JOC Article

Palladium-Catalyzed Synthesis of Nucleoside Adducts from Bay- and Fjord-Region Diol Epoxides

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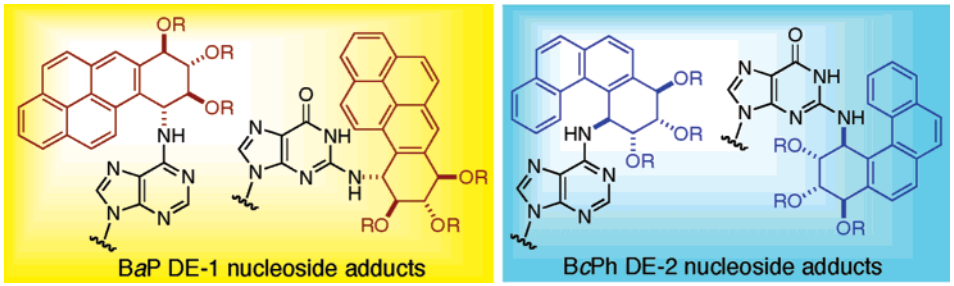

Palladium-catalyzed C−N bond formation has been utilized to synthesize covalent 2′-deoxyadenosine (dA) and 2′-deoxyguanosine (dG) adducts of benzo[*a*]pyrene (B*a*P) series 1 (syn) and benzo[*c*]-phenanthrene (B*c*Ph) series 2 (anti) diol epoxides. For this, (±)-10α-amino-7*β*,8α,9*β*-trisbenzoyloxy-7,8,9,10-tetrahydro B*a*P and (±)-1*β*-amino-2α,3α,4*β*-trisbenzoyloxy-1,2,3,4-tetrahydro B*c*Ph were coupled with 6-halo-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine and O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2-bromo-2′-deoxyinosine, using a (±)-BINAP−Pd complex and Cs_2CO_3. For the synthesis of the dA adducts, both the 6-chloro- as well as the 6-bromopurine nucleoside derivatives were analyzed for the C−N coupling reaction with the hydrocarbon amino tribenzoates. With the B*a*P amino tribenzoate, the 6-chloronucleoside provided satisfactory results, whereas the 6-bromo analogue proved to be superior with the B*c*Ph amino tribenzoate. Overall, lower yields of the dA adducts were obtained with the more hindered fjord-region B*c*Ph amino tribenzoate as compared to the bay-region B*a*P amino tribenzoate. In contrast to reactions leading to the dA adducts, the C−N reactions of both B*a*P and B*c*Ph amino tribenzoates with the 2-bromo-2′-deoxyinosine derivative proceeded in comparable yields. This seems to indicate that such Pd-catalyzed adduct forming reactions at the C-6 position may be influenced by steric constraints of the amine component, whereas those at the C-2 position are less sensitive. Diastereomeric adduct pairs were separated and characterized by spectral methods and by comparisons to adducts produced by direct displacement reactions as well as those formed from DNA alkylation by diol epoxides.

Introduction

Polycyclic aromatic hydrocarbons (PAHs) are ubiquitous environmental pollutants that result from activities of a modern society. Among the multiple metabolic pathways,[1−4] many PAHs that contain a bay- or a fjord-region undergo metabolic activation to four diol epoxides[4] that are thought to exert their carcinogenic activity by alkylation of cellular DNA.[5−7] This reaction with DNA proceeds by C−O bond scission of the

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(1) Earlier studies on PAHs and carcinogenesis have been reviewed in: (a) *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure−Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC Press: Boca Raton, FL, 1988; Vols. I and II. (b) *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Harvey, R. G., Ed.; Cambridge University Press: Cambridge, 1991. *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283: Washington, DC, 1985. (c) For a detailed survey of the chemistry of polycyclic aromatic hydrocarbons, please see: *Polycyclic Aromatic Hydrocarbons*; Harvey, R. G., Ed.; Wiley-VCH: New York, 1997.

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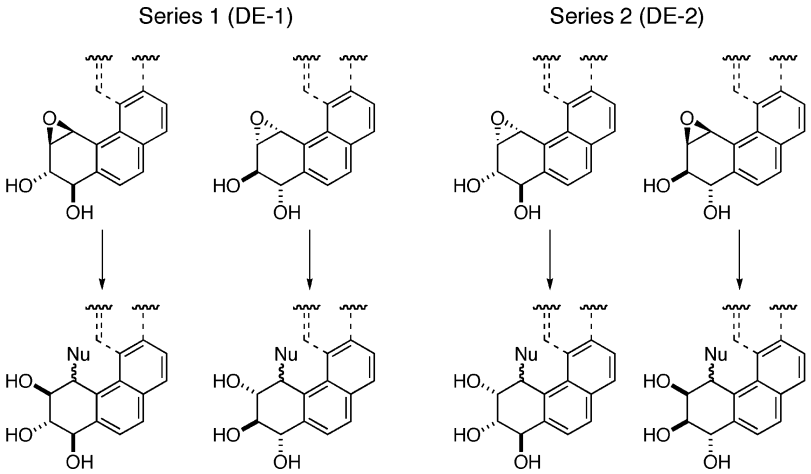
SCHEME 1. Cis/Trans Ring Opening of Four Isomeric Diol Epoxides



oxirane, followed by cis and trans attack by the exocyclic amino groups of the purine bases (Scheme 1).[6,7]

DNA alkylation upon metabolism of any PAH results in the formation of 16 purine nucleoside adducts.[6,7] To probe the structural and biological properties of individual diol epoxide−DNA lesions, access to site-specifically modified DNA containing stereochemically defined diol epoxide adducts is critical. Thus, substantial effort has been directed to the development of methods leading to diol epoxide adducted DNA.[8,9] Reactions of diol epoxides with nucleosides or nucleotides are not productive avenues for the synthesis of these adducts.[8a] Therefore, the total synthesis approach requires reversing the nucleophile/electrophile roles of the nucleoside and the PAH. Reactions of electrophilic purine nucleosides with amino PAH derivatives lead to the covalent diol epoxide−nucleoside adducts that can, after appropriate functionalization, be incorporated into DNA oligomers by solid-phase synthesis methods.[8] Typically, only fluorinated purine nucleosides possess sufficient reactivity to undergo S_NAr displacement reactions with the relatively unreactive amino derivatives of polycyclic aromatic hydrocarbons.[9b,10] However, syntheses of 6-fluoropurine-2′-deoxyriboside[11] and 2-fluoro-2′-deoxyinosine[12] are non-trivial, multistep procedures.

Pd-catalyzed C−N bond formation is growing in significance for the modification of nucleosides,[13] and several biologically important nucleoside adducts have been synthesized via its application.[14] Our interest in Pd-catalyzed synthesis of diol epoxide−nucleoside adducts stemmed from several important considerations, such as the cumbersome synthesis of reactive fluorinated nucleosides usually required for displacement reactions with the axially constrained and hindered PAH amines and the fact that some displacement reactions leading to the diol epoxide nucleoside adducts are not particularly efficient. Access to chloro- and bromonucleosides is easier,[11,14a,15,16] and Pd-catalyzed C−N bond formation presents a potentially facile approach to this important class of biologically relevant, modified nucleosides.

We[17] and others[18] have independently reported Pd-catalyzed synthesis of nucleoside adducts from the carcinogenic (±)-B*a*P

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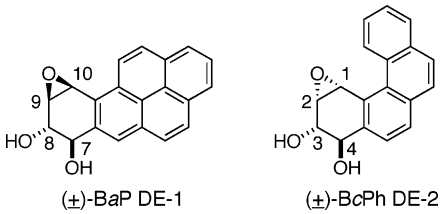


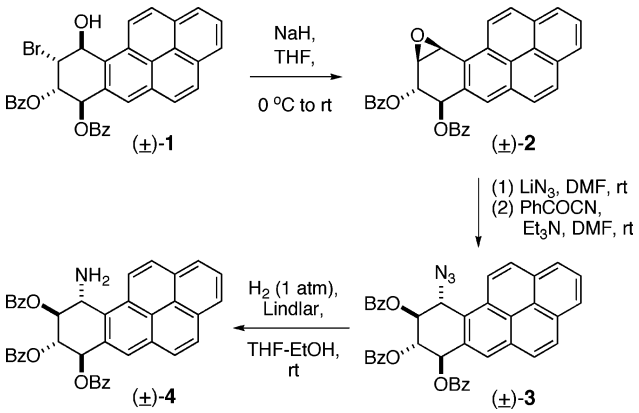
FIGURE 1. Bay- and fjord-region diol epoxides of B*a*P and B*c*Ph.

DE-2. Therefore, the current investigation focused on the synthesis of adducts from the stereoisomeric (±)-B*a*P DE-1 (a bay-region derivative) and from (±)-B*c*Ph DE-2 (a fjord-region compound; Figure 1), representing two structurally different paradigms. This also provided an opportunity to understand on a comparative basis the efficiency of catalysis reactions on chloro- and bromonucleosides. Pd-catalyzed amination of a trissilyl protected 6-chloropurine nucleoside with aliphatic amines was reported to proceed in good yield, but reactions with the less nucleophilic aryl amines were low-yielding.[19] Prior work has shown that the direct displacement reactions of hindered PAH amines with 6-chloropurine nucleoside are inefficient.[9b,10] On the other hand, two PAH amines underwent efficient Pd-catalyzed coupling with 6-chloro-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine,[17] and both chloro- and bromonucleosides were effective coupling partners in C−N bond formation with azole nitrogens.[20] On the basis of these results, we decided to assess the effectiveness of 6-bromo- and 6-chloro-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine for Pd-catalyzed C−N bond forming reactions with bay- and fjord-region amino PAH derivatives. In this paper, we discuss: (a) the efficiencies of 2′-deoxyadenosine adduct syntheses by C−N bond formation with the two C-6 halopurine 2′-deoxyribonucleosides, (b) the synthesis of 2′-deoxyguanosine adducts of the two PAH diol epoxides, (c) a comparison of the various reactions, and (d) an assessment of the stereochemical integrity in the Pd-catalyzed reactions.

