 30%), and Cs_2CO_3 (42.5 mg, 0.13 mmol). The resulting mixture was purged with argon, sealed, heated to 80−90 °C, and stirred for 24 h. The reaction was stopped, the solvent was evaporated off, and the product was purified by chromatography on silica gel. Elution with hexanes/EtOAc (3:2) gave **7a** (38.0 mg) and **8a** (56.0 mg, 53.4%): ^{1}H NMR ($CDCl_3$) δ 0.23 (s,6H), 0.35 (s, 6H), 1.05 (s, 9H), 1.17 (s, 9H), 2.11 (s, 3H), 2.15 (s, 3H), 2.65 (ddd, 1H, J = 2.2, 6.0, 14.0 Hz), 3.00−3.06 (m, 1H), 4.38−4.40 (m, 2H), 4.47 (dd, 1H, J = 5.5, 13.4 Hz), 5.48 (dd, 1H, J = 3.0, 3.0 Hz), 6.48 (dd, 1H, J = 6.0, 6.0 Hz), 7.41 (dd, 1H, J = 7.5, 7.5 Hz), 7.48 (dd, 1H, J = 7.5, 7.5 Hz), 7.71 (d, 1H, J = 9.0 Hz), 7.77 (d, 1H, J = 9.0 Hz), 7.87 (s, 1H), 7.97(d, 1H, J = 9.0 Hz), 7.98 (s, NH, 1H), 8.02 (d, 1H, J = 9.0 Hz), 8.30 (s, 1H), 8.37 (s, 1H), 8.48 (s, 1H), 9.57 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.6, 18.6, 18.8, 20.8, 20.9, 26.2, 37.4, 63.7, 74.5, 82.5, 84.6, 119.9, 120.0, 121.2, 122.0, 125.0, 125.4, 125.8, 126.6, 126.7, 127.1, 128.0, 128.2, 128.5, 128.8, 131.0, 131.1, 131.8, 138.8, 140.2, 144.6, 149.5, 153.0, 153.3, 170.3, 170.5; HRMS ($M + Na^+$) calcd for $C_{44}H_{55}N_5O_7Si_2Na$ 844.3538, found 844.3535.

***N*^{6}-[1-(3,4-bis-*O*-TBDMS-7-methylbenz[*a*]anthracenyl)]-3′,5′-bis-*O*-acetyl-2′-deoxyadenosine (8b).** Yield = 40%; ^{1}H NMR ($CDCl_3$) δ 0.24 (s,6H), 0.36 (s, 6H), 1.05 (s, 9H), 1.18 (s, 9H), 2.10 (s, 3H), 2.15 (s, 3H), 2.65 (ddd, 1H, J = 2.0, 6.0, 14.5 Hz), 2.96−3.06 (m, 1H), 4.36−4.47 (m, 3H), 5.47 (dd, 1H, J = 3.5, 3.5 Hz), 6.46 (dd, 1H, J = 6.0, 6.0 Hz), 7.39 (dd, 1H, J = 7.5, 7.5 Hz), 7.53 (dd, 1H, J = 7.5, 7.5 Hz), 7.70 (d, 1H, J = 8.5 Hz), 7.94 (s, 1H), 7.95 (s, 1H), 8.05 (dd, 2H, J = 10.0, 10.0 Hz), 8.23 (d, 1H, J = 8.5 Hz), 8.41 (br, 1H), 8.50 (s, 1H), 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.6, 14.4 (CH_3), 18.6, 18.7, 20.7, 20.9, 26.2, 37.3, 63.7, 64.3, 74.5, 82.5, 84.5, 119.3, 120.0, 121.1, 121.8, 122.7, 123.7, 123.9, 124.9, 125.7, 127.5, 127.9, 128.5, 128.7, 129.6, 129.9, 130.1, 131.1, 138.8, 139.7, 144.5, 149.4, 152.8, 153.2, 170.3, 170.4; HRMS (M^+) calcd for $C_{45}H_{57}N_5O_7Si_2$ 835.3797, found 835.3806.

