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Modular, Metal-Catalyzed Cycloisomerization Approach to Angularly Fused Polycyclic Aromatic Hydrocarbons and Their Oxidized Derivatives

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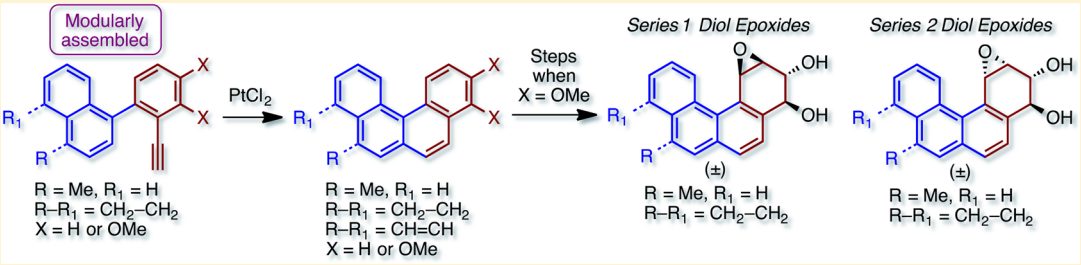
Supporting Information



ABSTRACT: Palladium-catalyzed cross-coupling reactions of 2-bromobenzaldehyde and 6-bromo-2,3-dimethoxybenzaldehyde with 4-methyl-1-naphthaleneboronic acid and acenaphthene-5-boronic acid gave corresponding *o*-naphthyl benzaldehydes. Corey–Fuchs olefination followed by reaction with *n*-BuLi led to various 1-(2-ethynylphenyl)naphthalenes. Cycloisomerization of individual 1-(2-ethynylphenyl)naphthalenes to various benzo[*c*]phenanthrene (B*c*Ph) analogues was accomplished smoothly with catalytic $PtCl_2$ in PhMe. In the case of 4,5-dihydrobenzo[*l*]acephenanthrylene, oxidation with DDQ gave benzo[*l*]acephenanthrylene. The dimethoxy-substituted benzo[*c*]phenanthrenes were demethylated with BBr_3 and oxidized to the *o*-quinones with PDC. Reduction of these quinones with $NaBH_4$ in THF/EtOH in an oxygen atmosphere gave the respective dihydrodiols. Exposure of the dihydrodiols to *N*-bromoacetamide in THF-H_2O led to bromohydrins that were cyclized with Amberlite IRA 400 HO^- to yield the series 1 diol epoxides. Epoxidation of the dihydrodiols with *m*CPBA gave the isomeric series 2 diol epoxides. All of the hydrocarbons as well as the methoxy-substituted ones were crystallized and analyzed by X-ray crystallography, and these data are compared to other previously studied B*c*Ph derivatives. The methodology described is highly modular and can be utilized for the synthesis of a wide variety of angularly fused polycyclic aromatic hydrocarbons and their putative metabolites and/or other derivatives.

INTRODUCTION

One of the classical methods for the synthesis of compounds containing a phenanthrene moiety is oxidative photocyclization.[1−8] In this approach, *cis*/*trans* stilbene-like molecules are subjected to photochemical ring closure to yield dihydroaromatic systems, which then undergo oxidation with catalytic I_2 and air to yield the fully aromatized final products. The high value of this method has led to improvements in order to attain cleaner reactions and better product yields. The most notable of these improvements are the use of propylene oxide[9] or THF[10] as sponges for the liberated HI. More recently, C–H bond activation to yield substituted stilbenes, followed by oxidative-photochemical cyclization has been reported, wherein $PhI(OAc)_2$ was used as the oxidant.[11] The power of photocyclization chemistry is exemplified in the range of compounds that can be synthesized, and recent reviews provide relevant representative examples.[12,13]

Despite the broad applicability of the photocyclization approach, there are scenarios in which this method cannot be readily applied. One case would be the unavailability of appropriate precursors for the photocyclization. Thus, alternative methods have been developed for the assembly of molecules containing a phenanthrene subunit. Some representative examples are cyclization reactions using electrophiles, such as ICl[14] and IBF_4,[15] Pd-catalyzed annulation,[16] intramolecular olefin metathesis,[17] Friedel–Crafts type reactions of geminal difluoroalkenes in $FSO_3H{\cdot}SbF_5$ (magic acid),[18] Rh(II)-catalyzed dimerization of carbenes formed from bis tosylhydrazones,[19] *t*-BuOK-mediated intramolecular cyclization of 1-(2-methylaryl)-3,4-dihydronaphthalene-2-carbaldehydes in the presence of light,[20] intramolecular Diels–Alder reaction of allenyl alcohols obtained by $AuCl_3$-catalyzed rearrangement of homopropargylic alcohols,[21] Ru-catalyzed benzannulation processes,[22] and Pd-mediated C–H bond-activation and arylation.[23] $PtCl_2$, $AuCl_3$, $GaCl_3$, $InCl_3$, as well as designed Pt

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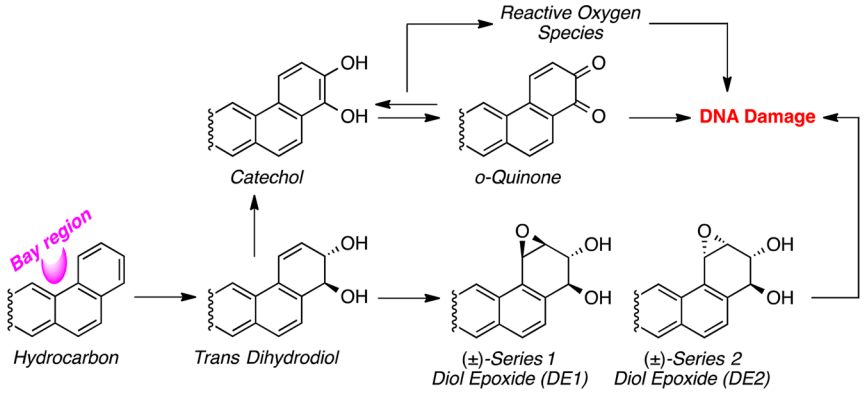
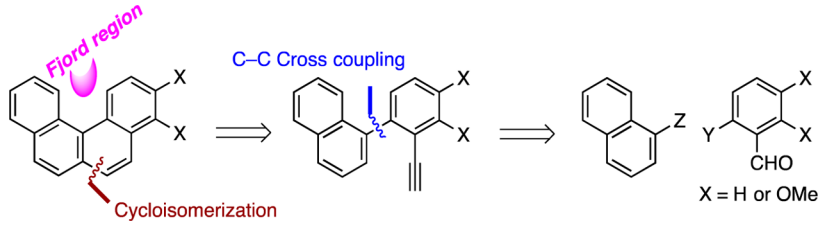
Scheme 1. Oxidative Metabolism of Polycyclic Aromatic Hydrocarbons and DNA Damage



Scheme 2. Retrosynthetic Analysis of the Proposed Approach



and Au catalysts have been evaluated for the 6-endo-dig cyclization of *o*-ethynylbiaryl systems.[24−26] The combination of $PtCl_2/PtCl_4$ has been reported for hydroarylation-cycloisomerization.[27]

For studies on the molecular mechanisms of chemical carcinogenesis by polycyclic aromatic hydrocarbons (PAHs), simple and facile routes to the hydrocarbons and their metabolites are necessary. PAHs are products of incomplete combustion of organic matter and are widely distributed in the environment. Because of their ubiquitous presence, they pose a significant health risk. Among this large family of compounds, alternant hydrocarbons possessing a bay or fjord region are particularly important. In mammalian systems, bay- and fjord-region-containing polycyclic aromatic hydrocarbons are metabolically converted to proximate carcinogens, dihydrodiols, by the combined actions of CYP450 and epoxide hydrolase.[28] Further oxidation of the dihydrodiols by CYP450 produces four isomeric electrophilic diol epoxides, which then covalently modify DNA.[28,29] Dihydrodiols are also implicated in dihydrodiol dehydrogenase-mediated redox cycles, resulting in the formation of DNA damaging reactive oxygen species and *o*-quinones (Scheme 1).[30,31]

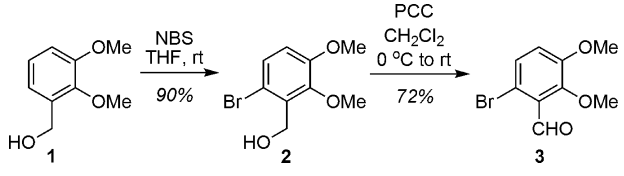
Substituted chrysenes and benzo[*c*]phenanthrenes (B*c*Phs) have been of significant interest in chemical carcinogenesis and access to these ring systems is available by photocyclization of appropriate 1- and 2-styryl naphthalenes, respectively.[32−34] Introduction of methoxy substituents into the angular ring then allows for the conversion of the hydrocarbons to their oxidized metabolites, the dihydrodiols and diol epoxides, via *o*-quinones.[33−36] Despite the convenience of the photochemical approach, availability of starting materials can be a limitation. Thus, we decided to explore the utility of $PtCl_2$- and $AuCl_3$-mediated cycloisomerization of *o*-ethynylbiaryls as a method to access unusual polycyclic aromatic hydrocarbons and their putative metabolites.

RESULTS AND DISCUSSION

We chose to demonstrate the metal-mediated cycloisomerization approach via the modular synthesis of two remotely functionalized B*c*Ph derivatives as well as their putative dihydrodiol and diol epoxide metabolites. The retrosynthetic analysis is shown in Scheme 2. In fact, this approach has been used for the synthesis of B*c*Ph in a demonstration of the chemistry.[24]

In the present case, the key would be the identification of suitable building blocks that can be used to modularly assemble various polycyclic hydrocarbon derivatives, which can then be elaborated to the oxidized metabolites. In Scheme 2, either building block could serve as the electrophile in the cross coupling with the other serving as the nucleophile. Because various arylboronic acids and related derivatives are readily available, either commercially or by synthesis, these were selected as the nucleophiles for the cross-coupling step. Thus, 2-bromobenzaldehyde and 6-bromo-2,3-dimethoxybenzaldehyde were chosen as the electrophilic cross-coupling partners. Whereas the former is commercially available, the latter (a known compound[37]) can be readily prepared on a multigram scale (Scheme 3). Bromination of 2,3-dimethoxybenzyl alcohol with NBS in THF gave the known 6-bromo-2,3-dimethoxybenzyl alcohol (**2**),[38] which upon oxidation with PCC in CH_2Cl_2,[39] then gave required aldehyde **3**.

Scheme 3. Synthesis of 6-Bromo-2,3-dimethoxybenzaldehyde as a Key Building Block



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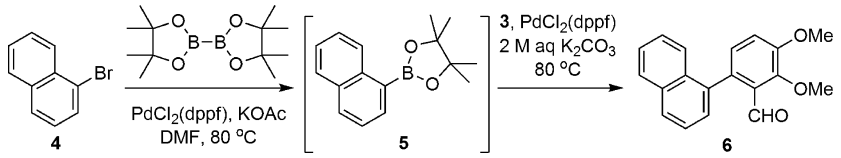
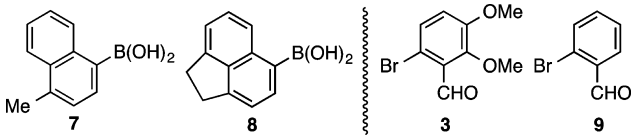
Scheme 4. Initial Tests on the in Situ Formation of a Boronate Ester and Cross Coupling

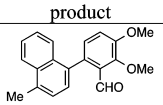
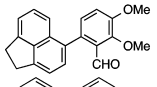
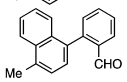
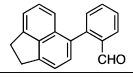


Because synthesis of biaryls via in situ formation of arylboronates has been reported,[40] we initially considered the formation of pinacol boronate esters from aryl halides[41] for cross coupling with bromo aldehyde **3**. Along these lines, initial experiments were conducted on 1-bromonaphthalene as a representative example (Scheme 4). Reaction of 1-bromonaphthalene (**4**) with bis(pinacolato)diboron was performed using $PdCl_2$(dppf)/KOAc in DMF at 80 °C, followed by cross coupling with aldehyde **3** as per the literature.[41] Although product **6** could be obtained in respectable 79−86% yields, extensive and repeated column chromatography was necessary to obtain pure product. Thus, this approach was discontinued.