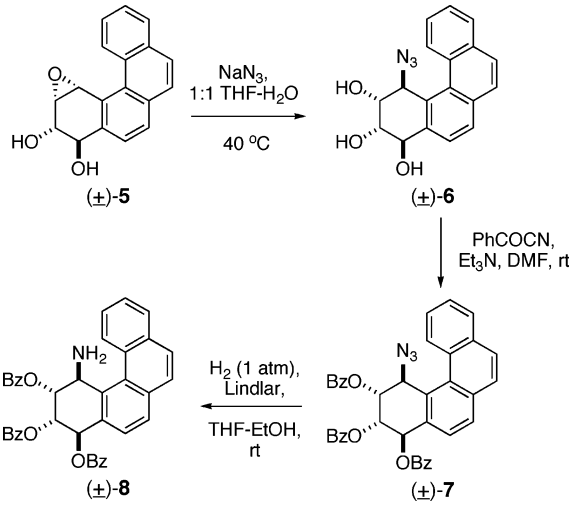
Results and Discussion

Synthesis of B*a*P Amino Tribenzoate. Many PAH amino triols and amino triacyl derivatives that are suitable precursors to the nucleoside−diol epoxide adducts can be stereoselectively synthesized by ring-opening reactions of the diol epoxides themselves.[8,9b,10,21] As shown in Scheme 2, in the present case, known bromohydrin (±)-**1** was synthesized via reaction of B*a*P dihydrodibenzoate[22] with NBS/NaOAc in ∼30% H_2O−THF[23] and cyclized to the epoxide (±)-**2**[23] with NaH in dry THF (Cs_2CO_3 in THF can be used, but the ensuing reactions are not very clean). Ring-opening of **2** to the azidotriol dibenzoate was performed with LiN_3 in DMF at room temperature, and the resulting crude material was directly converted to the azido tribenzoate (±)-**3**.[21b] Finally, the reduction of the azide moiety with H_2 and the Lindlar catalyst yielded the amino tribenzoate (±)-**4** (use of excess catalyst was required for efficient conversion; Pd−C could also be used but was less efficient and PtO_2 was ineffective).

SCHEME 2. Synthesis of B*a*P Amino Tribenzoate



SCHEME 3. Synthesis of B*c*Ph Amino Tribenzoate



Synthesis of B*c*Ph Amino Tribenzoate. Synthesis of the B*c*Ph amino tribenzoate (±)-**8** commenced from B*c*Ph DE-2 [(±)-(**5**)] (Scheme 3).[24] Because of its low solvolytic reactivity, as we had reported earlier,[25] the ring opening of (±)-**5** was conducted in THF−H_2O. These conditions eliminate non-benzylic ring opening by the azide, a feature that was observed when DMF was used as a solvent.[25] Conversion of the azidotriol (±)-**6** to the triester (±)-**7** was accomplished with PhCOCN/Et_3N in DMF.[21b] Again, catalytic reduction with H_2 and excess Lindlar catalyst yielded the amino tribenzoate (±)-**8**.

Coupling of the B*a*P and B*c*Ph Amino Tribenzoates with C-6 Halo Purine 2′-Deoxyribosides. Once the amino tribenzoates (±)-**4** and (±)-**8** were synthesized, the next step was the analysis of their coupling with each of the halo nucleosides 6-chloro- and 6-bromo-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine (**9** and **10**). For this, we selected conditions that we have successfully used previously

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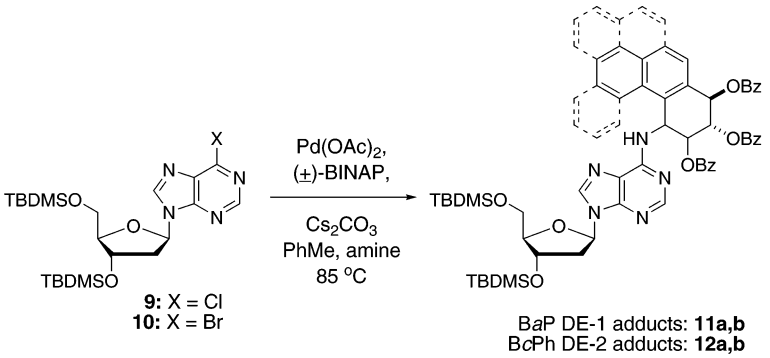
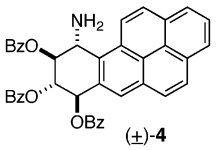
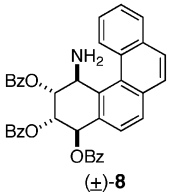
TABLE 1. Coupling of Amino Tribenzoates (±)-4 and (±)-8 with the Two C-6 Halo Nucleosides 9 and 10[a]



9: X = Cl
10: X = Br

B*a*P DE-1 adducts: **11a,b**
B*c*Ph DE-2 adducts: **12a,b**

entry	amine	mmol	nucleoside	molar [nucleoside]	time (h)	adducts, yield[b]
1	 (±)-**4**	0.032	**9**	0.028	22	**11a,b:** 32%
2		0.044	**9**	0.04	8	**11a,b:** 43%
3		0.028	**9**	0.1	4	**11a,b:** 59%
4		0.024	**10**	0.1	4	**11a,b:** 57%
5		0.222	**9**	0.1	5	**11a,b:** 73%
6	 (±)-**8**	0.028	**9**	0.025	6	**12a,b:** 37%
7		0.029	**9**	0.1	4	**12a,b:** 36%
8		0.026	**10**	0.1	4	**12a,b:** 50%
9		0.265	**10**	0.1	4	**12a,b:** 45%

[a] Reactions were conducted in PhMe at 85 °C. [b] Yield is of isolated, purified products and represents the combined yield of diastereomeric adduct pairs.

for the synthesis of B*a*P DE-2 adducts with 2′-deoxyadenosine.[17] The C−N bond formation was conducted with 1.1 molar equiv of amine with the combination of 10 mol % $Pd(OAc)_2$/30 mol % (±)-BINAP/1.4 molar equiv of Cs_2CO_3 in toluene as the solvent. The results of these reactions are compiled in Table 1.

The results in Table 1 show some interesting features and also provide meaningful comparisons between the reactions of the two amines. In the case of the B*a*P amino tribenzoate (±)-**4**, the reactions appeared to be dependent upon the concentration of the nucleoside (limiting reagent), and the coupling yield increased with concentration (entries 1−3). When comparing yields of **11a**,**b** from the reactions of the two halo nucleosides, as we had demonstrated in an earlier communication,[17] chloronucleoside **9** underwent C−N bond formation in comparable yield to the bromo analogue **10** (entry 3 vs 4). In contrast to these results, reactions with B*c*Ph amino tribenzoate (±)-**8** appeared to be different. The nucleoside concentration had a smaller influence on the product yield, and more notably, reactions with bromonucleoside **10** provided superior results. Yields of adducts **12a**,**b** from the more hindered fjord-region B*c*Ph amino tribenzoate were lower than those from the bay-region B*a*P derivative.

Coupling of the B*a*P and B*c*Ph Amino Tribenzoates with *O*^{6}-Benzyl-2-bromo-2′-deoxyinosine. Since we have faced difficulties in the preparation of 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2-chloro-2′-deoxyinosine,[26] the readily available 2-bromo analogue **13**[14a] was used to synthesize the 2′-deoxyguanosine adducts. Using the same catalyst composition described previously for the synthesis of the 2′-deoxyadenosine adducts, C−N bond formation between PAH amino tribenzoates (±)−**4**, (±)−**8**, and **13** was conducted at a nucleoside concentration of 0.1 M. The results from these experiments are shown in Table 2.

The most noteworthy feature in Table 2 is the observation that comparably good product yields were obtained from the two amino benzoates. This contrasts with the results in Table 1 where the yield of the 2′-deoxyadenosine adducts from the more hindered B*c*Ph amino tribenzoate was lower than that from the B*a*P amino tribenzoate. This result seems to imply that some subtle influences, possibly steric features associated with the PAH amines, come into play in C−N bond formation at the C-6 position of purine nucleosides but that such effects do not seem to influence C−N bond formation at the C-2 position. Most impressively, good yields of both B*a*P and B*c*Ph adducts are realized via this method. Although these compounds can be directly used for DNA assembly by methods we have previously described,[8d] for reasons indicated later, unequivocal structure confirmation was undertaken.