***N*^{6}-[1-(3,4-bis-*O*-TBDMS-7,12-dimethylbenz[*a*]anthracenyl)]-3′,5′-bis-*O*-acetyl-2′-deoxyadenosine (8c).** Yield = 46.0%; ^{1}H NMR ($CDCl_3/D_2O$) δ 0.18 (s, 3H), 0.30 (s, 3H), 0.38 (s, 3H), 0.46 (s, 3H), 1.09 (s, 6H), 1.18 (s, 6H), 2.12 (s, 1.5H), 2.14 (s, 1.5H), 2.18 (s, 1.5H), 2.19 (s, 1.5H), 2.66−2.68 (m, 1H), 2.75 (s, 1.5H), 2.76 (s, 1.5H), 2.96−3.16 (m, 1H), 3.06 (s, 3H), 4.39−4.43 (m, 2H), 4.48−4.50 (m, 1H), 5.49−5.52 (m, 1H), 6.47 (dd, 0.5H, J = 6.5, 6.5 Hz), 6.51 (dd, 0.5H, J = 6.5, 6.5 Hz), 7.57−7.64 (m, 2H), 7.82−7.91 (m, 3H), 8.10−8.13 (m, 1H), 8.33 (d, 1H, J = 8.5 Hz), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.9, −3.6, −3.4, −3.3, 14.3, 18.7, 18.9, 20.8, 20.9, 21.0, 26.2 and 26.3, 37.2 and 37.6, 63.7 and 63.8, 74.4 and 74.5, 82.5 and 82.6, 84.4 and 84.7, 113.2, 117.0, 121.1, 121.5, 122.7, 124.9, 125.3, 125.4, 125.6, 125.7, 126.4, 127.2, 127.9, 128.4, 128.9, 130.5, 130.8, 131.9, 137.3, 138.4, 138.7, 145.7, 149.0, 151.9, 153.0, 170.3 and 170.4, 170.5 and 170.6; HRMS ($M + Na^+$) calcd for $C_{46}H_{59}N_5O_7Si_2Na$ 872.3851, found 872.3857.

***N*^{6}-[1-(Benz[*a*]anthracene-3,4-dionyl)]-2′-deoxyadenosine (2a).** To a solution of **8a** (24.0 mg, 0.03 mmol) in CH_2Cl_2 (3 mL) was added a catalytic amount of tetramethylguandine/MeOH solution, and the mixture was stirred at room temperature for 1.5 h. TLC indicated reaction to be complete. The product was purified by chromatography on silica gel. Elution with CH_2Cl_2/methanol (15:1) gave the deacetylated product (19.0 mg, 90.7%), ^{1}H NMR ($CDCl_3/D_2O$) δ 0.21 (s, 6H), 0.34 (s, 6H), 1.01 (s, 9H), 1.15 (s, 9H), 2.39 (dd, 1H, J = 5.0, 8.0 Hz), 3.21 (m, 1H), 3.82 (d, 1H, J = 12.5 Hz), 4.03 (d, 1H, J = 12.5 Hz), 4.28 (app s, 1H), 4.75 (app s, 1H), 4.84 (d, 1H, J = 5.0 Hz), 6.41 (dd, 1H, J = 5.0, 9.0 Hz), 7.43 (t, 1H, J = 8.0 Hz), 7.49 (t, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 10.0 Hz), 7.78 (d, 1H, J = 10.0 Hz), 7.86 (s, 1H), 7.96 (d, 1H, J = 8.5 Hz), 7.98 (d, 1H, J = 8.5 Hz), 8.01 (s, 1H), 8.31 (s, 1H), 8.45 (s, 1H), 9.49 (s, 1H).

The deacetylated product (16.0 mg, 0.022 mmol) was dissolved in DMF/H_2O (5:2) (3.5 mL), and to the solution was added KF (5.1 mg, 0.088 mmol). The mixture was stirred at room temperature for 30 min, and the solvent was evaporated. The dark colored residue was dissolved in MeOH and purified by chromatography on silica gel. Elution with CH_2Cl_2/MeOH (3:1) afforded **2a** (10.0 mg, 92%): ^{1}H NMR (CD_3OD) δ 2.52 (m, 1H), 2.91 (ddd, 1H, J = 6.5, 6.5, 13.5 Hz), 3.79 (dd, 1H, J = 3.0, 12.0 Hz), 3.88 (dd, 1H, J = 2.5, 12.0 Hz), 4.11 (d, 1H, J = 2.5 Hz), 4.65 (s, 1H), 5.57 (s, 1H), 6.60 (dd, 1H, J = 6.5, 6.5 Hz), 7.46 (dd, 1H, J = 8.0, 8.0 Hz), 7.53 (dd, 1H, J = 8.0, 8.0 Hz), 8.02 (dd, 2H, J = 7.5, 7.5 Hz), 8.15 (d, 1H, J = 8.0 Hz), 8.23 (d, 1H, J = 8.0 Hz), 8.49 (s, 1H), 8.57 (s, 1H), 8.74 (s, 1H), 10.70 (s, 1H); ^{13}C NMR (CD_3OD) δ 41.62, 63.5, 72.85, 86.92, 89.78, 104.51, 121.94, 125.90, 126.96, 127.73, 128.02, 128.70, 129.07, 130.83, 132.38, 133.02, 133.20, 133.58, 133.78, 134.29, 135.40, 144.47, 152.17, 153.41, 162.84, 165.80, 167.47, 188.92; HRMS ($M + Na^+$) calcd for $C_{28}H_{21}N_5O_5$-Na 530.1440, found 530.1456.

