New Synthetic Approaches to Polycyclic Aromatic Hydrocarbons and Their Carcinogenic Oxidized Metabolites: Derivatives of Benzo[*s*]picene, Benzo[*rst*]pentaphene, and Dibenzo[*b,def*]chrysene

Fang-Jie Zhang, Cecilia Cortez, and Ronald G. Harvey*

Ben May Institute for Cancer Research, University of Chicago, Chicago, Illinois 60637

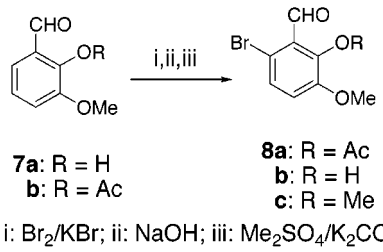
Received November 22, 1999

A new synthetic approach to polycyclic aromatic compounds is described that entails in the key steps double Suzuki coupling of PAH bisboronic acid derivatives with *o*-bromoaryl aldehydes to furnish aryl dialdehydes that are converted to larger polycyclic aromatic ring systems by either (a) conversion to diolefins by Wittig reaction followed by photocyclization or (b) reductive cyclization with triflic acid and 1,3-propanediol. This synthetic method provides convenient access to as many as three different polycyclic aromatic ring systems from a single Suzuki coupled intermediate. It was utilized to synthesize substituted derivatives of benzo[*s*]picene, benzo[*rst*]pentaphene, dibenzo[*b,def*]chrysene, and 13,14-dihydro-benz[*g*]indeno[2,1-*a*]fluorene, as well as the putative carcinogenic bisdihydrodiol metabolites of benzo[*s*]picene, benzo[*rst*]pentaphene, and dibenzo[*b,def*]chrysene.

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants produced in the combustion of organic matter.[1,2] Some PAHs, such as benzo[*a*]pyrene, are potent carcinogens that are implicated in the causation of lung cancer in cigarette smokers, as well as other cancers.[1a,3]

The mechanism of PAH carcinogenesis involves metabolic activation by P450 mono-oxygenase enzymes to PAH dihydrodiol intermediates that are transformed to PAH diol epoxides in which the epoxide ring resides in a sterically crowded bay or fjord molecular region. The latter serves to protect the reactive epoxide function from further enzymatic degradation. The PAH diol epoxides react with DNA to form covalent adducts that lead to mutations ultimately resulting in the induction of tumors.[1a,4] There is evidence that as many as three additional mechanistic pathways may also play a role.[1a] These include (1) one-electron oxidation to radical-cation intermediates that react with DNA, resulting in depurination;[5,6] (2) dihydrodiol dehydrogenase catalyzed dehydrogenation of dihydrodiols to quinones that combine with DNA or enter into a redox cycle with O_2 to generate reactive oxygen species that attack DNA;[7] and (3) formation of benzylic alcohol derivatives (by oxidation of methyl substituents or by biomethylation)[8] that are in turn converted by sulfotransferase enzymes to benzylic sulfate esters that attack DNA.[9] There is also evidence that more polar PAH metabolites, such as bisdihydrodiols, contribute to the carcinogenicity of PAHs that possess two or more sterically crowded bay or fjord regions in the molecule (e.g., dibenz[*a,j*]anthracene).[10]

Scheme 1



Investigations of the mechanisms of PAH carcinogenesis at the molecular-genetic level have been hampered by a deficiency of efficient methods for synthesis of PAHs

(1) (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis;* Cambridge University Press: Cambridge, England, 1991. (b) Harvey, R. G. In *The Handbook of Environmental Chemistry*, Volume 3, Part I: *PAHs and Related Compounds*; Hutzinger, O., Editor-in-Chief, Neilson, A., Volume Ed., Springer: Berlin, Heidelberg, 1997; Chapter 1, pp 1−54.

(2) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*; Wiley-VCH: New York, 1997.

(3) Denissenko, M. F.; Pao, A.; Tang, M.; Pfeifer, G. P. *Science* **1996**, *274*, 430. Pfeifer, G. P.; Denissenko, M. F. *Environ. Mol. Carcin.* **1998**, *31*, 197. Denissenko, M. F.; Chen, J. X.; Tang, M.; Pfeifer, G. P. *Proc. Natl. Acad. Sci. U.S.A.* **1997**, *94*, 3893. Chen, J. X.; Zheng, Y.; West, M.; Tang, M. *Cancer Res.* **1998**, *58*, 2170.

(4) Conney, A. H. *Cancer Res.* **1982**, *42*, 4875. Dipple, A.; Moschel, R. C.; Bigger, C. A. H. In *Chemical Carcinogens*, 2nd ed.; Searle, C. E., Ed.; ACS monograph no. 182, American Chemical Society: Washington, DC, 1984; pp 63−84. Harvey, R. G.; Geacintov, N. E. *Acc. Chem. Res.* **1988**, *21*, 66. Harvey, R. G. *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Symposium Series monograph 283,; American Chemical Society: Washington, DC, 1985.

(5) Cavalieri, E. L.; Rogan, E. G. *Xenobiotica* **1995**, *25*, 677.

(6) Recent evidence suggests that the depurination pathway may be of relatively minor importance in the mechanism of PAH carcinogenesis: Melendez-Colon, V.; Luch, A.; Seidel, A.; Baird, W. *Carcinogenesis* **1999**, *20*, 1885.

(7) Smithgall, T. E.; Harvey, R. G.; Penning, T. M. *Cancer. Res.* **1988**, *48*, 1227. Flowers-Geary, L.; Harvey, R. G.; Penning, T. M. *Chem. Res. Toxicol.* **1993**, *6*, 252. Penning, T. M.; Ohnishi, S. T.; Ohnishi, T.; Harvey, R. G. *Chem. Res. Toxicol.* **1996**, *9*, 84. Burczynski, M. E.; Harvey, R. G.; Penning, T. M. *Biochemistry* **1998**, *37*, 6781.

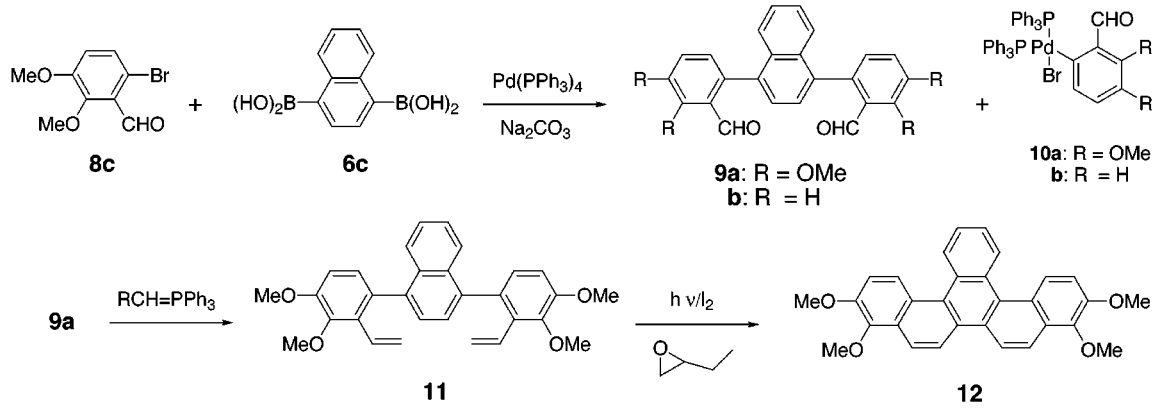
(8) Flesher, J.; Myers, S. R.; Blake, J. W. In *Polynuclear Aromatic Hydrocarbons*; Cooke, M., Dennis, A. J., Eds.; Battelle Press: Columbus, OH, 1986; pp 271−284.

(9) Glatt, H.; Pauly, K.; Frank, H.; Seidel, A.; Oesch, F.; Harvey, R. G.; Werle-Schneider, G. *Carcinogenesis* **1994**, *15*, 2605. Surh, Y.; Liem, A.; Miller, E. C.; Miller, J. *Carcinogenesis* **1989**, *10*, 1519.

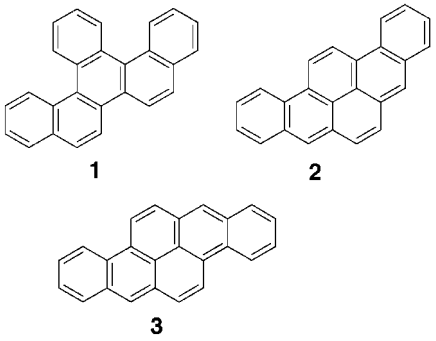
(10) Carcinogenic PAHs with more than one bay or fjord molecular region include dibenzo[*a,c*]anthracene, dibenzo[*a,h*]anthracene, dibenzo[*a,j*]anthracene, dibenzo[*b,def*]chrysene, dibenzo[*a,e*]aceanthrylene, dibenzo[*def,p*]chrysene, and benzo[*rst*]pentaphene. For references to the role of bisdihydrodiols in the mechanism of carcinogenesis of these PAHs, see: Harvey, R. G.; Dai, W.; Zhang, J.-T.; Cortez, C. *J. Org. Chem.* **1998**, *63*, 8118. Zhang, J.-T.; Dai, W.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 8125. Zhang, J.-T.; Harvey, R. G. *Tetrahedron* **1999**, 55, 625.