Structure Confirmation of the Synthetic PAH Diol Epoxide−Nucleoside Adducts. In products **11a**,**b** and **12a**,**b**, the benzoates in each pair of diastereomeric adducts were cleaved with NH_3/MeOH, and the resulting trihydroxy compounds were acetylated (Scheme 4). In the case of **14a**,**b** and **15a**,**b**, the previously described acyl group interchange was followed by removal of the *O*^{6}-benzyl group by hydrogenolysis (Scheme 4). Small amounts of the diastereomeric adducts were

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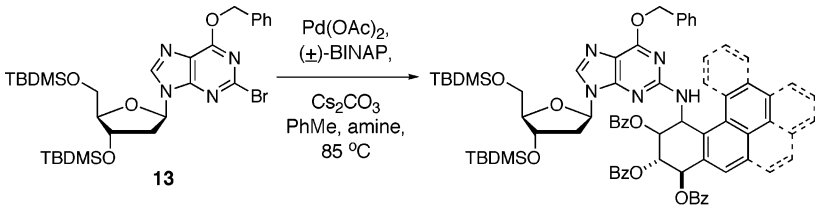
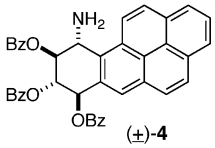
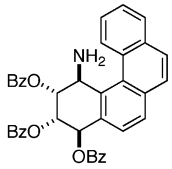
TABLE 2. Coupling of Amino Tribenzoates (±)-4 and (±)-8 with 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2-bromo-2′-deoxyinosine 13[a]

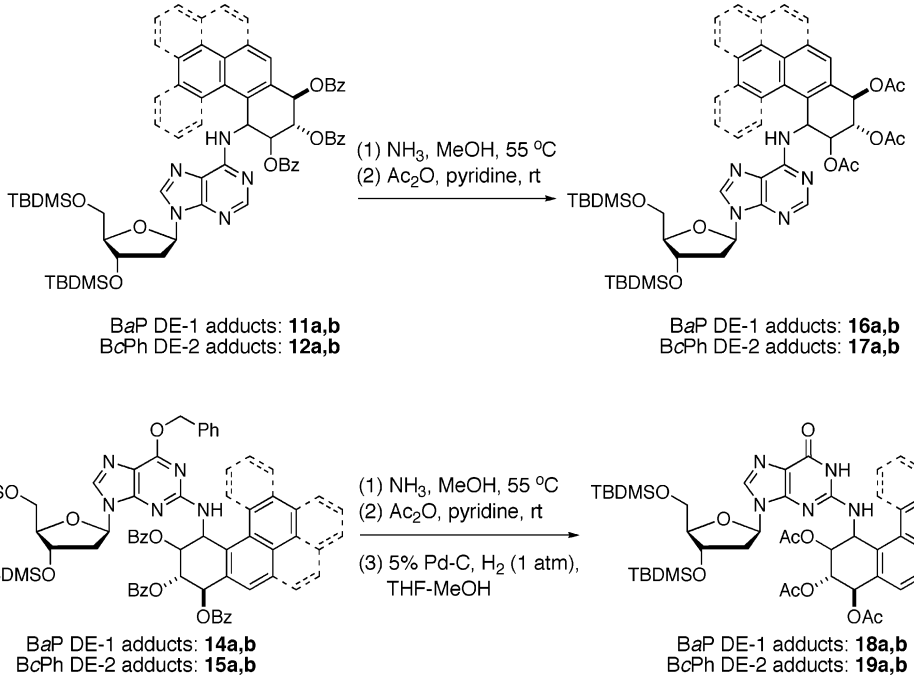


BaP DE-1 adducts: **14a,b**
BcPh DE-2 adducts: **15a,b**

entry	amine	mmol	time (h)	adducts, yield[b]
1	 (±)-**4**	0.023	18	**14a,b:** 68%
2		0.222	16	**14a,b:** 73%
3	 (±)-**8**	0.029	18	**15a,b:** 68%
4		0.265	16	**15a,b:** 70%

[a] Reactions were conducted in PhMe at 85 °C at a 0.1 M concentration of the nucleoside. [b] Yield is of isolated, purified products and represents the combined yield of diastereomeric adduct pairs.

SCHEME 4. Preparation of Adduct Triacetates for Characterization



separated by preparative TLC after these manipulations, and as described in the next section, the disilyl triacetates **16a**−**19b** were analyzed in detail.

Evaluation of Stereochemical Integrity in the Adduct Forming Reactions. The presence of a hydrogen atom α to the amino group raises the possibility of a loss of stereochemical integrity, and a loss of chirality in Pd-mediated C−N bond formation via *β*-hydride migration has been documented in the literature.[27] The use of a bis-phosphine ligand provides amelioration of this problem, possibly by closing open coordination sites at the metal center.[27] In the present cases, stereochemical integrity is of utmost importance since loss of chirality at the amine bearing carbon would alter the structure and conformation of the biologically important adducts that are to be used for structure−biological studies.

(27) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 8451−8458.

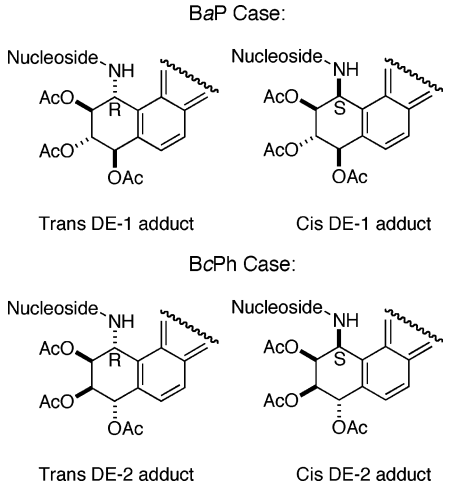


FIGURE 2. Loss of stereochemical integrity would result in the cis rather than the trans adducts.

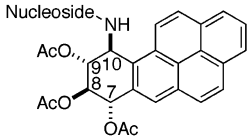
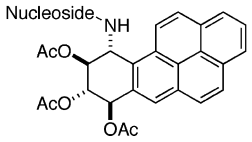
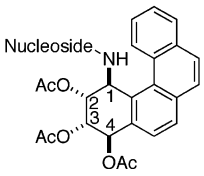
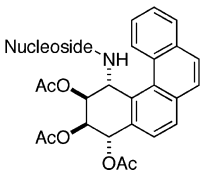
In our preliminary communication where we had initially disclosed studies on Pd-mediated C−N bond formation as a route to carcinogen−nucleoside conjugates,[17] we had addressed this potential problem by comparison of the products to those that were synthesized by displacement of fluoride from a fluoronucleoside. In the present cases, chirality attrition would result in a cis relative stereochemical arrangement of the nucleoside and the adjacent acetoxyl group (Figure 2). Chiro-optical methods alone would not be adequate to distinguish between trans and cis products due to close similarities in their CD spectra.[28]

Therefore, the coupling constants of the tetrahydro ring protons in the adducts obtained by the Pd-catalyzed method (Table 3) were compared to cis and trans adducts that are known in the literature and/or have been unequivocally synthesized (see the Supporting Information for this data). In the B*a*P case, the trans ring-opened 2′-deoxyadenosine adducts (**16a**,**b**) synthesized in this study showed $J_{7,8} = 5.8-6.0$, $J_{8,9} = 6.6-6.9$, and $J_{9,10} = 3.9-4.2$ Hz, and these are consistent with those for adducts derived from 6-fluoro-9-[3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-*erythro*-pentofuranosyl]purine ($J_{7,8} = 6.2$, $J_{8,9} = 7.0$, and $J_{9,10} = 4.0$ Hz). The latter products are derived via a S_NAr mechanism, where chirality attrition is not a question. Further, the *J* values of the trans adducts are quite different from those of the isomeric cis compounds, where they are $J_{7,8} = 7.9-8.0$, $J_{8,9} = 11.5$, and $J_{9,10} = 4.5$ Hz.[9e] The coupling constants for the trans ring-opened 2′-deoxyguanosine adducts (**18a**,**b**) obtained in the present study were $J_{7,8} = 6.5-6.9$, $J_{8,9} = 6.5-7.0$, and $J_{9,10} = 4.0-4.4$ Hz. Not only are these values very similar to those reported for the adducts obtained from 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2-fluoro-2′-deoxyinosine by fluoride displacement ($J_{7,8} = 6.1-6.9$, $J_{8,9} = 6.6-6.8$, and $J_{9,10} = 3.9-4.4$ Hz),[29] but again these are also markedly different from those of the isomeric cis ring-opened adducts ($J_{7,8} = 8.2$, $J_{8,9} = 11.8$, and $J_{9,10} = 2.2$ Hz).[30]

In the B*c*Ph case, the differences in the *J* values for the isomeric cis and trans ring-opened adducts are smaller. Thus, data for the 2′-deoxyadenosine adducts (**17a**,**b**) were compared to those reported for the products arising from fluoride displacement chemistry[25] as well as adduct peracetates obtained from alkylation of DNA by (±)-B*c*Ph DE-2,[31] and a very close match was observed (see the Supporting Information for a comprehensive tabulation). Best comparisons for the 2′-deoxyguanosine adducts (**19a**,**b**) were data for the peracetates of adducts derived from DNA alkylation by (±)-B*c*Ph DE-2.[31] The observed coupling constants for **19a**,**b** are $J_{3,4} = 8.5-8.9$, $J_{2,3} = 2.6-2.7$, and $J_{1,2} = 4.3-4.4$ Hz, and these match well with $J_{3,4} = 8.4-8.5$, $J_{2,3} = 1.6-2.6$, and $J_{1,2} = 4.1-4.5$ Hz reported for the corresponding adduct peracetates (see the Supporting Information).