***N*^{6}-[1-(7-Methylbenz[*a*]anthracene-3,4-dionyl)]-2′-deoxyadenosine (2b).** Yield = 91%; ^{1}H NMR (CD_3OD) δ 2.50 (ddd, 1H, J = 3.2, 6.1, 13.4 Hz), 2.86−2.92 (m, 1H), 3.11 (m, 3H), 3.77 (dd, 1H, J = 3.2, 12.0 Hz), 3.88 (dd, 1H, J = 3.2, 12.0 Hz), 4.09 (dd, 1H, J = 3.2, 6.3 Hz), 4.63 (m, 1H), 5.55 (s, 1H), 6.58 (t, 1H, J = 6.8, 6.8 Hz), 7.43 (t, 1H, J = 7.0, 7.0 Hz), 7.55 (t, 1H, J = 8.0, 8.0 Hz), 8.00 (d, 1H, J = 8.0 Hz), 8.16 (d, 1H, J = 9.2 Hz), 8.29 (d, 1H, J = 8.9 Hz), 8.56 (s, 1H), 8.56 (d, 1H, J = 8.2 Hz), 8.71 (s, 1H), 10.56 (s, 1H); ^{13}C NMR (DMSO) δ 14.5 (CH_3), 48.9, 62.1, 70.1, 71.2, 84.2, 88.4, 103.5, 120.7, 124.9, 125.2, 126.2, 127.4, 127.5, 128.6, 129.9, 130.5, 130.7, 130.8, 131.9, 132.1, 132.8, 143.2, 151.4, 152.6, 160.9, 162.2, 163.3, 186.4; HRMS ($M + Na^+$) calcd for $C_{29}H_{23}N_5O_5Na$ 544.1597, found 544.1603.

***N*^{6}-[1-(7,12-Dimethylbenz[*a*]anthracene-3,4-dionyl)]-2′-deoxyadenosine (2c).** Yield = 19%; ^{1}H NMR (DMSO-d_6 + D_2O) δ 2.29−2.32 (m, 1H), 2.70−2.74 (m, 1H), 3.02 (s, 6H), 3.48−3.61 (m, 2H), 3.87−3.90 (m, 1H), 4.40−4.47 (m, 1H), 5.34 (s, 1H), 6.38 (dd, 1H, J = 6.8, 6.8 Hz), 7.52 (dd, 1H, J = 7.0, 7.0 Hz), 7.59 (dd, 1H, J = 7.0, 7.0 Hz), 7.84 (d, 1H, J = 9.0 Hz), 8.14 (d, 1H, J = 9.0 Hz), 8.32 (d, 1H, J = 9.0 Hz), 8.37 (d, 1H, J = 9.0 Hz), 8.40 (s, 1H), 8.54 (s, 1H); ^{13}C NMR (DMSO-d_6 + D_2O) δ 14.3, 24.4, 61.9, 71.0, 84.1, 88.1, 98.1, 119.8, 125.1, 125.5, 125.9, 126.1, 127.0, 127.3, 127.5, 130.8, 131.0, 131.6, 131.8, 134.7, 139.2, 142.0, 151.0, 152.4, 161.9, 163.6, 168.5, 168.6, 186.7; HRMS ($M - H$) calcd for $C_{30}H_{24}N_5O_5$ 534.1777, found 534.1770.