10.1021/jo9918044 CCC: $19.00
Published on Web 05/31/2000

Scheme 2

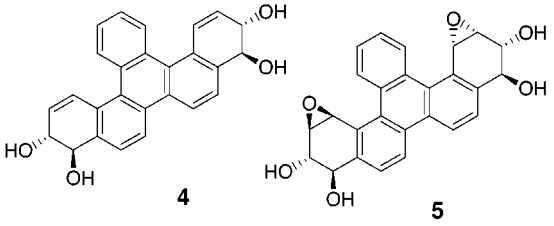


and their oxidized metabolites.[1,2] We now report a new synthetic approach that involves in the key steps double Suzuki coupling and triflic acid catalyzed reductive cyclization. This method was used to synthesize putative carcinogenic metabolites of benzo[*s*]picene (**1**), benzo[*rst*]-pentaphene (**2**), and dibenzo[*b,def*]chrysene (obsolete name, dibenzo[*a,h*]pyrene) (**3**).

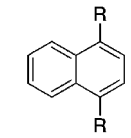


Results

The general synthetic approach entails double Suzuki coupling of a PAH bisboronic acid derivative with a suitably substituted aryl bromide. This is illustrated by its application to the synthesis of the bisdihydrodiol (**4**) and diol epoxide (**5**) derivatives of benzo[*s*]picene. The



key intermediate in this synthesis is 3,4,9,10-tetramethoxybenzo[*s*]picene (**12**) (Scheme 2). The 1,4-bisboronic acid derivative of naphthalene (**6c**), required as one of the starting compounds for the preparation of **12**, was itself synthesized from 1,4-dibromonaphthalene (**6a**) via



6a: R = Br
b: R = $B(OMe)_2$
c: R = $B(OH)_2$

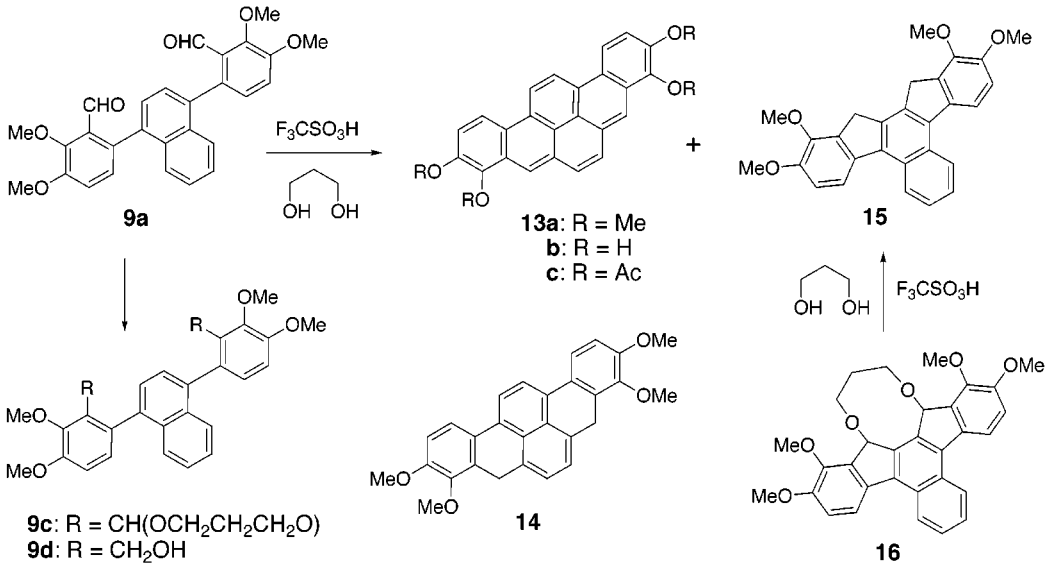
reaction with Mg and $B(OMe)_3$ followed by acidic hydrolysis.[11] The other starting compound 6-bromo-2,3-dimethoxybenzaldehyde (**8c**) was synthesized from 3-methoxysalicylaldehyde (**7a**) (Scheme 1) via acetylation of the phenolic hydroxyl group followed by selective bromination of the product (**7b**) with Br_2 and KBr in the 6-position to yield (**8a**).[12] Compound **8a** was converted to its methyl ether derivative (**8c**) by hydrolysis with 10% KOH to the phenol (**8b**) followed by reaction of the latter with dimethyl sulfate.[13] Direct synthesis of **8c** through bromination of 2,3-dimethoxybenzaldehyde was less satisfactory, affording a mixture of 5-bromo-2,3-dimethoxybenzaldehyde and **8c** (1.7:1).

Double Suzuki coupling of the aryl bromide **8c** with naphthalene 1,4-bisboronic acid (**6c**) was carried out in the presence of $Pd(PPh_3)_4$ in DME by the published procedure.[14] The yield of the dialdehyde product (**9a**) obtained by this procedure was moderate (20%). However, it was dramatically improved (to >90%) by a modified procedure that entailed use of sodium carbonate as a base and water as a cosolvent.[15] The principal product was shown by TLC and ^{1}H NMR analysis to be a mixture of stereoisomers of **9a** in the ratio of 35:65. Formation of isomers is apparently due to steric restriction of rotation between the two outer substituted aryl rings and the central naphthalene ring of **9a**. An additional product identified as the palladium complex **10a** on the basis of its elemental analysis and its ^{1}H and ^{13}C spectra was also isolated. This complex evidently arises from reaction between **8c** and $Pd(PPh_3)_4$. It is surprisingly stable in that it can be purified by column chromatography on silica gel and is resistant to hydrolysis by heating in aqueous solution.

Analogous double Suzuki coupling of 2-bromobenzaldehyde with **6c** in the presence of $Pd(PPh_3)_4$ in DME by the modified procedure afforded the corresponding dialdehyde product lacking the methoxy substituents (**9b**) in good yield (91%), but the analogous palladium complex

(11) Allen, L. M.; Roscoe, C. W. *J. Pharm. Sci.* **1969**, *58*, 368.
(12) Wriede, U.; Fernandez, M.; West, K. F.; Harcourt, D.; Moore, H. W. *J. Org. Chem.* **1987**, *52*, 4485.
(13) Kametani, T.; Honda, T.; Inoue, H.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1221.
(14) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
(15) Sharp, M. J.; Cheng, W.; Snieckus, V. *Tetrahedron* Lett. **1987**, *28*, 5093.
(16) 1,2-Epoxybutane serves to block competing secondary reactions by scavenging the HI produced: Liu, L. B.; Yang, B. W.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769.

Scheme 3



10b could not be isolated. To test the role of the palladium complex in the Suzuki coupling reaction with **6c**, **10a** was reacted with **6c** in the presence of Na_2CO_3. The dialdehyde coupling product **9a** was obtained in about 50% yield, confirming that **10a** is a likely intermediate in the Suzuki coupling.

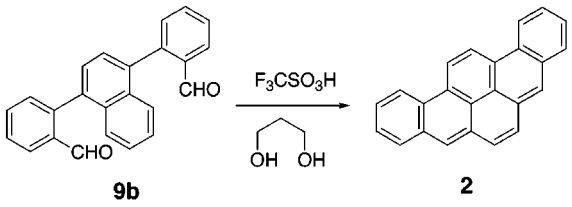
Wittig reaction of **9a** with the phosphonium salt prepared from methyltriphenylphosphonium bromide and *n*-butyllithium took place smoothly to furnish the diolefin **11** in 91% yield. Photochemical oxidative cyclodehydrogenation of **11** in dilute benzene solution (1.8×10^{-3} M) in the presence of iodine and 1,2-epoxybutane[16] gave 3,4,9,10-tetramethoxybenzo[*s*]picene (**12**) as the sole cyclized product in 81% yield.[17,18] Compound **12** prepared by this route was identical in its physical and spectral properties, including its ^{1}H NMR spectrum, with an authentic sample prepared by a synthetic route not involving Suzuki coupling.[18b] Conversion of tetramethoxybenzo[*s*]picene (**12**) to the bisdihydrodiol (**4**) and bis-*anti*-diol epoxide (**5**) derivatives of benzo[*s*]picene was reported previously.[19]

In principle, cyclodehydration of the dialdehyde intermediate (**9a**) might be expected to provide synthetic access to 3,4,9,10-tetramethoxybenzo[*rst*]pentaphene (**13a**) (Scheme 3), a convenient synthetic precursor of the unknown 3,4,9,10-bisdihydrodiol of benzo[*rst*]pentaphene. However, cyclodehydration of polycyclic aromatic aldehydes is seldom useful synthetically because of the low yields obtained. Consistent with this experience, acid-catalyzed cyclodehydration of **9a**, even under relatively dilute conditions, afforded mainly polymeric products. In view of this difficulty, we investigated a potential alternative approach involving reductive Friedel−Crafts cyclization of **9a** with trifluoromethanesulfonic acid (triflic acid) and 1,3-propanediol by the procedure of Fukuzawa et al.[20] The product of this reaction was not the expected 5,8-dihydro derivative (**14**). Instead, there was obtained the fully aromatic parent compound **13a** accompanied by the PAH compound arising from the alternative mode of cyclization, 1,2,11,12-tetramethoxy-13,14-dihydrobenz[*g*]-indeno[2,1-*a*]fluorene (**15**). The ^{1}H NMR spectrum of **13a** was relatively simple as a result of its symmetry. It exhibited characteristic singlets at δ 9.07, 8.59, and 7.81, which were assigned to the meso region $H_{5,8}$ aromatic protons, the K-region $H_{6,7}$ protons, and the bay region $H_{13,14}$ protons, respectively, and additional peaks consistent with this assignment. The product **15** presumably arises from reductive cyclization of the aldehyde functions of **9a** to the adjacent positions of the naphthalene ring system. The ^{1}H NMR spectrum of **15** showed a singlet at δ 4.06 for four methylene protons, consistent with either the assigned structure **15** or the alternative structure **14**. However, structure **14** could be ruled out by the chemical shift pattern of the remaining aromatic protons, which showed a doublet of doublets at δ 8.81 and a doublet at δ 8.06 assigned to the sterically hindered fjord region $H_{4,5}$ and $H_{8,9}$ protons, respectively, and an additional doublet of doublets at δ 7.65 and a doublet at δ 7.06 assigned to the $H_{6,7}$ and $H_{3,10}$ protons, respectively, as well as two singlets at δ 3.98 and 4.04 for the methyl protons. Moreover, attempted dehydrogenation of this compound over a palladium catalyst failed to yield the fully aromatic PAH compound **13a**, affording only recovered **15**.

