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A general route for ^{13}C-labeled fluorenols and phenanthrenols via palladium-catalyzed cross-coupling and one-carbon homologation

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A series of ^{13}C-labeled polyaromatic hydrocarbons (PAHs), fluorenols and phenanthrenols were synthesized from commercially available ^{13}C-labeled starting material giving rise to M + 6 isotopomers. This was accomplished using key palladium-catalyzed cross-coupling and one-carbon homologation strategies. The conditions for these reactions were optimized, and the new chemical routes are efficient in the number of chemical steps, can be scaled to afford gram quantities and occur in good yields based on the ^{13}C label. These labeled compounds as precursors for more complex PAHs and are useful as internal standards in mass spectrometry and NMR spectroscopy studies for monitoring environmental contamination and biological exposure to PAHs and their metabolites.

Keywords: polyaromatic hydrocarbons; palladium-catalyzed cross-coupling; one-carbon homologation; mass spectral standards; uniformly ^{13}C-labeled benzene and Friedel–Crafts reactions

Introduction

Polyaromatic hydrocarbons (PAHs) make up a class of compounds implicated in carcinogenesis and found to be prevalent in the environment. The most potent carcinogenic members contain four to six benzo rings. These PAHs have structural features such as crowded bay or fjord regions which enhance biological activities (Figure 1).[1]

One of the most potent carcinogens known is derivatives of the benzo[*a*]pyrene family. Strong correlation with carcinogenic activity is found with oxidized versions of benzo[*a*]pyrene. Metabolism by oxidases is found to give rise to epoxides, which are more reactive than the parent benzo[*a*]pyrene. Interestingly, the enzymatic reactions proceed with high regioselectivities and stereoselectivities, and these highly reactive intermediates then proceed to attack cellular targets such as DNA. The covalent attachment of PAHs to DNA can lead to significant damage to the cell. Persistent lesions give rise to cellular signals, lead to apoptosis. In addition, during replication, transcription errors can provide a whole host of deleterious cellular events. As cytoxicity is usually accompanied by gross changes in the structure of the DNA helix, which serves to block the reading of the oligomer by RNA and DNA polymerases, mutagenic lesions can give rise to errors in the transcription process.

We have recently been interested in the study of the process of the intercalation of PAHs into oligomeric deoxynucleic acids (DNA), and the effect and extent of soft π•••H–X (X = C, N, O) and C–H•••O hydrogen bonding interactions have on the structure of the DNA. In addition, we believe many of these intermediates are useful in monitoring and quantitating the presence of PAHs in biological systems and the environment by mass spectral methods. This report details our synthetic efforts toward a comprehensive approach to stable isotope labeling of PAHs. Because deuterium labeling of PAHs is problematic in terms of stability (dilution of the label), ^{13}C labeling is required in many cases. Our concept then begins with a reasonable source of ^{13}C label starting with U-^{13}C benzene. While making mass spectral standards and the studies of PAHs and DNA interactions, we needed to synthesize M + 4 labeled fluorenols and phenanthrenols. There are few existing methods[1] for ^{13}C labeling, however for our site-specific labeling, these are not feasible in terms of both time and cost. Here, we report a new general route to ^{13}C-labeled fluorenols and phenanthrenols by using a key palladium-catalyzed cross-coupling step followed by a one-carbon homologation (Figure 2).[2]

The synthetic route to 9-fluorenol **3** is shown in Scheme 1.

2-Iodobenzoyl chloride smoothly underwent Friedel–Crafts

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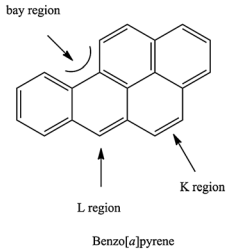


Figure 1. Carcinogenic hot spots in the molecular architecture of benzopyrenes and derivatives.

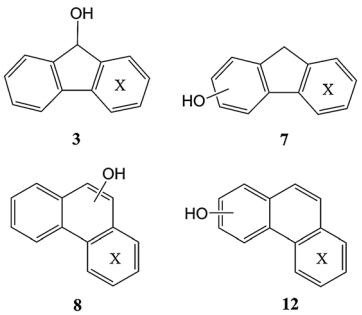


Figure 2. Synthesized ^{13}C labeling polyaromatic hydrocarbons.