These comparisons led us to the conclusion that chirality scrambling was not a problem within the detection limits of the analyses used. An interesting observation that stemmed from these studies is that the B*a*P adducts **16a**,**b** showed a solvent-dependent conformational change that is reflected in the coupling constants of the tetrahydro ring protons. The $J_{7,8} = 5.8-6.0$, $J_{8,9} = 6.6-6.9$, and $J_{9,10} = 3.9-4.2$ Hz observed in acetone-d_6 dramatically changed to $J_{7,8} = 3.1$, $J_{8,9} = 3.3-3.6$, and $J_{9,10} = 2.9$ Hz in $CDCl_3$. Since the coupling constants provide an understanding of the orientation of the substituents in the tetrahydrobenzo ring, a decrease in the values is an indication of substantially more axially disposed substituents in $CDCl_3$ as compared to acetone-d_6.

TABLE 3. Coupling Constants for Tetrahydro Ring Protons in the Adducts[a]

benzo[*a*]pyrene series	*2′-deoxyadenosine adducts*	*2′-deoxyguanosine adducts*[d]
	**16a** (10*S*)	**18a** (10*S*)
	$J_{9,10} = 4.2^b$ (2.9)[c]	$J_{9,10} = 4.4$
	$J_{8,9} = 6.9^b$ (3.3)[c]	$J_{8,9} = 7.0$
	$J_{7,8} = 6.0^b$ (3.1)[c]	$J_{7,8} = 6.9$
	**16b** (10*R*)	**18b** (10*R*)
	$J_{9,10} = 3.9^b$ (2.9)[c]	$J_{9,10} = 4.0$
	$J_{8,9} = 6.6^b$ (3.6)[c]	$J_{8,9} = 6.5$
	$J_{7,8} = 5.8^b$ (3.1)[c]	$J_{7,8} = 6.5$
benzo[*c*]phenanthrene series	*2′-deoxyadenosine adducts*	*2′-deoxyguanosine adducts*[d]
	**17a** (1*S*)	**19a** (1*S*)
	$J_{1,2} = 4.5^b$ (3.3)[c]	$J_{1,2} = 4.4$
	$J_{2,3} = 2.9^b$ (2.9)[c]	$J_{2,3} = 2.7$
	$J_{3,4} = 8.3^b$ (7.3)[c]	$J_{3,4} = 8.5$
	**17b** (1*R*)	**19b** (1*R*)
	$J_{1,2} = 4.1^b$ (3.7)[c]	$J_{1,2} = 4.3$
	$J_{2,3} = 2.4^b$ (2.9)[c]	$J_{2,3} = 2.6$
	$J_{3,4} = 8.3^b$ (7.4)[c]	$J_{3,4} = 8.9$

[a] Data obtained at 500 MHz under ambient conditions. [b] Obtained in acetone-d_6. [c] Obtained in deacidified $CDCl_3$. [d] Obtained in DMSO-d_6.

(28) Cheng, S. C.; Hilton, B. D.; Roman, J. M.; Dipple, A. *Chem. Res. Toxicol.* **1989**, *2*, 334−340.

(29) See the Supporting Information to: Custer, L.; Zajc, B.; Sayer, J. M.; Cullinane, C.; Phillips, D. R.; Cheh, A. M.; Jerina, D. M.; Bohr, V. A.; Mazur, S. J. *Biochemistry* **1999**, *38*, 569−581.

(30) Kroth, H.; Yagi, H.; Seidel, A.; Jerina, D. M. *J. Org. Chem.* **2000**, *65*, 5558−5564.

(31) Agarwal, S. K.; Sayer, J. M.; Yeh, H. J. C.; Pannell, L. K.; Hilton, B. D.; Pigott, M. A.; Dipple, A.; Yagi, H.; Jerina, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2497−2504.

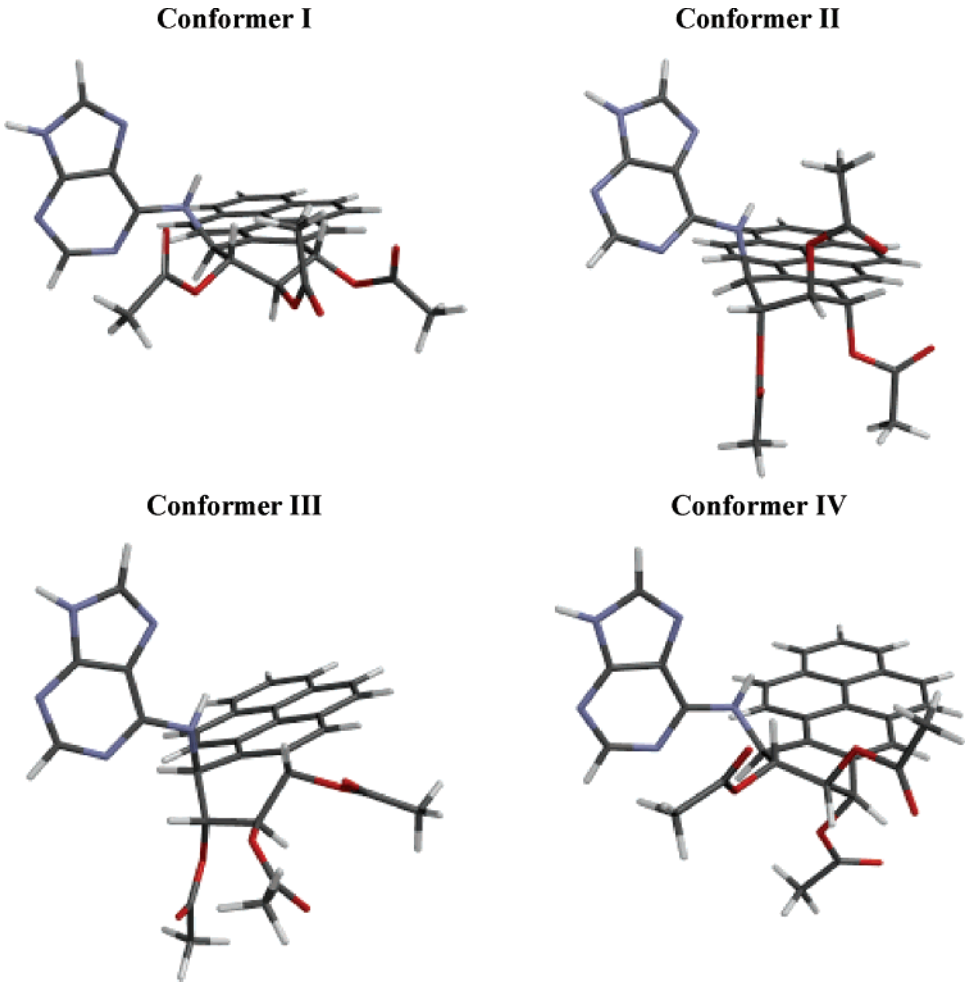


FIGURE 3. Possible conformations of the 10*S* B*a*P DE-1 deoxyadenosine adduct **16a** (generated via MacSpartan Pro V 1.0.3). For simplicity, the saccharide of the nucleoside has been replaced with a hydrogen atom.

In evaluating the conformational equilibria of the B*a*P DE-1 adducts **16a**,**b**, the NMR coupling constants were compared to those of products obtained by a trans ring opening of B*a*P DE-1 with various nucleophiles.[23] There are four principal conformers that can be considered for **16a**,**b**, and those for the 10*S* diastereomer (**16a**) are shown in Figure 3. Among these, half-chair conformer **I** was generated by imposing large dihedral angles between vicinal protons, and the structure was optimized. For conformers **II**−**IV**, possible dihedral angle constraints were imposed based upon the observed *J* values, and the structures were optimized followed by further minimization using semi-empirical AM1. Conformer **I** that has all equatorial substituents can be readily eliminated since this should display large coupling constants between all the axial protons and would require a quasi-equatorial orientation of the bay-region purine substituent as well (for this reason, no further AM1 minimization was considered). This analysis is comparable to that reported for the ring-opening products of B*a*P DE-1.[23] A half-chair conformer **II** appears to be preferred in $CDCl_3$, a solvent of lower polarity, and dihedral angles (absolute values) after AM1 minimization are $H_7-C-C-H_8 = 55.3$, $H_8-C-C-H_9 = 48.4$, and $H_9-C-C-H_{10} = 54.6$. A possible stabilizing feature in such a conformer could be an intramolecular hydrogen bond between the NH proton and the axial acyl group on the same face. In analogy to the conformation of **16a**, a C-10 anilino adduct arising by a trans ring opening of B*a*P DE-1 has also been proposed to exist in a conformation with all axial substituents in $CDCl_3$, possibly stabilized by an intramolecular hydrogen bond.[23] In the more polar acetone-d_6, there are two possible conformers that could account for the observed *J* values. These are **III**, where the absolute values of the dihedral angles in the minimized structure are $H_7-C-C-H_8 = 147.4$, $H_8-C-C-H_9 = 145.6$, and $H_9-C-C-H_{10} = 48.4$, and **IV** with dihedral angles $H_7-C-C-H_8 = 35.4$, $H_8-C-C-H_9 = 144.7$, and $H_9-C-C-H_{10} = 136.7$. Both **III** and **IV** adopt a boat or a flattened half chair conformation, and this analysis is again comparable to that reported for the trans ring-opening products of B*a*P DE-1.[23] In conformer **III**, the C-7 and C-8 substituents are diequatorially disposed, whereas in conformer **IV**, these are diaxial. Between **III** and **IV**, the latter also has a quasi-equatorial purine substituent in the sterically congested bay-region (quasi-axial in **III**). These reasons render **III** more preferable to **IV**. In the case of the B*c*Ph adducts **17a**,**b**, although small differences in the coupling constants were observed in $CDCl_3$ and acetone-d_6, these were not as dramatic. Such an analysis was not conducted with the 2′-deoxyguanosine adducts as a good line shape for these is typically only observed in DMSO-d_6 and not in $CDCl_3$.