The yields of **13a** and **15** obtained from reductive cyclization of **9a** with triflic acid and 1,3-propanediol in 1,2-dichloroethane by the original procedure of Fukuzawa et al.[20] (Method A) were modest (15% and 13%, respectively). Substitution of other acids (CF_3CO_2H, H_2SO_4, $Sc(OTf)_3$, or $BF_3{\cdot}Et_2O$) for triflic acid proved even less satisfactory, affording only polymeric products. The use of CH_2Cl_2 or CH_3NO_2 as solvents in place of 1,2-dichloroethane resulted in formation of complex mixtures of polar products of uncertain identity. However, use of dioxane in place of dichloroethane as the solvent (Method B) doubled the yield of **13a** (31%), and instead of **15** there was obtained a new compound (25%) identified as **16**, a cyclic diether derivative of **15**. Compound **16** was converted to **15** by heating with 1,3-propanediol and a catalytic amount of triflic acid in 1,2-dichloroethane. This reaction failed to take place in dioxane. These findings

(17) Mallory, F. B.; Mallory, C. W. *Org. React.* **1984**, *30*, 1.
(18) (a) Zhang, F.-J.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 2773. (b) Zhang, F.-J.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 1168.
(19) The bisdihydrodiol (**1**) was obtained as a mixture of diastereomers consisting of a meso isomer and a racemic mixture of enantiomers.
(20) Fukuzawa, S.; Tsuhimoto, T.; Hiyama, T. *J. Org. Chem.* **1997**, *62*, 151.

Scheme 4



9b **2**

suggest that **16** is an intermediate in the formation of **15**. Although **16** is stable in dioxane, it readily undergoes reduction to **15** in 1,2-dichloroethane. In confirmation of this hypothesis, when reductive cyclization of **9a** in 1,2-dichloroethane was monitored by TLC, compound **16** was detected as an initially formed product, which disappeared over time and was replaced by **15**.

Two other compounds that might conceivably participate as intermediates in the reductive cyclization of the dialdehyde **9a** are its diacetal (**9c**) and the related dialcohol 1,4-bis(2-hydroxymethyl-3,4-dimethoxyphenyl)-naphthalene (**9d**) (Scheme 3). The diacetal **9c** was synthesized from **9a** by reaction with 1,3-propanediol catalyzed by *p*-toluenesulfonic acid. The dialcohol **9d** was prepared by reduction of **9a** with excess $NaBH_4$. Reaction of **9c** with triflic acid in 1,2-dichloroethane under the conditions for reductive cyclization took place readily to afford compounds **13a** and **15** in essentially the same ratio as previously obtained. This is consistent with intermediacy of the diacetal **9c** in the reductive cyclization of **9a**. However, the dialcohol **9d** failed to react under the same conditions, indicating that it is unlikely to be an intermediate in reductive cyclization of **9a**.

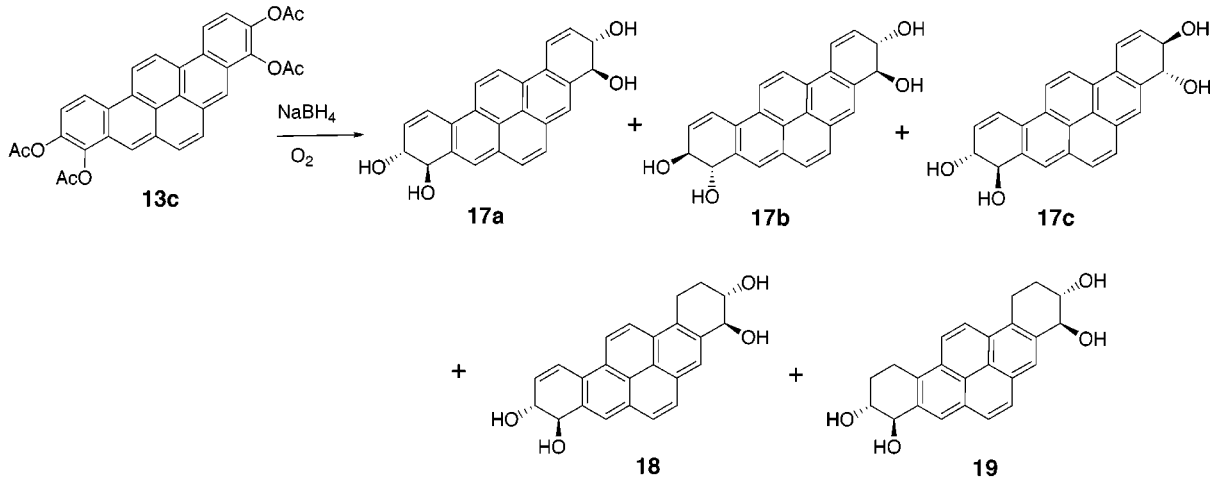
Synthesis of benzo[*rst*]pentaphene (**2**) was accomplished via analogous reductive cyclization of the unsubstituted dialdehyde **9b** with 1,3-propanediol and triflic acid in 1,2-dichloroethane (Scheme 4). This PAH was the sole major product; the PAH expected to be formed by the alternative mode of cyclization was not detected. The regioselectivity of cyclization is clearly dependent upon the nature of the substituents in the precursor.

Conversion of 3,4,9,10-tetramethoxybenzo[*rst*]pentaphene (**13a**) to the corresponding bisdihydrodiol (**17**) proceeded via initial demethylation with BBr_3 to yield the corresponding biscatechol, 3,4,9,10-tetrahydroxybenzo[*rst*]pentaphene (**13b**). In view of the sensitivity of PAH catechols to autoxidation, **13b** was isolated and characterized as its tetraacetate derivative (**13c**). Direct reduction of **13c** to the bisdihydrodiol by treatment with a large excess of $NaBH_4$ in EtOH with O_2 bubbling through the solution (Scheme 5) by the usual procedure[21,22] furnished *trans*-3,4-*trans*-9,10-tetrahydroxy-3,4,9,10-tetrahydrobenzo[*rst*]pentaphene (**17**) as a mixture of isomers (**17a**−**c**) along with the overreduced products **18** and **19**. The ratio of **18** to **19** was found to be dependent upon both the amount of $NaBH_4$ and reaction time. Optimum yield of the bisdihydrodiol was favored by a low ratio of $NaBH_4$ and relatively short reaction time, but some degree of over- or under-reduction could not be avoided. However, **17** was obtained in good yield free of **18** and **19** by a modified procedure that entailed monitoring the reaction by HPLC to ensure complete conversion of **13c** to products, followed by acetylation of the crude product mixture, and dehydrogenation with DDQ in refluxing benzene to yield the tetraacetate derivative of **17**. Hydrolysis gave the pure bisdihydrodiol **17**, which exhibited a tendency to undergo autoxidation in air and light.

The bisdihydrodiol **17** was obtained as a mixture of the symmetrical meso isomer (**17a**) and a racemic pair of enantiomers (**17b** and **17c**). HPLC showed two peaks corresponding to the meso and racemic forms. Each of the isomers of **17** has the potential for the dihydrodiol functions to exist as mixtures of diequatorial and diaxial conformers. However, for most PAH dihydrodiols, conformational interconversion is known to occur with relative facility at room temperature in the absence of steric restrictions, and the conformers tend to exist in dynamic equilibrium that favors a predominance of the diequatorial conformers.[23] The ^1H and ^{13}C NMR spectra of the isomers of **17** showed only a single set of peaks for each isomer, consistent with the anticipated facility of interconversion of the diaxial and diequatorial conformers at ordinary temperatures. The ^1H spectrum of the mixture of the corresponding tetraacetate derivatives showed two sets of peaks for the H_1 and the H_2 protons consistent with the presence of the meso and racemic forms. An analogous mixture of meso and racemic isomers was obtained previously in the related synthesis of the bisdihydrodiol derivative of benzo[*s*]picene (**4**).[18b,19]

