JOC Article

Synthesis of Pyrene and Benzo[*a*]pyrene Adducts at the Exocyclic Amino Groups of 2′-Deoxyadenosine and 2′-Deoxyguanosine by a Palladium-Mediated C−N Bond-Formation Strategy

Mahesh K. Lakshman,*,§ Felix N. Ngassa,† Suyeal Bae,‡ Dennis G. Buchanan,§ Hoh-Gyu Hahn,⊥ and Heduck Mah*,‡

Department of Chemistry, City College of CUNY, 138th Street at Convent Avenue, New York, New York 10031-9198, Department of Chemistry, University of North Dakota, Grand Forks, North Dakota 58202-9024, Department of Chemistry, Kyonggi University, Suwon 442-760, Korea, and Organic Chemistry Laboratory, Korea Institute of Science and Technology, P.O. Box 131, Cheongryang, Seoul 136-791, Korea

lakshman@sci.ccny.cuny.edu; hdma@kuic.kyonggi.ac.kr

Received April 2, 2003

Single-electron oxidation of the carcinogenic hydrocarbon benzo[*a*]pyrene (B*a*P) is thought to result in a radical cation intermediate and this species has been proposed to cause alkylation at the nitrogens of the purine nucleobases. Although several different nucleoside adducts have been isolated as arising from this mode of metabolic activation, there are no selective, total syntheses of the stable exocyclic amino group adducts formed by the single-electron oxidation of any hydrocarbon with the purine 2′-deoxynucleosides to date. In this paper we disclose the synthesis of the model adducts N^6-(1-pyrenyl)-2′-deoxyadenosine and N^2-(1-pyrenyl)-2′-deoxyguanosine as well as the first synthesis of the carcinogen-linked nucleoside derivatives N^6-(6-benzo[*a*]pyrenyl)-2′-deoxyadenosine and N^2-(6-benzo[*a*]pyrenyl)-2′-deoxyguanosine via a palladium-mediated C−N bond formation. Two different coupling strategies were attempted: coupling of an aryl bromide with a suitably protected nucleoside and the coupling of an arylamine with a suitable halonucleoside. The former had somewhat limited applicability in that only N^6-(1-pyrenyl)-2′-deoxyadenosine was prepared by this method; on the other hand, the latter was more general. However, there are noteworthy differences in the amination reactions at the C-6 and C-2 positions. Reactions at the C-6 resulted in the competing formation of a 1:2 amine−nucleoside adduct in addition to the desired monoaryl nucleoside. Such a dimer formation was not observed at the C-2. The C-2 adducts, however, displayed an interesting conformational behavior.

Introduction

By virtue of their environmental prevalence, several polycyclic aromatic hydrocarbons (PAHs) pose a health threat to humans.[1] Benzo[*a*]pyrene (B*a*P), an alternant, bay-region containing hydrocarbon, is one such contaminant that is known to be a potent carcinogen and has attracted research interest for several decades. In mammalian systems, two possible modes of metabolic activation have been proposed for this hydrocarbon as responsible sources for its tumorigenicity (Scheme 1). In the first, B*a*P is converted by the combined actions of cytochrome P450 and epoxide hydrolase to four isomeric diol epoxides (referred to as the monooxygenation pathway).[2] These electrophiles, in the presence of DNA undergo epoxide bond-scission leading to benzylic carbocations that are then trapped by the amino groups of adenine and guanine within DNA.[3] In the second proposed metabolic activation, B*a*P undergoes loss of a single

* Corresponding authors. M.K.L.: phone (212) 650-7835, fax (212) 650-6107. H.M.: phone +82-31-249-9631, fax +82-31-249-9605
§ City College of CUNY.
† University of North Dakota.
‡ Kyonggi University.
⊥ Korea Institute of Science and Technology.

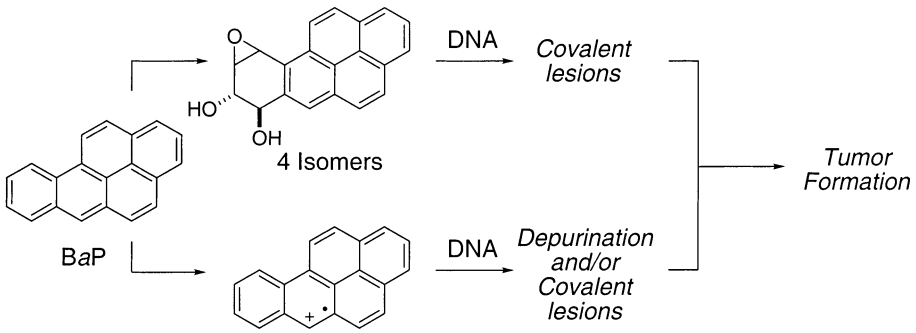
(1) PAH carcinogenesis has been reviewed in: (a) *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure−Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC Press: Boca Raton, FL, 1988; Vols. I and II. (b) *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Harvey, R. G., Ed.; Cambridge University Press: Cambridge, UK, 1991. (c) *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symp. Ser. 283: Washington, DC, 1985.

(2) Reviewed in: (a) Thakker, D. R.; Levin, W.; Wood, A. W.; Conney, A. H.; Yagi, H.; Jerina, D. M. In *Drug Stereochemistry, Analytical Methods and Pharmacology*; Wainer, I. W., Drayer, D. E., Eds.; Marcel Dekker: New York, 1988; pp 271−296. (b) Jerina, D. M.; Sayer, J. M.; Agarwal, S. K.; Yagi, H.; Levin, W.; Wood, A. W.; Conney, A. H.; Pruess-Schwartz, D.; Baird, W. M.; Pigott, M. A.; Dipple, A. In *Biological Reactive Intermediates III*; Kocsis, J. J., Jollow, D. J., Witmer, C. M., Nelson, J. O., Snyder, R., Eds.; Plenum Press: New York, 1986; pp 11−30. (c) Jerina, D. M.; Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Ittah, Y.; Thakker, D. R.; Wood, A. W.; Chang, R. L.; Levin, W.; Conney, A. H. In *Biological Reactive Intermediates II, Part A*; Snyder, R., Parke, D. V., Kocsis, J. J., Jollow, D. J., Gibson, C. G., Witmer, C. M., Eds.; Plenum Press: New York, 1986; pp 501−523.

(3) (a) Dipple, A. In *DNA Adducts: Identification and Biological Significance*; Hemminki, K., Dipple, A., Shuker, D. E. G., Kadlubar, F. F., Sagerbäck, D., Bartsch, H., Eds.; Scientific Publication No. 125; International Agency for Research on Cancer: Lyon, 1994; pp 107−129. (b) Szeliga, J.; Dipple, A. *Chem. Res. Toxicol.* **1998**, *11*, 1−11. (c) Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M. In *Biological Reactive Intermediates IV*; Witmer, C. M., Snyder, R., Jollow, D. J., Kalf, G. F., Kocsis, J. J., Sipes, I. G., Eds.; Plenum Press: New York, 1991; pp 533−553.

10.1021/jo030113b CCC: $25.00
Published on Web 06/20/2003

SCHEME 1



electron resulting in a radical-cation that is again trapped by the nitrogens of the DNA bases.[4] It has been postulated that a variety of enzymatic systems cause single-electron oxidation of B*a*P and that a variety of nucleoside and predominantly purine adducts are formed by such enzymatic activation. For instance, activation of B*a*P by horseradish peroxidase has yielded N-7 adducts of adenine and guanine, an N-3 adduct of adenine, as well as a C-8 adduct of guanine where the B*a*P is linked to the nucleobase via its C-6.[5] Microsomal activation also produces much of the same adducts (except for the N-3 adenine adduct) as well as the adducts from the diol epoxide activation pathway.[5] Interestingly, cytochrome P450, which is largely implicated in the oxidative metabolism of B*a*P leading to diol epoxides, has also been found to produce single-electron oxidation of B*a*P. Thus, the N-7 guanine adduct of B*a*P has been isolated from metabolic activation by this enzyme,[5] and this adduct has also been detected in the urine and feces of rats treated with B*a*P.[6] In addition, several of the aforementioned adducts have been found in the mouse skin and rat mammary gland and are formed in vitro by rat liver microsomal activation.[5,7−9] Formation of single-electron oxidation products from B*a*P has been ascribed to its low ionization potential,[10] and in every single adduct the B*a*P moiety is appended to the nucleobase solely at its C-6 position. This is consistent with the formation of a carbocationic center at this position.[11]

A primary difference in the DNA adducts resulting from the monooxygenation metabolism of B*a*P and the single electron-oxidation pathway is the following. In the former stable nucleoside adducts are produced involving the exocyclic amino groups of the nucleobases, whereas in the latter most of the identified adducts are unstable and undergo deglycosylation leading to isolation of the B*a*P-nucleobase conjugates. Thus, in the case of the diol epoxides the covalent DNA lesions have been deemed responsible for the terminal tumorigenic event. On the other hand, in the case of single-electron oxidation, the abasic sites resulting from alkylation-depurination are considered important.[5] For instance, c-Harvey-*ras* mutations in mouse skin papillomas have been related to replication at abasic sites in DNA.[12] On the basis of these factors substantial effort from several research groups has been directed toward the synthesis of nucleoside adducts of the various B*a*P metabolites. The diol epoxide-nucleoside adducts are not only markers for comparisons with metabolism studies, but several have also been used in DNA assembly for producing site-specifically modified DNA oligomers that are critical for structural, biological, and biochemical studies.[13] On the other hand, most of the effort on the synthesis of single-electron oxidation adducts (largely B*a*P-nucleobase adducts) has been for the generation of markers for metabolism studies.[5,10,14] It is these studies that drew our attention to the single-electron oxidative metabolism of B*a*P. Several electrochemical oxidation methods that have been used to generate the nucleobase adducts in several instances also yield nucleoside adducts. Two specific cases that pertain to B*a*P and its higher angular ring analogue dibenzo[*a*,*l*]pyrene (DB[*a*,*l*]P) are as follows. Anodic oxidation of the former in the presence of 2′-deoxyguanosine yielded in addition to the C-8 and N-7 guanine adducts three nucleoside adducts where B*a*P was linked via its C-6 to the C-8, N-3, and the exocyclic amino group of the nucleobase.[15a] Similarly, anodic oxidation of DB[*a*,*l*]P in

(4) (a) Cavalieri, E.; Rogan, E. In *Polycyclic Aromatic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symp. Ser. No. 283: Washington, DC, 1985; pp 290−305. (b) Cavalieri, E.; Rogan. E. *Environ. Health Perspect.* **1985**, *64*, 69−84.

