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

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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 (BcPh) analogues was accomplished smoothly with catalytic PtCl₂ 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 BBr₃ and oxidized to the *ortho*-quinones with PDC. Reduction of these quinones with NaBH₄ in THF/EtOH in an oxygen atmosphere gave the respective dihydrodiols. Exposure of the dihydrodiols to *N*-bromoacetamide in THF–H₂O 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 BcPh 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.

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Notes

The authors declare no competing financial interest.

SUPPORTING INFORMATION

¹H and ¹³C 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.jo.5b00931.

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 I₂ 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 oxide⁹ or THF¹⁰ 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 ICl¹⁴ and IBF₄,¹⁵ Pd-catalyzed annulation,¹⁶ intramolecular olefin metathesis,¹⁷ Friedel-Crafts type reactions of geminal difluoroalkenes in FSO₃H•SbF₅ (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 AuCl₃-catalyzed rearrangement of homopropargylic alcohols,²¹ Ru-catalyzed benzannulation processes,²² and Pd-mediated C–H bond-activation and arylation.²³ PtCl₂, AuCl₃, GaCl₃, InCl₃, as well as designed Pt and Au catalysts have been evaluated for the 6-endo-dig cyclization of *o*-ethynylbiaryl systems.^{24–26} The combination of PtCl₂/PtCl₄ 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 a 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 (BcPhs) 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 the *ortho*-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 PtCl₂- and AuCl₃-mediated cycloisomerization of *ortho*-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 BcPh 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 BcPh 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 compound³⁷) can be readily prepared on the 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 CH₂Cl₂,³⁹ then gave required aldehyde **3**.

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 halides⁴¹ 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 PdCl₂(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 $\text{Pd}(\text{PPh}_3)_4$ and CsF in DME at reflux. The product structures and yields are summarized in Table 1.

In earlier work,⁴² similar biaryl aldehydes were elaborated to either oxiranes (reaction with $\text{Me}_2\text{S}=\text{CH}_2$) or methoxyethenes (reaction with $\text{MeOCH}=\text{PPh}_3$), which upon exposure to suitable Brønsted 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*-TsN₃ (1.2 molar equiv), and K_2CO_3 (3 molar equiv), under literature conditions⁴³ 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 alkynylation⁴⁴ 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 BcPh **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 BcPh, 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 BcPh 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*]phenanthrene (5-MBcPh), 4,5-dihydrobenzo[*l*]acephenanthrylene ($\text{H}_2\text{B}[l]\text{A}$), 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 the *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 BcPh 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** 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 ¹H 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 BcPh ($J = 10.8$ Hz in CD_3OD)⁴⁶ and the 1,4-difluoro derivative (DFBcPh, $J = 11.0$ Hz in acetone-*d*₆).³⁴ Unlike the dihydrodiol of 1,4-

dimethylbenzo[*c*]phenanthrene (DMBcPh),³³ compounds **24** and **25** did not demonstrate *P* and *M* hydrocarbon helicity, and these were similar to dihydrodiols of BcPh and DFBcPh.

Exposure of dihydrodiols **24** and **25** to *N*-bromoacetamide (NBA) in THF-H₂O 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 between the resonance at δ4.82 ppm and the upfield resonance of the ABq at δ7.96 ppm led to the unequivocal assignment of the former resonance as H-4. The doublet at δ4.36 ppm was assigned to H-1 on the basis of its NOESY cross peak with the doublet at δ9.19 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 (δ3.95 ppm) and H-4 (δ4.82 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 (δ4.83 ppm) and H-11 (δ3.90 ppm) and a weak interaction between H-9 and H-12 (δ4.45 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 quasidaxial 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 BcPh, *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 BcPh 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 BcPh scaffold (Figure 2).

We have not previously synthesized the series 1 diol epoxide from DMBcPh 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 DFBcPh.³⁴ In comparison to the series 1 diol epoxide of BcPh, the corresponding diol epoxide from DFBcPh 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 BcPh series 1 diol epoxide in acetone-*d*₆ is comparable to that in DMSO-*d*₆³⁴). This difference between the two hydrocarbons is likely due to the extreme out-of-plane distortion of DFBcPh.³⁴ The series 1 diol epoxide of benzo[*ghi*]fluoranthene (B[*ghi*]F), a compound that is expected to be more planar than both

BcPh and DFBcPh, surprisingly, also shows a much smaller coupling constant between its carbinol protons ($J = 2.1$ Hz),⁴⁹ identical to that observed with DFBcPh. By contrast, the hydroxyl group conformation in the series 1 diol epoxides of both 5-MBcPh [(±)-**26**] and H₂B[l]A [(±)-**27**] are comparable to that in BcPh.