The more traditional cross coupling of boronic acids was then considered. 4-Methyl-1-naphthaleneboronic acid (**7**) and acenaphthene-5-boronic acid (**8**) were selected for further elaboration to the respective hydrocarbons as well as the putative metabolites. Although both boronic acids are commercially available, they are relatively expensive. Hence, these were prepared by lithiation of commercially available 1-bromo-4-methylnaphthalene as well as 5-bromoacenaphthene, followed by reaction with $B(OMe)_3$, and hydrolysis (89% yield of compound **7** and 77% yield of compound **8**). Each boronic acid was cross coupled with the bromo aldehydes **3** and **9** using $Pd(PPh_3)_4$ and CsF in DME at reflux. The product structures and yields are summarized in Table 1.

Table 1. Products of the C−C Cross Coupling and Yields



entry	cross-coupling partners	product	yield
1	**7** + **3**		**10:** 83%
2	**8** + **3**		**11:** 92%
3	**7** + **9**		**12:** 83%
4	**8** + **9**		**13:** 74%

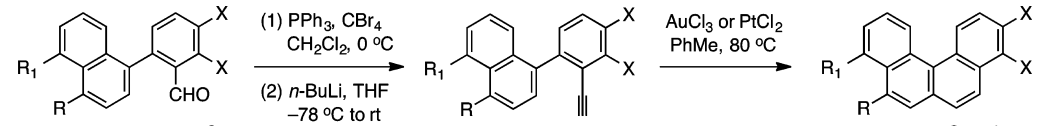
In earlier work,[42] similar biaryl aldehydes were elaborated to either oxiranes (reaction with $Me_2S{=}CH_2$) or methoxyethenes (reaction with $MeOCH{=}PPh_3$), which upon exposure to suitable Bronsted or Lewis acids underwent cyclization and aromatization to polycyclic hydrocarbons. In the present method, alkynylation was the next step in the sequence. Initially, the Bestmann−Ohira alkynylation was attempted on aldehyde **10**. Use of dimethyl-2-oxopropylphosphonate (1.2 molar equiv), *p*-TsN_3 (1.2 molar equiv), and K_2CO_3 (3 molar equiv), under literature conditions[43] led to a 55% isolated yield of the alkyne. The use of NaH caused a drastic reduction in the yield (39%). By comparison, the Corey−Fuchs two-step alkynylation[44] gave far superior results (97% yield for the gem-dibromide and 81% yield for the alkynylation, 78% overall). Thus, this became the preferred method to access the requisite cyclization precursors. The overall methodology up to the cyclization step is shown in Scheme 5.

Generally, good yields were obtained over two steps leading to alkynyl products **14**−**17** (56−78%). At this stage, both $AuCl_3$ and $PtCl_2$ were evaluated for the cyclization. Although 5 mol % $AuCl_3$ in PhMe at 80 °C gave 84% yield of dimethoxy B*c*Ph **18**, the yield of analogue **19** with this catalyst was 59%. In contrast, 5 mol % $PtCl_2$ in PhMe at 80 °C gave compounds **18** and **19** in comparable yields of 75 and 72%, respectively. Additional test reactions were conducted on the cyclization of 1-(2-ethynylphenyl)naphthalene. Here, in PhMe at 80 °C, $PtCl_2$ gave a 69% yield of B*c*Ph, which is comparable to the yield reported in the literature,[24] whereas $AuCl_3$ gave only 45% yield. On the basis of these results, as well as the hygroscopic nature of $AuCl_3$, $PtCl_2$ appears to be a suitable catalyst. Cyclization of alkynes **16** and **17** with $PtCl_2$ led to B*c*Ph derivatives **20** and **21** in yields of 81 and 69%, respectively.

At this stage, we had completed the synthesis of the precursors to the putative oxidized metabolites of 5-methylbenzo[*c*]phenanthrenene (5-MB*c*Ph), 4,5-dihydrobenzo[*l*]acephenanthrylene ($H_2B[l]A$), and the parent hydrocarbons. As shown in Scheme 6, demethylation of compounds **18** and **19** with BBr_3 gave catechols, which were directly converted to *o*-quinones **22** and **23**, respectively, by oxidation with PDC. Both quinones showed characteristic fjord-region quinonoid proton resonances (d, J = 10.5 Hz), which corresponded well with other quinones of B*c*Ph and its derivatives.[32e,33,34]

Reduction of quinones **22** and **23** with $NaBH_4$ in EtOH, under an oxygen atmosphere,[33−35] led to dihydrodiols (±)-**24**

Scheme 5. Synthesis of the Various Polycyclic Aromatic Hydrocarbons



10: R = Me, R_1 = H, X = OMe
11: R–R_1 = CH_2–CH_2, X = OMe
12: R = Me, R_1 = X = H
13: R–R_1 = CH_2–CH_2, X = H

14: R = Me, R_1 = H, X = OMe (*78%*)
15: R–R_1 = CH_2–CH_2, X = OMe (*78%*)
16: R = Me, R_1 = X = H (*61%*)
17: R–R_1 = CH_2–CH_2, X = H (*56%*)

18: R = Me, R_1 = H, X = OMe (*84%, 75%*)
19: R–R_1 = CH_2–CH_2, X = OMe (*59%, 72%*)
20: R = Me, R_1 = X = H (*81%*)
21: R–R_1 = CH_2–CH_2, X = H (*69%*)

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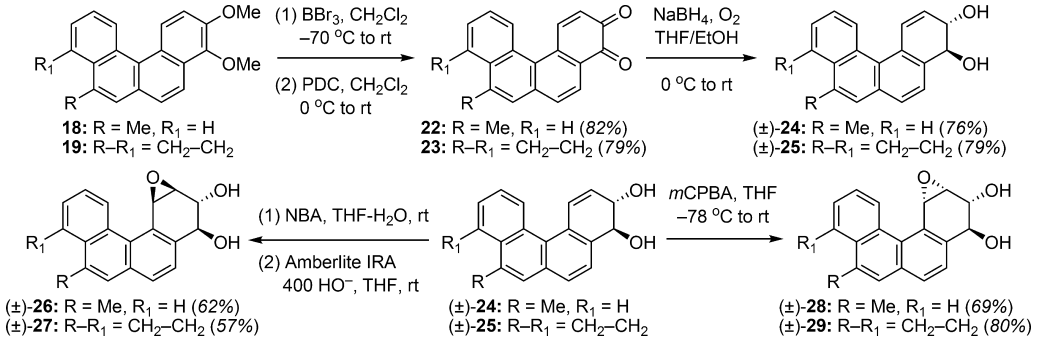
Scheme 6. Synthesis of the Dihydrodiols and Diol Epoxides of 5-MB*c*Ph and H_2B[*l*]A



and (±)-**25**, respectively. Diastereoselective conversion of the dihydrodiols to the diol epoxides, based upon literature procedures,[45] depends upon the trans hydroxyl groups being predominantly diequatorial. Thus, the conformations of dihydrodiols **24** and **25** were evaluated by ^{1}H NMR spectroscopy. In both cases, the hydroxyl groups were predominantly diequatorially disposed as indicated by the >11 Hz coupling constant between the carbinol protons in acetone-d_6. This is comparable to the coupling constant observed for the carbinol protons in B*c*Ph (J = 10.8 Hz in CD_3OD)[46] and the 1,4-difluoro derivative (DFB*c*Ph, J = 11.0 Hz in acetone-d_6).[34] Unlike the dihydrodiol of 1,4-dimethylbenzo[*c*]phenanthrene (DMB*c*Ph),[33] compounds **24** and **25** did not demonstrate *P* and *M* hydrocarbon helicity, and these were similar to dihydrodiols of B*c*Ph and DFB*c*Ph.

Exposure of dihydrodiols **24** and **25** to *N*-bromoacetamide (NBA) in THF-H_2O gave the respective bromotriols in 97 and 95% yield. Cyclization of the bromotriols to the series 1 diol epoxides (±)-**26** and (±)-**27** was accomplished with the hydroxide form of Amberlite IRA 400. Yields in the epoxidation step were 64% for **26** and 60% for **27**. Synthesis of the series 2 diol epoxides was accomplished by exposure of the dihydrodiols to *m*CPBA in dry THF. Thus, (±)-**24** gave (±)-**28** in 69% yield and (±)-**25** gave (±)-**29** in 80% yield.

NOESY spectra for the series 1 diol epoxides (±)-**26** and (±)-**27** were evaluated to support the relative stereochemistry (Figure 1). For compound (±)-**26**, NOESY cross peaks

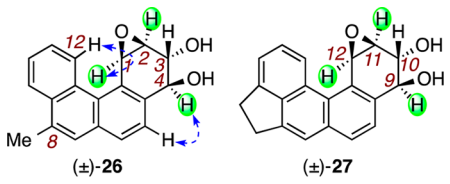


Figure 1. NOESY correlations between protons leading to assignments (dashed blue lines) and relative stereochemical arrangement of substituents (green ovals).

between the resonance at δ 4.82 ppm and the upfield resonance of the ABq at δ 7.96 ppm led to the unequivocal assignment of the former resonance as H-4. The doublet at δ 4.36 ppm was assigned to H-1 on the basis of its NOESY cross peak with the doublet at δ 9.19 ppm (H-12), which was coupled to a proton that produced a triplet resonance. The rest of the tetrahydrobenzo protons were easily assigned on the basis of their coupling constants. In diol epoxide (±)-**26**, the relative stereochemistry of H-2 (δ 3.95 ppm) and H-4 (δ 4.82 ppm) was *cis* based on the NOESY interaction (shown in green ovals in Figure 1). This was further supported by the additional weak interaction between H-1 and H-4. Similarly, and as compared to compound (±)-**26**, in diol epoxide (±)-**27**, interaction between H-9 (δ 4.83 ppm) and H-11 (δ 3.90 ppm) and a weak interaction between H-9 and H-12 (δ 4.45 ppm) were observed (see the Supporting Information for spectra).

From a conformation standpoint, in the absence of unusual factors, bay-region series 1 diol epoxides of polycyclic aromatic hydrocarbons generally exhibit a quasidiaxial arrangement of the hydroxyl groups, and in the series 2 isomers, these are quasidiequatorial.[28c] Typically, series 2 diol epoxides, with quasiequatorial hydroxyl groups, are tumorigenic, whereas the series 1 isomers are not.[28,29] In the case of B*c*Ph, *both* series 1 and series 2 diol epoxides exhibit quasidiequatorial hydroxyl groups due to steric buttressing in the fjord region of the hydrocarbon.[47] Correspondingly, this has important implications on the biological activity, and the (+)-series 1 B*c*Ph diol epoxide enantiomer showed high tumor-initiating ability in the mouse skin model.[48] It would therefore be instructive to compare the conformational preferences of the various diol epoxides synthesized to date that contain the B*c*Ph scaffold (Figure 2).

We have not previously synthesized the series 1 diol epoxide from DMB*c*Ph because of complications related to the *P*/*M* helicity elicited by its dihydrodiol.[33] However, we have synthesized both series 1 and 2 diol epoxides of DFB*c*Ph.[34] In comparison to the series 1 diol epoxide of B*c*Ph, the corresponding diol epoxide from DFB*c*Ph shows a significantly smaller coupling constant between the carbinol protons (Figure 2), indicative of a predominantly diaxial orientation of the hydroxyl groups in the latter (the coupling constant between the carbinol protons for the B*c*Ph series 1 diol epoxide in acetone-d_6 is comparable to that in DMSO-d_6[34]). This difference between the two hydrocarbons is likely due to the extreme out-of-plane distortion of DFB*c*Ph.[34] The series 1 diol epoxide of benzo[*ghi*]fluoranthene (B[*ghi*]F), a compound that is expected to be more planar than both B*c*Ph and DFB*c*Ph, surprisingly, also shows a much smaller coupling constant between its carbinol protons (J = 2.1 Hz),[49] identical to that observed with DFB*c*Ph. By contrast, the hydroxyl group conformation in the series 1 diol epoxides of both 5-MB*c*Ph [(±)-**26**)] and H_2B[*l*]A [(±)-**27**)] are comparable to that in B*c*Ph.