(5) Chen, L.; Devanesan, P. D.; Higginbotham, S.; Ariese, F.; Jankowiak, R.; Small, G. J.; Rogan, E. G.; Cavalieri, E. L. *Chem. Res. Toxicol.* **1996**, *9*, 897−903.

(6) Rogan, E. G.; RamaKrishna, N. V. S.; Higginbotham, S.; Cavalieri, E. L.; Jeong, H.; Jankowiak, R.; Small, G. J. *Chem. Res. Toxicol.* **1990**, *3*, 441−444.

(7) Rogan, E. G.; Devanesan, P. D.; RamaKrishna, N. V. S.; Higginbotham, S.; Padmavathi, N. S.; Chapman, K.; Cavalieri, E. L.; Jeong, H.; Jankowiak, R.; Small, G. J. *Chem. Res. Toxicol.* **1993**, *6*, 356−363.

(8) Todorovic, R.; Ariese, F.; Devanesan, P.; Jankowiak, R.; Small, G. J.; Rogan, E.; Cavalieri, E. *Chem. Res. Toxicol.* **1997**, *10*, 941−947.

(9) Devanesan, P. D.; RamaKrishna, N. V. S.; Todorovic, R.; Rogan, E. G.; Cavalieri, E. L.; Jeong, H.; Jankowiak, R.; Small, G. J. *Chem. Res. Toxicol.* **1992**, *5*, 302−309.

(10) Rogan, E. G.; Cavalieri, E. L.; Tibbels, S. R.; Cremonesi, P.; Warner, C. D.; Nagel, D. L.; Tomer, K. B.; Cerny, R. L.; Gross, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 4023−4029.

(11) (a) Rochlitz, J. *Tetrahedron* **1967**, *23*, 3043−3048. (b) Jeftic, L.; Adams, R. N. *J. Am. Chem. Soc.* **1970**, *92*, 1332−1337. (c) Johnson, M. D.; Calvin, M. *Nature* **1973**, *241*, 271−272.

(12) Chakravarti, D.; Pelling, J. C.; Cavalieri, E. L.; Rogan, E. G. *Proc. Natl. Acad. Sci.* **1995**, *92*, 10422−10426.

(13) For some examples on the site-specific modification of DNA by diol epoxides, please see: (a) Lakshman, M. K.; Chaturvedi, S. *Carcinogenesis* **1996**, *17*, 2747−2752. (b) Kim, S. J.; Stone, M. P.; Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1992**, *114*, 5480−5481. (c) Steinbrecher, T.; Becker, A.; Stezowski, J. J.; Oesch, F.; Seidel, A. *Tetrahedron Lett.* **1993**, *34*, 1773−1774. (d) Lee, H.; Luna, E.; Hinz, M.; Stezowski, J. J.; Kiselyov, A. S.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 5604−5613. (e) Mao, B.; Xu, J.; Li, B.; Margulis, L. A.; Smirnov, S.; Ya, N. Q.; Coutney, S.; Geacintov, N. E. *Carcinogenesis* **1995**, *16*, 357−365. (f) DeCorte, B. L.; Tsarouhtsis, D.; Kuchimanchi, S.; Cooper, M. D.; Horton, P.; Harris, C. M.; Harris. T. M. *Chem. Res. Toxicol.* **1996**, *9*, 630−637. (g) Kroth, H.; Yagi, H.; Seidel, A.; Jerina, D. M. *J. Org. Chem.* **2000**, *65*, 5558−5564.

(14) Hanson, A. A.; Rogan, E. G.; Cavalieri, E. L. *Chem. Res. Toxicol.* **1998**, *11*, 1201−1208.

the presence of 2′-deoxyadenosine yielded the N-1 and N-7 adducts of adenine where DB[*a*,*l*]P was linked to the nucleobase via the C-10 position (this position corresponds to the C-6 of B*a*P).[15b] In addition, a 2′-deoxyadenosine adduct was also isolated to an extent of 26%, with the C-10 position of DB[*a*,*l*]P linked to the exocyclic amino group of the purine.[15b]

On the basis of these observations, and despite the controversial nature of the single-electron-oxidation metabolism, we reasoned that it was perhaps likely that minor stable nucleoside adducts of hydrocarbons such as B*a*P produced by this pathway may not have been isolated. However, synthesis of these adducts would contribute not only to the database of markers for metabolic studies, but these could be readily used for site-specific modification of DNA. Thus, this raises the possibility for side-by-side comparisons of diol epoxide and single-electron-oxidation adducts of any single hydrocarbon within specific DNA contexts. Such studies could be instructive about the relative importance of stable adducts arising from both metabolic pathways in the overall scheme of tumorigenesis. In addition, our syntheses also constitute a continued evaluation of Pd-mediated C−N bond formation within the domain of nucleoside modification leading to complex, biologically important paradigms.

Results and Discussion

Over the recent years Pd-catalyzed C−N bond formation has become an effective method for the synthesis of a large assortment of compounds,[16,17] and this method has begun to find applicability for previously unknown functionalization of nucleosides as well.[18] Thus, the syntheses of 2′-deoxyadenosine and 2′-deoxyguanosine analogues that contain modifications at the exocyclic amino groups (N6 and N2, respectively) as well as the C-8 aminated purine nucleosides have been achieved.[19−26]

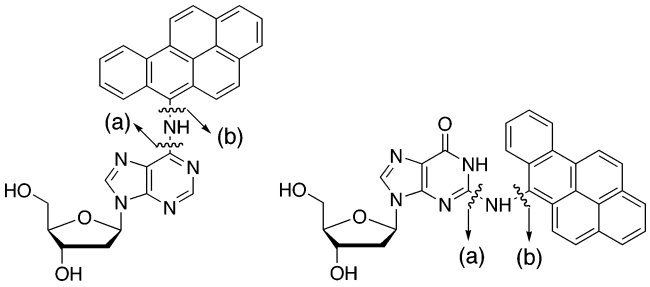


FIGURE 1. Two possible disconnection modes for the assembly of the benzo[*a*]pyrene 2′-deoxyadenosine and 2′-deoxyguanosine adducts.

For such nucleoside modification two alternative approaches have been reported; (a) coupling of a suitable halo nucleoside with an amino group donor,[19−25] and (b) coupling of a suitably protected nucleoside with an aryl halide or triflate. Although method b has found applicability with only *o*-nitro aryl halides and triflates,[26] we were curious whether extended aromatic systems would find applicability through this route. Therefore, in the present study we anticipated evaluation of both approaches and Figure 1 shows disconnections (a) and (b) representing the two.

On the basis of known chemistry, it was difficult to determine a priori which of the two approaches would prove satisfactory, and for the sake of simplicity initial optimization experiments with 1-bromopyrene and 1-aminopyrene (**1** and **2**, Figure 2) were planned. It was plausible that results obtained from the pyrene models would direct the experimentation with the B[*a*]P derivatives **3** and **4**. The commercial availability of **1** and **2** further justified their use.[27] In contrast, compounds **3** and **4** required syntheses as follows; 6-bromo B[*a*]P **3** was synthesized by bromination of B[*a*]P[28] and 6-amino B[*a*]P **4** was prepared by nitration of B[*a*]P followed by reduction.[29] Syntheses of the nucleoside precursors for testing the two approaches shown in Figure 1 are also convenient as **6** is derived from **5**[19,30] and **8** from **7**.[20,21] With all of the requisite starting materials at hand (Figure 2), the next stage was the evaluation of coupling partners as well as catalytic systems required to accomplish the syntheses.

Synthesis of *N*^{6}-(1-Pyrenyl)- 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine: (a) Pd-Mediated Coupling of 1-Bromopyrene (1) with 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (5). The commercial availability of **1** and the simple one-step

(15) (a) Ramakrishna, N. V. S.; Gao, F.; Padmavathi, N. S.; Cavalieri, E. L.; Rogan, E. G.; Cerny, R. L.; Gross, M. L. *Chem. Res. Toxicol.* **1992**, *5*, 293−302. (b) Li, K.-M.; Byun, J.; Gross, M. L.; Zamzow, D.; Jankowiak, R.; Rogan, E. G.; Cavalieri, E. L. *Chem. Res. Toxicol.* **1999**, *12*, 749−757.

(16) Reviewed in: (a) Hartwig, J. F. *Synlett* **1997**, 329−340. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (c) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1999**, *31*, 805−818. (d) Hartwig, J. F. *Acc. Chem. Res.* **1999**, *31*, 852−860. (e) Frost, C. G.; Mendonca, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2615−2623. (f) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146. (g) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: New York, 2000; pp 195−262. (h) Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041−2075.

(17) For some examples, see: (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609−3612. (b) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348−1350. (c) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (d) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216. (e) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369−7370. (f) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367−2370. (g) Bei, X.; Guram, A. S.; Turner, H. W.; Weinberg, W. H. *Tetrahedron Lett.* **1999**, *40*, 1237−1240. (h) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575−5580. (i) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729−7737.

(18) Reviewed in: Lakshman, M. K. *J. Organomet. Chem.* **2002**, *653*, 234−251.

(19) Lakshman, M. K.; Keeler, J. C.; Hilmer, J. H.; Martin, J. Q. *J. Am. Chem. Soc.* **1999**, *121*, 6090−6091.

(20) Harwood, E. A.; Sigurdsson, S. T.; Edfeldt, N. B. F.; Reid, B. R.; Hopkins, P. B. *J. Am. Chem. Soc.* **1999**, *121*, 5081−5082.

(21) Harwood, E. A.; Hopkins, P. B.; Sigurdsson, S. T. *J. Org. Chem.* **2000**, *65*, 2959−2964.

(22) Bonala, R.; Shishkina, I. G.; Johnson, F. *Tetrahedron Lett.* **2000**, *41*, 7281−7284.