***N*²-[1-(3,4-bis-*O*-TBDMS-benz[*a*]anthracenyl)]-3′,5′-bis-*O*-acetyl-*O*⁶-benzyl-2′-deoxyguanosine (14a).** To a solution of **7a** (120.0 mg, 0.24 mmol) and **13** (106.0 mg, 0.24 mmol) in anhydrous toluene (5 mL) in a sealing tube were added $Pd(OAc)_2$ (5.4 mg, 0.024 mmol), BINAP (44.8 mg, 0.072 mmol), and Cs_2CO_3 (78.0 mg, 0.24 mmol) in order. The mixture was purged with argon and then stirred at 85 °C for 48 h. The solvent was evaporated, and the product was purified by chromatography on a silica gel column. Elution with hexanes/EtOAc (3/2) afforded **7a** (35.0 mg) and **14a** (129 mg, 84%, based on converted **7a**): ^{1}H NMR ($CDCl_3$) δ 0.17 (s, 6H), 0.20 (s, 6H), 1.04 (s, 9H), 1.15 (s, 9H), 2.03 (s, 3H), 2.10 (s, 3H), 2.31 (m, 1H), 2.67 (m, 1H), 4.12 ∼ 4.22 (m, 3H), 5.20 (app s), 5.45 (s, 2H), 6.26 (dd, 1H, J = 7.5, 7.5 Hz), 7.20 ∼ 7.36 (m, 5H), 7.38 (dd, 1H, J = 8.0, 8.0 Hz), 7.45 (s, 1H), 7.48 (dd, 1H, J = 7.5, 7.5 Hz), 7.68 (d, 1H, J = 8.0 Hz), 7.74 (d, 1H, J = 8.0 Hz), 7.76 (s, 1H), 7.96 (d, 1H, J = 8.0 Hz), 8.02 (d, 1H, J = 8.5 Hz), 8.29 (s, 1H), 9.62 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.4, 18.8, 20.8, 21.1, 26.3, 26.34, 29.8, 36.7, 63.6, 68.0, 74.9, 82.3, 84.3, 116.6, 121.0, 121.4, 122.2, 125.4, 125.5, 125.9, 126.4, 126.8, 127.2, 128.0, 128.2, 128.4, 128.5, 128.7, 128.9, 130.3, 131.0, 131.1, 131.8, 136.4, 137.6, 140.4, 144.7, 153.7, 157.4, 161.1, 170.3, 170.5; HRMS (M + H$^+$) calcd for $C_{51}H_{62}N_5O_8Si_2$ 928.4137, found 928.4130.

***N*²-[1-(3,4-bis-*O*-TBDMS-7-methylbenz[*a*]anthracenyl)]-3′,5′-bis-*O*-acetyl-*O*⁶-benzyl-2′-deoxyguanosine (134b).** Yield = 82%. ^{1}H NMR ($CDCl_3$) δ 0.19 (s,3H, Si−CH_3), 0.22 (s,3H), 0.32 (s, 3H), 0.33 (s,3H), 1.05 (s, 9H), 1.17 (s, 9H), 2.02 (s, 3H), 2.11 (s, 3H), 2.28−2.32 (m, 1H), 2.65−2.70 (m, 1H), 3.08 (s, 3H), 4.08−4.22 (m, 3H), 5.22 (app. br, 1H), 5.47 (s, 2H), 6.27 (dd, 1H, J = 6.5, 6.5 Hz), 7.25−7.53 (m, 8H), 7.69 (d, 1H, J = 8.0 Hz), 7.76 (s, 1H), 8.07 (dd, 2H, J = 10.0, 10.0 Hz), 8.22 (d, 1H, J = 8.0 Hz), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −3.6, −3.5, 14.1, 18.6, 20.6, 20.8, 20.9, 26.1, 26.2, 36.5, 60.3, 63.4, 67.9, 74.7, 82.2, 84.2, 116.4, 120.5, 121.2, 121.9, 122.6, 123.8, 123.9, 124.9, 125.6, 127.5, 127.8, 128.2, 128.3, 128.7, 129.5, 129.6, 129.9, 130.1, 131.1, 136.2, 137.4, 139.8, 144.4, 153.5, 157.1, 160.9, 170.0, 170.3; HRMS (M$^+$) calcd for $C_{52}H_{63}N_5O_8Si_2$ 941.4215, found 941.4194.

***N*²-[1-(Benz[*a*]anthracene-3,4−dionyl)]-2′-deoxyguanosine (3a). Debenzylation. Method A.** To a solution of **14a** (80 mg, 0.088 mmol) in MeOH (10 mL) was added Lindlar catalyst (5% Pd on calcium carbonate, poisoned by lead, 10 mg). The suspension was stirred at room temperature for 48 h under hydrogen. TLC indicated that about half the **14a** remained unreacted, but further conversion failed to take place over longer time. Addition of more catalyst did not improve the yield. The catalyst was removed by filtration, and the product was purified by chromatography on a silica gel column. Elution with hexanes/EtOAc/CH_2Cl_2/MeOH (5:5:5:1) provided **14a** (40.0 mg, conversion 50%) and the debenzylated product (32.0 mg, 89%, based on converted **14a**): ^{1}H NMR (CD_3-OD) δ 0.18 (s, 3H), 0.25 (s, 3H), 0.34 (s, 3H), 0.40 (s, 3H), 1.07 (s, 9H), 1.17 (s, 9H), 1.72 (dd, 1H, J = 5.2, 14.0 Hz), 2.17 (m, 1H), 3.36 (dd, 1H, J = 5.1, 5.1 Hz), 3.74 (dd, 1H, J = 5.7, 12.0 Hz), 3.91 (dd, 1H, J = 5.5, 5.5 Hz), 4.74 (d, 1H, J = 5.8 Hz), 5.85 (dd, 1H, J = 6.2, 6.5 Hz), 7.29 (s, 1H), 7.40 (dd, 1H, J = 7.0, 7.0 Hz), 7.46 (dd, 1H, J = 8.5, 8.5 Hz), 7.65 (s, 1H), 7.80 (d, 1H, J = 9.4 Hz), 7.82 (d, 1H, J = 8.6 Hz), 7.96 (d, 1H, J = 8.1 Hz), 8.05 (d, 1H, J = 9.4 Hz), 8.34 (s, 1H), 9.56 (s, 1H).