Evaluation of the series 2 diol epoxides (Figure 2) shows a general uniformity in the hydroxyl group orientation, which are quasidiequatorial, with the carbinol coupling constants in the 8.0−8.7 Hz range. Remarkably, the more planar B[*ghi*]F as well as the highly nonplanar DFB*c*Ph and DMB*c*Ph diol epoxides have comparable conformations (diastereomeric *P* and *M*

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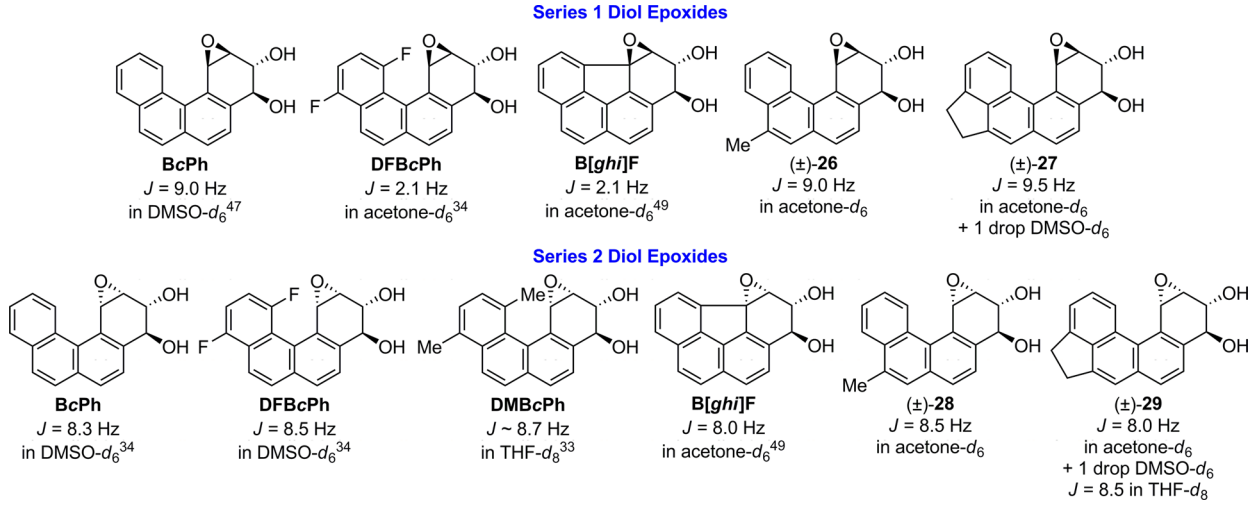
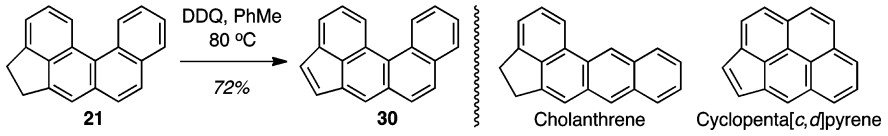


Figure 2. Various diol epoxides having the B*c*Ph structure and the coupling constants of their carbinol protons.

Scheme 7. Synthesis of Benzo[*l*]acephenanthrylene and the Structures of the Related Hydrocarbons Cholanthrene and Cyclopenta[*c,d*]pyerene



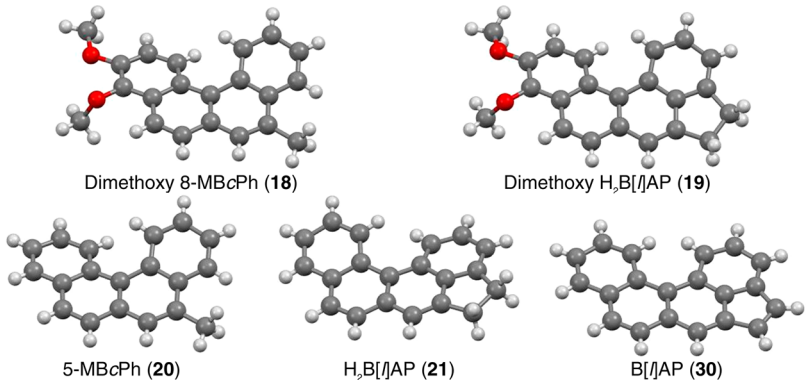


Figure 3. Crystal structures of several of the synthesized B*c*Ph derivatives.

helical dihydrodiols from DMB*c*Ph have very similar carbinol coupling constants[33]). From this evaluation it appears that, among the B*c*Ph analogues, conformations of the series 1 diol epoxides have a greater dependence on subtle differences in molecular structure, whereas the series 2 diol epoxides appear generally independent of it.

Because we have synthesized H_2B[*l*]AP (**21** in Scheme 5), an isomer of the carcinogen cholanthrene,[50] we decided to dehydrogenate compound **21** to benzo[*l*]acephenanthrylene (B[*l*]AP, **30**). Compound **30** is related to cyclopenta[*c,d*]-pyrene, a powerful mutagen and carcinogen.[51] Exposure of B*c*Ph derivative **21** to DDQ in PhMe at 80 °C gave B[*l*]AP (**30**) in 72% yield (Scheme 7). Compound **21** has previously been synthesized in 24−42% yields via a Wittig reaction/photocyclization approach starting from 1-indanone.[52] By comparison, the three-step yield of **21** obtained herein was 36%. A marginally better yield (by 12%) was obtained for the conversion of H_2B[*l*]AP (**21**) to B[*l*]AP **30** as compared to the literature.[52]

To gain greater insight into the new hydrocarbons synthesized, we undertook X-ray crystallographic analysis. Figure 3 shows the structures of 5-MB*c*Ph (**20**), H_2B[*l*]AP (**21**), B[*l*]AP (**30**), as well as the two dimethoxy compounds **18** and **19**. From these structures, the molecular distortion in B*c*Ph derivatives **18**−**21** is clearly evident, but compound **30** is significantly more planar.

Table 2 provides quantitative data on the plane angles between the four aromatic rings of B*c*Ph, 1,4-DFB*c*Ph, 1,4-DMB*c*Ph, 5-MB*c*Ph, H_2B[*l*]AP, B[*l*]AP, as well as the two methoxy derivatives **18** and **19**. As can be seen from the **A**−**D** plane angles of the unsubstituted hydrocarbons in this table, nonplanarity decreases in the order 1,4-DMB*c*Ph > 1,4-DFB*c*Ph > B*c*Ph > 5-MB*c*Ph > H_2B[*l*]AP > B[*l*]AP. What is perhaps surprising is that a remote substitution, namely a methyl group at the C-5 position of B*c*Ph, actually produces a decrease in overall nonplanarity of the B*c*Ph structure by ~3°. The ethylene bridge in H_2B[*l*]AP causes a further flattening of the molecule, and finally, B[*l*]AP is only distorted by ~2°. The **A**−**B** plane

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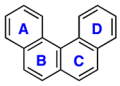
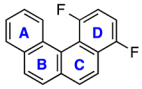
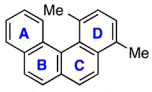
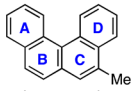
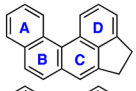
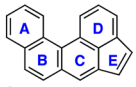
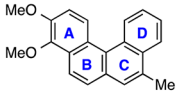
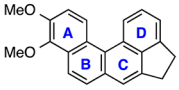
Table 2. Crystallographically Determined Plane Angles in B*c*Ph and its Analogues[a]

compound	A–B	A–C	A–D	B–C	B–D	C–D	C–E	D–E
	10.26°	18.12°	26.68°	7.87°	16.55°	8.83°	--	--
	10.2°	21.7°	33.5°	11.9°	23.6°	12.0°	--	--
	11.66°	24.70°	36.65°	13.07°	25.02°	12.45°	--	--
	9.79°	16.09°	23.27°	6.30°	13.81°	8.24°	--	--
	7.53°	12.70°	18.72°	5.19°	11.20°	6.13°	--	--
	0.60°	1.59°	2.20°	1.00°	1.62°	0.62°	0.45°	0.25°
	9.06°	16.58°	26.04°	7.52°	17.02°	9.53°	--	--
	6.61°	12.18°	18.30°	5.57°	11.70°	6.15°	--	--

[a]Data for B*c*Ph, DFB*c*Ph, and DMB*c*Ph were obtained from refs 33 and 34.

angles in B*c*Ph, 1,4-DFB*c*Ph, and 1,4-DMB*c*Ph are in the 10–12° range. Remote functionalization reduces this angle to <10°. There are wide variations in the other plane angles. Among the dimethoxy-substituted compounds, in the case of 3,4-dimethoxy-8-methyl B*c*Ph **18** there is an increase in overall molecular nonplanarity as compared to the parent hydrocarbon **20** as seen from the greater **A**–**D** plane angle. In contrast, in corresponding H_2B[*l*]AP derivative **19**, the **A**–**D** plane angle is slightly decreased compared to that of its parent hydrocarbon **21**.

These data show that the molecular distortion in such hydrocarbons can be manipulated not only via introduction of substituents into the angular rings but also via introduction of more remote substituents. As we have previously shown,[33,34] metabolic activation processes are influenced by molecular distortion with highly nonplanar polycyclic aromatic hydrocarbons undergoing poorer oxidative metabolism to DNA-alkylating, angular-ring diol epoxide metabolites. Thus, one is tempted to propose that the greater planarization of 5-MB*c*Ph and H_2B[*l*]AP should result in greater metabolic conversion to the angular-ring metabolites, this of course is not considering other possible metabolism pathways.

CONCLUSIONS

Herein, we have demonstrated the applicability of Pt-catalyzed (or in some cases Au-catalyzed) cycloisomerization reactions of 1-(2-ethynylphenyl)naphthalenes to yield benzo[*c*]-phenanthrene analogues that are otherwise not easy to access. The approach utilizes catalysis chemistry for two key transformations, namely, the synthesis of the biaryl core and the cyclization step. The method is highly modular wherein the use of 2-bromobenzaldehyde leads to the parent hydrocarbons, whereas the easily prepared 6-bromo-2,3-dimethoxybenzaldehyde allows access to the oxidative metabolites, such as *o*-quinone, trans dihydrodiol, as well as the series 1 and series 2 diol epoxides, which are of biological interest. In the context of the potential biological properties of these new compounds, the conformational preferences of the newly synthesized series 1 and series 2 diol epoxides have been compared to known data from other related B*c*Ph derivatives. In addition, we have comparatively assessed the crystallographically derived molecular structures of the new compounds, as well as those previously reported. We anticipate the utilization of these new compounds for metabolism and DNA binding studies, and on the chemical side, we expect that the methodology will draw broad interest in organic synthesis approaches.

EXPERIMENTAL SECTION

General Experimental Considerations. Thin-layer chromatography was performed on 250 μm glass-backed silica gel plates or 200 μm aluminum-foil-backed silica gel plates. Column chromatographic purifications were performed on 230–400 mesh silica gel. Commercially available compounds were used without further purification. THF was distilled over LAH and then redistilled over Na prior to use. PhMe was distilled over Na. CH_2Cl_2 and DME were distilled over CaH_2. Hexanes and EtOAc were distilled over anhydrous $CaSO_4$. Air and/or moisture-sensitive liquids and solutions were transferred via syringe under inert gas. ^{1}H NMR spectra were recorded at 500 MHz in the solvents indicated and are referenced to residual protonated solvent resonances. ^{13}C NMR spectra were recorded at 125 MHz in the solvents indicated and are referenced to the solvent resonances. Chemical shifts (δ) are reported in parts per million (ppm), and coupling constants (J) are in hertz (Hz). Standard abbreviations are used to designate resonance multiplicities.

*6-Bromo-2,3-dimethoxybenzyl Alcohol (**2**).*[38] In an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was placed 2,3-dimethoxybenzyl alcohol (**1**) (4 g, 23.8 mmol) in dry THF (18 mL). Recrystallized NBS (4.66 g, 26.2 mmol) was added, and the suspension was stirred at room temperature for 30 min at which time TLC showed the reaction to be complete. The THF was evaporated

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under reduced pressure, and the residue was dissolved in Et_2O. The insoluble succinimide was removed by filtration, and the resulting ethereal layer was washed twice with 2N aqueous NaOH. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Recrystallization of the product using 1:1 EtOAc-hexanes yielded a white, gummy solid that needed purification. Chromatographic purification on a silica gel column packed in hexanes and eluted with 20% EtOAc in hexanes afforded compound **2** as a whitish solid (5.33 g, 90% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.21; mp 75−76 °C (lit.[38] mp 76 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 9.0 Hz, 1H), 6.77 (d, J = 9.0 Hz, 1H), 4.83 (d, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.85 (s, 3H), 2.32 (t, J = 7.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.3, 148.8, 133.9, 127.9, 114.8, 113.4, 61.7, 60.4, 56.0.

*6-Bromo-2,3-dimethoxybenzaldehyde (**3**).*[37] In an oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar was placed 6-bromo-2,3-dimethoxybenzyl alcohol (**2**) (2 g, 8.09 mmol) in dry CH_2Cl_2 (10 mL). The solution was cooled to 0 °C, and PCC (3.49 g, 16.2 mmol) was added. The orange suspension was stirred at 0 °C for 5 min and then at room temperature for 5 h, at which time TLC showed the reaction to be complete. The black suspension was filtered through Celite, and the residue was washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure to give a yellowish solid. The crude product was chromatographed on a silica gel column packed in hexanes sequentially eluted with 20% CH_2Cl_2 in hexanes and 50% CH_2Cl_2 in hexanes. Compound **3** was obtained as a whitish-yellow solid (1.43 g, 72% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.32; mp 82−83 °C (lit.[37a] mp 83−85 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.37 (s, 1H), 7.37 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6, 152.9, 152.3, 129.5, 128.7, 117.7, 112.9, 62.5, 56.4.