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 DFBcPh and DMBcPh diol epoxides have comparable conformations (diastereomeric *P* and *M* helical dihydrodiols from DMBcPh have very similar carbinol coupling constants³³). From this evaluation it appears that, among the BcPh 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 H₂B[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 BcPh 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 H₂B[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-MBcPh (**20**), H₂B[l]AP (**21**), B[l]AP (**30**), as well as the two dimethoxy compounds **18** and **19**. From these structures, the molecular distortion in BcPh 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 BcPh, 1,4-DFBcPh, 1,4-DMBcPh, 5-MBcPh, H₂B[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-DMBcPh > 1,4-DFBcPh > BcPh > 5-MBcPh > H₂B[l]AP > B[l]AP. What is perhaps surprising is that a remote substitution, namely a methyl group at the C-5 position of BcPh, actually produces a decrease in overall nonplanarity of the BcPh structure by ~3°. The ethylene bridge in H₂B[l]AP causes a further flattening of the molecule, and finally, B[l]AP is only distorted by ~2°. The A–B plane angles in BcPh, 1,4-DFBcPh, and 1,4-DMBcPh 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 BcPh **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 the corresponding H₂B[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 the 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-MBcPh and H₂B[I]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 BcPh 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 μ m glass-backed silica gel plates or 200 μ m 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. CH₂Cl₂ and DME were distilled over CaH₂. Hexanes and EtOAc were distilled over anhydrous CaSO₄. Air and/or moisture-sensitive liquids and solutions were transferred via syringe under inert gas. ¹H NMR spectra were recorded at 500 MHz in the solvents indicated and are referenced to residual protonated solvent resonances. ¹³C 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 under reduced pressure and the residue was dissolved in Et₂O. 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 Na₂SO₄, 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* (SiO₂/20% EtOAc in hexanes): 0.21; mp 75–76 °C (lit.³⁸ mp 76 °C). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 CH₂Cl₂ (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 CH₂Cl₂. 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% CH₂Cl₂ in hexanes and 50% CH₂Cl₂ in hexanes. Compound **3** was obtained as a whitish-yellow solid (1.43 g, 72% yield). *R_f* (SiO₂/20% EtOAc in hexanes): 0.32; mp 82–83 °C (lit.^{37a} mp 83–85 °C). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 PdCl₂(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* (SiO₂/20% 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 Na₂CO₃ (0.51 mL, 12.2 mmol), and PdCl₂(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 Et₂O and washed twice with water followed by brine. The organic layer was dried over anhydrous Na₂SO₄ 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% CH₂Cl₂ in hexanes and 20% EtOAc in hexanes. Compound **6**

was obtained as a whitish-yellow solid (141 mg, 79% yield). R_f (SiO₂/20% EtOAc in hexanes): 0.29; mp 119–121 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₁₉H₁₇O₃ [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-naphthalenboronic acid (**7**) (1.67 g, 8.98 mmol), CsF (3.47 g, 22.8 mmol), and Pd(PPh₃)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 twice with EtOAc. The combined organic layer was dried over anhydrous Na₂SO₄ 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 CH₂Cl₂. Compound **10** was obtained as a yellow-light brown solid (2.08 g, 83% yield). R_f (SiO₂/CH₂Cl₂): 0.44; mp 146–148 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₀H₁₈O₃Na [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(PPh₃)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% CH₂Cl₂ in hexanes and CH₂Cl₂ afforded compound **11** as a light brownish solid (5.96 g, 92% yield). R_f (SiO₂/CH₂Cl₂): 0.32; mp 122–125 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₁H₁₈O₃Na [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(PPh₃)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% CH₂Cl₂ in hexanes afforded compound **12** as a yellow solid (1.34 g, 83% yield). *R_f* (SiO₂/10% EtOAc in hexanes): 0.62; mp 102–104 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₁₈H₁₅O [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(PPh₃)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% CH₂Cl₂ in hexanes afforded compound **13** as a yellow-orange solid (4.66 g, 74% yield). *R_f* (SiO₂/CH₂Cl₂): 0.51; mp 120–122 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₁₉H₁₅O [M + H]⁺, 259.1117; found, 259.1119.