Method B. To a solution of **14a** (80 mg, 0.088 mmol) in MeOH (10 mL) was added 1,4-cyclohexadiene (1.0 mL) and Pd black. The resulting suspension was stirred at room temperature for 1 h (TLC indicated reaction was complete). Pd black was filtered off (caution, may catch fire), and the filtrate was concentrated to give the debenzylated product (65 mg, 90%) sufficiently pure for the next step.

Deacetylation. To a solution of the above residue (30 mg, 0.036 mmol) in MeOH (5 mL) was added tetramethylguandine (15.0 mg). The mixture was stirred at room temperature for 1.5 h, and then purified by chromatography on silica gel eluted with hexanes/EtOAc/CH_2Cl_2/MeOH (5:5:5:2) to give the deacetylated product (24.0 mg, 91%): ^{1}H NMR (CD_3OD) δ 0.24 (s, 6H), 0.36 (s, 3H), 0.37 (s, 3H), 1.07 (s, 9H), 1.19 (s, 9H), 2.02 (m, 1H), 2.33 (m, 1H), 3.44(dd, 1H, J = 5.0, 12.0 Hz), 3.48 (dd, 1H, J = 3.8, 12.0 Hz), 3.81 (d, 1H, J = 3.6 Hz), 4.18 (t, 1H, J = 3.0 Hz), 6.07 (t, 1H, J = 6.6 Hz), 7.34 (s, 1H), 7.47 (dd, 1H, J = 7.2, 7.2 Hz), 7.50 (dd, 1H, J = 7.50, 7.50 Hz), 7.81 (d, 1H, J = 9.4 Hz), 7.91 (d, 1H, J = 8.2 Hz), 7.94 (s, 1H), 8.00 (d, 1H, J = 8.2 Hz), 8.05 (d, 1H, J = 8.2 Hz), 8.38 (s, 1H), 9.61 (s, 1H).

Removal of TBDMS. To a solution of the deacetylated product (24 mg, 0.032 mmol) in DMF (5 mL) and water (2 mL) was added KF (7.5 mg, 0.12 mmol), and the solution was stirred at room temperature for 1.5 h. The solvent was evaporated off, and the product was purified by chromatography on silica gel. Elution with EtOAc/CH_2Cl_2 /MeOH (1/1/1) gave **3a** (16 mg, 96%): ^{1}H NMR (CD_3OD) δ 2.45 (ddd, 1H, J = 3.0, 6.0, 13.0 Hz), 2.83 (ddd, 1H, J = 6.0, 6.0, 13.0 Hz), 3.71 (dd, 1H, J = 4.0, 12.5 Hz), 3.84 (dd, 1H, J = 2.5, 12.0 Hz), 4.02 (d, 1H, J = 2.5 Hz), 4.55 (t, 1H, J = 3.0 Hz), 5.98 (s, 1H), 6.39 (t, 1H, J = 7.0 Hz), 7.46 (dd, 1H, J = 8.0, 8.0 Hz), 7.51 (dd, 1H, J = 8.0, 8.0 Hz), 7.98 (d, 1H, J = 8.0 Hz), 8.08 (d, 1H, J = 8.5 Hz), 8.09 (d, 1H, J = 8.0 Hz), 8.15 (d, 1H, J = 9.0 Hz), 8.17 (s, 1H), 8.43 (s, 1H), 10.55 (s, 1H);13 C NMR (CD_3OD) δ 40.19, 62.04, 71.37, 85.44, 88.12, 102.58, 120.04, 120.35, 125.44, 126.15, 126.51, 127.13, 127.32, 129.37, 130.85, 131.45, 131.68, 132.21, 132.77, 133.81, 138.26, 149.45, 158.34, 159.70, 166.87, 168.87, 178.89, 187.05; HRMS (M + Na$^+$) calcd for $C_{28}H_{21}N_5O_6Na$ 546.1390, found 546.1410.