*2,3-Dimethoxy-6-naphthalen-1-yl-benzaldehyde (**6**). Step 1: Synthesis of 4,4,5,5-Tetramethyl-2-(naphthalen-1-yl)-1,3,2-dioxaborolane.* In an oven-dried reaction vial equipped with a magnetic stirring bar was placed $PdCl_2$(dppf) (29.5 mg, 0.040 mmol) in dry DMF (4.0 mL). Bis(pinacolato)diboron (342 mg, 1.36 mmol), KOAc, (360 mg, 3.67 mmol), and 1-bromonaphthalene (**4**) (254 mg, 1.22 mmol) were added. The vial was flushed with nitrogen gas and allowed to stir in a sand bath at 80 °C for 14 h, at which time TLC showed consumption of the starting material and the formation of a new spot. R_f (SiO_2/20% EtOAc in hexanes): 0.13.

Step 2: Synthesis of 2,3-Dimethoxy-6-naphthalen-1-yl-benzaldehyde. To the reaction mixture obtained in step 1 were added 6-bromo-2,3-dimethoxybenzaldehyde (**3**) (150 mg, 0.612 mmol), 2 M aqueous Na_2CO_3 (0.51 mL, 12.2 mmol), and $PdCl_2$(dppf) (29.5 mg, 0.040 mmol). The vial was flushed with nitrogen gas and allowed to stir in a sand bath at 80 °C for 21 h at which time TLC showed the reaction to be complete. The mixture was diluted with Et_2O and washed twice with water followed by brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a black solid. The crude product was chromatographed several times on a silica gel column packed in hexanes sequentially eluted with 20% CH_2Cl_2 in hexanes and 20% EtOAc in hexanes. Compound **6** was obtained as a whitish-yellow solid (141 mg, 79% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.29; mp 119−121 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.88 (t, J = 8.0 Hz, 2H), 7.51−7.45 (m, 3H), 7.38 (t, J = 8.0 Hz, 1H), 7.32 (d, J = 7.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 152.9, 150.7, 137.1, 135.2, 133.6, 132.8, 129.9, 128.5, 128.2, 127.7, 127.5, 126.5, 126.1, 125.9, 125.3, 116.7, 62.4, 56.4. HRMS (ESI/TOF) m/z: calcd for $C_{19}H_{17}O_3$ [M + H]$^+$, 293.1172; found, 293.1178.

*2,3-Dimethoxy-6-(4-methyl-naphthalen-1-yl)benzaldehyde (**10**).* In an oven-dried 100 mL round-bottom flask equipped with a magnetic stirring bar was placed 6-bromo-2,3-dimethoxybenzaldehyde (**3**) (2 g, 8.16 mmol) in dry DME (40 mL). 4-Methyl-1-naphthaleneboronic acid (**7**) (1.67 g, 8.98 mmol), CsF (3.47 g, 22.8 mmol), and $Pd(PPh_3)_4$ (377 mg, 0.326 mmol) were added. The resulting yellow suspension was stirred at reflux under a nitrogen atmosphere for 16 h, at which time TLC showed the reaction to be complete. The resulting black reaction mixture was diluted with EtOAc and washed twice with water. The aqueous layer was extracted with EtOAc twice. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give an orange residue. The crude product was chromatographed on a silica gel column packed in hexanes sequentially eluted with 10% EtOAc in hexanes and CH_2Cl_2. Compound **10** was obtained as a yellow-light brown solid (2.08 g, 83% yield). R_f (SiO_2/CH_2Cl_2): 0.44; mp 146−148 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.91 (s, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.53−7.50 (m, 2H), 7.39 (t, J = 8.0 Hz, 1H), 7.35 (d, J = 7.0 Hz, 1H), 7.22−7.19 (m, 2H), 7.08 (d, J = 8.5 Hz, 1H), 4.01 (s, 3H), 3.98 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.2, 152.2, 150.4, 135.4, 135.1, 134.4, 132.6, 132.5, 129.8, 127.4, 127.2, 126.4, 125.93, 125.91, 125.7, 124.5, 116.5, 62.2, 56.2, 19.6. HRMS (ESI/FTICR) m/z: calcd for $C_{20}H_{18}O_3Na$ [M + Na]$^+$, 329.1148; found, 329.1141.

*6-Acenaphthen-5-yl-2,3-dimethoxybenzaldehyde (**11**).* As described for the synthesis of compound **10**, compound **11** was prepared by the reaction of 6-bromo-2,3-dimethoxybenzaldehyde (**3**) (5 g, 20.4 mmol), acenaphthene-5-boronic acid (**8**) (4.44 g, 22.4 mmol), CsF (8.68 g, 57.1 mmol), and $Pd(PPh_3)_4$ (943 mg, 0.816 mmol) in dry DME (105 mL). The reaction mixture was stirred at reflux under a nitrogen atmosphere for 24 h and then worked up as described for compound **10**. Chromatographic purification using a silica gel column packed in hexanes sequentially eluted with 50% CH_2Cl_2 in hexanes and CH_2Cl_2 afforded compound **11** as a light brownish solid (5.96 g, 92% yield). R_f (SiO_2/CH_2Cl_2): 0.32; mp 122−125 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.94 (s, 1H), 7.38 (t, J = 7.0 Hz, 1H), 7.31−7.25 (m, 4H), 7.20 and 7.13 (AB_q, J = 8.3 Hz, 2H), 4.00 (s, 3H), 3.97 (s, 3H), 3.47−3.41 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.4, 152.6, 150.2, 146.2, 146.1, 139.2, 135.0, 132.0, 130.8, 129.8, 129.5, 128.3, 127.4, 120.6, 119.5, 118.8, 116.6, 62.2, 56.2, 30.6, 30.2. HRMS (ESI/FTICR) m/z: calcd for $C_{21}H_{18}O_3Na$ [M + Na]$^+$, 341.1148; found, 341.1149.

*2-(4-Methylnaphthalen-1-yl)benzaldehyde (**12**).* As described for the synthesis of compound **10**, compound **12** was prepared by the reaction of 2-bromobenzaldehyde (**9**) (1.2 g, 6.49 mmol), 4-methyl-1-naphthaleneboronic acid **7** (1.33 g, 7.13 mmol), CsF (2.76 g, 18.16 mmol), and $Pd(PPh_3)_4$ (300 mg, 0.259 mmol) in dry DME (33 mL). The reaction mixture was stirred at reflux under a nitrogen atmosphere for 18 h and then worked up as described for compound **10**. Chromatographic purification using a silica gel column packed in hexanes sequentially eluted with hexanes and 30% CH_2Cl_2 in hexanes afforded compound **12** as a yellow solid (1.34 g, 83% yield). R_f (SiO_2/10% EtOAc in hexanes): 0.62; mp 102−104 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.63 (s, 1H), 8.10 (d, J = 7.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.59−7.54 (m, 2H), 7.51 (d, J = 8.5 Hz, 1H), 7.44 (t, J = 6.5 Hz, 2H), 7.40 (d, J = 7.5 Hz, 1H), 7.30 (d, J = 7.0 Hz, 1H), 2.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.2, 144.6, 135.1, 135.0, 133.7, 133.6, 132.8, 132.5, 131.9, 128.1, 128.0, 127.0, 126.5, 126.4, 126.0, 125.8, 124.5, 19.6. HRMS (ESI/TOF) m/z: calcd for $C_{18}H_{15}O$ [M + H]$^+$, 247.1117; found, 247.1121.

*2-(1,2-Dihydroacenaphthylen-5-yl)benzaldehyde (**13**).* As described for the synthesis of compound **10**, compound **13** was prepared by the reaction of 2-bromobenzaldehyde (**9**) (4.5 g, 24.32 mmol), acenaphthene-5-boronic acid (**8**) (5.30 g, 26.75 mmol), CsF (10.34 g, 68.10 mmol), and $Pd(PPh_3)_4$ (1.12 g, 0.973 mmol) in dry DME (123 mL). The reaction mixture was stirred at reflux under a nitrogen atmosphere for 23 h and then worked up as described for compound **10**. Chromatographic purification using a silica gel column packed in hexanes sequentially eluted with hexanes and 50% CH_2Cl_2 in hexanes afforded compound **13** as a yellow-orange solid (4.66 g, 74% yield). R_f (SiO_2/CH_2Cl_2): 0.51; mp 120−122 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.56 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 8.0 Hz, 1H), 7.36−7.33 (m, 3H), 7.28 (d, J = 8.5 Hz, 1H), 3.48 (br s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 192.4, 146.8, 146.3, 144.1, 139.2, 134.8, 133.6, 131.8, 131.0, 130.8, 130.2, 128.8, 127.9, 127.2, 120.6, 119.8, 118.8, 30.5, 30.2. HRMS (ESI/TOF) m/z: calcd for $C_{19}H_{15}O$ [M + H]$^+$, 259.1117; found, 259.1119.

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*1-(2-Ethynyl-3,4-dimethoxyphenyl)-4-methylnaphthalene (**14**). Step 1: Synthesis of 1-[2-(2,2-Dibromovinyl)-3,4-methoxyphenyl]-4-methylnaphthalene.* In an oven-dried 50 mL round-bottom flask equipped with a magnetic stirring bar was placed PPh_3 (7.71 g, 29.4 mmol) in dry CH_2Cl_2 (8.0 mL). The mixture was cooled to 0 °C; CBr_4 (4.87 g, 14.7 mmol) was added, and the mixture was stirred for 10 min at 0 °C. Aldehyde **10** (1.8 g, 5.87 mmol) dissolved in dry CH_2Cl_2 (14.0 mL) was added slowly. The mixture was flushed with nitrogen gas and allowed to stir at 0 °C for 2 h, at which time TLC showed the reaction to be complete. The mixture was diluted with CH_2Cl_2 and washed twice with brine followed by twice with H_2O. The aqueous layer was extracted twice with CH_2Cl_2. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give an orange residue. Chromatographic purification on a silica gel column packed in CH_2Cl_2 eluted with CH_2Cl_2 afforded the vinyl dibromide as a foamy, yellow solid (2.63 g, 97% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.56. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 8.5 Hz, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 7.0 Hz, 1H), 7.39 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 7.0 Hz, 1H), 7.23 (d, J = 7.0 Hz, 1H), 7.07−7.02 (m, 3H), 3.95 (s, 3H), 3.88 (s, 3H), 2.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.1, 146.2, 135.9, 134.0, 133.9, 132.8, 132.7, 131.9, 130.9, 127.2, 126.65, 126.61, 126.0, 125.50, 125.47, 124.4, 112.2, 93.7, 61.1, 55.9, 19.6.

*Step 2: Synthesis of 1-(2-Ethynyl-3,4-dimethoxyphenyl)-4-methylnaphthalene (**14**).* In an oven-dried 25 mL three-neck round-bottom flask equipped with a magnetic stirring bar was placed the vinyl dibromide obtained in step 1 (200 mg, 0.433 mmol) in dry THF (1.0 mL) under a nitrogen atmosphere. The mixture was cooled to −78 °C, and a 1.6 M solution of *n*-BuLi in hexanes (0.68 mL, 1.08 mmol) was added dropwise. The mixture was allowed to stir at −78 °C for 5 h and then for 1 h at room temperature, at which time TLC showed the reaction to be complete. The mixture was quenched with cold water and extracted with Et_2O three times. The combined organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give an orange-yellow oily solid. Chromatographic purification on a silica gel column packed in hexanes eluted with 10% EtOAc in hexanes afforded compound **14** as a yellowish-white solid (106 mg, 81% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.38; mp 155−156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.0 Hz, 1H), 7.40 (t, J = 7.5 Hz, 1H), 7.36 and 7.32 (AB_q, J = 6.8 Hz, 2H), 7.04 and 7.01 (AB_q, J = 8.8 Hz, 2H), 4.00 (s, 3H), 3.95 (s, 3H), 2.93 (s, 1H), 2.74 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.8, 151.2, 137.1, 136.4, 134.0, 132.5, 132.2, 127.1, 126.9, 126.4, 125.9, 126.5, 126.4, 124.2, 117.8, 112.7, 84.5, 78.5, 61.1, 56.1, 19.6. HRMS (ESI/FTICR) m/z: calcd for $C_{21}H_{18}O_2Na$ $[M + Na]^+$, 325.1199; found, 325.1197.