Conclusion

In summary, our studies show that Pd-mediated amination chemistry is an effective method leading to nucleoside adducts

of PAH diol epoxides. This method appears to be broadly applicable to the synthesis of bay- and fjord-region diol epoxide−nucleoside adducts and in the present case has led to the synthesis of nucleoside adducts from B*a*P DE-1 and B*c*Ph DE-2. There are some interesting differences in these reactions. The adduct forming reactions of the less hindered amino tribenzoate derived from B*a*P DE-1 provided good yields of the N^6-2′-deoxyadenosine adducts, whereas corresponding reactions with the more hindered amino tribenzoate derived from B*c*Ph DE-2 were lower yielding. This suggests that subtle factors, possibly steric congestion, associated with the PAH amino tribenzoates are at play in these reactions. Also, reactions with the B*a*P amino tribenzoate proceeded well with the C-6 chloronucleoside, whereas those with the B*c*Ph amino tribenzoate proceeded better with the C-6 bromonucleoside. In each case, the pure adduct diastereomers were separated after replacement of the PAH benzoyl groups with acetyl esters. Quite in contrast to reactions at the C-6 position, C−N bond−forming reactions of both B*a*P and B*c*Ph amino tribenzoates at the C-2 position of silyl protected O^6-benzyl-2-bromo-2′-deoxyinosine proceeded in comparably good yields. This seems to suggest that structural factors associated with the PAH component are not quite as critical in reactions at the C-2 position. Here again, the benzoyl groups on PAH were replaced with acetyls, and facile debenzylation delivered the PAH diol epoxide 2′-deoxyguanosine adducts quite efficiently. The adduct diastereomers were readily separated after the O^6 deprotection. The pure adduct diastereomers from each reaction were compared with known compounds. On the basis of these comparisons, it was rationalized that loss of chirality at the amine bearing carbon does not compete with product formation. This factor is important from the standpoint that these compounds are to be used for structural and biochemical experimentation after incorporation into DNA oligomers. Chemistry leading to site-specific DNA modification by these diol epoxide−nucleoside adducts is underway, and results are forthcoming.

Experimental Procedures

(±)-7*β*,8α-Bisbenzoyloxy-9α-bromo-10*β*-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (1).[23] To a solution of (±)-7*β*,8α-bisbenzoyloxy-7,8-dihydrobenzo[*a*]pyrene[22] (1.4 g, 2.8 mmol) in THF−H_2O (350 mL/140 mL) were added freshly recrystallized *N*-bromosuccinimide (654 mg, 3.6 mmol) and NaOAc (695 mg, 8.4 mmol). The mixture was stirred under N_2 gas at room temperature under subdued light. TLC showed the reaction to be complete after 18 h, and the solvents were evaporated. The residue was dissolved in ethyl acetate and washed twice with water. The organic layer was separated, dried over Na_2SO_4, and evaporated. The resulting product was chromatographed on silica gel using CH_2Cl_2, and product obtained was then washed twice with 1:1 ether−hexane to afford 1 g (60%) of (±)-**1** as a white powder.

(±)-7*β*,8α-Bisbenzoyloxy-9*β*,10*β*-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (2).[23] A stirring suspension of NaH (24 mg, 1 mmol) in THF (5 mL) was flushed with N_2 gas and cooled in an ice bath. Compound **1** (300 mg, 0.507 mmol) was added, and the mixture turned brownish. After stirring at 0 °C for 1 h, the mixture was allowed to warm to room temperature over 30 min. TLC indicated the reaction to be complete. The mixture was diluted with 1:1 Et_2O−EtOAc and washed twice with water. The organic layer was dried over Na_2SO_4 and evaporated to leave a solid. This solid was washed twice with 1:1 Et_2O−hexane with sonication to yield 217 mg (84%) of (±)-**2** as a pinkish powder.

(±)-10α-Azido-7*β*,8α,9*β*-trisbenzoyloxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (3).[21b] The diol epoxide dibenzoate (±)-**2** (657 mg, 1.28 mmol) and LiN_3 (629.6 mg, 12.86 mmol) were allowed to stir in DMF (15 mL) at room temperature overnight. The mixture was diluted with EtOAc and washed with water. The organic layer was dried over Na_2SO_4 and evaporated. This crude material was directly benzoylated by the addition of dry DMF (30 mL) and dry Et_3N (1.5 mL, 10.7 mmol) followed by benzoyl cyanide (0.839 g, 6.4 mmol). The mixture was allowed to stir at room temperature for 30 min, quenched with methanol, and diluted with EtOAc. The mixture was washed twice with brine, and the organic layer was dried over Na_2SO_4 and evaporated. The resulting yellow oil was chromatographed on a silica gel column using CH_2Cl_2. The product was washed twice with 1:1 Et_2O−hexane to yield 513 mg (61%) of (±)-**3** as a white powder.

(±)-10α-Amino-7*β*,8α,9*β*-trisbenzoyloxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (4).[21b] To a suspension of Lindlar catalyst (875 mg) in 1:1 THF−EtOH (70 mL) was added the azidotribenzoate (±)-**3** (175 mg, 0.27 mmol). The suspension was stirred under a hydrogen balloon for 2 h and 20 min, at which time TLC indicated that all starting material had been consumed. The mixture was filtered through Celite, and the solvents were evaporated. The resulting pinkish oil was chromatographed on a silica gel column using 1:100 MeOH−CH_2Cl_2, and the resulting product was washed twice with 1:1 Et_2O−hexane to yield 121 mg (72%) of (±)-**4** as a white powder.

(±)-1*β*-Azido-2α,3α,4*β*-trihydroxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (6).[25] B*c*Ph diol epoxide (±)-**5** (244 mg, 0.876 mmol) and sodium azide (569.9 mg, 8.76 mmol) were stirred in 1:1 THF−H_2O (100 mL) at 40 °C. TLC showed disappearance of the starting material after 40 h. The mixture was extracted with EtOAc. The aqueous layer was extracted one more time with EtOAc, and the combined organic layers were washed with water, dried over Na_2SO_4, and evaporated. The product was taken up in the minimum volume of Et_2O and added to hexane under sonication. The precipitated product was isolated and treated in the same manner one more time. The resulting white powder was dried to yield 225 mg (80%) of (±)-**6**.

(±)-1*β*-Azido-2α,3α,4*β*-trisbenzoyloxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (7). The azido triol (±)-**6** (39.5 mg, 0.123 mmol) was dissolved in dry DMF (1.5 mL). Dry Et_3N (171.5 μL, 1.23 mmol) and benzoyl cyanide (161.3 mg, 1.23 mmol) were added, and the reaction mixture was allowed to stir for 45 min at room temperature. The reaction was quenched with sat aq $NaHCO_3$, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated. The product was chromatographed on silica gel using 2:1 toluene−CH_2Cl_2. Finally, some minor impurities were removed by washing the product twice with 1:1 Et_2O−hexane. This process yielded 47 mg (60%) of (±)-**7** as a white powder. R_f (SiO_2/2:1 toluene−CH_2Cl_2) = 0.53. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.00 (d, 1H, Ar−H, J = 8.8), 8.14 (d, 2H, Ar−H, J = 8.3), 8.01 (d, 1H, Ar−H, J = 8.3), 7.97 (d, 2H, Ar−H, J = 8.3), 7.82 (d, 1H, Ar−H, J = 8.8), 7.79−7.68 (m, 7H), 7.58 (t, 1H, Ar−H, J = 7.7), 7.53 (t, 1H, Ar−H, J = 7.4), 7.48 (t, 1H, Ar−H, J = 7.4), 7.47 (d, 1H, Ar−H, J = 7.8), 7.46 (d, 1H, Ar−H, J = 7.8), 7.36 (t, 2H, Ar−H, J = 7.8), 7.31 (t, 2H, Ar−H, J = 7.4), 7.14 (d, 1H, H4, J = 7.3), 6.35 (dd, 1H, H3, J = 7.3, 2.6), 6.18 (dd, 1H, H2, J = 4.9, 2.6), 5.97 (d, 1H, H1, J = 4.9). HRMS calculated for $C_{39}H_{31}N_4O_6$ ($M^+ + NH_4$): 651.2238, found: 651.2239.