***N*²-[1-(7-Methylbenz[*a*]anthracene-3,4-dionyl)]-2′-deoxyguanosine (3b).** ^{1}H NMR (DMSO-d_6) δ 2.18−2.28 (m, 1H), 2.64−2.70 (m, 1H), 3.05 (s, 3H), 3.32−3.61 (m, 2H), 3.83 (br, 1H), 4.35 (br. 1H), 5.18 (br, 1H), 5.29 (br, 1H), 5.71 (s, 1H), 6.26 (t, 1H, J = 4.2 Hz), 7.51 (t, 1H, J = 7.5, 7.5 Hz), 7.60 (t, 1H, J = 6.8, 6.8 Hz), 8.00 (d, 1H, J = 9.0 Hz), 8.13 (s, 1H, $H_{guanine}$-8), 8.15 (d, 1H, J = 9.0 Hz), 8.31 (d, 1H, J = 8.8 Hz), 8.50 (d, 1H, J = 9.0 HZ), 10.44 (s, 1H, H-12); ^{13}C NMR (DMSO-d_6) δ 14.1 (CH_3), 62.3, 71.3, 83.8, 88.3, 101.7 (?), 120.1, 120.9, 124.9, 125.8, 126.3, 127.4, 127.8, 130.1, 130.5, 130.6, 130.7, 131.0, 131.9, 132.0, 132.3, 134.4, 137.9, 150.1, 156.5, 157.9, 158.2, 165.4, 187.7; HRMS (M$^+$) calcd for $C_{29}H_{23}N_5O_6$ 537.1648, found 537.1675.

1-Amino-3,4-diacetoxybenz[*a*]anthracene (16a). Hydrogen gas was bubbled through a solution of **5a** (80 mg, 0.29 mmol) and 5% Pd/C (10.0 mg) in DMF (5 mL) for 30 min (TLC indicated reaction to be complete). To the resulting suspension were added Ac_2O (59 mg, 0.58 mmol) and K_2CO_3, and the mixture was stirred at room temperature for 30 min. Then it was poured into water (100 mL), the Pd/C was filtered off, and the solution was extracted with EtOAc. Purification by flash chromatography on a silica gel column eluted with hexane/ EtOAc (3:1) gave **16a** (86 mg, 82.3%): ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.47 (s, 3H), 4.50 (br, 2H), 6.86 (s, 1H), 7.46 (d, 1H, J = 9.2 Hz), 7.57 (m, 2H), 7.64 (d, 1H, J = 9.2 Hz), 8.03 (m, 2H), 8.23 (s, 1H), 9.54 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.3, 20.7, 109.8, 117.1, 119.2, 124.5, 125.8, 125.9, 126.9, 127.3, 127.5, 128.5, 129.0, 130.3, 130.6, 130.9, 131.8, 140.3, 144.3, 168.4, 169.0; HRMS (M + Na$^+$) calcd for $C_{22}H_{17}NO_4Na$ 382.1055, found 382.1055.

1-Amino-3,4-diacetoxy-7-methyl-benz[*a*]anthracene (16b). Yield = 83%; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.46 (s, 3H), 2.87 (s, 3H), 4.30 (br, 2H), 6.78 (s, 1H), 7.42 (d, 1H, J = 9.7 Hz), 7.53 (t, 1H, J = 6.8 Hz), 7.58 (t, 1H, J = 6.8 Hz), 7.88 (d, 1H, J = 9.6 Hz), 7.97 (d, 1H, J = 8.1 Hz), 8.20 (d, 1H, J = 8.5 Hz), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3 (CH_3), 20.5 (CH_3CO), 20.9 (CH_3-CO), 109.7, 117.5, 118.9, 123.1, 124.2, 125.1, 125.4, 125.8, 126.9, 128.3, 128.4, 129.4, 129.9, 130.1, 130.4, 131.2, 140.3, 144.4, 168.6, 169.2; HRMS (M$^+$) calcd for $C_{23}H_{19}NO_4$ 373.1314, found 373.1325.