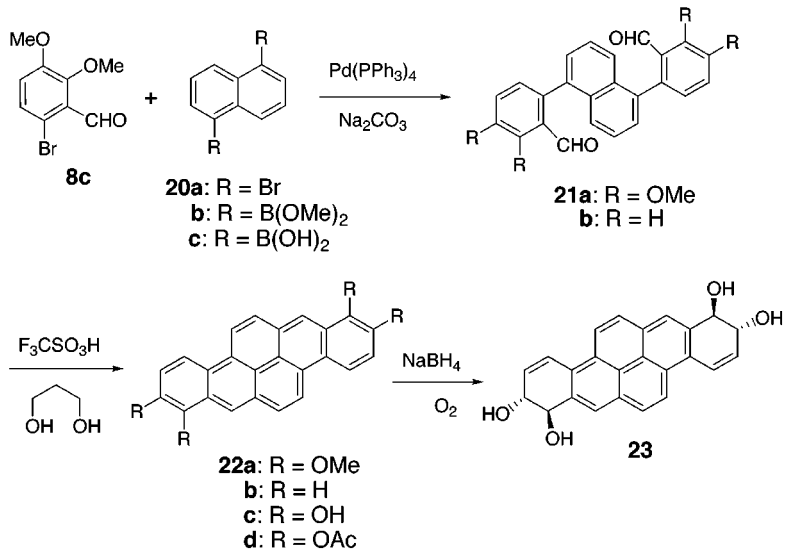
Extension of this approach to the synthesis of 1,2,8,9-tetramethoxydibenzo[*b*,*def*]chrysene (**22a**) was also examined (Scheme 6). The 1,5-bisboronic acid derivative of naphthalene (**20c**) required as starting compound was

Scheme 5



13c **17a** **17b** **17c** **18** **19**

Scheme 6



synthesized from 1,5-dibromonaphthalene[24] (**20a**) via reaction with Mg and $B(OMe)_3$ followed by acidic hydrolysis of the resulting 1,5-bisboronate (**20b**).[11] Double Suzuki coupling of **8c** with **20c** in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in aqueous DME by the procedure employed for **9a** furnished the corresponding dialdehyde (**21a**). The ^{1}H NMR spectrum of **21a** showed it to be a mixture of stereoisomers (35:65). As in the case of **9a**, formation of isomers is a consequence of steric restriction of rotation between the bulky aryl substituents and the central naphthalene ring.

Reductive Friedel−Crafts cyclization of the dialdehyde **21a** with triflic acid and 1,3-propanediol in dioxane gave 1,2,8,9-tetramethoxydibenzo[*b*,*def*]chrysene (**22a**) as the sole identifiable product. Neither the PAH compound analogous to **15** from the alternative mode of cyclization nor a product analogous to **16** was detected. The poor solubility of **22a** made its separation from polymeric products and its purification by chromatography difficult. The ^{1}H NMR spectrum of **22a** was entirely consistent with its structural assignment, exhibiting a characteristic singlet at δ 8.95 assigned to the meso region $H_{7,14}$ aromatic protons, doublets at δ 8.88, 8.78, and 8.34 for the remaining aromatic protons, and additional peaks consistent with this assignment. Reductive cyclization of the unsubstituted dialdehyde **21b** with triflic acid and 1,3-propanediol under similar conditions furnished dibenzo[*b*,*def*]chrysene (**22b**) as the principal product.

Conversion of **22a** to the bisdihydrodiol of dibenzo[*b*,*def*]chrysene (**23**) via a sequence of steps analolgous to that employed for the synthesis of **17**, i.e., demethylation to the biscatechol (**22c**), acetylation to the tetraacetate (**22d**), and reduction with $NaBH_4$, was successful. Despite the relatively poor solubility of the tetraacetate **22d** (and other compounds in this series), it was efficiently reduced to **23** under appropriate reaction conditions (large excess of $NaBH_4$, use of CH_2Cl_2 as cosolvent, and relatively short reaction time [2 h]). Formation of over-reduced products was minimal under these conditions.

Discussion

A new synthetic approach to PAHs is described that entails in the key steps double Suzuki coupling of a PAH bisboronic acid derivative with an *o*-bromoaryl aldehyde and conversion of the primary dialdehyde product to a larger polycyclic aromatic ring system through either (a) Wittig reaction followed by oxidative photocyclization or (b) triflic acid catalyzed reductive cyclization. The former sequence is illustrated by synthesis of 3,4,9,10-tetramethoxybenzo[*s*]picene (**12**) and its conversion to the bisdihydrodiol of benzo[*s*]picene (**4**). Double Suzuki coupling of the aryl bromide **8c** with naphthalene 1,4-bisboronic acid (**6c**) in the presence of $Pd(PPh_3)_4$ by a modified procedure using aqueous Na_2CO_3 furnished smoothly the dialdehyde product **9a** in good yield (Scheme 2). Wittig reaction of **9a** with methylenetriphenylphosphorane provided the diolefin (**11**), which underwent photochemical cyclodehydrogenation to yield **12**. Alternatively, the dialdehyde **9a** was converted to 3,4,9,10-tetramethoxybenzo[*rst*]pentaphene (**13a**) via triflic acid catalyzed reaction with 1,3-propanediol in 1,2-dichloroethane. Compound **13a** arises from double intramolecular cyclization into the *peri* positions of the adjacent ring. It was accompanied by 1,2,11,12-tetramethoxy-13,14-dihydrobenz[*g*]indeno[2,1-*a*]fluorene (**15**) formed by double cyclization into the β-positions of the same ring. Similar reaction of **9a** in dioxane afforded **13a** in higher yield, but compound **15** was not detected as a product. Instead, the second major product was a new compound identified as **16**, a cyclic diether derivative of **15**. Compound **16** was converted to **15** by triflic acid catalyzed reaction with 1,3-propanediol. Thus, this synthetic methodology provides convenient synthetic access to three different PAH ring systems, **12** or **13a** and **15**.

The use of Suzuki coupling for the synthesis of PAH ring systems has been reported by Kumar[25] and by Rice

(21) Dai, W.; Abu-Shqara, E.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 4905. Platt, K.; Oesch, F. *Synthesis* **1982**, 459.

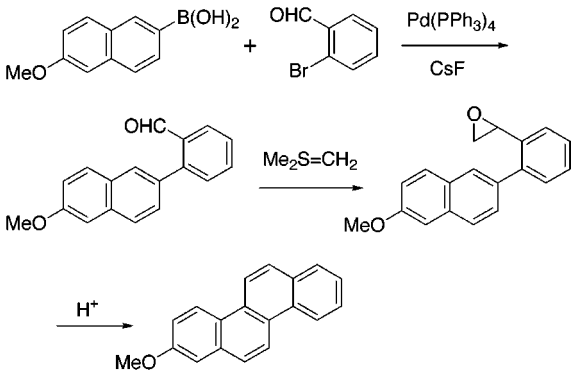
(22) Oxygen serves to recycle hydroquinone intermediates formed by isomerization of the primary reduction product back to quinone.

(23) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenesis;* Cambridge University Press: Cambridge, England, 1991; Chapter 13, pp 306−329. Harvey, R. G. In *Cyclohexenes, Cyclohexadienes, and Related Hydroaromatics*; Rabideau, P. W., Ed.; VCH: New York, 1989; pp 267−298.

(24) Harvey, R. G.; Pataki, J., Cortez, C.; Di Raddo, P.; Yang, C. *J. Org. Chem.* **1991**, *56*, 1210.

(25) Kumar, S. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3157.

Scheme 7

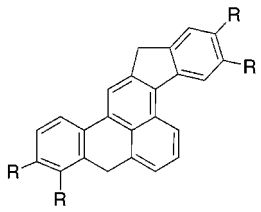


and Cai.[26] The synthetic approach described herein is more closely related to Kumar's method, which entails Suzuki cross-coupling of an *o*-bromoaryl aldehyde followed by conversion of the aldehyde function of the product into the related ethylene oxide and acid-catalyzed cyclization of the latter (Scheme 7). The novel variations on this synthetic theme introduced herein expand the scope of Suzuki coupling to the synthesis of a broader range of polycyclic aromatic ring systems.

Formation of the fully aromatic PAH benzo[*rst*]pentaphene (**2**) and its 3,4,9,10-tetramethoxy derivative **13a** in the reactions of the dialdehydes **9a** and **9b** with 1,3-propanediol and triflic acid (Schemes 3 and 4) rather than their 5,8-dihydro derivatives (e.g., **14**), though unexpected, is not inconsistent with the mechanism for reductive cyclization proposed by Fukusawa et al.[20] According to this concept, the aldehyde functions undergo initial acid-catalyzed reaction with 1,3-propanediol to form the corresponding cyclic diacetals (e.g., **24**) (Scheme 8). Protonation of an oxygen atom of the diacetal followed by ring opening affords a benzylic cationic intermediate that may attack the adjacent aromatic ring system to generate a bisether intermediate (**25**). 1,3-Shift of hydride from the alkoxy carbon to the benzylic carbon atom leads to formation of a partially reduced monoether (**26**) with loss of 3-hydroxypropanal. Compound **26** undergoes conversion to the fully aromatic compound **2** via acid-catalyzed elimination of 1,3-propanediol facilitated by aromatization of the PAH ring system. Elimination of 1,3-propanediol is evidently energetically more favorable than a second 1,3-hydride shift with loss of a second 3-hydroxypropanal to furnish 5,8-dihydro-**17**. Similar considerations explain the formation of the 3,4,9,10-tetramethoxy derivative of benzo[*rst*]pentaphene (**13a**) rather than its 5,8-dihydro derivative (e.g., **14**) in the triflic acid catalyzed reaction of the dialdehyde **9a**.