*5-(2-Ethynyl-3,4-dimethoxyphenyl)acenaphthene (**15**). Step 1: Synthesis of 5-[2-(2,2-Dibromovinyl)-3,4-dimethoxyphenyl]-acenaphthene.* As described for the synthesis of compound **14**, the vinyl dibromide was prepared from PPh_3 (824 mg, 3.14 mmol), CBr_4 (521 mg, 1.57 mmol), and aldehyde **11** (200 mg, 0.628 mmol) in dry CH_2Cl_2 (2.3 mL) at 0 °C over 2 h. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes sequentially eluted with 50% CH_2Cl_2 in hexanes and CH_2Cl_2 afforded the vinyl dibromide as a foamy, yellow solid (284 mg, 96% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.47. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.34 (m, 2H), 7.30−7.28 (m, 3H, superimposed with the $CHCl_3$ resonance), 7.14 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.48−3.40 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.0, 146.1, 145.6, 139.4, 134.1, 133.0, 132.3, 130.7, 130.2, 129.4, 127.8, 126.6, 120.9, 119.1, 118.7, 112.21, 112.20, 93.6, 61.0, 55.9, 30.5, 30.1.

*Step 2: Synthesis of 5-(2-Ethynyl-3,4-dimethoxyphenyl)-acenaphthene (**15**).* As described for the synthesis of compound **14**, compound **15** was prepared from the vinyl dibromide (1.99 g, 4.19 mmol) using a 1.6 M solution of *n*-BuLi in hexanes (6.54 mL, 10.5 mmol) in dry THF (10 mL) at −78 °C for 5 h and then for 1 h at room temperature. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes eluted with 10% EtOAc in hexanes afforded compound **15** as a yellow solid (1.06 g, 81% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.42; mp 154−156 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44−7.36 (m, 3H), 7.32 (d, J = 7.0 Hz, 1H), 7.27 (d, J = 6.0 Hz, 1H), 7.10 and 7.02 (AB_q, J = 8.3 Hz, 2H), 4.01 (s, 3H), 3.94 (s, 3H), 3.44 (br s, 4H), 2.99 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.7, 151.4, 145.0, 145.7, 139.3, 136.4, 133.3, 130.4, 129.3, 127.7, 126.3, 121.3, 119.1, 118.7, 117.5, 112.8, 84.5, 78.7, 61.1, 56.1, 30.5, 30.2. HRMS (ESI) m/z: calcd for $C_{22}H_{18}O_2Na$ $[M + Na]^+$, 337.1199; found, 337.1198.

*1-(2-Ethynylphenyl)-4-methylnaphthalene (**16**). Step 1: Synthesis of 1-(2-(2,2-Dibromovinyl)phenyl)-4-methylnaphthalene.* As described for the synthesis of compound **14**, the vinyl dibromide was prepared using PPh_3 (6.39 g, 24.36 mmol), CBr_4 (4.04 g, 12.18 mmol), and aldehyde **12** (1.2 g, 4.87 mmol) in dry CH_2Cl_2 (18 mL) at 0 °C for 2 h. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes and eluted with hexanes afforded the vinyl dibromide as a yellow oily solid (1.939 g, 99% yield). R_f (SiO_2/50% CH_2Cl_2 in hexanes): 0.76. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 8.5 Hz, 1H), 7.81−7.79 (m, 1H), 7.55−7.33 (m, 7H), 7.22 (d, J = 7.5 Hz, 1H), 6.94 (s, 1H), 2.76 (br s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1, 136.9, 136.1, 135.4, 134.5, 132.6, 131.8, 131.1, 128.8, 128.2, 127.3, 127.2, 126.6, 126.0, 125.8, 125.7, 124.4, 90.6, 19.6.

*Step 2: Synthesis of 1-(2-Ethynylphenyl)-4-methylnaphthalene (**16**).* As described for the synthesis of compound **14**, compound **16** was prepared from the vinyl dibromide (2.08 g, 5.17 mmol) using a 1.6 M solution of *n*-BuLi in hexanes (8.07 mL, 12.92 mmol) in dry THF (12 mL) at −78 °C for 5 h and then for 1 h at room temperature. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes and eluted with hexanes afforded compound **16** as an orange-yellow solid (773 mg, 62% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.61; mp 72−74 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (d, J = 8.5 Hz, 1H), 7.67 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.51 (t, J = 7.0 Hz, 1H), 7.46−7.42 (m, 2H), 7.39 (t, J = 7.5 Hz, 2H), 7.35 (t, J = 7.0 Hz, 2H), 2.76 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7, 136.8, 134.2, 134.2, 133.2, 132.6, 131.9, 131.0, 128.5, 127.2, 126.9, 126.8, 126.0, 125.5, 124.3, 122.6, 82.7, 80.2, 19.9. HRMS (EI/TOF) m/z: calcd for $C_{19}H_{14}$ $[M]^+$, 242.1096; found, 242.1094.

*5-(2-Ethynylphenyl)-1,2-dihydroacenaphthene (**17**). Step 1: Synthesis of 5-(2-(2,2-Dibromovinyl)phenyl)-1,2-dihydroacenaphthene.* As described for the synthesis of compound **14**, the vinyl dibromide was prepared using PPh_3 (12.69 g, 48.39 mmol), CBr_4 (8.02 g, 24.19 mmol), and aldehyde **13** (2.5 g, 9.68 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C for 2 h. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes and eluted with hexanes afforded the vinyl dibromide as a yellow solid (3.774 g, 94% yield). R_f (SiO_2/50% CH_2Cl_2 in hexanes): 0.68. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81−7.79 (m, 1H), 7.46−7.42 (m, 2H), 7.42−7.37 (m, 2H), 7.34−7.27 (m, 4H), 7.01 (s, 1H), 3.49−3.43 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.2, 146.1, 139.5, 139.3, 137.2, 135.1, 133.1, 131.0, 130.1, 129.5, 129.0, 128.3, 128.1, 127.1, 120.9, 119.5, 118.8, 90.4, 30.5, 30.2.

*Step 2: Synthesis of 5-(2-Ethynylphenyl)-1,2-dihydroacenaphthylene (**17**).* As described for the synthesis of compound **14**, compound **17** was prepared from the vinyl dibromide (3.5 g, 8.45 mmol) using a 1.6 M solution of *n*-BuLi in hexanes (13.2 mL, 21.13 mmol) in dry THF (20 mL) at −78 °C for 5 h and then for 1 h at room temperature. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes and eluted with hexanes afforded compound **17** as a whitish-yellow solid (1.282 g, 60% yield). R_f (SiO_2/10% EtOAc in hexanes): 0.53; mp 86−87 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.68 (d, J = 7.5 Hz, 1H), 7.45 (t, J = 7.0 Hz, 2H), 7.43−7.36 (m, 4H), 7.34 (d, J = 7.5 Hz, 1H), 7.29−7.28 (m, 1H), 3.55 (br s, 4H), 2.84 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 146.0, 143.1, 139.3, 133.7, 133.4, 130.9, 130.1, 129.2, 128.5, 127.8, 127.1, 122.2, 121.2, 119.2, 118.7, 83.0, 80.1, 30.6, 30.2. HRMS (ESI/TOF) m/z: calcd for $C_{20}H_{15}$ $[M + H]^+$, 255.1168; found, 255.1170.

*3,4-Dimethoxy-8-methylbenzo[c]phenanthrene (**18**). Using $PtCl_2$.* In an oven-dried reaction vial equipped with a magnetic stirring bar

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was placed alkyne **14** (40 mg, 0.132 mmol) in dry PhMe (0.6 mL). $PtCl_2$ (1.8 mg, 6.77 μmol) was added. The vial was flushed with nitrogen gas, and the mixture was allowed to stir in a sand bath at 80 °C for 17 h, at which time TLC showed the reaction to be complete. The mixture was filtered through Celite, and the residue was washed with CH_2Cl_2. Chromatographic purification on a silica gel column packed in hexanes eluted with 50% CH_2Cl_2 in hexanes afforded compound **18** as a yellow solid (29.8 mg, 75% yield).

Using $AuCl_3$. In an oven-dried reaction vial equipped with a magnetic stirring bar was placed alkyne **14** (30 mg, 0.100 mmol) in dry PhMe (0.43 mL). $AuCl_3$ (1.5 mg, 4.94 μmol) was added. The vial was flushed with nitrogen gas, and the mixture was allowed to stir in a sand bath at 80 °C for 24 h, at which time TLC showed the reaction to be complete. Workup as described above and chromatographic purification on a silica gel column packed in hexanes and eluted with 50% CH_2Cl_2 in hexanes afforded compound **18** as a yellow solid (25.3 mg, 84% yield). R_f (SiO_2/50% CH_2Cl_2 in hexanes): 0.28; mp 143−144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.08−9.06 (m, 1H), 8.80 (d, *J* = 9.3 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.17−8.15 (m, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.67−7.65 (m, 3H), 7.40 (d, *J* = 9.5 Hz, 1H), 4.07 (s, 3H), 4.06 (s, 3H), 2.80 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6, 143.3, 133.2, 132.3, 132.3, 130.3, 129.6, 128.9, 128.4, 127.1, 127.0, 126.5, 125.7, 125.5, 124.42, 124.39, 120.7, 113.5, 61.4, 56.6, 19.7. HRMS (ESI/FTICR) *m*/*z*: calcd for $C_{21}H_{18}O_2Na$ [M + Na]$^+$, 325.1199; found, 325.1198.

*9,10-Dimethoxy-4,5-dihydrobenzo[l]acephenanthrylene (**19**). Using $PtCl_2$.* As described for the synthesis of compound **18**, compound **19** was prepared by a reaction of alkyne **15** (30 mg, 0.095 mmol) and $PtCl_2$ (1.27 mg, 4.77 μmol) in dry PhMe (0.42 mL) at 80 °C over 21 h. Workup and chromatographic purification on a silica gel column packed in hexanes and eluted with 50% CH_2Cl_2 in hexanes afforded compound **19** as a yellow solid (21.7 mg, 72% yield).

Using $AuCl_3$. As described for the synthesis of compound **18**, compound **19** was prepared by a reaction of alkyne **15** (30 mg, 0.095 mmol) and $AuCl_3$ (1.45 mg, 4.78 μmol) in dry PhMe (0.42 mL) at 80 °C over 29 h. Workup and chromatographic purification on a silica gel column packed in hexanes and eluted with 50% CH_2Cl_2 in hexanes afforded compound **19** as a yellow solid (17.8 mg, 59% yield). R_f (SiO_2/20% EtOAc in hexanes): 0.32; mp 154−155 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (d, *J* = 9.0 Hz, 1H), 8.84 (d, *J* = 8.5 Hz, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.66 (t, *J* = 7.0 Hz, 1H), 7.63 (s, 1H), 7.47 (d, *J* = 7.0 Hz, 1H), 7.44 (d, *J* = 9.0 Hz, 1H), 4.07 (d, 3H), 4.06 (d, 3H), 3.52−3.48 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.5, 146.1, 144.4, 139.3, 132.5, 128.8, 128.5, 128.2, 128.1, 126.9, 126.8, 124.9, 123.43, 123.37, 120.5, 120.4, 120.2, 113.6, 61.4, 56.6, 30.7, 29.4. HRMS (ESI/FTICR) *m*/*z*: calcd for $C_{22}H_{18}O_2Na$ [M + Na]$^+$, 337.1199; found, 337.1195.

*5-Methylbenzo[c]phenanthrene (**20**).* As described for the synthesis of compound **18**, compound **20** was prepared by a reaction of alkyne **16** (771 mg, 3.183 mmol) and $PtCl_2$ (42.3 mg, 0.159 mmol), in dry PhMe (14 mL) at 80 °C over 24 h. Workup and chromatographic purification on a silica gel column packed in hexanes and eluted with hexanes afforded compound **20** as a yellow solid (626 mg, 81% yield). R_f (SiO_2/hexanes): 0.18; mp 74−76 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.14 (d, *J* = 8.5 Hz, 1H), 9.07 (d, *J* = 8.5 Hz, 1H), 8.20−8.18 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.71−7.65 (m, 4H), 7.59 (t, *J* = 7.6 Hz, 1H), 2.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.3, 133.1, 133.1, 130.8, 130.5, 130.2, 128.5, 128.4, 127.9, 127.5, 127.1, 126.5, 126.4, 126.1, 125.8, 125.7, 125.4, 124.4, 19.8. HRMS (ESI/TOF) *m*/*z*: calcd for $C_{19}H_{15}$ [M + H]$^+$, 243.1168; found, 243.1168.