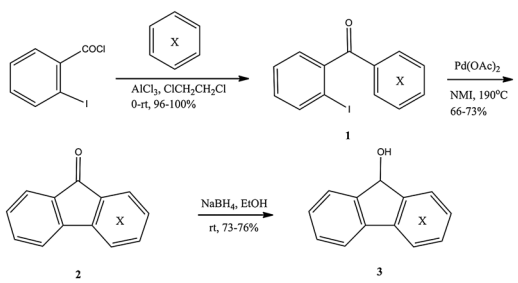
acylation with uniformly ^{13}C-labeled benzene as illustrated in Scheme 1. The cyclization of the resulting benzophenone **1** was achieved by palladium (II) acetate catalyzed cross-coupling to afford 9-fluorenone **2** in good overall yield.[3] 9-Fluorenol **3** was obtained by reduction of 9-fluorenone **2** with sodium borohydride.[4]

3-, 4-, 5-, and 6-Methoxy-2-bromofluorenone **4a**, **4b**, **4c**, **4d** were synthesized from the corresponding methoxy substituted 2-bromobenzoyl chloride. The general synthetic route for the first step is illustrated in Scheme 2.

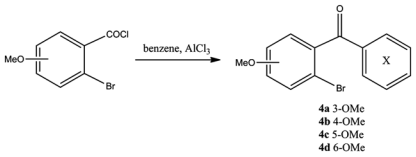
The Friedel–Crafts reaction between 4-methoxy-2-bromobenzoyl chloride and benzene in chlorinated solvents gave rise to the desired product 4-methoxybenzophenone **4b** albeit in diminished yields (13–35%). Simply by changing the solvent to nitromethane gave rise to significantly improved yields (72%).

Cross-coupling of the substituted bromobenzophenone using palladium acetate as a catalyst afforded the corresponding annulated fluorenones **5**, as illustrated in Scheme 3 in 57–92% yields.

As shown in Scheme 4, the cyclization of 2-bromo-3-methoxybenzophenone using palladium acetate and sodium carbonate in N,N-dimethylacetamide gave rise to a mixture of



Scheme 1. Synthesis of $^{13}C_6$ 9-fluorenol **3**.



Scheme 2. Synthesis of $^{13}C_6$ 3-, 4-, 5- and 6-methox-2-bromobenzophenones.

4-methoxyfluorenone **5a** and dehydrohalogenation product 3-methoxybenzophenone in a 2:3 ratio and in low combined yield (30–40%). Improvement in the selectivity of the reaction was observed by the addition of triphenylphosphine to the catalyst affording **5a** at higher yield of 76% accompanied with less than 6% of dehydrohalogenation product.

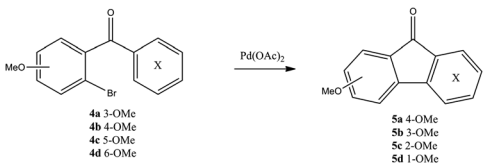
However, for the cyclization of 2-bromo-6-methoxybenzophenone, use of triphenylphosphine as a ligand gave rise to a 1:1 mixture of 1-methoxyfluorenone **5a** and the dehydrohalogenation product 2-methoxybenzophenone. By substituting the phosphorus-based ligand with tricyclohexyl-phosphine tetrafluoroborate[5] the product to by-product ratio increased to 3:1.

The methoxyl substituted 9-fluorenones **5** were reduced to fluorenes **6** by palladium on carbon with hydrogen under pressure and heat at about 60 °C.[6] Demethylation of the methoxy groups using boron tribromide provided the desired fluorenols **7** (Scheme 5).

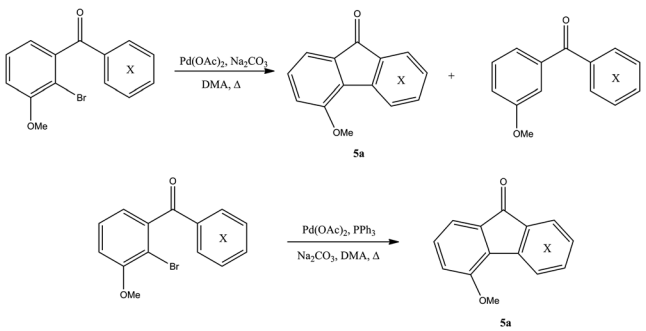
The synthesis of 9-phenanthrenol **8** started with 9-fluorenone **2** that was constructed according to Scheme 1 using a ring expansion homologation reaction. 9-Fluorenone **2** reacted with trimethylsilyldiazomethane in the presence of boron trifluoride to form the 9-phenanthrenol **8** in one step (Scheme 6).[7]

Likewise, the synthesis of 1-, 2-, 3- and 4-methoxyphenanthrenes **11** started from the corresponding 1-, 2-, 3- and 4-methoxyfluorenones **5** as shown in Scheme 7.