Formation of the unusual cyclic ether product **16** in the reaction of **9a** with triflic acid and 1,3-propanediol in dioxane, but not in 1,2-dichloroethane, is also consistent with the proposed mechanism. The most plausible origin of **16** is via initial formation of the bisether derivative of **15** analogous to **25** followed by acid-catalyzed reduction with loss of 3-hydroxypropanal by one of the ether functions leading to formation of **16** through reaction of the benzylic cation formed by the resulting partially reduced monoether with the second alcohol function. From a synthetic viewpoint, formation of the ether derivative **16** does not detract from the utility of the method, since reaction in dioxane affords higher yields and **16** may be readily converted to **15** by heating with 1,3-propanediol and triflic acid.

In the reductive cyclization of **9a**, only the symmetrical products of double cyclization to the same ring (e.g., **13a** and **15**) were detected as significant products. The unsymmetrical PAH compound that might be expected to be formed by partial cyclization in each direction (e.g., **27**) was not found, although minor amounts may have

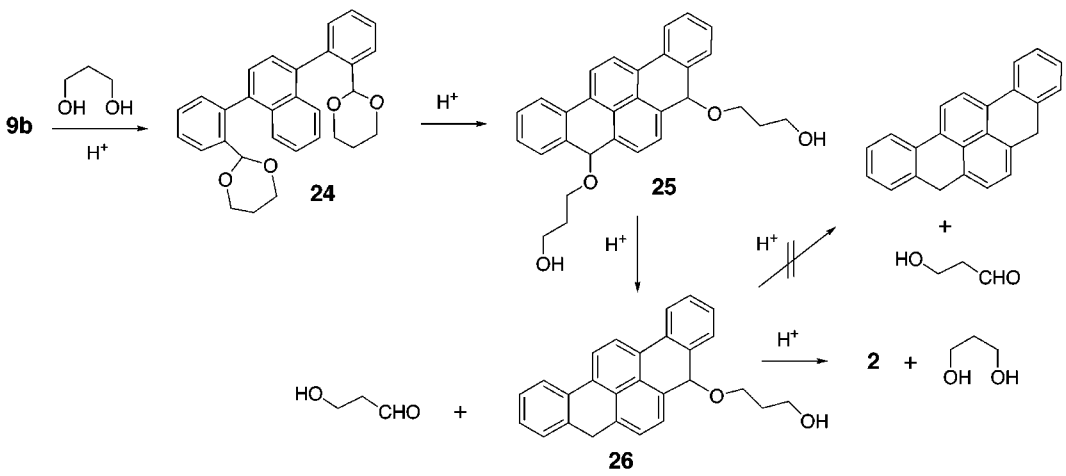


27

been formed. The reason that symmetrical cyclization is favored is that the primary partially cyclized intermediate tends to favor substitution in the same ring by the alkyl substitution effect.

This synthetic methodology appears to be potentially broad in scope. It differs from older well-established synthetic approaches to PAH ring systems, such as the Haworth synthesis,[1a,2,27] in that it entails direct formation of covalent bonds between aromatic rings in the primary step. In this respect, it complements photochemical cyclodehydrogenation of diaryolefins[17] wherein covalent bond formation between aromatic rings to form a new

Scheme 8



ring is the final step. The synthetic method entailing Suzuki coupling is more versatile than the photochemical method because it is more amenable to large scale preparations and because it allows a choice of methods for cyclization. Two methods of cyclization are described herein: (1) conversion of an aldehyde function to a vinyl group followed by photocyclization, and (2) direct reductive cyclization of an aldehyde substituent.

Although double Suzuki coupling was employed in all of the syntheses reported, dual coupling is not an essential feature of the synthetic method. There is no inherent reason that single, double, or even triple Suzuki coupling cannot be employed to synthesize a much larger range of polycyclic aromatic compounds.

Experimental Section

Materials and Methods. 6-Bromo-2,3-dimethoxybenzaldehyde (**8c**) was synthesized from 3-methoxysalicylaldehyde by acetylation, followed by bromination with Br_2 and KBr, hydrolysis, and treatment with dimethyl sulfate by the literature method.[12,13] 1,5-Dibromonaphthalene was synthesized by the procedure previously described.[24] THF was freshly distilled from sodium/benzophenone ketal.

The NMR spectra were recorded on 400 or 500 MHz spectrometers in $CDCl_3$ with tetramethylsilane as internal standard unless stated otherwise. Integration was consistent with all structural assignments. Mass spectra (MS) and HRMS were performed by the University of Illinois at Urbana−Champaign, School of Chemical Sciences. The UV spectra were measured with a Perkin-Elmer Lambda 6 spectrometer. All melting points are uncorrected. ***Caution***: Benzo[*s*]picene, benzo[*rst*]pentaphene, and dibenzo[*b*,*def*]chrysene exhibit carcinogenic activity in animal assays. These PAHs and their dihydrodiol, diol epoxide, and higher oxidized metabolites are potentially hazardous and should be handled with care in accordance with *NIH Guidlines for the Laboratory Use of Chemical Carcinogens*.

1,4-Bis(naphthalenylboronic acid) (6c). A solution of 1,4-dibromonaphthalene (14.25 g, 50 mmol) in freshly distilled anhydrous THF (150 mL) was added dropwise with stirring to Mg turnings (3.6 g, 150 mmol) in a 2 L, three-neck flask equipped with a condenser and a dropping funnel under argon. It was necessary to initiate reaction by adding a few crystals of iodine to 30 mL of the solution and warming to 45 °C. The remaining 120 mL of solution was added over a period of 30 min, and then the solution was warmed to 65 °C and allowed to reflux for 12 h. The resulting light green slurry was allowed to cool to room temperature, and then it was immersed in a dry ice−acetone bath and cooled to −65 °C. Trimethyl borate (250 mmol) in dry THF (50 mL) was added dropwise with stirring over 1h, then the mixture was slowly warmed to room temperature and stirred overnight. The mixture was then cooled in a dry ice bath and hydrolyzed with 2 N HCl. After decomposition of the excess Mg turnings, the solution was extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). After removal of the solvent, the residue was recrystallized from ether to give **6c** as a white solid (4.2 g). The mother liquid was recrystallized from ether−hexane to afford the second crop of **6c** as a yellowish solid (1.8 g), mp > 300 °C: ^{1}H NMR (DMSO, 500 MHz) δ 7.50−7.60 (m, 2H), 7.65 (s, 2H), 8.25−8.45 (m, 4H) [after addition of D_2O, changed to 8.30−8.40 (m, 2H)].

1,4-Bis(2-formyl-3,4-dimethoxyphenyl)naphthalene (9a). To a solution of 6-bromo-2,3-dimethoxybenzaldehyde (**8c**) (6.47 g, 25 mmol) in DME (80 mL) was added $Pd(PPh_3)_4$ (1.0 g, 0.86 mmol), and the mixture was stirred under argon for 15 min. A solution of **6c** (2.16 g, 10 mmol) in EtOH (20 mL) was added, the mixture was stirred for another 15 min, and then 2 M aqueous Na_2CO_3 (100 mL)was added. The resulting mixture was refluxed for 20 h under argon and cooled, and the organic solvent was removed under reduced pressure. The resulting suspension was extracted with CH_2Cl_2 and dried over $MgSO_4$, and the solvent was evaporated. The residue was chromatographed on silica gel eluted with CH_2Cl_2 and then with CH_2Cl_2/EtOAc (90:10) to yield the palladium complex **10a** (600 mg) as a yellow solid, mp 213 °C (CH_2Cl_2/MeOH): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.30 (s, 3), 3.64 (s, 3), 6.45 (d, 1, J = 8.0 Hz), 7.06 (d, 1, J = 8.0 Hz), 7.22−7.29 (m,12), 7.30−7.35 (m, 6), 7.57−7.64 (m, 12), 9.45 (s, 1); ^{13}C NMR (125 MHz) δ 56.47, 61.79, 117.72, 127.66, 127.69, 127.73, 129.72, 129.92 (br), 130.90, 131.08, 131.26, 133.34 (br), 134.66, 134.71, 134.76, 148.89, 153.61, 156.28, 191.28; UV (THF) λ_{max} 298 (ϵ 24 730) nm. Anal. Calcd for $C_{45}H_{39}BrO_3P_2Pd$: C, 61.69; H, 4.49; Br, 9.12. Found: C, 61.83; H, 4.49; Br, 9.25. Further elution gave **9a** (4.1 g, 90%) as a yellow solid, mp 207−209 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.97 (s, 2), 3.98 (s, 4), 4.02 (s, 2), 4.03 (s, 4), 7.12 (d, 1, J = 8.5 Hz), 7.16 (d, 1, J = 9.0 Hz), 7.22 (d, 1, J = 9.0 Hz), 7.23 (d, 1, J = 8.5 Hz), 7.31−7.39 (m, 4), 7.51−7.56 (m, 2), 9.97 (s, 1), 10.00 (s, 1); ^{13}C NMR (125 MHz) δ 56.05, 62.09, 116.38, 116.51, 126.03, 126.07, 126.22, 126.60, 126.71, 127.11, 127.43, 129.47, 129.56, 132.42, 132.47, 134.67, 134.86, 136.7, 150.23, 150.39, 152.65, 152.76, 190.76, 191.12; UV (THF) λ_{max} 305 (ϵ 16 850) nm. Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 73.55; H, 5.35.