(±)-1*β*-Amino-2α,3α,4*β*-trisbenzoyloxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (8). The azido tribenzoate (±)-**7** (239 mg, 0.38 mmol) and Lindlar catalyst (1.195 g) were stirred in 1:1 THF−EtOH (95 mL) under a hydrogen balloon for 2 h and 20 min while protected from light. TLC showed a disappearance of the starting material and the formation of a new spot. The mixture was filtered through Celite, and the residue was washed twice with EtOAc. The filtrate was dried over Na_2SO_4, and the solvents were evaporated. The compound was purified by chromatography on a silica gel column using 95:5 toluene−EtOAc. Finally, some minor contaminants were removed by washing the product with 1:1 Et_2O−hexane

to provide 199 mg (87%) of (±)-**8** as a white powder. R_f (SiO_2/95:5 toluene−EtOAc) = 0.26. ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.51 (d, 1H, Ar−H, J = 8.6), 8.13 (d, 2H, Ar−H, J = 7.8), 7.97 (d, 2H, Ar−H, J = 7.8), 7.93 (t, 2H, Ar−H, J = 7.6), 7.77 (d, 1H, Ar−H, J = 8.6), 7.75 (d, 2H, Ar−H, J = 7.7), 7.72 (t, 2H, Ar−H, J = 8.3), 7.66 (d, 1H, Ar−H, J = 8.1), 7.65 (t, 1H, Ar−H, J = 7.3), 7.57 (t, 1H, Ar−H, J = 7.6), 7.50 (t, 1H, Ar−H, J = 7.6), 7.47 (t, 1H, Ar−H, J = 7.7), 7.46 (d, 1H, Ar−H, J = 7.7), 7.44 (d, 1H, Ar−H, J = 7.6), 7.35 (t, 2H, Ar−H, J = 7.6), 7.30 (t, 2H, Ar−H, J = 7.7), 7.06 (d, 1H, H4, J = 7.8), 6.65 (dd, 1H, H3, J = 7.8, 2.5), 6.04 (app. t, 1H, H2, J = 3.5), 5.55 (d, 1H, H1, J = 4.4). HRMS calculated for $C_{39}H_{30}NO_6$ (M^+ + H): 608.2068, found: 608.2070.

***N*^{6}-[10-(7,8,9-Trisbenzoyloxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (11a,b). (a) Pd-Mediated Coupling of 9 and (±)-4.** Into an oven-dried, screw-capped vial equipped with a stirring bar were placed $Pd(OAc)_2$ (4.6 mg, 20.5 μmol) and (±)-BINAP (37.7 mg, 60.5 μmol). Toluene (2 mL) was added, and the mixture was stirred at room temperature for 5 min. Cs_2CO_3 (92.0 mg, 0.282 mmol) followed by (±)-**4** (140.0 mg, 0.222 mmol) and then chloronucleoside **9** (100.6 mg, 0.202 mmol) were added. The vial was flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 85 °C. The reaction was monitored by TLC and judged to be complete after 5 h, at which time the mixture was cooled, diluted with Et_2O, and washed twice with brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. Chromatography of the crude mixture on a silica gel column using 4:40:56 acetone−hexane−CH_2Cl_2 yielded 161 mg (73%) of the diastereomeric mixture of adducts **11a**,**b** as a white powder. R_f **11a**,**b** (SiO_2/4:40:56 acetone−hexane−CH_2Cl_2) = 0.61.

(b) Pd-Mediated Coupling of 10 and (±)-4. A similar C−N reaction between bromonucleoside **10** (11.7 mg, 21.5 μmol) and (±)-**4** (15.0 mg, 23.7 μmol) was conducted using $Pd(OAc)_2$ (0.5 mg, 2.2 μmol), (±)-BINAP (4.0 mg, 6.4 μmol), and Cs_2CO_3 (9.9 mg, 30.4 μmol) in toluene (0.21 mL). This reaction was complete within 4 h and yielded, after purification, 13.4 mg (57%) of the adduct diastereomers as a white powder.

Synthesis and Characterization of *N*^{6}-[10-(7,8,9-Trisacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (16a,b). The diastereomeric mixture of adducts **11a**,**b** (10 mg) was dissolved in MeOH saturated with NH_3 (2.5 mL). The reaction was allowed to proceed for 15 h at 55 °C at which time TLC showed the reaction to be complete. The mixture was cooled to room temperature and carefully evaporated. The product was dried under vacuum to give 8 mg of crude material. This crude material was taken in pyridine (100 μL) and acetic anhydride (100 μL), and a few crystals of DMAP were added, and the mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with Et_2O and washed with 1 M aq HCl, sat aq $NaHCO_3$, and twice with water. The organic layer was dried over Na_2SO_4, and the mixture was evaporated to yield 9 mg of a crude mixture of diastereoisomers **16a**,**b** that was separated using preparative TLC (SiO_2, 1 mm, 20 cm × 20 cm and elution with 92:8 CH_2Cl_2−EtOAc) to yield 3.2 mg of the less-polar adduct and 2.8 mg of the more-polar adduct (combined yield of 72%).

The less-polar diastereomer was the 10*S* isomer (**16a**) as determined by the presence of a positive band at 282 nm in its CD spectrum. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (s, 1H, purine−H2), 8.29 (d, 1H, Ar−H11, J = 9.4), 8.21 (d, 1H, Ar−H1 or H3, J = 7.8), 8.18 (d, 1H, Ar−H3 or H1, J = 7.8), 8.19 (s, 1H, Ar−H6), 8.09 (d, 1H, Ar−H5, J = 9.2), 8.08 (d, 1H, Ar−H4, J = 9.2), 8.06 (s, 1H, purine−H8), 8.05 (d, 1H, Ar−H12, J = 9.4), 8.02 (t, 1H, Ar−H2, J = 7.8), 6.77 (dd, 1H, H10, J = 9.1, 2.9), 6.67 (d, 1H, H7, J = 3.1), 6.46 (t, 1H, H1′, J = 6.3), 6.23 (d, 1H, NH, J = 9.1), 5.69 (t, 1H, H8, J = 3.3), 5.64 (t, 1H, H9, J = 2.9), 4.59 (app. q, 1H, H3′, J = 4.9), 4.00 (app. q, 1H, H4′, J = 3.7), 3.87 (dd, 1H, H5′, J = 11.4, 4.2), 3.75 (dd, 1H, H5″, J = 11.4, 3.1), 2.64 (app. quint, 1H, H2′, J = 13.1, 5.4), 2.46 (ddd, 1H, H2″, J = 13.1, 5.8, 4.5), 2.18, 2.11, 2.05 (3s, 9H, $OCOCH_3$), 0.92, 0.86 (2s, 18H, *tert*-Bu), 0.11, 0.10, 0.05, 0.03 (4s, 12H, $SiCH_3$). HRMS calcd for $C_{48}H_{62}N_5O_9Si_2$ (M^+ + H) 908.4081, found 908.4090.

The more-polar diastereomer was the 10*R* isomer (**16b**) as determined by the presence of a negative band at 282 nm in its CD spectrum. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.62 (s, 1H, purine−H2), 8.35 (d, 1H, Ar−H11, J = 9.4), 8.21 (d, 1H, Ar−H1 or H3, J = 7.6), 8.17 (d, 1H, Ar−H3 or H1, J = 7.6), 8.20 (s, 1H, Ar−H6), 8.10 (d, 1H, Ar−H5, J = 9.2), 8.06 (s, 1H, purine−H8), 8.08 (d, 1H, Ar−H4, J = 9.2), 8.03 (d, 1H, Ar−H12, J = 9.4), 8.02 (t, 1H, Ar−H2, J = 7.6), 6.76 (br, 1H, H10), 6.67 (d, 1H, H7, J = 3.1), 6.46 (t, 1H, H1′, J = 6.4), 6.22 (br d, 1H, NH, J = 7.9), 5.69 (t, 1H, H8, J = 3.6), 5.64 (t, 1H, H9, J = 2.9), 4.62 (app. q, 1H, H3′, J = 4.3), 4.00 (app. q, 1H, H4′, J = 3.7), 3.88 (dd, 1H, H5′, J = 11.4, 4.3), 3.77 (dd, 1H, H5″, J = 11.4, 3.0), 2.63 (app. quint, 1H, H2′, J = 13.1, 6.2), 2.43 (ddd, 1H, H2″, J = 13.1, 6.0, 4.6), 2.18, 2.09, 2.04 (3s, 9H, $OCOCH_3$), 0.91, 0.86 (2s, 18H, *tert*-Bu), 0.094, 0.092, 0.05, 0.04 (4s, 12H, $SiCH_3$). HRMS calcd for $C_{48}H_{62}N_5O_9Si_2$ (M^+ + H) 908.4081, found 908.4084.

***N*^{6}-[1-(2,3,4-Trisbenzoyloxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrenyl)]-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (12a,b). (a) Pd-Mediated Coupling of 10 and (±)-8.** Into an oven-dried, screw-capped vial equipped with a stirring bar were placed $Pd(OAc)_2$ (5.4 mg, 24.1 μmol) and (±)-BINAP (45.0 mg, 72.3 μmol). Toluene (2.4 mL) was added, and the mixture was stirred at room temperature for 5 min. Cs_2CO_3 (109.9 mg, 0.337 mmol) followed by (±)-**8** (161.0 mg, 0.265 mmol) and then bromonucleoside **10** (131.0 mg, 0.241 mmol) were added. The vial was flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 85 °C. The reaction was monitored by TLC and judged to be complete after 4 h, at which time the mixture was cooled, diluted with Et_2O, and washed twice with brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. Chromatography of the crude mixture on a silica gel column using 99:1 CH_2Cl_2−EtOAc yielded 116 mg (45%, 75% based upon recovered (±)-**8**) of the diastereomeric mixture of adducts **12a**,**b** as a white powder. R_f **12a**,**b** (SiO_2/99:1 CH_2Cl_2−EtOAc) = 0.37.