*4,5-Dihydrobenzo[l]acephenanthrylene (**21**).*[52] As described for the synthesis of compound **18**, compound **21** was prepared by the reaction of alkyne **17** (1.07 g, 4.207 mmol) and $PtCl_2$ (56 mg, 0.210 mmol) in dry PhMe (18 mL) at 80 °C over 24 h. Workup and chromatographic purification on a silica gel column packed in hexanes sequentially eluted with hexanes and 10% CH_2Cl_2 in hexanes afforded compound **21** as a pale reddish-brown solid (716 mg, 69% yield). R_f (SiO_2/hexanes): 0.16; mp 125−126 °C (lit.[52] mp 123−124). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (d, *J* = 8.5 Hz, 1H), 8.94 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.88 and 7.83 (AB_q, *J* = 8.5 Hz, 2H), 7.72−7.68 (m, 2H), 7.65 (s, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 1H), 3.53−3.48 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.1, 145.1, 139.2, 133.7, 132.8, 131.3, 129.0, 128.6, 128.3, 127.7, 127.3, 127.0, 126.2, 125.3, 124.8, 123.5, 120.6, 120.2, 30.7, 29.4. HRMS (ESI/TOF) *m*/*z*: calcd for $C_{20}H_{15}$ [M + H]$^+$, 255.1168; found, 255.1170.

*8-Methylbenzo[c]phenanthrene-3,4-dione (**22**). Step 1: Demethylation.* In an oven-dried 15 mL two-neck round-bottom flask equipped with a magnetic stirring bar was placed catechol dimethyl ether **18** (30.24 mg, 0.1 mmol) in dry CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. The mixture was cooled to −70 °C, and a 1 M solution of BBr_3 in pentane (0.3 mL, 0.3 mmol) was added. The purple-pink suspension was stirred at −70 °C for 5 min, then allowed to warm to room temperature and stirred for 2 h. TLC showed completion of the reaction, and the mixture was by quenched with ice and cold water. The mixture was diluted with CH_2Cl_2, and the layers were separated. The organic layer was washed several times with brine and cold water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude catechol as a reddish solid. R_f (SiO_2/CH_2Cl_2): 0.16.

Step 2: Oxidation. In an oven-dried 25 mL three-neck round-bottom flask equipped with a magnetic stirring bar was placed the crude catechol (27.43 mg, 0.1 mmol) in dry CH_2Cl_2 (2 mL). The mixture was cooled to 0 °C, and PDC (104.4 mg, 0.3 mmol) was added. The mixture was stirred at room temperature for 4 h, at which time TLC showed the reaction to be complete. The mixture was filtered through Celite, and the reddish orange filtrate was evaporated under reduced pressure to give a reddish solid. This product was chromatographed on a silica gel column packed in CH_2Cl_2 and sequentially eluted with CH_2Cl_2 and 5% MeOH in CH_2Cl_2. Compound **22** was obtained as a reddish-orange solid (22.3 mg, 82% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.82; mp 204−210 °C (dec. with charring). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.39 (d, *J* = 10.5 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.81 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.76 (dt, *J* = 1.0, 8.0 Hz, 1H), 7.71 (s, 1H), 6.51 (d, *J* = 10.5 Hz, 1H), 2.72 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 180.6, 178.9, 143.7, 137.1, 137.0, 133.3, 131.9, 130.5, 129.6, 129.2, 128.6, 128.4 128.1, 126.4, 126.3, 126.1, 125.7, 125.1, 19.4. HRMS (ESI/TOF) *m*/*z*: calcd for $C_{19}H_{13}O_2$ [M + H]$^+$, 273.0910; found, 273.0912.

*4,5-Dihydrobenzo[l]acephenanthrylene-9,10-dione (**23**). Step 1: Demethylation.* As described for the synthesis of compound **22**, compound **23** was prepared from catechol dimethyl ether **19** (31.4 mg, 0.1 mmol) using a 1 M solution of BBr_3 in pentane (0.3 mL, 0.3 mmol) in dry CH_2Cl_2 (1.5 mL). Workup gave a reddish-orange solid of the crude catechol. R_f (SiO_2/CH_2Cl_2): 0.07.

Step 2: Oxidation. As described for the synthesis of compound **22**, compound **23** was prepared by oxidation of the crude catechol (28.6 mg, 0.1 mmol) with PDC (112.7 mg, 0.3 mmol) in dry CH_2Cl_2 (2.0 mL). Workup and chromatographic purification on a silica gel column packed in CH_2Cl_2 and eluted with CH_2Cl_2 afforded compound **23** as a dark red solid (22.5 mg, 79% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.81; mp 159−162 °C (dec. with charring). ^{1}H NMR (500 MHz, acetone-d_6): δ 8.84 (d, *J* = 10.5 Hz, 1H), 8.36 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.76 (t, *J* = 7.0 Hz, 1H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.65 (s, 1H), 6.58 (d, *J* = 10.5 Hz, 1H), 3.54−3.48 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 180.0, 178.0, 149.5, 146.8, 143.7, 139.6, 139.3, 135.9, 133.1, 130.7, 129.3, 127.7, 127.4, 125.9, 125.6, 123.7, 120.3, 119.9, 30.6, 29.4. HRMS (ESI/TOF) *m*/*z*: calcd for $C_{20}H_{13}O_2$ [M + H]$^+$, 285.0910; found, 285.0914.

*(±)-Trans-8-methyl-3,4-dihydrobenzo[c]phenanthrene-3,4-diol ((±)**24**).* In an oven-dried 200 mL round-bottom flask equipped with a magnetic stirring bar was placed quinone **22** (134.8 mg, 0.5 mmol) in dry THF (9 mL) and EtOH (60 mL). The mixture was cooled to 0 °C, sparged with O_2 for 15 min, and then $NaBH_4$ (187.3 mg, 5.0 mmol) was added portionwise. The yellow mixture was allowed to stir at room temperature while being sparged with O_2 for 4 h and was then allowed to stir under an O_2 balloon for 15 h protected from light. The mixture was again cooled to 0 °C, sparged with O_2 for 15 min, and

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another aliquot of $NaBH_4$ (187.3 mg, 5.0 mmol) was added portionwise. The mixture was allowed to stir at room temperature while being sparged with O_2 for 5 h, at which time TLC showed the reaction to be complete. The mixture was concentrated to a third of its volume. The addition of ice and cold water resulted in a creamy yellow suspension. The mixture was transferred to a separatory funnel; EtOAc was added to dissolve the solids, and the mixture was washed three times with H_2O. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a whitish-orange solid. This solid was suspended in cold Et_2O and sonicated to yield dihydrodiol (±)-**24** as a whitish solid, which was collected by filtration (104.5 mg, 76% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.35. ^{1}H NMR (500 MHz, acetone-d_6): δ 8.63 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.71–7.64 (m, 2H), 7.61 (s, 1H), 7.27 (d, J = 10.5 Hz, 1H), 6.31 (dd, J = 1.5, 10.0 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.69 (br d, J = 5.5 Hz, 1H), 4.64 (br d, J = 11.5 Hz, 1H), 4.42 (br, 1H), 2.73 (s, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 137.9, 133.4, 133.0, 132.21, 132.20, 130.2, 129.0, 128.8, 127.4, 127.1, 126.9, 126.8, 126.4, 125.6, 124.9, 74.9, 71.4, 19.7. HRMS (ESI/TOF) m/z: calcd for $C_{19}H_{16}O_2Na$ [M + Na]$^+$, 299.1043; found, 299.1043.

*(±)-Trans-4,5,9,10-tetrahydrobenzo[l]acephenanthrylene-9,10-diol ((±)-**25**).* As described for the synthesis of dihydrodiol (±)-**24**, dihydrodiol (±)-**25** was prepared by reduction of quinone **23** (180 mg, 0.633 mmol) with $NaBH_4$ (239.5 mg, 6.33 mmol) added portionwise in two equal aliquots, in THF (10.5 mL) and EtOH (72.5 mL), in the presence of O_2 over 24 h. The crude yellow solid obtained upon workup as described for (±)-**24** was suspended in cold Et_2O and sonicated to afford dihydrodiol (±)-**25** as an off-white solid, which was collected by filtration (144.5 mg, 79% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.26. ^{1}H NMR (500 MHz, acetone-d_6): δ 8.41 (d, J = 8.0 Hz, 1H), 7.92 and 7.85 (AB_q, J = 7.8 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.52–7.47 (m, 2H), 6.34 (d, J = 10.5 Hz, 1H), 4.75 (d, J = 11.5 Hz, 1H), 4.67 (br, J = 5.0 Hz, 1H), 4.60 (d, J = 11.5 Hz, 1H), 4.40 (br, 1H), 3.48–3.41 (m, 4H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 145.7, 143.9, 139.1, 137.1, 134.7, 133.6, 129.9, 128.7, 128.2, 128.1, 126.4, 124.9, 124.5, 124.4, 121.9, 120.1, 74.9, 71.4, 30.6, 28.9. HRMS (ESI/TOF) m/z: calcd for $C_{20}H_{16}O_2Na$ [M + Na]$^+$, 311.1043; found, 311.1043.

*(±)-1β,2β-Epoxy-3α,4β-dihydroxy-8-methyl-1,2,3,4-tetrahydrobenzo[c]phenanthrene ((±)-**26**). Step 1: Synthesis of (±)-2α-Bromo-8-methyl-1β,3α,4β-trihydroxyl-1,2,3,4-tetrahydrobenzo[c]phenanthrene.* In an oven-dried reaction vial equipped with a magnetic stirring bar was placed dihydrodiol (±)-**24** (20.0 mg, 72.38 μmol) in dry THF (3.0 mL) and H_2O (1.5 mL). Recrystallized *N*-bromoacetamide (29.95 mg, 0.217 mmol) was added, and the mixture was stirred at room temperature under subdued light for 25 h, at which time TLC showed the reaction to be complete. The orange mixture was evaporated to half its volume, diluted with Et_2O, and washed sequentially with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et_2O containing a little hexanes afforded the bromo triol as a white solid (26.2 mg, 97% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.20.

*Step 2: Cyclization to (±)-1β,2β-Epoxy-3α,4β-dihydroxy-8-methyl-1,2,3,4-tetrahydrobenzo[c]phenanthrene ((±)-**26**).* In an oven-dried reaction vial equipped with a magnetic stirring bar was placed the bromo triol obtained above (15.3 mg, 40.99 μmol) in dry THF (1.6 mL). Amberlite IRA 400 HO^- (248.5 mg) was added, and the mixture was stirred at room temperature under subdued light for 4 h, at which time TLC showed the reaction to be complete. The Amberite was filtered off, and the filtrate obtained was evaporated under reduced pressure to give a white solid. Trituration with cold Et_2O afforded diol epoxide (±)-**26** as a white solid (7.7 mg, 64% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.39. ^{1}H NMR (500 MHz, acetone-d_6): δ 9.19 (d, J = 7.5 Hz, 1H), 8.17 (d, J = 8.0 Hz, 1H), 7.98 and 7.96 (AB_q, J = 8.3 Hz, 2H), 7.76–7.69 (m, 2H), 7.68 (s, 1H), 4.87 (br, 1H, D_2O exchangeable), 4.82 (d, J = 9.0 Hz, 1H), 4.66 (br, 1H, D_2O exchangeable), 4.36 (d, J = 4.0 Hz, 1H), 3.95 (dd, J = 2.0, 4.5 Hz, 1H), 3.84 (dd, J = 1.5, 9.0 Hz, 1H), 2.74 (s, 3H). The following resonances were observed to sharpen upon exchange with D_2O: 4.82 (d, J = 9.0 Hz, 1H), 4.36 (d, J = 4.5 Hz, 1H), 3.95 (dd, J = 2.0, 4.5 Hz, 1H), 3.84 (dd, J = 2.0, 9.0 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ 136.4, 133.4, 132.5, 132.40, 132.37, 130.2, 129.2, 127.8, 127.1, 126.7, 125.8, 124.8, 124.6, 113.9, 72.4, 72.1, 62.4, 50.9, 19.0. HRMS (ESI/TOF) m/z: calcd for $C_{19}H_{16}O_3Na$ [M + Na]$^+$, 315.0992; found, 315.0992.