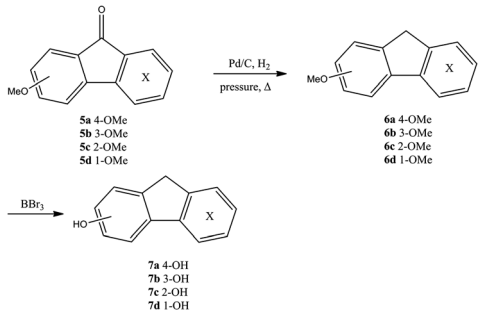
Following the one-carbon homologation, the methoxy substituted 9-phenanthrenols **9** were converted to the corresponding aryl triflates **10**. Reaction of the aryl triflates with palladium acetate, triphenyphosphine, triethylamine and formic acid in DMF gave rise to methoxy substituted phenanthrenes



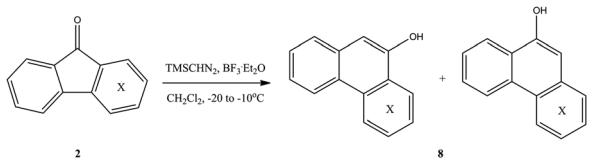
Scheme 3. Synthesis of $^{13}C_6$ fluorenones **5**.



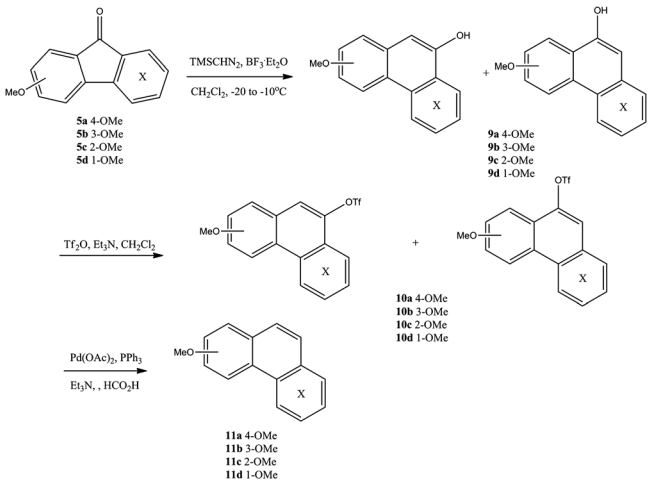
Scheme 4. Synthesis of $^{13}C_6$ 4-methoxyfluorenone **5d**.



Scheme 5. Synthesis of $^{13}C_6$ fluorenol **7**.



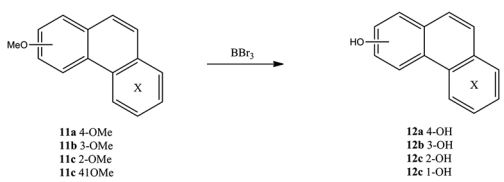
Scheme 6. Synthesis of $^{13}C_6$ 9-phenanthrenol **8**.



Scheme 7. Synthesis of $^{13}C_6$ 1-, 2-, 3- and 4-methoxyphenanthrenes **11**.

11 in good to excellent yields.[8] 1-, 2-, 3- and 4-Phenanthrenols **12** were obtained by conventional demethylation with boron tribromide (Scheme 8).

In conclusion, we report an efficient and reliable route to the synthesis of M + 6 isotope-labeled fluorenols and phenanthrenols by using uniformly ^{13}C-labeled benzene as the only carbon **13** source. The procedure provides a quick access to these compounds. These new stable isotope-labeled PAHs and intermediates are ideally suited for further elaboration to more complex and biologically and environmentally important PAHs. Current efforts in our laboratories are underway for construction of these PAHs. In addition, these compounds will be useful for the detection, quantitation and environmental monitoring of exposures to PAH agents.



Scheme 8. Synthesis of $^{13}C_6$ 1-, 2-, 3- and 4-phenanthrenols **12**.

Experimental

General

All reactions were carried out under argon. All solvents or reagents were used as received. Uniformly ^{13}C-labeled benzene was purchased either from Cambridge Isotope Laboratories, Inc. (Andover, MA, USA) or Isotec, Inc. (Miamisburg, OH, USA). Flash column chromatography was carried out using Merck Kieselge 60 (Darmstadt, Germany) (230–400 mesh) silica gel. Proton and carbon NMR spectra were recorded on Bruker Avance 300 spectrometer (Billerica, MA, USA) using an internal deuterium lock. Chemical shifts are quoted in parts per million downfield from tetramethylsilane. Carbon NMR spectra were recorded with broad proton decoupling. Mass spectra were recorded on a ThermoFinnigan PolarisQ TraceGC instrument (San Jose, CA, USA), and elemental analyses were recorded on a ThermoFinnigan Flash 1112 Series EA CHNSO Analyzer.

2-Iodobenzoyl chloride and 2-bromo-5-methoxybenzoyl chloride were purchased from Aldrich Chemical Company (St. Louis, MO, USA) and Lancaster Synthesis Inc. (Windham, NH, USA), respectively. 2-Bromo-3-methoxybenzoyl chloride, 2-bromo-4-methoxybenzoyl chloride and 2-bromo-6-methoxybenzoyl chloride were made from their corresponding acids by treatment with thionyl chloride.