1-Bromo-3,4-diacetoxybenz[*a*]anthracene (17a). To a solution of **16a** (36 mg, 0.01 mmol) in CH_2Br_2 (25 mL) in a dry ice bath (−35 °C) was injected by syringe a solution of *t*-BuONO (31 mg, 0.03 mmol) in CH_2Br_2 (2 mL) (2.0 mL) followed by addition of a solution of TMSBr in CH_2Br_2 (2.0 mL). The resulting mixture was stirred at −35 °C for 1.0 h, then allowed to warm to 0 °C, and poured into saturated sodium bicarbonate solution. Extraction with CH_2Cl_2 followed by flash chromatography on a silica gel column eluted with hexane/EtOAc (5:1) gave **17a** (22 mg, 53%): ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.52 (s, 3H), 7.63 (m, 3H), 7.86 (d, 1H, J = 9.2 Hz), 7.95 (s, 1H), 8.05 (d, 1H, J = 9.0 Hz), 8.18 (d, 1H, J = 9.0 Hz), 8.36 (s, 1H), 10.50 (s, 1H).

1-Bromo-3,4-diacetoxy-7-methylbenz[*a*]anthracene (17b). ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.51 (s, 3H), 3.02 (s, 3H), 7.50−7.63 (m, 3H), 8.07 (d, 1H, J = 8.5 Hz), 8.14 (d, 1H, J = 10.0 Hz), 8.27 (d, 1H, J = 8.5 Hz), 8.69 (d, 1H, J = 9.0 Hz), 8.95 (s, 1H).

1-Bromo-3,4-dibenzyloxybenz[*a*]anthracene (18a). To a solution of **17a** (21 mg, 0.05 mmol) in DMF (5.0 mL), a catalytic amount 18-crown-6, and benzyl bromide (171 mg, 0.1 mmol) under argon was added KOH (5.7 mg, 1.0 mmol). The reaction mixture was stirred at room temperature for 1.0 h and then poured into ice−water (50 mL). The resulting yellow precipitate was collected by filtration to give **18a** (25 mg, 95.0%) pure enough for the next step: ^{1}H NMR ($CDCl_3$) δ 5.20 (s, 2H), 5.31 (s, 2H), 7.38−7.60 (m,12H), 7.73 (d, 1H, J = 12.0 Hz), 7.76 (s, 1H), 8.00 (d, 1H, J = 10.0 Hz), 8.03 (dd, 1H, J = 2.8, 6.5 Hz), 8.15 (dd, 1H, J = 2.8, 6.5 Hz), 8.30 (s, 1H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 71.5, 75.7, 114.3, 120.2, 121.8, 123.7, 125.6, 126.0, 126.2, 126.3, 127.1, 127.6, 127.8, 128.1, 128.2, 128.4, 128.5, 128.6, 128.8, 129.0, 130.0, 130.9, 131.0, 131.4, 136.2, 137.1, 143.1, 148.9; HRMS (M + Na^+) calcd for $C_{32}H_{23}BrO_2Na$ 541.0774, found 541.0770.

1-Bromo-3,4-dibenzyloxy-7-methylbenz[*a*]anthracene (18b). Yield = 91%; ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 5.28 (s, 2H), 5.31 (s, 2H), 7.39−7.57 (m, 12H), 7.73 (s, 1H), 8.00 (d, 1H, J = 10.0 Hz), 8.08 (d, 1H, J = 10.0 Hz), 8.12 (d, 1H, J = 8.0 Hz), 8.28 (d, 1H, J = 8.0 Hz), 10.18 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4 (CH_3), 71.5 (CH_2), 75.7 (CH_2), 114.3, 119.9, 121.8, 124.1, 124.3, 124.8, 124.9, 125.3, 126.1, 127.5, 127.6, 128.1, 128.2, 128.5, 128.6, 129.3, 129.6, 129.7, 130.3, 130.4, 136.3, 137.2, 142.9, 148.9; HRMS (M + H^+) calcd for $C_{33}H_{26}BrO_2$ 533.1116, found 533.1132.

***N*^{6}-[1-(3,4-Dibenzyloxybenz[*a*]anthracenyl)]-2′-deoxyadenosine (19a).** To a solution of **18a** (5.2 mg, 0.01 mmol) in DMSO (20.0 μL) were added adenine hydrate (2.7 mg, 0.01 mmol), CuI (0.4 mg, 0.002 mmol), *N*,*N*′-dimethylethylenediamine (0.2 mg, 0.002 mmol), and Cs_2CO_3 (3.3 mg, 0.01 mmol). The flask was flushed with argon, and the solution was heated at 110 °C for 8 h. After completion of the reaction, the mixture was diluted with EtOAc and subjected to silica gel flash chromatography with EtOAc/CH_2Cl_2/MeOH (6/6/1) to give **19a** (5.6 mg, 82%): ^{1}H NMR (CD_3OD) 2.47 (m, 1H), 2.88 (m, 1H), 3.78 (dd, 1H, J = 3.5, 7.8 Hz), 3.89 (dd, 1H, J = 3.5, 7.8 Hz), 4.12 (m, 1H), 4.62 (m, 1H), 5.18 (s, 2H), 5.29 (s, 2H), 6.52 (dd, 1H, J = 6.0, 6.0 Hz), 7.34−7.56 (m, 13H), 7.62 (s, 1H), 7.73 (d, 1H, J = 9.5 Hz), 7.94 (d, 1H, J = 8.5 Hz), 8.00 (d, 1H, J = 9.5 Hz), 8.13 (s, 1H), 8.28 (s, 1H), 8.50 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (CD_3OD) δ 41.7, 63.7, 72.4, 73.1, 76.9, 87.3, 90.0, 117.4, 121.8, 123.0, 126.4, 126.8, 127.1, 127.8, 128.3, 129.1, 129.2, 129.3, 129.4, 129.5, 129.6, 129.8, 132.4, 132.6, 132.7, 133.3, 138.4, 139.0, 143.9, 150.8, 153.5; HRMS (M + H^+) calcd for $C_{42}H_{36}N_5O_5$ 690.2716, found 690.2738.