(23) Wang, Z.; Rizzo, C. J. *Org. Lett.* **2001**, *3*, 565−568.

(24) Schoffers, E.; Olsen, P. D.; Means, J. C. *Org. Lett.* **2001**, *3*, 4221−4223.

(25) Meier, C.; Gräsl, S. *Synlett* **2002**, 802−804.

(26) De Riccardis, F.; Bonala, R. R.; Johnson, F. *J. Am. Chem. Soc.* **1999**, *121*, 10453−10460.

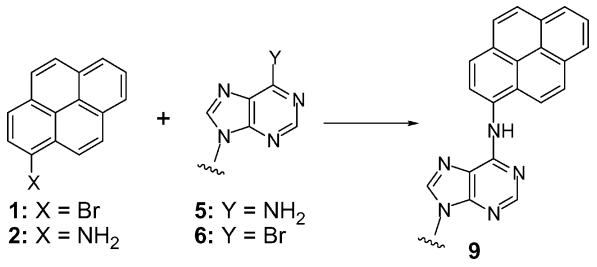
(27) 1-Bromopyrene and 1-aminopyrene are commercially available from one or more sources.

(28) Dewhurst, F.; Kitchen, D. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 710−712.

(29) Fieser, L. F.; Hershberg, E. B. *J. Am. Chem. Soc.* **1939**, *61*, 1565−1574.

(30) In ref 19 the use of CBr_4 for the synthesis of the bromo nucleoside is an error, $CHBr_3$ is the correct reagent.

TABLE 1. Optimization Experiments for the Synthesis of N^6-(1-Pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (9)



entry	X	Y	Pd species	ligand[a]	base	solvent	time (h), temp (°C)	result[b,c]
1	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe	16.5, 90	81% yield, relatively pure product
2	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe	4, 90	89% yield, clean product
3	Br	NH_2	$Pd_2(dba)_3$	**L-2**	K_3PO_4	PhMe	18, 90	after 18 h more catalyst was added and reaction continued for another 2 h; 41% yield, impure product and pyrene byproduct were observed
4	Br	NH_2	$Pd_2(dba)_3$	**L-2**	*t*-BuONa	PhMe	18, 90	after 18 h more catalyst was added and reaction continued for another 2 h; 24% yield, impure product and pyrene byproduct were observed
5	Br	NH_2	$Pd(OAc)_2$	**L-3**	*t*-BuONa	PhMe	4.5, rt then 16, 90	no reaction
6	Br	NH_2	$Pd(OAc)_2$	**L-3**	K_3PO_4	PhMe	20, 90	no reaction
7	Br	NH_2	$Pd(OAc)_2$	**L-4**	*t*-BuONa	PhMe	21, 90	no reaction
8	Br	NH_2	$Pd(OAc)_2$	**L-4**	K_3PO_4	PhMe	21, 90	no reaction
9	NH_2	Br	$Pd_2(dba)_3$	**L-2**	K_3PO_4	1,2-DME	2, 80	52% yield, clean product
10	NH_2	Br	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	1,2-DME	1, 80	73% yield, somewhat impure product
11	OTf	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe	24, 90	substantial unreacted starting materials

[a] Ligands: **L-1** = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; **L-2** = 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl; **L-3** = 2-(dicyclohexylphosphino)biphenyl; **L-4** = 2-(di-*tert*-butylphosphino)biphenyl. [b] Reactions were monitored by TLC. [c] In the cases where yields are cited, yield refers to that of product isolated after chromatography.

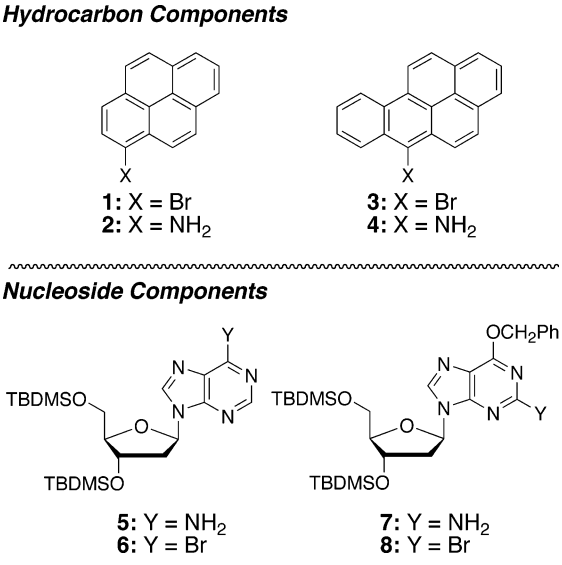


FIGURE 2. The hydrocarbon and nucleoside coupling components used in the synthesis of the pyrene and benzo[*a*]pyrene nucleoside adducts.

silylation of 2′-deoxyadenosine led to initial experimentation with these two substrates. To determine an appropriate catalytic system several parameters needed to be varied. These were the Pd species, the ligand, the base, and the solvent. The results of this optimization are shown in entries 1−8 of Table 1. It is clear from this table that the use of $Pd(OAc)_2$/**L-1**/Cs_2CO_3 in toluene at 90 °C resulted in an effective reaction leading to the N^6-(1-pyrenyl) adduct **9** within 4 h (entry 2). On the other hand, use of the $Pd_2(dba)_3$/**L-2** system with either K_3PO_4 or *t*-BuO^-Na^+ resulted in low yield and the formation of the reduction product pyrene (entries 3 and 4). Consistent with our previous observations[31] on aryl amination at the C-6 position, use of **L-3** and **L-4** is essentially ineffective.

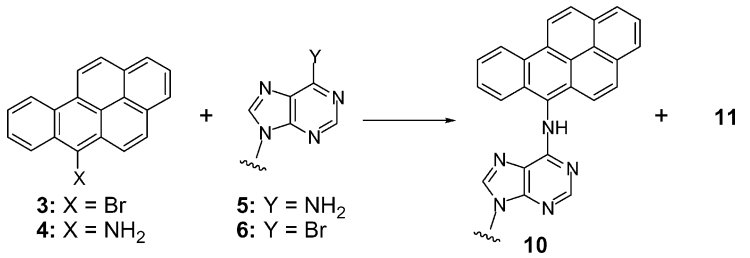
(b) Pd-Mediated Coupling of 1-Aminopyrene (2) with 6-Bromo-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-erythropentofuranosyl]purine (6). On the basis of our previous report,[19] commercially available 1-aminopyrene was coupled with bromo nucleoside **6**. The results of two optimization experiments are shown in entries 9 and 10 of Table 1. Using conditions we had previously described, the combination of $Pd_2(dba)_3$/**L-2**/K_3PO_4 in 1,2-DME at 80 °C afforded a modest 52% yield of **9** in 2 h. On the other hand, use of $Pd(OAc)_2$/**L-1**/Cs_2CO_3 in 1,2-DME produced an improved yield but a decrease in product quality.

(c) Pd-Mediated Coupling of 1-Pyrenyl Triflate with 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (5). In a single experiment (entry 11 in Table 1) the coupling of 1-pyrenyl triflate[32] with protected 2′-deoxyadenosine **5** was attempted utilizing the catalytic system that had provided positive results above. After 24 h at 90 °C substantial amounts of starting materials were present, indicating that even triflates of polyaromatic phenols are poor coupling partners in C−N bond

(31) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779−7787.

(32) 1-Pyrenyl triflate was prepared by reaction of 1-hydroxypyrene with triflic anhydride in CH_2Cl_2 in the presence of 2,6-lutidine at −30 to −35 °C.

TABLE 2. Optimization Experiments for the Synthesis of N^6-(6-Benzo[*a*]pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (10)



entry	X	Y	Pd species	ligand[a]	base	solvent	time (h), temp (°C)	result[b,c]
1	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe	24, 100	insignificant reaction
2	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	1,2-DME	24, 80	insignificant reaction
3	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	1,4-dioxane	43, 100	insignificant reaction (∼12% product isolated)
4	Br	NH_2	$Pd(OAc)_2$	**L-1**	*t*-BuONa	1,4-dioxane	43, 100	no reaction
5	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe-THF (1:1)	72, 100	insignificant reaction
6	NH_2	Br	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe	16, 80	%**10**:%**11** = 20.3:25.7; total 46%
7	NH_2	Br	$Pd_2(dba)_3$	**L-2**	K_3PO_4	1,2-DME	18, 80	%**10**:%**11** = 38.6:10.3; total 48.9%
8	NH_2	Br	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	1,2-DME	18, 80	%**10**:%**11** = 29.5:22; total 51.5%
9	NH_2	Br	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	1,4-dioxane	5.5, 100	%**10**:%**11** = 51.3:15; total 66.3%
10	NH_2	Br	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe-THF (1:1)	21, 100	%**10**:%**11** = 15.9:24.8; total 40.7%

[a] Ligands: **L-1** = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; **L-2** = 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl; **L-3** = 2-(dicyclohexylphosphino)biphenyl; **L-4** = 2-(di-*tert*-butylphosphino)biphenyl. [b] Reactions were monitored by TLC. [c] In the cases where yields are cited, yield refers to that of product isolated after chromatography.

formation. No further experimentation was conducted with this substrate.

Synthesis of N^6-(6-Benzo[*a*]pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine: (a) Pd-Mediated Coupling of 6-Bromobenzo[*a*]pyrene (3) with 3′,5′-Bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (5). On the basis of the result that the N^6-(1-pyrenyl) adduct **9** could be synthesized from 1-bromopyrene and **5**, we anticipated that a similar approach using 6-bromo B[*a*]P would provide the simplest access to the N^6-(6-benzo[*a*]pyrenyl) adduct as well. Furthermore, the required 6-bromo B[*a*]P was available in one step from B[*a*]P.[28] Thus, the coupling of **3** with **5** was attempted with the $Pd(OAc)_2$/**L-1**/Cs_2CO_3 combination that had proven successful in the reaction of 1-bromopyrene. Surprisingly insignificant reaction was observed. This led to the evaluation of slightly modified conditions, the results of which are summarized in entries 1−5 of Table 2. Considering that solubility of 6-bromo B[*a*]P could be a factor leading to inefficient coupling, solvents such as 1,2-DME, 1,4-dioxane, and toluene−THF combinations were tested. None proved satisfactory and not much product formation was observed even after prolonged reaction times in these cases. Thus, coupling of 6-bromo B[*a*]P (**3**) with the 2′-deoxyadenosine derivative **5** does not appear to be a viable route to the N6 adduct, which contrasts with the good result obtained with 1-bromopyrene.