1,4-Bis(2-formyl-phenyl)naphthalene (9b). This synthesis was carried out on a 5.5 mmol scale by the procedure for **9a**. Chromatography of the product on a silica gel column eluted with hexane/CH_2Cl_2 (8:2, 1:1) gave **9b** (1.68 g, 91%) as a white solid, mp 168 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.47 (m, 2), 7.47−7.54 (m, 4), 7.54−7.65 (m, 4), 7.70−7.79 (m, 2), 8.14 (d, 2, J = 9.5 Hz), 9.70 (s, 0.8), 9.71 (s, 1); ^{13}C NMR (125 MHz) δ 126.28, 126.96, 127.00, 127.22, 127.23, 127.29, 128.40, 131.59, 131.70, 132.64, 133.71, 133.79, 134.74, 136.08, 136.10, 143.68, 143.74, 191.58, 191.84; UV (THF) λ_{max} 298 (ϵ 14 550) nm. Anal. Calcd for $C_{24}H_{16}O_2$: C, 85.69; H, 4.80. Found: C, 85.48; H, 4.84.

Reaction of the Palladium Complex 10a with 6c. To a suspension of **10a** (110 mg, 0.126 mmol) in DME (4 mL) was added a solution of **6c** (13.6 mg, 0.063 mmol) in EtOH (0.5 mL), and the mixture was stirred for 15 min at room temperature under Ar. TLC showed no reaction occurred. Then 2 M aqueous Na_2CO_3 (2 mL) was added, the resulting mixture was heated at reflux for 20 min under Ar, and a black palladium solid formed. The usual workup gave the dialdehyde **9a** (13 mg, 48%), identical by ^{1}H NMR with an authentic sample.

1,4-Bis(2-vinyl-3,4-dimethoxyphenyl)naphthalene (11). To a solution of methyltriphenylphosphonium bromide (1.78 g, 5 mmol) in 30 mL of dry THF was added 2 mL of a 2.5 M *n*-butyllithium solution in hexane at room temperature under Ar. The resulting yellow solution was stirred for 15 min, then a solution of **9a** (684 mg, 1.5 mmol) in dry CH_2Cl_2 (12 mL) was added, and stirring was continued overnight at room temperature. Evaporation of the solvent under reduced pressure gave a solid residue, which was chromatographed on a silica gel column eluted with hexane/CH_2Cl_2 and then with CH_2Cl_2. Compound **11** (620 mg, 91%) was obtained as a white foam, mp 58−60 °C (hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.88 (s, 6), 3.97 (s, 6), 5.02−5.11 (m, 2), 5.43 (dd, 1, J = 18.0 and 2.0 Hz), 5.60 (dd, 1, J = 18.0 and 2.0 Hz), 6.34−6.50 (m, 2), 6.93−6.97 (m, 2), 7.02−7.08 (m, 2), 7.12−7.18 (m, 4), 7.52−7.57 (m, 2); UV (THF) λ_{max} 303 (ϵ 17 930) nm; EI MS *m*/*z* 452 (M^+). Anal. Calcd for $C_{30}H_{28}O_4$: C, 79.62; H, 6.24. Found: C, 79.37; H, 6.31.

3,4,9,10-Tetramethoxybenzo[*s*]picene (12). Argon was bubbled through a solution of **11** (410 mg, 0.91 mmol) and I_2 (461 mg, 1.82 mmol) in 500 mL of benzene for 15 min. Then 1,2-epoxybutane (15 mL) was added, and the mixture was irradiated with a Hanovia 450 W medium-pressure mercury lamp through a Pyrex filter with stirring for 4 h. TLC showed reaction to be complete. After removal of the solvent under vacuum, the residue was taken up in CH_2Cl_2, and the solution was washed with 10% aqueous $Na_2S_2O_3$, dried over $MgSO_4$, and evaporated to dryness. Chromatography on a short column of silica gel eluted with CH_2Cl_2 afforded **12** (320 mg, 81%) as

(26) Rice, J. E.; Cai, Z.-W. *J. Org. Chem.* **1993**, *58*, 1415.
(27) .Johnson, W. S. *Org. React.* **1944**, *2*, 114.

a white solid, mp 302−303 °C dec ($CHCl_3$), identical with an authentic sample: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.09 (s, 6), 4.10 (s, 6), 7.43 (d, 2, J = 9.0 Hz), 7.60−7.65 (m, 2),), 8.37 (d, 2, J = 9.0 Hz), 8.63 (d, 2, J = 9.0 Hz),), 8.75 (d, 2, J = 9.5 Hz), 8.90−8.94 (m, 2).

Diacetal of 9a (9c). A mixture of **9a** (912 mg, 2 mmol), 1,3-propanediol (456 mg, 6 mmol), *p*-toluenesulfonic acid (20 mg), and benzene (100 mL) was placed in a round-bottom flask, equipped with a Dean−Stark apparatus. The solution was refluxed with stirring for 2 h until no additional water was collected. The solution was cooled to room temperature, triethylamine (0.5 mL) was added, and the solvent was removed. The residue was dissolved in CH_2Cl_2, washed with 2 N NaOH, and dried over K_2CO_3. Evaporation of the solvent furnished pure **9c** (1.06 g, 93%) as a white solid, mp 104−107 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.04−1.14 (m, 2), 1.85−1.95 (m, 2), 3.25−3.51 (m, 4), 3.80−4.03 (m, 4), 3.94 (s, 6), 3.98 (s, 6), 5.38 (s, 1), 5.43 (s, 1), 7.03 (m, 4), 7.30−7.37 (m, 2), 7.39 (s, 1), 7.41 (s, 1), 7.60−7.68 (m, 2); ^{13}C NMR (125 MHz) δ 25.52, 25.68, 56.16, 56.24, 61.52, 67.06, 67.09, 67.12, 67.22, 100.18, 100.30, 113.01, 113.06, 125.08, 125.10, 126.77, 126.81, 126.90, 127.08, 131.29, 131.57, 132.57, 133.02, 133.08, 137.86, 137.98, 148.25, 148.48, 152.88, 153.00; UV (THF) λ_{max} 291 (ϵ 15 000) nm. Anal. Calcd for $C_{34}H_{36}O_8$: C, 71.31; H, 6.34. Found: C, 71.23; H, 6.45.

1,4-Bis(2-hydroxymethyl-3,4-dimethoxyphenyl)naphthalene (9d). To a solution of **9a** (150 mg, 0.33 mmol) in 10 mL of CH_2Cl_2/EtOH (v/v, 1:1) was added $NaBH_4$ (50 mg, 1.32 mmol). The mixture was stirred at room temperature for 1 h. TLC showed the reaction was complete. The reaction mixture was poured into ice−water, extracted with CH_2Cl_2, washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from CH_2Cl_2/hexane to give **9d** as a white solid (145 mg, 96%), mp 187−189 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.96 (s, 2), 3.97 (s, 4), 4.02 (s, 4), 4.03 (s, 2), 4.31 (d, 1, J = 12.0 Hz), 4.33 (d, 1, J = 11.0 Hz), 4.48 (d, 1, J = 12.0 Hz), 4.49 (d, 1, J = 12.0 Hz), 7.00 (d, 1, J = 8.0 Hz), 7.02 (d, 1, J = 8.0 Hz), 7.05 (d, 1, J = 8.5 Hz), 7.08 (d, 1, J = 8.5 Hz), 7.36−7.42 (m, 4), 7.54−7.60 (m, 2); ^{13}C NMR (125 MHz) δ 55.82, 59.01, 59.12, 61.24, 111.77, 111.81, 126.04, 126.07, 126.31, 126.35, 126.38, 126.46, 126.86, 132.70, 132.75, 132.77, 132.82, 133.56, 133.65, 137.50, 137.57, 147.77, 147.87, 151.97; UV (THF) λ_{max} 290 (ϵ 14 920) nm. Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.02; H, 6.13. Found: C, 72.72; H, 6.09.