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 PPh₃ (7.71 g, 29.4 mmol) in dry CH₂Cl₂ (8.0 mL). The mixture was cooled to 0 °C; CBr₄ (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 CH₂Cl₂ (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 CH₂Cl₂ and washed twice with brine, followed by twice with H₂O. The aqueous layer was extracted twice with CH₂Cl₂. The combined organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give an orange residue. Chromatographic purification on a silica gel column packed in CH₂Cl₂ eluted with CH₂Cl₂ afforded the vinyl dibromide as a foamy, yellow solid (2.63 g, 97% yield). *R_f* (SiO₂/20% EtOAc in hexanes): 0.56. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 three times with Et₂O. The combined organic layer was dried over anhydrous Na₂SO₄ 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* (SiO₂/20% EtOAc in hexanes): 0.38; mp 155–156 $^{\circ}\text{C}$. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₁H₁₈O₂Na [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 PPh₃ (824 mg, 3.14 mmol), CBr₄ (521 mg, 1.57 mmol), and aldehyde **11** (200 mg, 0.628 mmol) in dry CH₂Cl₂ (2.3 mL) at 0 $^{\circ}\text{C}$ over 2 h. Workup as described for compound **14** and chromatographic purification on a silica gel column packed in hexanes sequentially eluted with 50% CH₂Cl₂ in hexanes and CH₂Cl₂ afforded the vinyl dibromide as a foamy, yellow solid (284 mg, 96% yield). *R_f* (SiO₂/20% EtOAc in hexanes): 0.47. ¹H NMR (500 MHz, CDCl₃): δ 7.38–7.34 (m, 2H), 7.30–7.28 (m, 3H, superimposed with the CHCl₃ 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). ¹³C NMR (125 MHz, CDCl₃): 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* (SiO₂/20% EtOAc in hexanes): 0.42; mp 154–156 $^{\circ}\text{C}$. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₂H₁₈O₂Na [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 PPh₃ (6.39 g, 24.36 mmol), CBr₄ (4.04 g, 12.18 mmol), and aldehyde **12** (1.2 g, 4.87 mmol) in dry CH₂Cl₂ (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* (SiO₂/50% CH₂Cl₂ in hexanes): 0.76. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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* (SiO₂/20% EtOAc in hexanes): 0.61; mp 72–74 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₁₉H₁₄ [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 PPh₃ (12.69 g, 48.39 mmol), CBr₄ (8.02 g, 24.19 mmol), and aldehyde **13** (2.5 g, 9.68 mmol) in dry CH₂Cl₂ (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* (SiO₂/50% CH₂Cl₂ in hexanes): 0.68. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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* (SiO₂/10% EtOAc in hexanes): 0.53; mp 86–87 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₀H₁₅ [M + H]⁺, 255.1168; found, 255.1170.

3,4-Dimethoxy-8-methylbenzo[c]phenanthrene (18)

Using PtCl₂: In an oven-dried reaction vial equipped with a magnetic stirring bar was placed alkyne **14** (40 mg, 0.132 mmol) in dry PhMe (0.6 mL). PtCl₂ (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 CH₂Cl₂. Chromatographic purification on a silica gel column packed in hexanes eluted with 50% CH₂Cl₂ in hexanes afforded compound **18** as a yellow solid (29.8 mg, 75% yield).

Using AuCl₃: 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). AuCl₃ (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% CH₂Cl₂ in hexanes afforded compound **18** as a yellow solid (25.3 mg, 84% yield). *R_f* (SiO₂/50% CH₂Cl₂ in hexanes): 0.28; mp 143–144 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₁H₁₈O₂Na [M + Na]⁺, 325.1199; found, 325.1198.

9,10-Dimethoxy-4,5-dihydrobenzo[*l*]acephenanthrylene (19)

Using PtCl₂: As described for the synthesis of compound **18**, compound **19** was prepared by a reaction of alkyne **15** (30 mg, 0.095 mmol) and PtCl₂ (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% CH₂Cl₂ in hexanes afforded compound **19** as a yellow solid (21.7 mg, 72% yield).