(b) Pd-Mediated Coupling of 6-Aminobenzo[*a*]pyrene (4) with 6-Bromo-9-[2-deoxy-3,5-bis-*O*-(*tert*-butyldimethylsilyl)-*β*-D-erythropentofuranosyl]purine (6). The failure of method a above in yielding the requisite adduct, therefore, prompted a test of the approach involving coupling of 6-amino B[*a*]P **4**, available in two steps from B[*a*]P (nitration and reduction),[29] with bromo nucleoside **6**. With use of the catalytic system $Pd(OAc)_2$/**L-1**/Cs_2CO_3, which yielded the best result for the synthesis of the N^6-(1-pyrenyl) adduct, the coupling of **4** with **6** was conducted in toluene at 80 °C. This reaction led to consumption of starting materials and yielded a surprising result: the formation of two products with different fluorescent properties under UV light (365 nm). The *more mobile* product on silica gel had a greenish fluorescence whereas the *less mobile* one was bluish. These two products were separated and analyzed. The ^{1}H NMR data of the *more mobile* product clearly indicated a ratio of one B[*a*]P unit to a single nucleoside moiety, whereas in the *less mobile* product there were two nucleoside units to a single B[*a*]P. Mass spectral analysis also confirmed these structures. The dimeric compound (**11**, shown in Figure 3) showed sharp aromatic and aliphatic resonances. On the other hand, the aromatic signals in compound **10** were sharp and the aliphatic resonances were broadened (at ambient temperature in $CDCl_3$). It must be noted that formation of such dimeric products by further reaction of an initially formed species has been reported in Pd-catalyzed aminations of nucleosides.[26,33] However, this is the first case in nucleoside aryl

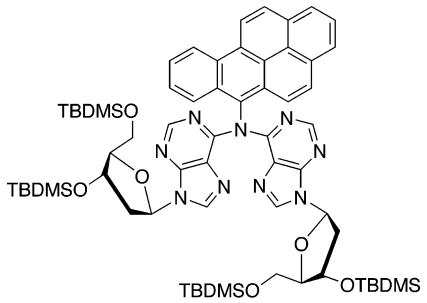


FIGURE 3. Structure of the dimer, benzo[*a*]pyrene dinucleoside adduct.

(33) De Riccardis, F.; Johnson, F. *Org. Lett.* **2000**, *3*, 293−295.

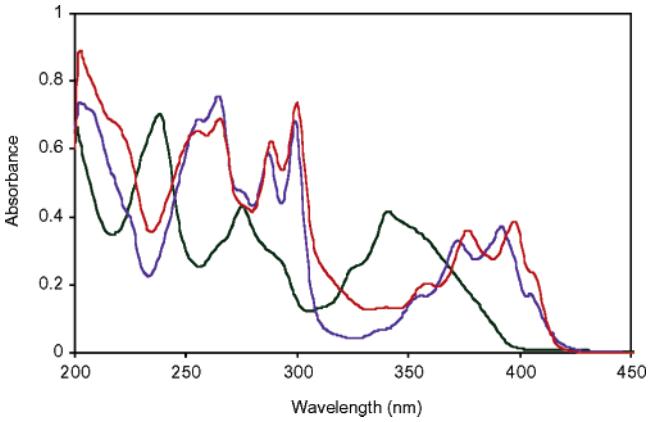


FIGURE 4. UV spectra of the pyrene (green), benzo[*a*]pyrene (blue), and dimeric benzo[*a*]pyrene (red) adducts in MeOH.

amination that a 2:1 adduct of nucleoside to arylamine has been observed.

Since this reaction had yielded two products of which only one was desired, a study was undertaken to evaluate whether the ratio of **10**:**11** could be altered by changing the catalytic system, base, or solvent. The results of these experiments are shown in entries 6−10 of Table 2. From this analysis it appeared that use of $Pd(OAc)_2$/**L-1**/Cs_2CO_3 in 1,4-dioxane at 100 °C provided the best ratio of **10** to **11** in a moderately good yield (**10**:**11** = 51.3:15, overall 66.3%).

While this work was in progress, Véliz and Beal reported that direct displacement of bromide from the C-6 position of acetyl (but not TBDMS)-protected purine nucleosides by arylamines offers a facile approach to C-6 amino aryl nucleosides.[34] This method seemed to offer the possibility that dimer formation could be suppressed, a factor that is important while considering scale-up. Their method utilizes 6 molar equiv of the arylamine in an alcohol medium, MeOH or EtOH. Whereas such large excesses can be utilized with commercially available arylamines, in the present case this was not possible. Thus, in our attempt, 3 molar equiv of **4** was allowed to react with 6-bromo-9-[2-deoxy-3,5-bis-*O*-acetyl-*β*-D-erythropentofuranosyl]purine[34] in MeOH at 65 °C over a 24-h period. Careful purification of the mixture returned mainly the bromo nucleoside as the major nucleoside material with no significant proportion of adduct-like compound. Perhaps solubility of the arylamine in MeOH is a factor, but no further attempts were made to utilize this method.

Some features of the UV Spectra of 9, 10, and 11. The UV spectra of compounds **9**−**11** are shown in Figure 4. As anticipated, the pyrene adduct **9** (shown in green) has substantially blue-shifted absorbances compared with the B[*a*]P analogue **10** (shown in blue). However, the dimeric nucleoside **11** (shown in red) and the monoadduct **10** show some interesting differences. Although the absorption bands of **10** and **11** in the 250−270 and 280−310 nm regions are very similar, the bands in the 350−410 nm region of **11** shown substantial bathochromic shifts compared to those of **10**.

Synthesis of N^6-(1-Pyrenyl) and N^6-(6-Benzo[*a*]-pyrenyl)-2′-deoxyadenosine (12 and 13) and Some

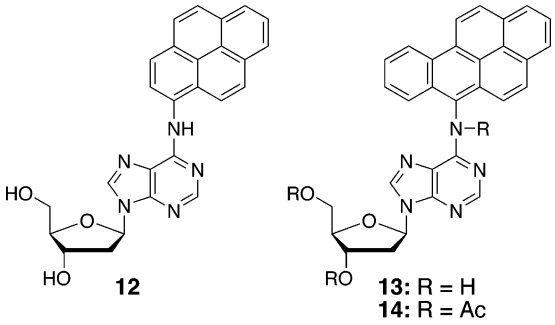


FIGURE 5. Structures of the N^6-(1-pyrenyl)- and N^6-(6-benzo[*a*]pyrenyl)-2′-deoxyadenosine and the triacetate of the latter.

Features of Their NMR Spectra. Small portions of the synthetically derived **9** and **10** were subjected to desilylation with *n*-$Bu_4N^+F^-$ in THF. The ^1H NMR spectra of the products **12** and **13** at room temperature in $CDCl_3$ show similarities, the most striking of which is the appearance of a doublet and triplet pattern for the diastereotopic H-5′ protons. Such a resonance pattern has been reported for purine 2′-deoxynucleosides in $CDCl_3$ and has been attributed to a possible intramolecular hydrogen bond between the 5′-hydroxyl proton and the N3 of the base.[35] However, the H-2′ resonances of **13** are somewhat broader compared to those of **12**, perhaps an influence of the added angular ring in the former. For additional characterization purposes, compound **13** (Figure 5) was acetylated with Ac_2O/pyridine/DMAP. Interestingly, this reaction yielded the *N*,*O*,*O*-triacetate **14** rather than the *O*,*O*-diacetate. This result is different compared to that from similar acetylation reactions of B[*a*]P diol epoxide adducts at the N6 position of 2′-deoxyadenosine where no *N*-acetylation is normally observed.[36]

Synthesis of N^2-(1-Pyrenyl)-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine: (a) Pd-Mediated Coupling of 1-Bromopyrene (1) with O^6-Benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (7). The coupling of **1** with **7** was conducted in a fashion similar to the reactions of **1** with **5**. Here again, reaction progress was observed in most cases (entries 1−7 of Table 3) resulting in good yields of **15** in some (Table 3, entries 1 and 3). However, in the higher yielding reactions product **15** was contaminated with inseparable impurities. In the few cases where pure **15** was isolated the yields of the product were not high (Table 3, entries 4, 5, and 7). Thus, the coupling of 1-bromopyrene with the O^6-protected 2′-deoxyguanosine analogue does not appear to be a practical method for the synthesis of the N^2-(1-pyrenyl)-2′-deoxyguanosine adduct.

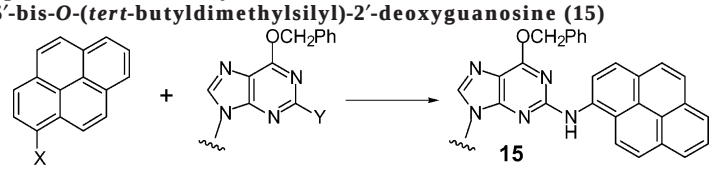
(b) Pd-Mediated Coupling of 1-Aminopyrene (2) with 2-Bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (8). Since coupling of the aryl halide with the amino group of the protected nucleoside did not seem to be the best route, the coupling

(34) Véliz, E. A.; Beal, P. A. *J. Org. Chem.* **2001**, *66*, 8592−8598.

(35) Lakshman, M. K.; Lehr, R. E. *Nucleosides Nucleotides* **1992**, *11*, 1039−1046.

(36) (a) Lakshman, M. K.; Sayer, J. M.; Jerina, D. M. *J. Am. Chem. Soc.* **1991**, *113*, 6589−6594. (b) Lakshman, M. K.; Sayer, J. M.; Jerina, D. M. *J. Org. Chem.* **1992**, *57*, 3438−3443. (c) Lakshman, M. K.; Sayer, J. M.; Yagi, H.; Jerina, D. M. *J. Org. Chem.* **1992**, *57*, 4585−4590.