Reductive Cyclization of 9a. Method A. To a mixture of **9a** (228 mg, 0.5 mmol) and 1,3-propanediol (114 mg, 1.5 mmol) in anhydrous 1,2-dichloroethane (150 mL) was added trifluoromethanesulfonic acid (triflic acid) (15 mg, 0.1 mmol). The solution was refluxed with stirring for 1 h and then cooled to room temperature. Triethylamine (0.5 mL) was added, and the solvent was removed. Chromatography of the residue on silica gel [CH_2Cl_2/hexane (1:1), CH_2Cl_2] gave **13a** followed by **15**. Compound **13a**; R_f = 0.78 (CH_2Cl_2/EtOAc, 20:1) as a yellow solid (32 mg, 15%); mp 308−309 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 125 MHz) δ 4.12 (s, 6), 4.15 (s, 6), 7.57 (d, 2, J = 8.5 Hz), 7.81 (s, 2), 8.59 (s, 2), 8.75 (d, 2, J = 8.5 Hz), 9.07 (s, 2); ^{13}C NMR (125 MHz) δ 56.77, 61.46, 114.23, 118.46, 119.28, 122.22, 124.50, 129.05; UV (THF) λ_{max} 408 (ϵ 62 570), 386 (42 930), 365.7 (18 790), 350 (17 130), 318 (63 820), 284 (30 714) nm. Anal. Calcd for $C_{28}H_{22}O_4$: C, 79.60; H, 5.25. Found: C, 79.50; H, 5.31. Compound **15**; R_f = 0.63 (CH_2Cl_2/EtOAc, 20:1) as a gray solid (27 mg, 13%), mp 286−287 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.98 (s, 6), 4.04 (s, 6), 4.06 (s, 4), 7.06 (d, 2, J = 8.5 Hz), 7.62−7.67 (m, 2), 8.05 (d, 2, J = 8.5 Hz), 8.78−8.83 (m, 2); ^{13}C NMR (125 MHz) δ 33.36, 56.16, 60.35, 111.64, 118.29, 124.52, 125.27, 126.26, 129.25, 134.88, 137.02, 137.37, 138.29, 145.53, 150.86; UV (THF) λ_{max} 384 (ϵ 34 000), 366 (35 300), 267 (34 000), 258 (32 770) nm. Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.60; H, 5.25. Found: C, 79.50; H, 5.31. **Method B.** To a solution of **9a** (228 mg, 0.5 mmol) and 1,3-propanediol (114 mg, 1.5 mmol) in freshly distilled anhydrous 1,4-dioxane (150 mL) was added triflic acid (15 mg, 0.1 mmol). The solution was refluxed with stirring for 1 h and then cooled to room temperature, Et_3N (0.5 mL) was added, and the solvent was evaporated under vacuum. Chromatography of the residue on a silica gel column eluted with CH_2Cl_2/hexane (1:1) then CH_2Cl_2 provided in turn **13a** and **16**. Compound **13a** (66 mg, 31%) was obtained as a yellow solid identical in its physical properties to **13a** from procedure A. Compound **16** was obtained as a pinkish solid (52 mg, 25%), mp 302−304 °C (CH_2Cl_2/hexane), R_f = 0.54 (CH_2Cl_2/EtOAc, 20:1): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.30−2.36 (m, 2), 3.97 (s, 6), 4.04 (s, 6), 4.44−4.50 (m, 2), 4.56−4.61 (m, 2), 5.98 (s, 2), 7.00 (d, 2, J = 8.5 Hz), 7.58−7.62 (m, 2), 7.92 (d, 2, J = 8.0 Hz), 8.65−8.70 (m, 2); ^{13}C NMR (125 MHz) δ 30.73, 56.12,61.00, 72.54, 79.51, 112.66, 118.62, 125.04, 125.86, 129.98, 133.15, 135.43, 139.69, 139.77, 146.71, 152.16; UV (THF) λ_{max} 397 (ϵ 28 470), 378 (29 260), 271 (30 000) nm. Anal. Calcd for $C_{31}H_{28}O_6$: C, 74.98; H, 5.68. Found: C, 74.87; H, 5.67.

Acid-Catalyzed Cyclization of the Diacetal 9c. Method A. To a solution of **9c** (200 mg, 0.35 mmol) in anhydrous 1,2-dichloroethane (100 mL) was added triflic acid (10.5 mg, 0.07 mmol), and the solution was refluxed with stirring for 1 h. Then it was cooled to room temperature, Et_3N (0.5 mL) was added, and the solvent was removed under vacuum. Chromatography of the residue on a silica gel column eluted with CH_2Cl_2/hexane (1:1) and then with CH_2Cl_2 provided in turn **13a** (20 mg, 13.5%) and **15** (20 mg, 13.5%). **Method B.** To a solution of **9c** (286 mg, 0.5 mmol) in freshly distilled anhydrous 1,4-dioxane (150 mL) was added triflic acid (15 mg, 0.1 mmol). The solution was refluxed with stirring for 45 min, then cooled to room temperature, and worked up as before to afford in turn **13a** (60 mg, 28.4%) and **16** (48 mg, 22.6%).

Benzo[*rst*]pentaphene (2). Method A. Reductive cyclization of **9b** (202 mg, 0.6 mmol) and purification of the product by chromatography on silica gel furnished on elution with CH_2Cl_2/hexane (2:8, 1:1) benzo[*rst*]pentaphene (**2**) as a yellow solid (78 mg, 43%), mp 278−280 °C (CH_2Cl_2/MeOH) (lit.[2] 280−282 °C): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74−7.85 (m, 4), 7.80 (s, 2), 8.22 (d, 2, J = 7.5 Hz), 8.32 (s, 2), 9.05 (d, 2, J = 8.5 Hz), 9.22 (s, 2). **Method B**. Reaction of **9b** (202 mg, 0.6 mmol) by this procedure gave **17** (45 mg, 37%) identical to that obtained by procedure A.

3,4,9,10-Tetraacetoxybenzo[*rst*]pentaphene (13c). To a solution of **13a** (260 mg, 0.62 mmol) in dry CH_2Cl_2 (200 mL) at −20 °C was added a solution of BBr_3 in CH_2Cl_2 (1 M, 12.4 mL). The mixture was stirred at −20 °C for 30 min and then at room temperature for 2 h. The mixture was cooled with dry ice, ice was added, and the organic solvent was removed at room temperature under reduced pressure. The aqueous suspension was extracted with EtOAc, and the combined EtOAc solution was washed with brine, dried over Na_2SO_4, and evaporated to dryness at room temperature. The solid residue was dissolved in pyridine (14 mL)/Ac_2O (10 mL) at −20 °C and then stirred at room temperature overnight. The mixture was poured into ice−water and extracted with CH_2Cl_2. The organic layer was washed with 1 N HCl and brine in turn and dried (Na_2SO_4). After removal of the solvent, the residue was applied to a short silica gel column and eluted with CH_2Cl_2 and CH_2Cl_2/EtOAc (95:5) to give **13c** (289 mg, 88%) as a yellow solid, mp 325−326 °C (CH_2Cl_2/hexane): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.43 (s, 6), 2.60 (s, 6), 7.69 (d, 2, J = 9.0 Hz), 7.83 (s, 2), 8.31 (s, 2), 8.95 (d, 2, J = 9.0 Hz), 9.16 (s, 2); ^{13}C NMR (125 MHz) δ 20.64, 20.90, 117.79, 121.51, 121.78, 122.69, 123.77, 126.07, 127.40, 127.70, 129.07, 130.89, 137.46, 139.90, 168.32, 168.45; UV (THF) λ_{max} 401 (ϵ 79 190), 389 (48 800), 359 (21 580), 337 (20 900), 320 (25 500), 301 (70 640), 288 (51 160), 276 (34 760) nm. Anal. Calcd for $C_{32}H_{22}O_8$: C, 71.90; H, 4.15. Found: C, 71.81; H, 4.13.

***trans*-3,4-*trans*-9,10-Tetrahydroxy-3,4,9,10-tetrahydrobenzo[*rst*]pentaphene (17). Method A**. A mixture of **13c** (10 mg, 0.019 mmol) and $NaBH_4$ (50 mg, 1.3 mmol) in 100 mL of EtOH/CH_2Cl_2 (v/v, 70:30) was stirred at room temperature with O_2 bubbling through for 2 h. The color of the solution changed from yellow to orange red. Then another 50 mg of $NaBH_4$ was added, and the solution was stirred for another 2 h. The color of the solution changed to light yellow. The solvent was removed under reduced pressure without

heating, and then cold water was added. The suspension was acidified and filtered. The solid product was dried and then triturated with EtOAc to furnish **17** as a yellow solid (4.5 mg, 66%), mp 220−225 °C (dec): ^{1}H NMR (DMSO, 500 MHz) δ 4.42 (d, 2, J = 10.0 Hz), 4.89 (d, 2, J = 10.5 Hz), 5.39 (d, 1, J = 5.0 Hz, OH), 5.84 (d, 1, J = 6.0 Hz, OH), 6.21 (d, 2, J = 10.5 Hz), 7.51 (d, 2, J = 9.5 Hz), 8.12 (s, 2), 8.39 (s, 2), 8.45 (s, 2); ^{13}C NMR (DMSO, 100 MHz) δ 72.16, 74.80, 122.72, 123.08, 123.48, 124.17, 125.74, 126.67, 127.87, 130.50, 135.16, 137.14; UV (THF) λ_{max} 394 (ϵ 47 360), 373 (35 550), 355 (16 875), 318 (21 420), 305 (21 400), 276 (25 800) nm; HRMS calcd for $C_{24}H_{18}O_4$ m/z 370.1205, found 370.1206. HPLC and NMR showed that **17** obtained by this procedure was contaminated by the over-reduced products **18** and **19**. Pure **17** was more efficiently prepared by Method B. **Method B**. A mixture **13c** (53.4 mg, 0.1 mmol) and $NaBH_4$ (200 mg, 5.3 mmol) in 200 mL of EtOH/CH_2Cl_2 (v/v, 50:50) was stirred at room temperature with O_2 bubbling through for 24 h. The solvent was removed under reduced pressure *without heating*, and then cold water was added. The suspension was acidified and filtered to afford a yellow solid. HPLC analysis using a Zorbax ODS (9.4 mm × 25 cm) column that was eluted isocratically with MeOH/0.02% TFA in water (v/v, 50:50) at a flow rate of 4 mL/min showed the product to be a mixture of **17** (retention times for isomers, 15.8 and 17.8 min) and products of further reduction (**18** and **19**). Compound **18** showed one peak at 14.1 min, and the retention times for the isomers of **19** were 11.4 and 19.0 min. The ratios of UV absorbency at Å260/Å370 were ∼1.2, 2.1, and 5 for compounds **17**, **18**, and **19**, respectively. This mixture was dissolved in pyridine (14 mL)/Ac_2O (10 mL) and heated overnight. The usual workup afforded a mixture of acetates of **17**, **18**, and **10**. This mixture was heated at reflux with DDQ (150 mg) in benzene for 20 h. After the usual workup, the crude product was purified on a silica gel column [CH_2Cl_2/hexane (1:1), CH_2Cl_2] to give the tetraacetate of **17** as a yellow solid (25 mg, 46% in total), mp 223−225 °C (CH_2Cl_2/MeOH): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.07 (s, 6), 2.17 (s, 6), 5.74 (m, 2), 6.32 (d, 1, J = 10.0 Hz), 6.33 (d, 1, J = 10.0 Hz), 6.55 (d, 2, J = 6.0 Hz), 7.69 (d, 2, J = 10.0 Hz), 8.00 (s, 2), 8.10 (s, 2), 8.37 (s, 2); ^{13}C NMR (125 MHz) δ 21.03, 21.18, 69.51, 71.74, 122.96, 125.18, 125.48, 125.56, 125.81, 126.22, 126.75, 128.02, 129.40, 131.26, 170.32, 170.32; UV (THF) λ_{max} 393 (ϵ 67 480), 372 (47 850), 354 (20 510), 315 (32 600), 302 (26 840), 276 (38 360) nm. Anal. Calcd for $C_{32}H_{26}O_8$: C, 71.36; H, 4.87. Found: C, 71.59; H, 4.93.