*(±)-11β,12β-Epoxy-4,5,9,10,11,12-hexahydrobenzo[l]acephenanthrylene-9β,10α-diol ((±)-**27**). Step 1: Synthesis of (±)-11α-Bromo-4,5,9,10,11,12-hexahydrobenzo[l]acephenanthrylene-9β,10α,12β-triol.* In an oven-dried reaction vial equipped with a magnetic stirring bar was placed dihydrodiol (±)-**26** (30.0 mg, 0.104 mmol) in dry THF (4.4 mL) and H_2O (2.2 mL). Recrystallized *N*-bromoacetamide (17.2 mg, 0.124 mmol) was added, and the mixture was allowed to stir at room temperature under subdued light for 19 h, at which time TLC showed the reaction to be complete. The orange mixture was evaporated to half its volume, diluted with Et_2O, and washed sequentially with H_2O and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a reddish-white solid. Trituration with cold Et_2O containing a little hexanes afforded the bromo triol as a pale reddish-white solid (39.1 mg, 95% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.16.

*Step 2: Cyclization to (±)-11β,12β-Epoxy-4,5,9,10,11,12-hexahydrobenzo[l]acephenanthrylene-9β,10α-diol ((±)-**27**).* In an oven-dried reaction vial equipped with a magnetic stirring bar was placed the bromo triol obtained above (39.1 mg, 0.101 mmol) in dry THF (4.0 mL). Amberlite IRA 400 HO^- (615.1 mg) was added and the mixture was stirred at room temperature under subdued light for 4 h, at which time TLC showed the reaction to be complete. The Amberite was filtered off, and the filtrate obtained was evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et_2O afforded diol epoxide (±)-**27** as a pale yellowish-white solid (18.7 mg, 60% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.32. ^{1}H NMR (500 MHz, acetone-d_6 + 1 drop DMSO-d_6): δ 8.80 (d, J = 8.5 Hz, 1H), 8.00 and 7.95 (AB_q, J = 8.3 Hz, 2H), 7.65 (t, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.55 (d, J = 7.0 Hz, 1H), 5.19 (br, 2H), 4.83 (d, J = 9.5 Hz, 1H), 4.45 (d, J = 4.4 Hz, 1H), 3.90 (dd, J = 2.0, 4.4 Hz, 1H), 3.68 (dd, J = 2.0, 9.5 Hz, 1H), 3.48–3.39 (m, 4H). ^{13}C NMR (125 MHz, acetone-d_6 + 1 drop DMSO-d_6): δ 156.5, 146.2, 145.6, 144.2, 139.2, 138.9, 129.7, 128.5, 128.0, 127.6, 124.2, 123.5, 121.7, 119.8, 73.1, 71.9, 61.9, 50.2, 30.2, and one resonance embedded in the acetone-d_6 resonance. HRMS (ESI/TOF) m/z: calcd for $C_{20}H_{16}O_3Na$ [M + Na]$^+$, 327.0992; found, 327.0997.

*(±)-1α,2α-Epoxy-3α,4β-dihydroxy-8-methyl-1,2,3,4-tetrahydrobenzo[c]phenanthrene ((±)-**28**).* In an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was placed dihydrodiol (±)-**24** (20.0 mg, 72.38 μmol) in THF (4 mL). The mixture was cooled to −78 °C, and purified *m*CPBA (125.8 mg, 0.729 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 h, at which time TLC showed the reaction to be complete. The mixture was evaporated to a third of its volume and diluted with EtOAc. The mixture was washed twice with each cold 1 M NaOH, H_2O, and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et_2O afforded diol epoxide (±)-**28** as a pale yellowish-white solid (14.6 mg, 69% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.37. ^{1}H NMR (500 MHz, acetone-d_6): δ 8.79 (d, J = 8.0 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.75 (dt, J = 1.5, 8.5 Hz, 1H), 7.72 (dt, J = 1.5, 8.5 Hz, 1H), 7.65 (s, 1H), 4.89 (br, 1H, D_2O exchangeable), 4.87 (d, J = 8.5 Hz, 1H), 4.80 (d, J = 4.5 Hz, 1H), 4.64 (br, 1H, D_2O exchangeable), 3.96 (br d, J = 8.5 Hz, 1H), 3.81 (dd, J = 1.8, 4.5 Hz, 1H), 2.75 (s, 3H). The following resonances were observed to sharpen upon exchange with D_2O: 4.84 (d, J = 8.5 Hz, 1H), 4.78 (d, J = 4.0 Hz, 1H), 3.96 (dd, J = 2.0, 8.5 Hz, 1H), 3.81 (dd, J = 2.0, 4.5 Hz, 1H). ^{13}C NMR (125 MHz, acetone-d_6): δ 139.8, 133.4, 133.3, 132.2, 132.1, 130.5, 128.2, 127.6, 126.8, 126.6, 125.2, 124.5, 123.4, 72.3, 70.6, 57.2, 54.7, 54.1, 18.8. HRMS (ESI/TOF) m/z: calcd for $C_{19}H_{16}O_3Na$ [M + Na]$^+$, 315.0992; found, 315.0995.

*(±)-11α,12α-Epoxy-4,5,9,10,11,12-hexahydrobenzo[l]acephenanthrylene-9β,10α-diol ((±)-**29**).* In an oven-dried 10 mL round-

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bottom flask equipped with a magnetic stirring bar was placed dihydrodiol (±)-**25** (30.0 mg, 0.104 mmol) in THF (6 mL). The mixture was cooled to −78 °C, and purified *m*CPBA (179.5 mg, 1.04 mmol) was added. The mixture was allowed to warm to room temperature and stirred for 2 h, at which time TLC showed the reaction to be complete. The mixture was evaporated to a third of its volume and diluted with EtOAc. The mixture was washed twice with each cold 1 M NaOH, H_2O, and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et_2O afforded diol epoxide (±)-**29** as a pale yellowish-white solid (25.5 mg, 80% yield). R_f (SiO_2/5% MeOH in CH_2Cl_2): 0.11. ^{1}H NMR (500 MHz, acetone-d_6 + 1 drop DMSO-d_6): δ 8.50 (d, J = 8.5 Hz, 1H), 7.93 and 7.89 (AB_q, J = 8.4 Hz, 2H), 7.63 (t, J = 7.8 Hz, 1H), 7.55−7.52 (m, 2H), 4.97 (d, J = 4.5 Hz, 1H), 4.77 (d, J = 8.0 Hz, 1H), 3.95 (dd, J = 2.0, 8.0 Hz, 1H), 3.79 (dd, J = 2.0, 4.5 Hz, 1H), 3.47−3.39 (m, 4H). ^{1}H NMR (500 MHz, THF-d_8): δ 8.50 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 7.78 (d, J = 8.3 Hz, 1H), 7.55 (t, J = 7.7 Hz, 1H), 7.48−7.42 (m, 2H), 4.92 (d, J = 4.4 Hz, 1H), 4.88 (d, J = 5.1 Hz, 1H), 4.70 (dd, J = 4.5, 8.5 Hz, 1H), 4.59 (d, J = 6.0 Hz, 1H), 3.82−3.77 (m, 1H), 3.68 (dd, J = 1.9, 4.5 Hz, 1H), 3.47−3.34 (m, 4H). ^{13}C NMR (125 MHz, THF-d_8): δ 146.2, 144.4, 139.9, 135.3, 130.1, 129.9, 129.0, 128.8, 128.3, 128.0, 124.6, 124.1, 122.1, 120.1, 73.2, 71.6, 57.3, 54.5, 31.1, 29.5. HRMS (ESI/TOF) m/z: calcd for $C_{20}H_{16}O_3Na$ $[M + Na]^+$, 327.0992; found, 327.0992.

Benzo[l]acephenanthrylene (30).[52] In an oven-dried reaction vial equipped with a magnetic stirring bar was placed 4,5-dihydrobenzo-[*l*]acephenanthrylene (**21**) (25.4 mg, 0.1 mmol) in dry PhMe (1 mL). DDQ (29.5 mg, 0.13 mmol) was added; the vial was flushed with nitrogen gas, and the mixture was stirred at 80 °C for 24 h. TLC showed the reaction to be complete, and the mixture was evaporated under a stream of nitrogen gas to give a dark yellow solid. The crude product was chromatographed on a column containing 1/4 basic alumina and 3/4 silica gel packed in hexanes and eluted with hexanes. Compound **30** was obtained as a yellow solid (18.1 mg, 72% yield). R_f (SiO_2/hexanes): 0.14; mp 109−111 °C from hexanes (lit.[52] mp 101−104 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.21 (d, J = 8.5 Hz, 1H), 8.96−8.93 (m, 1H), 8.09 (s, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.95 and 7.92 (AB_q, J = 8.5 Hz, 2H), 7.76−7.72 (m, 3H), 7.65 (dt, J = 1.0, 8.0 Hz, 1H), 7.23 (d, J = 5.0 Hz, 1H), 7.14 (d, J = 5.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 138.9, 134.0, 133.3, 131.9, 131.3, 129.3, 129.0, 128.7, 128.4, 128.1, 128.0, 127.3, 126.6, 126.5, 126.4, 126.0, 122.6. HRMS (ESI/TOF) m/z: calcd for $C_{20}H_{13}$ $[M + H]^+$, 253.1012; found, 253.1012.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for compounds **2**, **3**, **6**, **10**−**23**, (±)-**24**−(±)-**29**, and **30**, NOESY spectra for (±)-**26** and (±)-**27**, details of the X-ray crystallographic analysis, ORTEP figures, and CIF files for compounds **18**−**21** and **30**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00931.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Mallory, F. B.; Wood, C. S.; Gordon, J. T.; Lindquist, L. C.; Savitz, M. L. *J. Am. Chem. Soc.* **1962**, *84*, 4361−4362.
(2) Moore, W. A.; Morgan, D. D.; Stermitz, F. R. *J. Am. Chem. Soc.* **1963**, *85*, 829−830.
(3) Wood, C. S.; Mallory, F. B. *J. Org. Chem.* **1964**, *29*, 3373−3377.
(4) Mallory, F. B.; Wood, C. S.; Gordon, J. T. *J. Am. Chem. Soc.* **1964**, *86*, 3094−3102.
(5) Mallory, F. B.; Mallory, C. W. *J. Am. Chem. Soc.* **1972**, *94*, 6041−6048.
(6) Mallory, F. B.; Butler, K. E.; Evans, A. C.; Brondyke, E. J.; Mallory, C. W.; Yang, C.; Ellenstein, A. *J. Am. Chem. Soc.* **1997**, *119*, 2119−2124.
(7) Mallory, F. B.; Rudolph, M. J.; Oh, S. M. *J. Org. Chem.* **1989**, *54*, 4619−4626.
(8) For reviews, see: (a) Mallory, F. B.; Mallory, C. W. *Organic Reactions*; John Wiley & Sons, Inc.: Hoboken, NJ, 1984; Vol. *30*, p 1−456. (b) Laarhoven, W. H. *Pure Appl. Chem.* **1984**, *56*, 1225−1240. (c) Laarhoven, W. H. *Recl. Trav. Chim. Pays-Bas* **1983**, *102*, 185−204. (d) Muszkat, K. A. *Top. Curr. Chem.* **1980**, *88*, 89−143. (e) Floyd, A. J.; Dyke, S. F.; Ward, S. E. *Chem. Rev.* **1976**, *76*, 509−562.
(9) Liu, L.; Yang, B.; Katz, T. J.; Poindexter, M. K. *J. Org. Chem.* **1991**, *56*, 3769−3775.
(10) (a) Talele, H. R.; Chaudhary, A. R.; Patel, P. R.; Bedekar, A. V. *ARKIVOC* **2011**, *ix*, 15−39. (b) Talele, H.; Gohil, M. J.; Bedekar, A. V. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 1182−1186.
(11) Li, H.; He, K.-H.; Liu, J.; Wang, B.-Q.; Zhao, K.-Q.; Hu, P.; Shi, Z.-J. *Chem. Commun.* **2012**, *48*, 7028−7030.
(12) Jørgensen, K. B. *Molecules* **2010**, *15*, 4334−4358.
(13) Shen, Y.; Chen, C.-F. *Chem. Rev.* **2012**, *112*, 1463−1535.
(14) (a) Li, C.-W.; Wang, C.-I.; Liao, H.-Y.; Chaudhuri, R.; Liu, R.-S. *J. Org. Chem.* **2007**, *72*, 9203−9207. (b) Yao, T.; Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3511−3517. (c) Yao, T.; Campo, M. A.; Larock, R. C. *Org. Lett.* **2004**, *6*, 2677−2680.
(15) (a) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578−4593. (b) Goldfinger, M. B.; Swager, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 7895−7896.
(16) (a) Lin, Y.-D.; Cho, C.-L.; Ko, C.-W.; Pulte, A.; Wu, Y.-T. *J. Org. Chem.* **2012**, *77*, 9979−9988. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002−2009. (c) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. *J. Org. Chem.* **1997**, *62*, 7536−7537. (d) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941−1946.
(17) (a) Jones, S. B.; He, L.; Castle, S. L. *Org. Lett.* **2006**, *8*, 3757−3760. (b) Collins, S. K.; Grandbois, A.; Vachon, M. P.; Côté, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2923−2926. (c) Bonifacio, M. C.; Robertson, C. R.; Jung, J.-Y.; King, B. T. *J. Org. Chem.* **2005**, *70*, 8522−8526. (d) Iuliano, A.; Piccioli, P.; Fabbri, D. *Org. Lett.* **2004**, *6*, 3711−3714.
(18) Ichikawa, J.; Yokota, M.; Kudo, T.; Umezaki, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 4870−4873.
(19) Xia, Y.; Liu, Z.; Xiao, Q.; Qu, P.; Ge, R.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 5714−5717.
(20) Pathak, R.; Vandayar, K.; van Otterlo, W. A. L.; Michael, J. P.; Fernandes, M. A.; de Koning, C. B. *Org. Biomol. Chem.* **2004**, *2*, 3504−3509.
(21) Samanta, K.; Kar, G. K.; Sarkar, A. K. *Tetrahedron Lett.* **2012**, *53*, 1376−1379.
(22) (a) Shen, H.-C.; Tang, J.-M.; Chang, H.-K.; Yang, C.-W.; Liu, R.-S. *J. Org. Chem.* **2005**, *70*, 10113−10116. (b) Donovan, P. M.; Scott, L. T. *J. Am. Chem. Soc.* **2004**, *126*, 3108−3112.
(23) Paul, S.; Jana, R.; Ray, J. K. *Synlett* **2010**, 1463−1468.