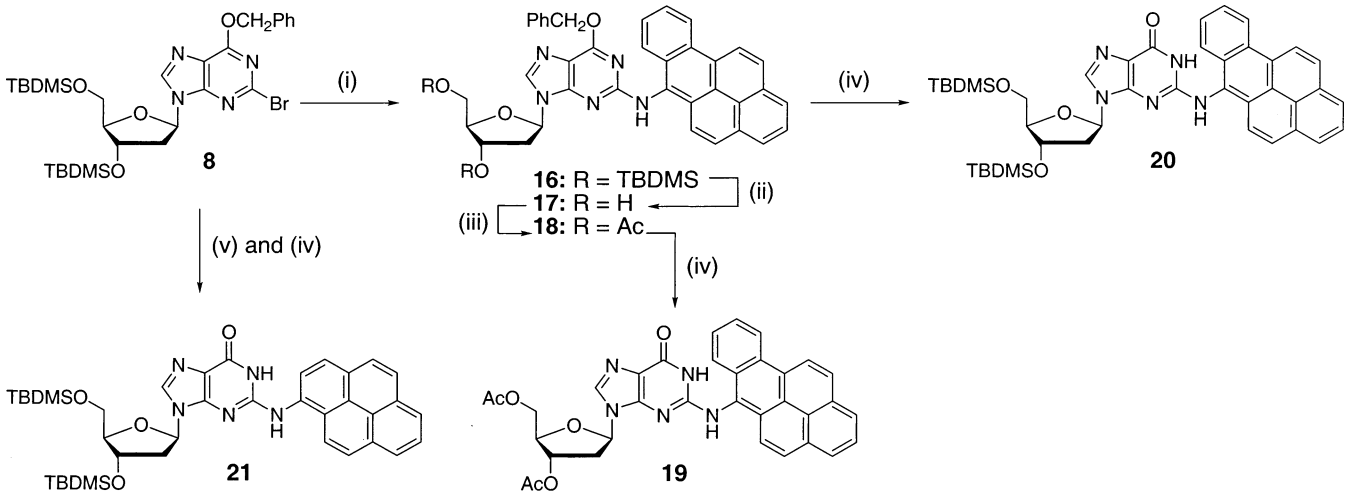
TABLE 3. Optimization Experiments for the Synthesis of N^2-(1-Pyrenyl)-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (15)



entry	X	Y	Pd species	ligand[a]	base	solvent	time (h), temp (°C)	result[b,c]
1	Br	NH_2	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	PhMe	3.5, 90	86% yield, impure product
2	Br	NH_2	$Pd_2(dba)_3$	**L-2**	K_3PO_4	PhMe	19, 90	37% yield, impure product
3	Br	NH_2	$Pd_2(dba)_3$	**L-2**	*t*-BuONa	PhMe	19, 90	70% yield, impure product
4	Br	NH_2	$Pd(OAc)_2$	**L-3**	*t*-BuONa	PhMe	24, 90	19% yield, relatively pure product but incomplete reaction
5	Br	NH_2	$Pd(OAc)_2$	**L-3**	K_3PO_4	PhMe	24, 90	28% yield, relatively pure product but incomplete reaction
6	Br	NH_2	$Pd(OAc)_2$	**L-4**	*t*-BuONa	PhMe	24, 90	31% yield, impure product and incomplete reaction
7	Br	NH_2	$Pd(OAc)_2$	**L-4**	K_3PO_4	PhMe	24, 90	23% yield, relatively pure product but incomplete reaction
8	NH_2	Br	$Pd(OAc)_2$	**L-1**	Cs_2CO_3	1,2-DME	18, 80	80% yield, clean product
9	NH_2	Br	$Pd_2(dba)_3$	**L-2**	K_3PO_4	1,2-DME	18, 80	75% yield, clean product

[a] Ligands: **L-1** = (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; **L-2** = 2-(dicyclohexylphosphino)-2′-(*N*,*N*-dimethylamino)-1,1′-biphenyl; **L-3** = 2-(dicyclohexylphosphino)biphenyl; **L-4** = 2-(di-*tert*-butylphosphino)biphenyl. [b] Reactions were monitored by TLC. [c] In the cases where yields are cited, yield refers to that of product isolated after chromatography.

SCHEME 2[a]



[a] Reagents and conditions: (i) **4**, $Pd(OAc)_2$, **L-1**, Cs_2CO_3, 1,4-dioxane, 90 °C; (ii) *n*-$Bu_4N^+F^-$, THF, rt; (iii) CH_2Cl_2, $(CH_3CO)_2O$, rt; (iv) 10% Pd-C, H_2, 1:1 THF−MeOH, rt; (v) **2**, $Pd(OAc)_2$, **L-1**, Cs_2CO_3, 1,2-DME, 80 °C.

of **2** with bromo nucleoside **8** was attempted. The two different catalytic systems that were tested (entries 8 and 9 of Table 3) were comparably effective in yielding product **15** of good purity. Thus, for 2′-deoxyguanosine modification the experiments indicated that coupling of the amino hydrocarbon with a halo nucleoside was substantially better than reactions with the opposite coupling partners.

Synthesis of N^2-(6-Benzo[*a*]pyrenyl)-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine: Pd-Mediated Coupling of 6-Aminobenzo[a]pyrene (4) with 2-Bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine (8). The reaction leading to N^2-(6-benzo[*a*]pyrenyl)-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (**16**) was carefully considered in light of the results obtained in the coupling of bromo nucleoside **6** with **4**. Since $Pd(OAc)_2$/**L-1**/Cs_2CO_3 in 1,4-dioxane had provided the best result for the synthesis of the 2′-deoxyadenosine adduct, this was the combination chosen in the present case. With use of this catalyst−solvent system, coupling of **4** with **8** proceeded to completion smoothly, within 5 h at 90 °C, to yield the desired adduct **16** in ca. 88% yield (Scheme 2). Interesting to note, in contrast to the synthesis of the adenine adduct no dimeric adduct was detected in this case.

Features of the NMR Spectra of N^2-(1-Pyrenyl)- and N^2-(6-Benzo[*a*]pyrenyl)-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (15 and 16), as Well as the Corresponding Deprotected 2′-Deoxyguanosine Derivatives. Adducted nucleoside derivatives of 2′-deoxyguanosine are often more polar

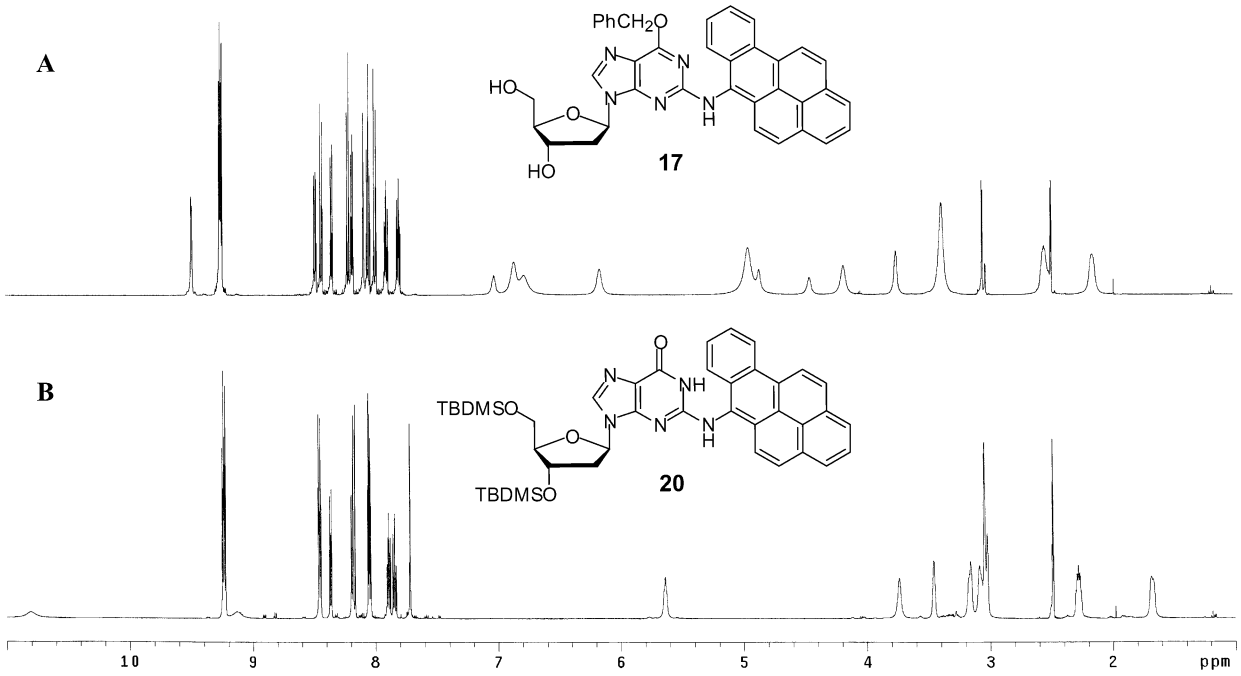


FIGURE 6. (A) ^{1}H NMR spectrum of N^2-(6-benzo[*a*]pyrenyl)-O^6-benzyl-2′-deoxyguanosine (**17**) in DMSO-d_6 at 80 °C. (B) Partial ^{1}H NMR spectrum of N^2-(6-benzo[*a*]pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (**20**) in DMSO-d_6 at 80 °C (not shown are the *tert*-butyldimethylsilyl resonances).

compared to the 2′-deoxyadenosine analogues, and this led us to consider characterization of the 2′-deoxyguanosine adducts containing protecting groups on the carbohydrate moiety. Initial effort was directed at the generation of the N^2-(1-pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (**21** in Scheme 2). This was achieved by catalytic hydrogenolysis of the O^6-benzyl protecting group. Whereas the ^{1}H NMR spectrum (in $CDCl_3$ at room temperature) of compound **15** showed excellent resolution of all signals, in the debenzylated product **21** the aliphatic resonances showed substantial broadening. FAB HRMS of **21** showed an expected 696.3427 ($M^+ + H$) signal.