(b) Pd-Mediated Coupling of 9 and (±)-8. A similar C−N reaction between chloronucleoside **9** (13.4 mg, 26.8 μmol) and (±)-**8** (17.9 mg, 29.5 μmol) was conducted using $Pd(OAc)_2$ (0.6 mg, 2.7 μmol), (±)-BINAP (5.0 mg, 8.0 μmol), and Cs_2CO_3 (12.2 mg, 37.4 μmol) in toluene (0.26 mL). This reaction was complete within 4 h and yielded, after purification, 10.5 mg (36%, 39% based upon recovered (±)-**8**) of the adduct diastereomers as a white powder.

Synthesis and Characterization of *N*^{6}-[1-(2,3,4-Trisacetoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrenyl)]-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (17a,b).[25] The diastereomeric mixture of adducts **12a**,**b** (10 mg) was dissolved in MeOH saturated with NH_3 (2.5 mL). The reaction was allowed to proceed for 15 h at 55 °C at which time TLC showed the reaction to be complete. The mixture was cooled to room temperature and carefully evaporated. The product was dried under vacuum to give 8.4 mg of crude material. This crude material was taken in pyridine (100 μL) and acetic anhydride (100 μL), and a few crystals of DMAP were added, and the mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with Et_2O and washed with 1 M aq HCl, sat aq $NaHCO_3$, and twice with water. The organic layer was dried over Na_2SO_4, and the mixture was evaporated to yield 8 mg of the mixture of diastereoisomers **17a**,**b** that was separated using preparative TLC (SiO_2, 1 mm, 20 cm × 20 cm and elution with 90:10 CH_2Cl_2−EtOAc) to yield 2.8 mg of the less-polar adduct and 2.9 mg of the more-polar adduct (combined yield of 69%).

The less-polar diastereomer was the 1*S* isomer (**17a**) as determined by the presence of a positive band at 248 nm in its CD spectrum. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.66 (s, 1H, purine−

H2), 8.52 (d, 1H, Ar−H12, J = 8.6), 8.09 (s, 1H, purine−H8), 7.98 (d, 1H, Ar−H6, J = 8.3), 7.87 (dd, 1H, Ar−H9, J = 8.1, 1.3), 7.78 (d, 1H, Ar−H8, J = 8.7), 7.74 (d, 1H, Ar−H7, J = 8.7), 7.54 (d, 1H, Ar−H5, J = 8.3), 7.50 (t, 1H, Ar−H10, J = 7.6), 7.23 (dd, 1H, Ar−H11, J = 8.6, 7.8), 6.54 (br s, 1H, NH), 6.51 (t, 1H, H1′, J = 6.3), 6.47 (d, 1H, H1, J = 3.3), 6.39 (d, 1H, H4, J = 7.3), 6.30 (t, 1H, H2, J = 2.9), 5.95 (dd, 1H, H3, J = 7.3, 2.9), 4.61 (app. quint, 1H, H3′, J = 4.3), 4.01 (app. q, 1H, H4′, J = 3.5), 3.86 (dd, 1H, H5′, J = 11.3, 4.1), 3.77 (dd, 1H, H5″, J = 11.3, 2.9), 2.62 (app. quint, 1H, H2′, J = 13.3. 6.2), 2.48 (ddd, 1H, H2″, J = 13.3, 6.1, 4.3), 2.24, 2.02, 1.89 (3s, 9H, $OCOCH_3$), 0.92, 0.89 (2s, 18H, *tert*-Bu), 0.12, 0.10, 0.07, 0.06 (4s, 12H, $SiCH_3$).

The more-polar diastereomer was the 1*R* isomer (**17b**) as determined by the presence of a negative band at 248 nm in its CD spectrum. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.65 (s, 1H, purine−H2), 8.56 (d, 1H, Ar−H12, J = 8.6), 8.03 (s, 1H, purine−H8), 7.98 (d, 1H, Ar−H6, J = 8.3), 7.87 (dd, 1H, Ar−H9, J = 8.0, 1.4), 7.78 (d, 1H, Ar−H8, J = 8.7), 7.73 (d, 1H, Ar−H7, J = 8.7), 7.55 (d, 1H, Ar−H5, J = 8.3), 7.50 (t, 1H, Ar−H10, J = 7.5), 7.25 (dd, 1H, Ar−H11, J = 8.5, 7.8), 6.54 (br s, 1H, NH), 6.47 (t, 1H, H1′, J = 6.6), 6.40 (d, 1H, H1, J = 3.7), 6.39 (d, 1H, H4, J = 7.4), 6.29 (t, 1H, H2, J = 3.7), 5.94 (dd, 1H, H3, J = 7.4, 2.9), 4.63 (app. quint, 1H, H3′, J = 3.8), 4.03 (app. q, 1H, H4′, J = 3.7), 3.89 (dd, 1H, H5′, J = 11.2, 4.4), 3.79 (dd, 1H, H5″, J = 11.2, 3.4), 2.69 (app. quint, 1H, H2′, J = 13.2. 6.2), 2.44 (ddd, 1H, H2″, J = 13.2, 6.0, 3.7), 2.23, 2.02, 1.89 (3s, 9H, $OCOCH_3$), 0.92, 0.89 (2s, 18H, *tert*-Bu), 0.12, 0.11, 0.07, 0.05 (4s, 12H, $SiCH_3$).

***N*^{2}-[10-(7,8,9-Trisbenzoyloxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (14a,b).** Into an oven-dried, screw-capped vial equipped with a stirring bar were placed $Pd(OAc)_2$ (4.5 mg, 20.0 μmol) and (±)-BINAP (37.7 mg, 60.6 μmol). Toluene (2.0 mL) was added, and the mixture was stirred at room temperature for 5 min. Cs_2CO_3 (92.0 mg, 0.282 mmol) followed by (±)-**4** (140.0 mg, 0.222 mmol) and then bromonucleoside **13** (131.0 mg, 0.202 mmol) were added. The vial was flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 85 °C. The reaction was monitored by TLC and judged to be complete after 16 h, at which time the mixture was cooled, diluted with Et_2O, and washed twice with brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. Chromatography of the crude mixture on a silica gel column using 4:40:56 acetone−hexane−CH_2Cl_2 yielded 176.2 mg (73%) of the diastereomeric mixture of adducts **14a**,**b** as a white powder. R_f **14a**,**b** (SiO_2/4:40:56 acetone−hexane−CH_2Cl_2) = 0.54.

Synthesis and Characterization of *N*^{2}-[10-(7,8,9-Trisacetoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrenyl)]-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (18a,b).[29] **(a) Step 1: Synthesis of the Adduct Triacetate.** The diastereomeric mixture of adducts **14a**,**b** (18.9 mg) was dissolved in MeOH saturated with NH_3 (2.5 mL). The reaction was allowed to proceed for 15 h at 55 °C, at which time TLC showed the reaction to be complete. The mixture was cooled to room temperature and carefully evaporated, and the product was dried under vacuum. This crude material was taken in pyridine (300 μL) and acetic anhydride (300 μL), and a few crystals of DMAP were added, and the mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with Et_2O and washed with 1 M aq HCl, sat aq $NaHCO_3$, and twice with water. The organic layer was dried over Na_2SO_4, and the mixture was evaporated to yield 11.5 mg of the mixture of the triacetyl adduct diastereoisomers that was purified by preparative TLC (SiO_2, 1 mm, 20 cm × 20 cm and elution with 95:5 CH_2Cl_2−EtOAc). This adduct mixture was used for the second step.

(b) Step 2: Debenzylation. To a solution of the adduct mixture (11.2 mg) in 1:1 THF−MeOH (0.12 mL) was added 5% Pd−C (5 mg). The reaction mixture was stirred under 1 atm H_2 pressure (balloon) for 5 h at which time TLC indicated the reaction to be complete. The mixture was filtered through Celite and evaporated to dryness. The two diastereoisomers were separated using preparative TLC (SiO_2, 1 mm, 20 cm × 20 cm and elution with 35:40:25 acetone−hexane−CH_2Cl_2) to yield 3.1 mg of the less-polar adduct and 3.2 mg of the more-polar adduct (combined yield of 43% over the two steps).

The less-polar diastereomer was the 10*S* isomer (**18a**) as determined by the presence of a positive band at 251 nm in its CD spectrum. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.68 (s, 1H, guanine ring NH), 8.35 (d, 1H, Ar−H3 or H1, J = 7.8), 8.31 (d, 1H, Ar−H1 or H3, J = 7.8), 8.29 (d, 1H, Ar−H11, J = 9.3), 8.24 (s, 2H, Ar−H4 and H5), 8.23 (s, 1H, Ar−H6), 8.22 (d, 1H, Ar−H12, J = 9.3), 8.11 (t, 1H, Ar−H2, J = 7.8), 7.95 (s, 1H, purine−H8), 7.30 (br s, 1H, exocyclic NH), 6.63 (d, 1H, H7, J = 6.9), 6.24 (t, 1H, H1′, J = 7.1), 6.18 (dd, 1H, H10, J = 7.5, 4.4), 5.85 (dd, 1H, H9, J = 7.0, 4.4), 5.42 (t, 1H, H8, J = 6.9), 4.50 (dt, 1H, H3′, J = 5.1, 4.6), 3.88 (dt, 1H, H4′, J = 5.4, 4.3), 3.79 (dd, 1H, H5′, J = 11.5, 5.3), 3.73 (dd, 1H, H5″, J = 11.5, 4.9), 2.55 (app. quint, 1H, H2′, J = 12.9, 6.4), 2.29 (ddd, 1H, H2″, J = 12.9, 6.6, 5.6), 2.27, 2.07, 1.98 (3s, 9H, $OCOCH_3$), 0.87, 0.85 (2s, 18H, *tert*-Bu), 0.06, 0.05, 0.44, 0.04 (4s, 12H, $SiCH_3$).