Using AuCl₃: As described for the synthesis of compound **18**, compound **19** was prepared by a reaction of alkyne **15** (30 mg, 0.095 mmol) and AuCl₃ (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% CH₂Cl₂ in hexanes afforded compound **19** as a yellow solid (17.8 mg, 59% yield). *R_f* (SiO₂/20% EtOAc in hexanes): 0.32; mp 154–155 °C. ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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. ^1H 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 (lit⁵² mp 123–124). ^1H 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 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 CH₂Cl₂ and sequentially eluted with CH₂Cl₂ and 5% MeOH in CH₂Cl₂. Compound **22** was obtained as a reddish-orange solid (22.3 mg, 82% yield). *R_f* (SiO₂/5% MeOH in CH₂Cl₂): 0.82; mp 204–210 °C (dec. with charring). ¹H 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). ¹³C 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 C₁₉H₁₃O₂ [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 BBr₃ in pentane (0.3 mL, 0.3 mmol) in dry CH₂Cl₂ (1.5 mL). Workup gave a reddish-orange solid of the crude catechol. *R_f* (SiO₂/CH₂Cl₂): 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 CH₂Cl₂ (2.0 mL). Workup and chromatographic purification on a silica gel column packed in CH₂Cl₂ and eluted with CH₂Cl₂ afforded compound **23** as a dark red solid (22.5 mg, 79% yield). *R_f* (SiO₂/5% MeOH in CH₂Cl₂): 0.81; mp 159–162 °C (dec. with charring). ¹H 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). ¹³C 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 C₂₀H₁₃O₂ [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 O₂ for 15 min, and then NaBH₄ (187.3 mg, 5.0 mmol) was added portionwise. The yellow mixture was allowed to stir at room temperature while being sparged with O₂ for 4 h and was then allowed to stir under an O₂ balloon for 15 h, protected from light. The mixture was again cooled to 0 °C, sparged with O₂ for 15 min, and another aliquot of NaBH₄ (187.3 mg, 5.0 mmol) was added portionwise. The mixture was allowed to stir at room temperature while being sparged with O₂ for 5 h, at which time TLC showed the reaction to be complete. The mixture was concentrated to a third of its volume. Addition of ice and cold water resulted in a creamy yellow suspension. The mixture was transferred to a separatory funnel and EtOAc was added to dissolve the solids, and the mixture was washed three times with H₂O. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give a whitish-orange solid. This solid was suspended in cold Et₂O and sonicated to yield dihydrodiol (±)-**24** as a whitish solid, which was collected by filtration (104.5 mg, 76% yield). *R_f* (SiO₂/5% MeOH in CH₂Cl₂): 0.35. ¹H 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 $\text{C}_{19}\text{H}_{16}\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$, 299.1043; found, 299.1043.

($\pm$)-*Trans*-4,5,9,10-tetrahydrobenzo[*l*]acephenanthrylene-9,10-diol (($\pm$)-25)—As described for the synthesis of dihydrodiol ($\pm$)-**24**, dihydrodiol ($\pm$)-**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 ($\pm$)-**24** was suspended in cold Et₂O and sonicated to afford dihydrodiol ($\pm$)-**25** as an off-white solid, which was collected by filtration (144.5 mg, 79% yield). R_f (SiO₂/5% MeOH in CH₂Cl₂): 0.26. ^1H 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 $\text{C}_{20}\text{H}_{16}\text{O}_2\text{Na}$ $[\text{M} + \text{Na}]^+$, 311.1043; found, 311.1043.

($\pm$)-1 β ,2 β -Epoxy-3 α ,4 β -dihydroxy-8-methyl-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene (($\pm$)-26)

Step 1: synthesis of ($\pm$)-2 α -bromo-8-methyl-1 β ,3 α ,4 β -trihydroxyl-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene: In an oven-dried reaction vial equipped with a magnetic stirring bar was placed dihydrodiol ($\pm$)-**24** (20.0 mg, 72.38 μmol) in dry THF (3.0 mL) and H₂O (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 Et₂O, and washed sequentially with H₂O and brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et₂O containing a little hexanes afforded the bromo triol as a white solid (26.2 mg, 97% yield). R_f (SiO₂/5% MeOH in CH₂Cl₂): 0.20.