In contrast to the pyrene adduct **15** the benzo[*a*]pyrene derivative **16** showed sharp signals for the aromatic protons but the sugar resonances were very broad signals, barely discernible from the baseline, in $CDCl_3$ at ambient. Increasing the temperature to 40 °C produced an increased intensity of the sugar resonances but the signals were still very broad. Changing the solvent to DMSO-d_6 produced results similar to those with $CDCl_3$ at both room temperature and 60 °C. Compound **16** was subjected to debenzylation, but significant signal broadening was observed in **20** (in $CDCl_3$ at room temperature). With a view to improving the signal resolution for product characterization, other derivatives were selected. Desilylation of **16** yielded the dihydroxy derivative **17**; however, this compound and its diacetate **18** both showed well-resolved aromatic resonances but very broad sugar signals along the baseline, in $CDCl_3$ at room temperature. The triacetate derivative (**22** in the Supporting Information) was prepared from **17** (Ac_2O, pyridine, DMAP) and this compound exhibited an interesting property. Whereas this triacetate showed extremely well resolved signals for both the aromatic and the sugar protons, duplicity of some signals was observed, and the phenomenon persisted in DMSO-d_6 at 80 °C (Figure 14 in the Supporting Information). This led us to consider the possibility that the significant signal broadening that was observed in adducted 2′-deoxyguanosine derivatives was a result of slow dynamic molecular motion at room temperature and that acetylation of the N2 froze out certain conformers. This is consistent with two other observations: the signal broadening in **21** (though not as pronounced as in the B[*a*]P adducts) and the signal broadening observed in the N6 B[*a*]P adduct **13** compared to the pyrene analogue **12** (in the case of **13** the H-2′ resonances showed substantial broadening). Therefore, we decided to reanalyze the ^{1}H NMR spectra of **16**−**20** in DMSO-d_6 at an elevated temperature (Figures 8−12 in the Supporting Information). At 80 °C **16** clearly showed sharp aromatic resonances; however, the aromatic resonances of the benzyl moiety as well as the benzylic methylene and remaining sugar protons were broad but discernible. The dihydroxy derivative **17** shows many of the same features but the two hydroxyl protons were also visible and were assigned by deuterium exchange. Figure 6A shows the ^{1}H NMR spectrum of **17**. Diacetate **18** also showed the same pattern described for **16** and **17**. Among the three derivatives **17** shows the best identifiable features of the glycosidic portion of the N2 adduct in the ^{1}H NMR spectrum.

Two other derivatives were analyzed by ^{1}H NMR in DMSO-d_6 at 80 °C, and these were compounds **19** and **20** where the O6 protection had been removed. In both cases the glycosidic protons were again clearly distinguishable although signal broadening was still observed. Among the two **20** appears to be slightly better and splitting for the 2′ protons can be observed (Figures 6B and 12 in the Supporting Information). From Figure 6A,B some interesting observations can be made. In these N2 aryl derivatives the B*a*P residue is not subject to a slow

dynamic exchange. On the other hand, the benzyl moiety of **17** and the carbohydrate protons of **17** and **20** are influenced even at 80 °C. What is notable is that despite the absence of the bulky *tert*-butyldimethylsilyl groups in **17** the carbohydrate resonances are broad. It also appears that removal of the O6 benzyl moiety from **16** produces slightly improved signal resolution in **20**, which still retains the *tert*-butyldimethylsilyl groups. Therefore, the silyl groups alone are not contributors to the signal broadening observed in these cases. HRMS data for all compounds in the 2′-deoxyguanosine series were consistent with the calculated results.

Thus, in comparison to the N^2-(1-pyrenyl)-2′-deoxyguanosine derivatives the N^2-(6-benzo[*a*]pyrenyl)-2′-deoxyguanosine analogues display some unique conformational properties. This seems to stem from the additional angular ring on the pyrene moiety at N2 leading to a substantial decrease in the conformational interchange rate and significant signal broadening of the sugar resonances. Whereas this type of pattern is also evident in the N6 adducts, the effect is far less pronounced perhaps due to a greater separation between the large hydrocarbon and the glycosidic portion.

Conclusions

In this report we have clearly demonstrated the assembly of biologically important, putative N6 2′-deoxyadenosine and N2 2′-deoxyguanosine adducts arising from the single-electron oxidation of B[*a*]P. For this purpose Pd catalysis offers a convenient route. It is of interest to note that reactions of simpler models are perhaps not representative of more elaborate reactants. For example, coupling of 1-bromopyrene with protected 2′-deoxyadenosine was quite successful and moderately so with 2′-deoxyguanosine; however, the chemistry does not readily apply to 6-bromo B[*a*]P. On the other hand, coupling of 1-aminopyrene and 6-amino B[*a*]P to bromo nucleosides produces the desired nucleoside adducts. But here again lies a difference; no dimeric adduct was observed with 1-aminopyrene but with 6-amino B[*a*]P an unusual dimeric adduct was obtained in addition to the desired product. Between reactions at the 6 and 2 positions of the purine, dimeric adduct formation seems to occur at the former by a second arylation of the initially formed 2′-deoxyadenosine adduct, but this does not appear to be the case with the 2′-deoxyguanosine analogue. Also, in comparing the pyrene and the B[*a*]P adducts the latter compounds, perhaps due to slower conformational exchange, show signal broadening in their ^{1}H NMR spectra. This feature is quite pronounced in the case of the N2 2′-deoxyguanosine adducts. Compound **13** has been incorporated into codon 61 of the human N-*ras* sequence (5′-CGGACAAGAAG), and studies on this modified DNA oligomer are currently in progress. Combined with our recently reported Pd-catalyzed synthesis of PAH epoxide adducts at the exocyclic amino groups of 2′-deoxyadenosine and 2′-deoxyguanosine,[37] this approach offers convenient access to PAH-nucleoside adducts formed via both the diol epoxide and the single-electron-oxidation metabolic activation pathways.

(37) Lakshman, M. K.; Gunda, P. *Org. Lett.* **2003**, *5*, 39−42.

Experimental Section

For the 2′-deoxyadenosine adducts, thin-layer chromatography was performed on 250-μm silica plates and routine column chromatographic purifications were performed on 200−300 mesh silica gel. Separations of **10** and **11** were performed on 230−400 mesh silica gel. For the 2′-deoxyguanosine series all chromatographic purifications were performed on 230−400 mesh silica gel. NMR spectra were recorded at 500 or 600 MHz in deacidified $CDCl_3$ (deacidification was performed by percolating $CDCl_3$ through a bed of solid $NaHCO_3$ and basic alumina) or DMSO-d_6 as indicated. Chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hz.

***N*^{6}-(1-Pyrenyl)- 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (9). Method A: Coupling of 1-Bromopyrene (1) with Protected 2′-Deoxyadenosine 5.** Into an oven-dried screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (1.5 mg, 6.68 μmol) and **L-1** (6.3 mg, 10.1 μmol). Toluene (0.68 mL) was added, the vial was flushed with N_2 gas, and the mixture was stirred at room temperature for ca. 5 min. To this mixture were added 1-bromopyrene (**1**, 19.1 mg, 67.9 μmol) and nucleoside **5** (49.0 mg, 0.102 mmol) followed by Cs_2CO_3 (31.0 mg, 95.1 μmol). The vial was again flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 92−94 °C. The reaction was monitored by TLC and judged to be complete in 4 h at which time the mixture was cooled, diluted with EtOAc, and extracted twice with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was loaded onto a silica gel column packed in CH_2Cl_2 and eluted with this solvent followed by 5% acetone in CH_2Cl_2. The N6 adduct **9** was isolated as a yellow foam (41.5 mg, 89.9%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.62 (d, 1H, J = 8.3); 8.50 (s, 1H); 8.28−8.25 (m, 3H); 8.21−8.18 (m, 3H); 8.13−8.00 (m, 4H); 6.54 (t, 1H, J = 6.5); 4.67 (m, 1H); 4.06 (m, 1H); 3.93 (dd, 1H, J = 4.1, 11.1); 3.82 (dd, 1H, J = 3.0, 11.1); 2.71 (app quint, 1H, J ∼ 6.5); 2.50 (ddd, 1H, J = 4.1, 6.1, 12.9); 0.96 and 0.95 (2s, 18H, *t*-Bu); 0.14 (s, 12H, $SiCH_3$). HRMS calcd for $C_{38}H_{50}N_5O_3Si_2$ ($M^+ + H$) 680.3452, found 680.3454. UV−vis λ_{max} (MeOH): 238, 275, and 341 nm.

Method B: Coupling of 1-Aminopyrene (2) with Bromo Nucleoside 6. Into an oven-dried screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (1.6 mg, 7.13 μmol), **L-1** (13.2 mg, 21.2 μmol), and Cs_2CO_3 (34.6 mg, 0.106 mmol). 1-Aminopyrene (**2**, 23.0 mg, 0.106 mmol) and bromo nucleoside **6** (38.5 mg, 70.8 μmol) were added followed by 1,2-DME (0.7 mL). The vial was flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 82−84 °C. The reaction was monitored by TLC and judged to be complete in 1 h at which time the mixture was cooled, diluted with EtOAc, and extracted with water. The aqueous layer was back extracted with EtOAc twice, and the organic layers were combined, dried over Na_2SO_4 and evaporated to dryness. The crude product was loaded onto a silica gel column packed in CH_2Cl_2 and eluted with this solvent to remove excess amine and another nonpolar material. Subsequent elution with 5% acetone−CH_2Cl_2 yielded the N6 adduct **9**, isolated as a greenish-yellow foam (35.0 mg, 73%). The ^{1}H NMR spectrum of this material was identical with that reported in Method A above, except that some minor impurities were also evident.