The more-polar diastereomer was the 10*R* isomer (**18b**) as determined by the presence of a negative band at 250 nm in its CD spectrum.^{1}H NMR (500 MHz, DMSO-d_6): δ 10.65 (s, 1H, guanine ring NH), 8.35 (d, 1H, Ar−H3 or H1, J = 7.8), 8.31 (d, 1H, Ar−H1 or H3, J = 7.8), 8.29 (d, 1H, Ar−H11, J = 9.3), 8.24 (s, 2H, Ar−H4 and H5), 8.23 (s, 1H, Ar−H6), 8.15 (d, 1H, Ar−H12, J = 9.3), 8.11 (t, 1H, Ar−H2, J = 7.8), 7.96 (s, 1H, purine−H8), 7.24 (br s, 1H, exocyclic NH), 6.63 (d, 1H, H7, J = 6.5), 6.23 (t, 1H, H1′, J = 6.7), 6.18 (dd, 1H, H10, J = 7.8, 4.0), 5.80 (dd, 1H, H9, J = 6.5, 4.0), 5.43 (t, 1H, H8, J = 6.5), 4.45 (m 1H, H3′), 3.83 (m, 1H, H4′), 3.75 (dd, 1H, H5′, J = 10.8, 7.3), 3.71 (dd, 1H, H5″, J = 10.8, 4.4), 3.08 (app. quint, 1H, H2′, J = 13.9, 6.6), 2.28 (ddd, 1H, H2″, J = 12.9, 7.2, 5.2), 2.25, 2.07, 1.99 (3s, 9H, $OCOCH_3$), 0.87, 0.64 (2s, 18H, *tert*-Bu), 0.10, 0.08, −0.02, −0.31 (4s, 12H, $SiCH_3$).

***N*^{2}-[1-(2,3,4-Trisbenzoyloxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrenyl)]-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (15a,b).** Into an oven-dried, screw-capped vial equipped with a stirring bar were placed $Pd(OAc)_2$ (5.4 mg, 24.1 μmol) and (±)-BINAP (45.0 mg, 72.3 μmol). Toluene (2.4 mL) was added, and the mixture was allowed to stir at room temperature for 5 min. Cs_2CO_3 (109.9 mg, 0.337 mmol) followed by (±)-**8** (161.0 mg, 0.265 mmol) and then bromonucleoside **13** (156.0 mg, 0.24 mmol) were added. The vial was flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 85 °C. The reaction was monitored by TLC and judged to be complete after 16 h, at which time the mixture was cooled, diluted with Et_2O, and washed twice with brine. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. Chromatography of the crude mixture on a silica gel column using 99:1 CH_2Cl_2−EtOAc yielded 197 mg (70%) of the diastereomeric mixture of adducts **15a**,**b** as a white powder. R_f **15a**,**b** (SiO_2/99:1 CH_2Cl_2−EtOAc) = 0.49.

Synthesis and Characterization of *N*^{2}-[1-(2,3,4-Trisacetoxy-1,2,3,4-tetrahydrobenzo[*c*]phenanthrenyl)]-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (19a,b).[32] **(a) Step 1: Synthesis of the Adduct Triacetate.** The diastereomeric mixture of adducts **15a**,**b** (23.1 mg) was dissolved in MeOH saturated with NH_3 (2.5 mL). The reaction was allowed to proceed for 15 h at 55 °C, at which time TLC showed the reaction to be complete. The mixture was cooled to room temperature and carefully evaporated, and the product was dried under vacuum. This crude material was taken in pyridine (300 μL) and acetic anhydride (300 μL), and a few crystals of DMAP were added, and the mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with Et_2O

(32) Kroth, H.; Yagi, H.; Sayer, J. M.; Kumar, S.; Jerina, D. M. *Chem. Res. Toxicol.* **2001**, *14*, 708−719.

and washed with 1 M aq HCl, sat aq $NaHCO_3$, and twice with water. The organic layer was dried over Na_2SO_4, and the mixture was evaporated to yield 16.0 mg of the mixture of the triacetyl adduct diastereoisomers that was purified by preparative TLC (SiO_2, 1 mm, 20 cm × 20 cm and elution with 95:5 CH_2Cl_2−EtOAc). This adduct mixture was used for the second step.

(b) Step 2: Debenzylation. To a solution of the adduct mixture (16.0 mg) in 1:1 THF−MeOH (0.16 mL) was added 5% Pd−C (5 mg). The reaction mixture was stirred under 1 atm H_2 pressure (balloon) for 5 h, at which time TLC indicated the reaction to be complete. The mixture was filtered through Celite and evaporated to dryness. The two diastereoisomers were separated using preparative TLC (SiO_2, 1 mm, 20 cm × 20 cm and elution with 35:35:30 acetone−hexane−CH_2Cl_2) to yield 4.4 mg of the less-polar adduct and 7.0 mg of the more-polar adduct (combined yield of 64% over the two steps).

The less-polar diastereomer was the 1*S* isomer (**19a**) as determined by the presence of a positive band at 257 nm in its CD spectrum. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.16 (s, 1H, guanine ring NH), 8.52 (d, 1H, Ar−H12, J = 8.9), 8.18 (d, 1H, Ar−H9, J = 8.4), 8.05 (d, 1H, Ar−H6, J = 8.2), 8.04 (s, 1H, purine−H8), 7.95 (d, 1H, Ar−H7, J = 8.8), 7.92 (d, 1H, Ar−H8, J = 8.8), 7.64 (br d, 1H, exocyclic NH, J = 6.5), 7.60 (t, 1H, Ar−H10, J = 7.4), 7.58 (d, 1H, Ar−H5, J = 8.2), 7.34 (t, 1H, Ar−H11, J = 8.2), 6.43 (d, 1H, H4, J = 8.5), 6.32 (t, 1H, H1′, J = 6.6), 6.06 (dd, 1H, H2, J = 4.4, 2.7), 6.04 (dd, 1H, H1, J = 6.5, 4.4), 5.74 (dd, 1H, H3, J = 8.5, 2.7), 4.50 (dt, 1H, H3′, J = 6.0, 3.7), 3.86 (app. q, 1H, H4′, J = 4.5), 3.77 (dd, 1H, H5′, J = 11.3, 5.2), 3.72 (dd, 1H, H5″, J = 11.3, 4.5), 2.68 (app. quint, 1H, H2′, J = 13.4, 7.7), 2.35 (ddd, 1H, H2″, J = 13.4, 6.4, 4.0), 2.23, 1.99, 1.90 (3s, 9H, $OCOCH_3$), 0.89, 0.83 (2s, 18H, *tert*-Bu), 0.07, 0.06, 0.058, 0.054 (4s, 12H, $SiCH_3$).

The more-polar diastereomer was the 1*R* isomer (**19b**) as determined by the presence of a negative band at 257 nm in its CD spectrum. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.24 (s, 1H, guanine ring NH), 8.44 (d, 1H, Ar−H12, J = 8.9), 8.19 (d, 1H, Ar−H9, J = 8.5), 8.06 (d, 1H, Ar−H6, J = 8.1), 8.03 (s, 1H, purine−H8), 7.97 (d, 1H, Ar−H7, J = 8.9), 7.93 (d, 1H, Ar−H8, J = 8.9), 7.87 (br s, 1H, exocyclic NH), 7.61 (t, 1H, Ar−H10, J = 7.4), 7.57 (d, 1H, Ar−H5, J = 8.1), 7.25 (t, 1H, Ar−H11, J = 8.3), 6.44 (d, 1H, H4, J = 8.9), 6.23 (dd, 1H, H1′, J = 9.2, 5.4), 6.10 (t, 1H, H2, J = 3.5), 5.95 (dd, 1H, H1, J = 6.4, 4.3), 5.75 (dd, 1H, H3, J = 8.9, 2.6), 4.38 (d, 1H, H3′, J = 5.1), 3.55 (t, 1H, H4′, J = 10.3), 3.76 (dd, 1H, H5′, J = 10.3, 4.4), 3.46 (dd, 1H, H5″, J = 10.3, 4.1), 3.23 (ddd, 1H, H2′, J = 13.4, 9.2, 4.9), 2.12 (dd, 1H, H2″, J = 13.4, 5.4), 2.24, 2.00, 1.95 (3s, 9H, $OCOCH_3$), 0.86, 0.52 (2s, 18H, *tert*-Bu), 0.08, 0.07, −0.54, −0.66 (4s, 12H, $SiCH_3$).

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Supporting Information Available: General experimental methods; tabulation of the coupling constant data for the tetrahydro ring protons in the B*a*P and B*c*Ph adducts; CD spectra of adduct pairs **16a**/**16b**, **17a**/**17b**, **18a**/**18b**, and **19a**/**19b**; and ^{1}H NMR spectra of (±)-**7**, (±)-**8**, **16a**, **16b**, **17a**, **17b**, **18a**, **18b**, **19a**, and **19b**. This information is available free of charge via the Internet at http://pubs.acs.org.

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