DOI: 10.1021/acs.joc.5b00931
J. Org. Chem. 2015, 80, 7435−7446

(24) (a) Mamane, V.; Hannen, P.; Fürstner, A. *Chem.—Eur. J.* **2004**, *10*, 4556—4575. (b) Fürstner, A.; Mamane, V. *J. Org. Chem.* **2002**, *67*, 6264—6267.
(25) (a) Wu, T.-L.; Chou, H.-H.; Huang, P.-Y.; Cheng, C.-H.; Liu, R.-S. *J. Org. Chem.* **2014**, *79*, 267—274. (b) Yamamoto, K.; Oyamada, N.; Xia, S.; Kobayashi, Y.; Yamaguchi, M.; Maeda, H.; Nishihara, H.; Uchimaru, T.; Kwon, E. *J. Am. Chem. Soc.* **2013**, *135*, 16526—16532. (c) Oyama, H.; Nakano, K.; Harada, T.; Kuroda, R.; Naito, M.; Nobusawa, K.; Nozaki, K. *Org. Lett.* **2013**, *15*, 2104—2107. (d) Wu, A.; Xu, D.; Lu, D.; Penning, T. M.; Blair, I. A.; Harvey, R. G. *Tetrahedron* **2012**, *68*, 7217—7233. (e) Walker, B. D.; Howgego, J.; Davis, A. P. *Synthesis* **2010**, 3686—3692. (f) Chen, T.-A.; Lee, T.-J.; Lin, M.-Y.; Sohel, S. M. A.; Diau, E. W.-G.; Lush, S.-F.; Liu, R.-S. *Chem.—Eur. J.* **2010**, *16*, 1826—1833. (g) Storch, J.; Čermák, J.; Karban, J. *Tetrahedron Lett.* **2007**, *48*, 6814—6816.
(26) (a) Kozma, Á.; Deden, T.; Carreras, J.; Wille, C.; Petuškova, J.; Rust, J.; Alcarazo, M. *Chem.—Eur. J.* **2014**, *20*, 2208—2214. (b) Carreras, J.; Gopakumar, G.; Gu, L.; Gimeno, A.; Linowski, P.; Petuškova, J.; Thiel, W.; Alcarazo, M. *J. Am. Chem. Soc.* **2013**, *135*, 18815—18823. (c) Hirano, K.; Inaba, Y.; Takasu, K.; Oishi, S.; Takemoto, Y.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2011**, *76*, 9068—9080. (d) Matsuda, T.; Moriya, T.; Goya, T.; Murakami, M. *Chem. Lett.* **2011**, *40*, 40—41.
(27) Storch, J.; Bernard, M.; Sýkora, J.; Karban, J.; Čermák, J. *Eur. J. Org. Chem.* **2013**, 260—263.
(28) For reviews, see: (a) *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Harvey, R. G., Ed.; Cambridge University Press: Cambridge, 1991. (b) *Polycyclic Aromatic Hydrocarbon Carcinogenesis: Structure-Activity Relationships*; Yang, S. K., Silverman, B. D., Eds.; CRC Press: Boca Raton, FL, 1988; Vols *I* and *II*. (c) 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. Reactivity and tumorigenicity of bay-region diol epoxides derived from polycyclic aromatic hydrocarbons. 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. (d) *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283: Washington, DC, 1985.
(29) (a) Melendez-Colon, V. J.; Luch, A.; Seidel, A.; Baird, W. M. *Carcinogenesis* **1999**, *20*, 1885—1891. (b) Szeliga, J.; Dipple, A. *Chem. Res. Toxicol.* **1998**, *11*, 1—11. (c) Dipple, A. Reactions of polycyclic aromatic hydrocarbons with DNA. 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, France, 1994; pp 107—129. (d) Jerina, D. M.; Chadha, A.; Cheh, A. M.; Schurdak, M. E.; Wood, A. W.; Sayer, J. M. Covalent bonding of bay-region diol epoxides to nucleic acids. 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.
(30) For reviews, see: (a) Bolton, J. L.; Trush, M. A.; Penning, T. M.; Dryhurst, G.; Monks, T. J. *Chem. Res. Toxicol.* **2000**, *13*, 135—160. (b) Penning, T. M.; Burczynski, M. E.; Hung, C.-F.; McCoull, K. D.; Palackal, N. T.; Tsuruda, L. S. *Chem. Res. Toxicol.* **1999**, *12*, 1—18.
(31) (a) Park, J.-H.; Mangal, D.; Tacka, K. A.; Quinn, A. M.; Harvey, R. G.; Blair, I. A.; Penning, T. M. *Proc. Natl. Acad. Sci. U. S. A.* **2008**, *105*, 6846—6851. (b) Park, J.-H.; Troxel, A. B.; Harvey, R. G.; Penning, T. M. *Chem. Res. Toxicol.* **2006**, *19*, 719—728. (c) Park, J.-H.; Gopishetty, S.; Szewczuk, L. M.; Troxel, A. B.; Harvey, R. G.; Penning, T. M. *Chem. Res. Toxicol.* **2005**, *18*, 1026—1037. (d) Yu, D.; Berlin, J. A.; Penning, T. M.; Field, J. *Chem. Res. Toxicol.* **2002**, *15*, 832—842. (e) Palackal, N. T.; Burczynski, M. E.; Harvey, R. G.; Penning, T. M. *Biochemistry* **2001**, *40*, 10901—10910. (f) McCoull, K. D.; Rindgen, D.; Blair, I. A.; Penning, T. M. *Chem. Res. Toxicol.* **1999**, *12*, 237—246.
(32) For examples, see: (a) Amsharov, K. Y.; Kabdulov, M. A.; Jansen, M. *Eur. J. Org. Chem.* **2009**, 6328—6335. (b) Sharma, A. K.; Amin, S. *Chem. Res. Toxicol.* **2005**, *18*, 1438—1443. (c) Harvey, R. G.; Dai, W.; Zhang, J.-Y.; Cortez, C. *J. Org. Chem.* **1998**, *63*, 8118—8124. (d) Plater, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2903—2909. (e) Misra, B.; Amin, S. *J. Org. Chem.* **1990**, *55*, 4478—4480. (f) Amin, S.; Camanzo, J.; Huie, K.; Hecht, S. S. *J. Org. Chem.* **1984**, *49*, 381—384. (g) Amin, S.; Hecht, S. S.; Hoffman, D. *J. Org. Chem.* **1981**, *46*, 2394—2398. (h) Browne, C. E.; Dobbs, T. K.; Hecht, S. S.; Eisenbraun, E. J. *J. Org. Chem.* **1978**, *43*, 1656—1660. (i) Nagel, D. L.; Kupper, R.; Antonson, K.; Wallcave, L. *J. Org. Chem.* **1977**, *42*, 3626—3628.
(33) Lakshman, M. K.; Kole, P. L.; Chaturvedi, S.; Saugier, J. H.; Yeh, H. J. C.; Glusker, J. P.; Carrell, H. L.; Katz, A. K.; Afshar, C. E.; Dashwood, W.-M.; Kenniston, G.; Baird, W. M. *J. Am. Chem. Soc.* **2000**, *122*, 12629—12636.
(34) Bae, S.; Mah, H.; Chaturvedi, S.; Jeknic, T. M.; Baird, W. M.; Katz, A. K.; Carrell, H. L.; Glusker, J. P.; Okazaki, T.; Laali, K. K.; Zajc, B.; Lakshman, M. K. *J. Org. Chem.* **2007**, *72*, 7625—7633.
(35) Platt, K. L.; Oesch, F. *J. Org. Chem.* **1983**, *48*, 265—268.
(36) For examples, see: (a) Ray, J. K.; Gupta, S.; Kar, G. K.; Roy, B. C.; Lin, J.-M.; Amin, S. *J. Org. Chem.* **2000**, *65*, 8134—8138. (b) Kumar, S.; Kim, T.-Y. *J. Org. Chem.* **2000**, *65*, 3883—3884. (c) Zhang, F.-J.; Harvey, R. G. *J. Org. Chem.* **1998**, *63*, 2771—2773. (d) Kiselyov, A. S.; Lee, H.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 6123—6128. (e) Kumar, S.; Kole, P. L.; Sehgal, R. K. *J. Org. Chem.* **1989**, *54*, 5272—5277. (f) Harvey, R. G.; Cortez, C.; Sugiyama, T.; Ito, Y.; Sawyer, T. W.; DiGiovanni, J. *J. Med. Chem.* **1988**, *31*, 154—159.
(37) (a) Dubost, E.; Fossey, C.; Cailly, T.; Rault, S.; Fabis, F. *J. Org. Chem.* **2011**, *76*, 6414—6420. (b) Bernardo, P. H.; Wan, K.-F.; Sivaraman, T.; Xu, J.; Moore, F. K.; Hung, A. W.; Mok, H. Y. K.; Yu, V. C.; Chai, C. L. L. *J. Med. Chem.* **2008**, *51*, 6699—6710.
(38) Qandil, A. M.; Ghosh, D.; Nichols, D. E. *J. Org. Chem.* **1999**, *64*, 1407—1409.
(39) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647—2650.
(40) Giroux, A.; Han, Y.; Prasit, P. *Tetrahedron Lett.* **1997**, *38*, 3841—3844.
(41) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508—7510.
(42) Kumar, S. *J. Org. Chem.* **1997**, *62*, 8535—8539.
(43) Roth, G. J.; Liepold, B.; Müller, S. G.; Bestmann, H. J. *Synthesis* **2004**, 59—62.
(44) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *13*, 3769—3772.
(45) Yagi, H.; Thakker, D. R.; Hernandez, O.; Koreeda, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1977**, *99*, 1604—1611.
(46) Croisy-Delcey, M.; Ittah, Y.; Jerina, D. M. *Tetrahedron Lett.* **1979**, *20*, 2849—2852.
(47) Sayer, J. M.; Yagi, H.; Croisy-Delcey, M.; Jerina, D. M. *J. Am. Chem. Soc.* **1981**, *103*, 4970—4972.
(48) Levin, W.; Chang, R. L.; Wood, A. W.; Thakker, D. R.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1986**, *46*, 2257—2261.
(49) Chang, H.-F.; Cho, B. *J. Org. Chem.* **1999**, *64*, 9051—9056.
(50) Law, L. W.; Lewisohn, M. *Cancer Res.* **1941**, *1*, 695—698.
(51) (a) Raveh, D.; Slaga, T. J.; Huberman, E. *Carcinogenesis* **1982**, *3*, 763—766. (b) Wood, A. W.; Levin, W.; Chang, R. L.; Huang, M.-T.; Ryan, D. E.; Thomas, P. E.; Lehr, R. E.; Kumar, S.; Koreeda, M.; Akagi, H.; Ittah, Y.; Dansette, P.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 642—649. (c) Eisenstadt, E.; Gold, A. *Proc. Natl. Acad. Sci. U. S. A.* **1978**, *75*, 1667—1669. (d) Neal, J.; Trieff, N. M. *Health Lab. Sci.* **1972**, *9*, 32—38.
(52) Plater, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2897—2901.

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