***N*^{6}-(6-Benzo[*a*]pyrenyl)- 3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyadenosine (10).** Into an oven-dried screw-cap vial equipped with a stirring bar were placed $Pd(OAc)_2$ (2.1 mg, 9.35 μmol) and **L-1** (17.18 mg, 27.6 μmol) in 1,4-dioxane (1 mL). The vial was flushed with N_2 gas and the mixture was stirred at room temperature for ca. 6 min. 6-Aminobenzo[*a*]pyrene (**4**, 49.2 mg, 0.184 mmol), the bromo nucleoside **6** (50.0 mg, 91.9 μmol), Cs_2CO_3 (44.94 mg, 0.138 mmol), and 1,4-dioxane (0.84 mL) were added, and the vial was again flushed with N_2 gas, sealed with a Teflon-lined cap, and heated in a sand bath that was maintained at 100−102 °C. After 5.5 h, at which time the reaction was judged to be

complete by TLC, the mixture was cooled, diluted with EtOAc, and washed with water. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The crude product was loaded onto a silica gel column (230−400 mesh) packed in CH_2Cl_2. The column was eluted with CH_2Cl_2 followed by 2% acetone−CH_2Cl_2. Three fractions were collected. The fastest eluting was residual 6-aminobenzo[*a*]pyrene, followed by the desired mono-adduct **10** and then the bis-adduct **11**. Mono-adduct **10** was obtained as a yellowish-brown solid (34.5 mg, 51.3%) whereas the bis-adduct **11** was obtained as a yellow solid (16.4 mg, 15%) after addition and evaporation of anhydrous pentane.

A larger scale reaction with **6** (101.7 mg, 0.187 mmol) and 6-aminobenzo[*a*]pyrene (**4**, 100 mg, 0.374 mmol) yielded the mono-adduct **10** in 49% yield and the bis-adduct in 19% yield. (In some reactions these compounds have been isolated as brown solids and in others as brown foams with a gray metallic sheen.)

Compound **10** ^{1}H NMR (600 MHz, $CDCl_3$): 9.10 (d, 1H, J = 8.4); 9.07 (d, 1H, J = 9.6); 8.42 (d, 1H, J = 8.4); 8.33 (d superimposed on br signal, 2H, J = 9.6); 8.23 (d, 1H, J = 7.8); 8.22 (br s, 1H); 8.14 (d, 1H, J = 9.0); 8.06 (d, 1H, J = 7.2); 7.96 (m, 2H); 7.88 (d, 1H, J = 9.0); 7.83 (t, 1H, J = 7.2); 7.72 (t, 1H, J = 7.2); 6.52 (br, 1H); 4.66 (br, 1H); 4.04 (br, 1H); 3.91 (br, 1H); 3.81 (br d, 1H, J = 9.0); 2.75 (br m, 1H); 2.48 (br m, 1H); 0.91 (br s, 18H, *t*-Bu); 0.11 (br s, 12H, $SiMe_3$). HRMS calcd for $C_{42}H_{52}N_5O_3Si_2$ (M^+ + H) 730.3609, found 730.3607. UV−vis λ_{max} (MeOH): 256, 265, 287, 299, 372, and 392 nm.

Compound **11** ^{1}H NMR (600 MHz, $CDCl_3$): 9.10 (m, 2H); 8.50 (s, 1H); 8.49 (s, 1H); 8.46 (d, 1H, J = 9.0); 8.34 (d, 1H, J = 9.0); 8.22 (d, 1H, J = 7.8); 8.19 (d, 1H, J = 9.6); 8.00 (d, 1H, J = 6.6); 7.93 (t, 1H, J = 7.2); 7.87 (s, 2H); 7.78 (d, 1H, J = 9.0); 7.75 (t, 1H, J = 7.8); 7.59 (t, 1H, J = 7.2); 6.42 (2 closely spaced t, 2H, J = 6.6 and 6.6); 4.56 (m, 2H); 3.96 (m, 2H); 3.75 (dd, 2H, J = 5.4, 10.8); 3.69 (dd, 2H, J = 3.6, 10.8); 2.67 (app quint, 2H, J ∼ 6.3); 2.39−2.36 (m, 2H); 0.88, 0.87, and 0.77 (3s, 36H, *t*-Bu); 0.065, −0.03, −0.038, −0.062, and −0.077 (5s, 24H, $SiMe_3$). HRMS calcd for $C_{64}H_{90}N_9O_6Si_4$ (M^+ + H) 1192.6091, found 1192.6066. UV−vis λ_{max} (MeOH): 255, 265, 288, 300, 377, and 398 nm.

***N*^{6}-(1-Pyrenyl)-2′-deoxyadenosine (12).** The disilyl pyrene adduct **9** (37 mg, 54.4 μmol) was dissolved in THF (0.55 mL) to produce a 0.1 M solution that was cooled to 0 °C in an ice bath. To this was added a 1 M solution of *n*-$Bu_4N^+F^-$ in THF (0.12 mL, 2.2 molar equiv) and the mixture was stirred at 0 °C for 90 min at which time the reaction was complete. The mixture was diluted with EtOAc, and washed three times with water. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting solid was chromatographed on a silica gel column packed in 5% MeOH−CH_2Cl_2, using the same solvent. The desilylated adduct **12** was obtained as an off-white powder (10.1 mg, 41%). ^{1}H NMR (600 MHz, $CDCl_3$): 8.52 (d, 1H, J = 8.4); 8.41 (s, 1H); 8.27 (br s, 1H); 8.24−8.22 (m, 2H); 8.19 (d, 1H, J = 7.8); 8.17 (d, 1H, J = 7.8); 8.10 (d, 1H, J = 9.0); 8.06 (AB_{quart}, 2H, J = 9.6); 8.00 (t, 1H, J = 7.8); 7.93 (s, 1H); 6.52 (d, 1H, J = 12.0); 6.38 (dd, 1H, J = 6.0); 4.82 (app d, 1H, J = 4.8); 4.24 (s, 1H); 3.99 (d, 1H, J = 13.2); 3.80 (app t, 1H, J ∼ 11.7); 3.16 (ddd, 1H, J = 5.4, 10.2, 15.0); 2.43 (app dd, 1H, J = 5.4, 13.2); 1.93 (br s, 1H). HRMS calcd for $C_{26}H_{22}N_5O_3$ (M^+ + H) 452.1723, found 452.1716.

***N*^{6}-(6-Benzo[*a*]pyrenyl)-2′-deoxyadenosine (13).** The disilyl benzo[*a*]pyrene adduct **10** (98.9 mg, 0.135 mmol) was dissolved in THF (1.36 mL) to produce a 0.1 M solution that was cooled to 0 °C in an ice bath. To this was added a 1 M solution of *n*-$Bu_4N^+F^-$ in THF (0.3 mL, 2.2 molar equiv) and the mixture was stirred at 0 °C for 3 h at which time the reaction was complete. The mixture was diluted with EtOAc, and washed three times with water. The organic layer was dried over Na_2SO_4, filtered, and evaporated to dryness. The resulting solid was chromatographed on a silica gel column packed in 5% MeOH−CH_2Cl_2, using the same solvent. The desilylated adduct **13** was obtained as a yellow solid upon addition and evaporation of anhydrous hexane to the material obtained by chromatography (49.0 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$): 9.10 (d, 1H, J = 8.4); 9.07 (d, 1H, J = 8.4); 8.38 (br, 1H); 8.34 (d, 1H, J = 9.6); 8.25 (d, 1H, J = 7.2); 8.16 (s, 1H); 8.13 (s, 1H); 8.10 (br, 1H); 8.08 (d, 1H, J = 7.2); 7.99−7.96 (m, 2H); 7.94 (d, 1H, J = 9.0); 7.84 (td, 1H, J = 1.2, 7.8); 7.73 (t, 1H, J = 7.2); 6.54 (d, 1H, J = 11.0); 6.41 (dd, 1H, J = 5.4, 9.0); 4.81 (br s, 1H); 4.24 (s, 1H); 3.96 (d, 1H, J = 13.2); 3.77 (app t, 1H, J ∼ 13.2); 3.18 (app septet, 1H); 2.36 (app dd, 1H, J = 5.4, 13.8); 1.89 (br s, 1H). HRMS calcd for $C_{30}H_{24}N_5O_3$ (M^+ + H) 502.1879, found 502.1897.

***N*^{2}-(1-Pyrenyl)-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (15). Method A: Coupling of 1-Bromopyrene (1) with Protected 2′-Deoxyguanosine 7.** Into a dry reaction flask equipped with a stirring bar were placed $Pd(OAc)_2$ (1.5 mg, 6.68 μmol), **L-1** (6.4 mg, 10.3 μmol), and anhydrous toluene (0.68 mL). The flask was flushed with N_2 gas and stirred for 5 min at room temperature. The protected 2′-deoxyguanosine **7** (59.8 mg, 0.102 mmol), 1-bromopyrene (**1**, 19.1 mg, 0.068 mmol), and Cs_2CO_3 (31.0 mg, 95.1 μmol) were added to the reaction flask, which was again flushed with N_2 gas, sealed, and stirred at 90° C for 3.5 h. The reaction mixture was then cooled to room temperature, diluted with EtOAc (20 mL), and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified on a silica gel column with 20% EtOAc−*n*-hexane to afford the desired adduct **15** as a brownish-yellow, oily product (46 mg, 86%). The ^{1}H NMR spectrum of this material was identical with that reported in Method B below except that some impurities were also evident.

Method B: Coupling of 1-Aminopyrene (2) with Bromo Nucleoside 8. Into a dry flask equipped with a stirring bar were placed 1-aminopyrene (**2**, 21.8 mg, 0.10 mmol), bromo nucleoside **8** (43.4 mg, 0.067 mmol), **L-1** (12.5 mg, 20.07 μmol), $Pd(OAc)_2$ (1.5 mg, 6.68 μmol), and Cs_2CO_3 (32.7 mg, 0.10 mmol). Anhydrous 1,2-dimethoxyethane (0.7 mL) was added and the flask was flushed with N_2 gas. The flask was sealed and the mixture was stirred at 80 ° C for 18 h. The flask was cooled to room temperature, diluted with EtOAc (20 mL), and washed with water. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness. The crude product was purified by flash chromatography on silica gel with CH_2Cl_2 and then 20% EtOAc−*n*-hexane to afford the adduct **15** as a greenish-yellow oil (42 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.55 (d, 1H, J = 8.3); 8.26 (d, 1H, J = 9.2); 8.19−8.16 (m, 3H); 8.11−8.00 and 7.75 (m and one br s, 6H); 7.33−7.32 (m, 2H); 7.26−7.22 (m, 3H); 6.41 (t, 1H, J = 6.4); 5.52 (AB_{quart}, 2H, J = 12.3); 4.57 (m, 1H); 4.01 (app q, 1H, J ∼ 3.6); 3.82 (dd, 1H, J = 4.2, 11.1); 3.78 (dd, 1H, J = 3.3, 11.1); 2.60 (app quint, 1H, J ∼ 6.5); 2.42 (ddd, 1H, J = 3.9, 6.1, 13.1); 0.93 (s, 18H, *t*-Bu), 0.11 and 0.098 (2s, 12H, $SiMe_3$); HRMS calcd for $C_{45}H_{56}N_5O_4Si_2$ (M^+ + H) 786.3871, found 786.3884.