***N*^{6}-[1-(3,4-Dibenzyloxy-7-methylbenz[*a*]anthracenyl)]-2′-deoxyadenosine (19b).** Yield = 79%; ^{1}H NMR (DMSO-d_6) δ 2.28−2.32 (m, 1H), 2.75−2.79 (m, 1H), 3.01 (s, 3H), 3.52−3.55 (m, 1H), 3.62−3.65 (m, 1H), 3.90 (br, 1H), 4.43 (br, 1H), 5.18 (s, 2H), 5.20 (d, 1H, J = 5.5 Hz), 5.31 (s, 2H), 5.34 (d, 1H, J = 3.5 Hz), 6.41 (t, 1H, J = 7.0 Hz), 7.35−7.58 (m, 13 H), 7.62 (s, 1H), 8.02 (d, 1H, J = 9.8 Hz), 8.07 (s, 1H), 8.17 (d, 1H, J = 9.8 Hz), 8.27 (d, 1H, J = 8.8 Hz), 8.55 (s, 1H), 9.67 (s, 1H), 10.41 (s, 1H); ^{13}C NMR (DMSO) δ 14.5 (CH_3), 62.3, 70.8, 71.3, 75.4, 84.4, 88.4, 120.8, 122.3, 124.7, 128.3, 128.5, 128.7, 128.8, 128.9, 129.4, 129.9, 130.1, 131.1, 137.2, 137.8, 141.7, 149.0, 152.6, 154.3; HRMS (M + Na^+) calcd for $C_{43}H_{37}N_5O_5Na$ 726.2692, found 726.2697.

***N*^{2}-[1-(3,4-Dibenzyloxybenz[*a*]anthracenyl)]-2′-deoxy-(6-benzyloxy)-guanosine (21a).** To a solution of **18a** (2.6 mg, 0.005 mmol) and 2′-deoxy-(6-benzyloxy)-guanosine (**20**) (1.8 mg, 0.007 mmol) were added Cs_2CO_3 and DMEDA (0.2 mg, 0.001 mmol), and the solution was stirred at 100 °C under argon for 4.0 h. The solution was cooled to ambient temperature, and water (10 mL) and NH_4OH (1.0 mL of 40% solution) were added. The resulting blue solution was extracted with EtOAc, and the extracts were combined, concentrated, and purified by flash chromatography on a silica gel column. Elution with CH_2Cl_2/MeOH (8:1) gave **21a** (2.3 mg, 57%): ^{1}H NMR (DMSO) δ 2.08−2.32 (m, 2H), 3.77 (m, 1H), 4.20 (m, 1H), 4.80 (m, 1H), 5.17 (s, 2H), 5.22 (m, 1H), 5.33 (s, 2H), 6.20 (m, 1H), 7.18−7.51 (m, 10 H), 7.57 (d, 1H, J = 7.5 Hz), 7.63 (d, 1H, J = 7.5 Hz), 7.68 (s, 1H), 7.82 (d, 1H, J = 10 Hz), 7.97 (d, 1H, J = 10 Hz), 8.02 (d, 1H, J = 8.0 Hz), 8.11 (s, 1H), 8.42 (s, 1H), 9.67 (s, 1H), 9.74 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 62.1, 67.1, 62.1, 70.8, 71.2, 75.4, 75.4, 83.6, 88.2, 116.3, 121.0, 125.6, 127.5, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 129.0, 129.1, 130.9, 131.6, 136.7, 137.3, 137.7, 149.3, 157.6, 160.2; HRMS (M + H^+) calcd for $C_{49}H_{42}N_5O_5$ 796.3130, found 796.3138.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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