Step 2: cyclization to ($\pm$)-1 β ,2 β -epoxy-3 α ,4 β -dihydroxy-8-methyl-1,2,3,4-tetrahydrobenzo[*c*]phenanthrene, ($\pm$)-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 Amberlite was filtered off, and the filtrate obtained was evaporated under reduced pressure to give a white solid. Trituration with cold Et₂O afforded diol epoxide ($\pm$)-**26** as a white solid (7.7 mg, 64% yield). R_f (SiO₂/5% MeOH in CH₂Cl₂): 0.39. ^1H 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, D₂O exchangeable), 4.82 (d, *J* = 9.0 Hz, 1H), 4.66 (br, 1H, D₂O 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 D₂O: 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). ¹³C 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 C₁₉H₁₆O₃Na [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 H₂O (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 Et₂O, and washed sequentially with H₂O and brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give a reddish-white solid. Trituration with cold Et₂O containing a little hexanes afforded the bromo triol as a pale reddish-white solid (39.1 mg, 95% yield). *R*_f (SiO₂/5% MeOH in CH₂Cl₂): 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 Amberlite was filtered off, and the filtrate obtained was evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et₂O afforded diol epoxide (±)-**27** as a pale yellowish-white solid (18.7 mg, 60% yield). *R*_f (SiO₂/5% MeOH in CH₂Cl₂): 0.32. ¹H 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). ¹³C 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 C₂₀H₁₆O₃Na [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, H₂O, and brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et₂O afforded diol epoxide ($\pm$)-**28** as a pale yellowish-white solid (14.6 mg, 69% yield). *R_f* (SiO₂/5% MeOH in CH₂Cl₂): 0.37. ¹H 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, D₂O exchangeable), 4.87 (d, *J* = 8.5 Hz, 1H), 4.80 (d, *J* = 4.5 Hz, 1H), 4.64 (br, 1H, D₂O 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 D₂O: 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). ¹³C 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 C₁₉H₁₆O₃Na [M + Na]⁺, 315.0992; found, 315.0995.

($\pm$)-11 α ,12 α -Epoxy-4,5,9,10,11,12-hexahydrobenzo[*l*]acephenanthrylene-9 β ,10 α -diol ($\pm$)-29****—In an oven-dried 10 mL round-bottom flask equipped with a magnetic stirring bar was placed dihydrodiol ($\pm$)-**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, H₂O, and brine. The organic layer was dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give a yellowish-white solid. Trituration with cold Et₂O afforded diol epoxide ($\pm$)-**29** as a pale yellowish-white solid (25.5 mg, 80% yield). *R_f* (SiO₂/5% MeOH in CH₂Cl₂): 0.11. ¹H 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). ¹H 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). ¹³C 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 C₂₀H₁₆O₃Na [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 ¼ basic alumina and ¾ silica gel packed in hexanes and eluted with hexanes. Compound **30** was obtained as a yellow solid (18.1 mg, 72% yield). *R_f* (SiO₂/hexanes): 0.14; mp 109–111 °C

from hexanes (lit⁵² mp 101–104 °C). ¹H NMR (500 MHz, CDCl₃): 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). ¹³C NMR (125 MHz, CDCl₃): 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 C₂₀H₁₃ [M + H]⁺, 253.1012; found, 253.1012.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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

Figure 2.
Various diol epoxides having the BcPh structure and the coupling constants of their carbinol protons.

Figure 3.
Crystal structures of several of the synthesized BcPh derivatives.

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

Scheme 2.
Retrosynthetic Analysis of the Proposed Approach

Scheme 3.

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

Scheme 4.

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

Scheme 5.

Synthesis of the Various Polycyclic Aromatic Hydrocarbons

Scheme 6.

Synthesis of the Dihydrodiols and Diol Epoxides of 5-MBcPh and H₂B[l]A

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

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%

Table 2

Crystallographically Determined Plane Angles in BcPh 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°	--	--

compound	A-B	A-C	A-D	B-C	B-D	C-D	C-E	D-E
	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°	--	--

^aData for BcPh, DFBcPh, and DMBcPh were obtained from references 33 and 34.