***N*^{2}-(6-Benzo[*a*]pyrenyl)-*O*^{6}-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (16).** The 2-bromo nucleoside **8** (430 mg, 0.66 mmol), 6-aminobenzo[*a*]pyrene (**4**, 183 mg, 0.69 mmol), $Pd(OAc)_2$ (14.8 mg, 66.0 μmol), **L-1** (124 mg, 0.2 mmol), and Cs_2CO_3 (322 mg, 0.99 mmol) were placed in a dry flask equipped with a magnetic stirring bar. Freshly distilled 1,4-dioxane (12 mL) was added and the mixture was stirred under N_2 gas at 90 °C for 5 h. Upon completion of the reaction as judged by TLC, the mixture was cooled to room temperature and then evaporated under reduced pressure to produce a dark-brown gummy solid. This material was directly purified by flash chromatography on a silica gel column with CH_2Cl_2 and 1:1 *n*-hexanes−EtOAc sequentially, to provide the protected adduct derivative **16** as a greenish-yellow foam (487.8 mg, 88.5%). ^{1}H NMR (600 MHz, DMSO-d_6 at 80 °C): 9.52 (s, 1H); 9.24 (d, 1H, J = 8.4); 9.23 (d, 1H, J = 9.0); 8.48 (d, 1H, J = 8.4); 8.42 (d, 1H, J = 8.4); 8.33 (d, 1H, J = 7.8); 8.19 (d, 1H, J = 9.0); 8.16 (d, 1H, J = 7.2); 8.03 (t, 1H, J =

7.8); 7.99 (s, 1H); 7.97 (d, 1H, J = 9.0); 7.88 (t, 1H, J = 7.8); 7.78 (t, 1H, J = 7.8); 7.10 and 6.97 (broad signals, 5H); 6.07 (br, 1H); 5.10 (br, 2H); 4.16 (m, 1H); 3.69 (br, 1H); 3.48 (br, 2H); 2.62 (br, 1H); 2.02 (br, 1H); 0.80 and 0.75 (2s, 18H, *t*-Bu); −0.076 and −0.086 (2s, 12H, $SiMe_3$). HRMS calcd for $C_{49}H_{58}N_5O_4Si_2$ (M^+ + H) 836.4027, found 836.4037.

***N*²-(6-Benzo[*a*]pyrenyl)-*O*⁶-benzyl-2′-deoxyguanosine (17).** A ∼0.015 M solution of the O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl) nucleoside **16** (232.8 mg, 0.278 mmol) in THF (19 mL) was prepared. To this was added a 1 M solution of *n*-$Bu_4N^+F^-$ in THF (0.61 mL, 2.2 molar equiv) and the mixture was stirred at room temperature. Upon completion of the reaction in 2 h the solvent was removed under reduced pressure. The residue was purified by flash chromatography on a silica gel column with 5% MeOH−CH_2Cl_2 to afford the O^6-benzyl nucleoside **17** as a yellow, foamy solid (168 mg, 99%). ^{1}H NMR (600 MHz, DMSO-d_6 at 80 °C): 9.49 (s, 1H); 9.26 (d, 1H, J = 8.4); 9.25 (d, 1H, J = 9.0); 8.48 (d, 1H, J = 8.4); 8.43 (d, 1H, J = 9.0); 8.34 (d, 1H, J = 7.2); 8.21 (d, 1H, J = 10.2); 8.18 (d, 1H, J = 7.2); 8.08 (s, 1H); 8.04 (t, 1H, J = 8.4); 7.99 (d, 1H, J = 9.6); 7.91 (t, 1H, J = 8.4); 7.80 (t, 1H, J = 7.8); 7.02−6.78 (3 br signals, 5H); 6.16 (br, 1H); 4.95 (br, 2H); 4.86 (br, 1H); 4.45 (br, 1H); 4.18 (br, 1H); 3.75 (br, 1H); 3.38 (br, 2H); 2.55 (br, 1H); 2.16 (br, 1H). HRMS calcd for $C_{37}H_{30}N_5O_4$ (M^+ + H) 608.2298, found 608.2300.

***N*²-(6-Benzo[*a*]pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (20).** To a solution of the O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl) nucleoside **16** (50.9 mg, 61 μmol) in 1:1 THF−MeOH (1.7 mL) was added 10% Pd-C (5 mg). The flask was evacuated and flushed with hydrogen, and this procedure was repeated three times. The reaction mixture was then stirred for 24 h under a hydrogen atmosphere (balloon). The mixture was filtered and evaporated under reduced pressure. Flash chromatographic purification of the crude material on a silica gel column with ethyl acetate and 5% MeOH−THF sequentially afforded the desired disilyl adduct **20** as a yellowish-white powder (41.6 mg, 91.5%). ^{1}H NMR (600 MHz, DMSO-d_6 at 80 °C): 10.80 (br, 1H); 9.24 (d, 1H, J = 8.4); 9.23 (d, 1H, J = 9.0); 9.13 (br, 1H); 8.46 (d, 1H, J = 9.0); 8.45 (d, 1H, J = 8.4); 8.36 (d, 1H, J = 7.8); 8.19 (d, 1H, J = 7.2); 8.17 (d, 1H, J = 9.0); 8.06 (d, 1H, J = 7.2); 8.05 (d, 1H, J = 9.0); 7.89 (t, 1H, J = 7.8); 7.84 (t, 1H, J = 7.8); 7.74 (s, 1H); 5.64 (br, 1H); 3.74 (br, 1H); 3.46 (br, 1H); 3.16 (br m, 1H); 3.09 (br m, 1H); 2.26−2.30 (app quint, 1H); 1.68 (m, 1H); 0.73 and 0.54 (2s, 18H, *t*-Bu); −0.18, −0.19, −0.30, and −0.36 (4s, 12H, $SiMe_3$). HRMS calcd for $C_{42}H_{52}N_5O_4Si_2$ (M^+ + H) 746.3558, found 746.3566.

***N*²-(1-Pyrenyl)-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine (21).** To a solution of the O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl) nucleoside **15** (47.9 mg, 0.061 mmol) in 1:1 THF−MeOH (3 mL) was added 10% Pd-C (25 mg). The flask was evacuated and flushed with hydrogen, and this procedure was repeated three times. The reaction mixture was then stirred for 18 h under a hydrogen atmosphere (balloon). Upon completion of the reaction, the mixture was filtered though a plug of Celite and then evaporated to dryness. Purification of the crude material by flash chromatography on a silica gel column with 5% MeOH−CH_2Cl_2 afforded the desired compound **21** as a brownish-white solid (10.9 mg, 25.7%). ^{1}H NMR (600 MHz, $CDCl_3$): 12.66 (br, 1H); 10.32 (br, 1H); 8.38 (d, 1H, J = 9.0); 8.24 (d, 1H, J = 7.8); 8.10 (d, 1H, J = 7.2); 8.07−7.96 (m, 5H); 7.91 (t, 1H, J = 7.5); 7.47 (br, 1H); 5.78 (br m, 1H); 3.98 (br s, 1H); 3.66 (br s, 1H); 3.37 (br d, 1H, J = 8.4); 3.25 (br m, 1H); 2.18 (br m, 1H); 1.91 (m, 1H); 0.67, 0.66 (2s, 18H, *t*-Bu); −0.22, −0.27 (2s, 12H, $SiMe_3$). HRMS calcd for $C_{38}H_{50}N_5O_4Si_2$ (M^+ + H) 696.3401, found 696.3427.

Acknowledgment. S.B. and H.M. are grateful to the Kyonggi University for partial financial support of this work (year 2000). M.K.L. is grateful for support from the NIH (NCI 1R15 CA094224-01) and a PSC-CUNY 33 award. We wish to thank Dr. Seo Jung Ju at Korea Basic Science Institute for assistance with mass spectral data, Dr. Surendra Chaturvedi (PrimeSyn Lab Inc., NJ) for assistance with DNA synthesis, and Dr. Mark Hail (Enovatia, NJ) for mass spectral analysis of the adducted oligomer.

Supporting Information Available: Synthetic procedures for N^6,3′,5′-triacetyl-N^6-(6-benzo[*a*]pyrenyl)-2′-deoxyadenosine (**14**), N^2-(6-benzo[*a*]pyrenyl)-O^6-benzyl-3′,5′-diacetyl-2′-deoxyguanosine (**18**), N^2-(6-benzo[*a*]pyrenyl)-3′,5′-diacetyl-2′-deoxyguanosine (**19**), and N^2-(6-benzo[*a*]pyrenyl)- N^2,3′,5′-triacetyl-O^6-benzyl-2′-deoxyguanosine (**22**) as well as proton NMR spectra for **9**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added in Proof

After this manuscript was accepted we became aware of a communication (Chakraborti, D.; Colis, L.; Schneider, R.; Basu, A. K. *Org. Lett.*, submitted) wherein the Pd-mediated coupling of bromo and bromo nitro pyrenes with O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyguanosine as well as amino and amino nitro pyrenes with 2-bromo-O^6-benzyl-3′,5′-bis-*O*-(*tert*-butyldimethylsilyl)-2′-deoxyinosine was studied. Despite some experimental differences, for bromopyrene the results paralleled our observations, whereas for the nitropyrenes, coupling of the halo aromatic with protected deoxyguanosine afforded good yields, indicating that even a remote nitro group was adequate for efficient coupling.

JO030113B