To a solution of the tetraacetate of **17** (15 mg, 0.028 mmol) in THF (6 mL)/MeOH (12 mL) was added 0.15 mL of solution of MeONa (25 wt % in MeOH) at room temperature. The resulting solution was stirred for 3 h, and then the mixture was poured into ice−water, acidified, and extracted with EtOAc. The organic layer was washed with brine and cold water and dried (Na_2SO_4). The solvent was removed under reduced pressure at room temperature, and the residue was triturated with EtOAc to give a yellow solid (8 mg, 78%), mp 220−225 °C (dec), identical in its physical properties to an authentic sample of **17** from Method A.

***trans*-3,4-*trans*-9,10-Tetrahydroxy-1,2,3,4,9,10,11,12-octahydrobenzo[*rst*]pentaphene (19).** A mixture **17** (10 mg, 0.019 mmol) and $NaBH_4$ (50 mg, 1.3 mmol) in 100 mL of EtOH/CH_2Cl_2 (v/v, 50:50) was stirred at room temperature with O_2 bubbling through for 24 h. Another 50 mg of $NaBH_4$ was added, and the solution was stirred for another 48 h during which time it became colorless. The solvent was removed under reduced pressure without heating, then cold water was added, and the suspension was acidified and filtered. The solid was dried and then triturated with EtOAc to furnish **19** (5 mg, 70%) as a gray solid, mp 224−227 °C (dec): ^{1}H NMR (DMSO, 500 MHz) δ 1.96 (m, 2), 2.26 (m, 2), 3.36 (m, 2), 3.48 (m, 2), 3.87 (m, 2), 4.70 (br d, 2, J = 6.0 Hz), 4.96 (d, 1, J = 3.5 Hz, OH), 5.55 (d, 1, J = 6.0 Hz), 7.98 (s, 2), 8.28 (s, 2), 8.31 (s, 2); ^{13}C NMR (125 MHz) δ 23.40, 27.25, 70.23, 72.96, 123.03, 123.06, 125.57, 126.47, 127.31, 129.04, 130.04, 136.85; HRMS calcd for $C_{24}H_{23}O_4$ m/z 375.1596, found 375.1591.

1,5-Bis(naphthalenylboronic acid) (20c). Preparation from 1,5-dibromonaphthalene[25] (8.0 g) was carried out by the procedure described for **6c**. Compound **20c** was obtained as a gray solid (38%), mp >370 °C: ^{1}H NMR (DMSO, 500 MHz) δ 7.42 (dd, 2, J = 6.9, 8.3 Hz), 7.65 (d, 2, J = 6.6 Hz, OH), 8.33 (d, 2, J = 8.2 Hz), 8.37 (br s, 2, QH, exchangeable with D_2O); ^{13}C NMR (DMSO, 125 MHz) δ 124.60, 129.93, 131.34, 135.30; UV (THF) λ_{max} 290 (ϵ 6 800), 239 (4 300) nm.

1,5-Bis(2-formyl-3,4-dimethoxyphenyl)naphthalene (21a). Preparation of **21a** from **8c** and **20c** was carried out by the procedure described for **9a**. Compound **21a** was obtained as a yellow solid (63%), mp 289−290 °C (CH_2Cl_2/hexane): ^{1}H NMR (500 MHz) δ 3.98 (s, 2), 4.00 (s, 4), 4.02 (s, 2), 4.03 (s, 4), 7.09 (d, 1, J = 8.0 Hz), 7.15 (d, 1, J = 8.5 Hz), 7.18−7.42 (m, 6), 7.50 (d, 1, J = 8.0 Hz), 7.55 (d, 1, J = 8.5 Hz), 9.95 (s, 1), 9.98 (s, 1); ^{13}C NMR (125 MHz) δ 56.13, 56.15, 62.17, 116.39, 116.59, 125.36, 125.44, 125.74, 125.87, 127.24, 127.35, 127.43, 127.72, 129.48, 129.69, 132.49, 135.00, 135.14, 137.03, 137.19, 150.29, 150.53, 152.69, 152.81, 190.93, 191.17; UV (THF) λ_{max} 304 (ϵ 12 080), 242 (29 600) nm. Anal. Calcd for $C_{28}H_{24}O_6$: C, 73.67; H, 5.30. Found: C, 73.58; H, 5.41.

1,2,8,9-Tetramethoxydibenzo[*b,def*]chrysene (22a). Reductive acid-catalyzed cyclization of **21a** was carried out by Method B for the analogous reaction of **9a**. To a mixture of **21a** (228 mg, 0.6 mmol) and 1,3-propanediol (114 mg, 1.5 mol) in freshly distilled anhydrous dioxane (150 mL) was added triflic acid (15 mg, 0.1 mmol). The solution was heated at reflux with stirring for 2 h, then it was cooled to room temperature, and triethylamine (0.5 mL) was added. The solvent was removed under reduced pressure, and the residue was chromatographed on a silica gel column eluted with CH_2Cl_2/hexane (1:1) to yield **22a** as a yellow solid (34 mg, 16%), mp 335 °C (dec): ^{1}H NMR (500 MHz) δ 4.14 (s, 6), 4.20 (s, 6), 7.65 (d, 2, J = 8.5 Hz), 8.34 (d, 2, J = 9.3 Hz), 8.78 (d, 2, J = 9.3 Hz), 8.88 (d, 2, J = 9.0 Hz), 8.95 (s, 2); UV (THF) λ_{max} 322 (ϵ 52 800), 310 (28 100) nm; HRMS calcd for $C_{28}H_{22}O_4$ m/z 422.1518, found 422.1509.

1,2,8,9-Tetraacetoxydibenzo[*b,def*]chrysene (22d). Conversion of **22a** to **22d** was carried out by the procedure described for **13c**. Compound **22d** was obtained as a green-yellow solid (85%), mp 347 °C (CH_2Cl_2/hexane) (dec): ^{1}H NMR (500 MHz) δ 2.43 (s, 6), 4.00 (s, 3.9), 4.62 (s, 6), 7.68 (d, 2, J = 9.5 Hz), 8.34 (d, 2, J = 9.5 Hz), 8.66 (s, 2), 8.89−9.00 (m, 4); UV (THF) λ_{max} 451 (ϵ 25 900), 425 (18 030), 314 (121 780), 301 (60 890), 259 (23 580) nm; HRMS calcd for $C_{32}H_{22}O_8$ m/z 534.1315, found 534.1304.

***trans*-1,2-*trans*-8,9-Tetrahydroxy-1,2,8,9-tetrahydrodibenzo[*b,def*]chrysene (23).** A mixture **22d** (10 mg, 0.019 mmol) and $NaBH_4$ (50 mg, 1.3 mmol) in 60 mL of EtOH/CH_2Cl_2 (v/v, 50:50) was stirred at room temperature with O_2 bubbling through for 2 h. The color changed from yellow to orange-red. Then another 50 mg of $NaBH_4$ was added, and the solution was stirred for another 4 h during which time the color changed to pale yellow. The solvent was removed *without heating*, then cold water was added, and the suspension was acidified and filtered. The solid was dried and triturated with EtOAc to furnish **23** as a yellow solid (5.0 mg, 71%), mp 222−226 °C (dec): ^{1}H NMR (DMSO, 500 MHz) δ 4.43 (d, 2, J = 10.0 Hz), 4.89 (d, 2, J = 10.5 Hz), 6.22 (d, 2, J = 10.0 Hz), 7.51 (d, 2, J = 10.0 Hz), 8.15 (d, 2, J = 9.5 Hz), 8.39 (s, 2), 8.43 (d, 2, J = 9.5 Hz); ^{13}C NMR (DMSO, 125 MHz) δ 71.75, 74.42, 122.29, 122.33, 122.51, 123.70, 125.90, 126.47, 127.90, 129.47, 134.71, 136.74; UV (THF) λ_{max} 401 (ϵ 36 900), 378 (38 990), 305 (22 500), 264 (39 690) nm; HRMS calcd for $C_{24}H_{18}O_4$ m/z 370.1205, found 370.1206.

HPLC analysis of **23** on a ZORBAX ODS column (9.4 mm × 25 cm) eluted isocratically with MeOH/0.02% TFA (v/v, 50:50) at a flow rate of 4 L/min showed the presence of two isomers with retention times of 11.5 and 12.6 min, respectively.

Acknowledgment. This research was supported by a grant from the National Cancer Institute (CA 67937).

JO9918044