General procedure for the preparation of benzophenones 1 and 4

In a 100-mL round bottom flask, was charged with 2-iodo or 2-bromomethoxy-substituted benzoyl chloride (10.0 mmol), 1,2-dichloroethane (10.0 mL), and $^{13}C_6$ benzene (0.841 g, 10.0 mmol). The reaction mixture was cooled in an ice bath, and aluminum chloride (1.467 g, 11.0 mmol) was added in one portion. The mixture was stirred at 0 °C for 5 min and allowed to warm to room temperature, and stirring was continued for 1–2 h or until thin layer chromatography (TLC) analysis showed a complete reaction. Water was slowly added to the reaction mixture while cooled with an ice bath. The mixture was extracted with dichloromethane, washed with brine and dried over sodium sulfate, filtered and concentrated. The residue was purified by flash chromatography with 3–10% ethyl acetate in hexanes to provide the desired product.

2-Iodobenzophenone 1 (96%)

^{1}H NMR ($CDCl_3$) δ 8.25–8.05 (m, 1H), 8.00–7.95 (dd, J = 8.07, 1.01 Hz, 1H), 7.95–7.82 and 7.42–7.30 (m, 1H), 7.82–7.70 (m, 1H), 7.75–7.52 (m, 1H), 7.50–7.45 (td, J = 7.50, 1.04 Hz, 1H), 7.37–7.30 (dd, J = 7.65, 1.73 Hz, 1H), 7.30–7.20 (m, 1H), 7.25–7.20 (td, J = 7.74, 1.70 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 197.20 (d, J = 51.77 Hz), 144.33 (d, J = 12.72 Hz), 139.68 (s), 135.8 (td, J = 55.57, 8.43 Hz), 133.80 (td, J = 52.61, 8.52 Hz), 130.50 (td, J = 58.98, 4.54 Hz), 128.50 (td, J = 52.55, 7.79 Hz), 92.19 (s). HRMS calculated 313.9899, found 313.9894.

(2-Bromo-3-methoxyphenyl)(phenyl)-methanone 4a (91%)

^{1}H NMR ($CDCl_3$) δ 8.25–8.05 (m, 1H), 7.96–7.85 and 7.32–7.45 (m, 1H), 7.85–7.70 (m, 1H), 7.65–7.53 (m, 1H), 7.38 (dd, J = 8.28, 7.56 Hz, 1H), 7.34–7.20 (m, 1H), 7.24 (dd, J = 8.28, 1.37 Hz, 1H), 6.98 (dd, J = 7.56, 1.35 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 156.00 (d, J = 15.57 Hz), 135.55 (m), 133.30 (m), 129.85 (m), 128.10 (m), 120.39, 112.62, 108.89, 56.45. HRMS calculated 296.0144, found 296.0141.

(2-Bromo-4-methoxyphenyl)(phenyl)methanone 4b (72%)

^{1}H NMR ($CDCl_3$) δ 8.18–8.05 (m, 1H), 7.95–7.85 and 7.32–7.45 (m, 1H), 7.80–7.70 (m, 1H), 7.65–7.50 (m, 1H), 7.39 (d, J = 8.52 Hz, 1H), 7.30–7.20 (m, 1H), 7.25 (d, J = 2.52 Hz, 1H), 6.97 (dd, J = 8.52, 2.52 Hz, 1H), 3.95 (s,

3H). ^{13}C NMR ($CDCl_3$) δ 136.51 (m), 132.98 (m), 129.82 (m), 127.91 (m), 118.29, 112.62, 55.31. HRMS calculated 296.0144, found 296.0146.

(2-Bromo-5-methoxyphenyl)(phenyl)methanone 4c (94%)

^{1}H NMR ($CDCl_3$) δ 8.22–8.05 (m, 1H), 7.90–7.80 and 7.40–7.28 (m, 1H), 7.80–7.65 (m, 1H), 7.65–7.50 (m, 1H), 7.51 (dd, *J* = 8.22, 0.88 Hz, 1H), 7.28–7.15 (m, 1H), 6.95–6.85 (m, 2H), 3.80 (s, 3H). ^{13}C NMR ($CDCl_3$) 195.38 (pd, *J* = 55.66, 3.97 Hz), 158.52 (s), 141.14 (d, *J* = 12.85 Hz), 135.58 (m), 133.71 (m), 130.03 (m), 128.39 (m), 117.09 (s), 114.02 (s), 109.36 (s), 55.44 (s). HRMS calculated 296.0144, found 296.0142.

(2-Bromo-6-methoxyphenyl)(phenyl)methanone 4d (78%)

^{1}H NMR ($CDCl_3$) δ 8.30–8.00 (m, 1H), 8.00–7.85 and 7.35–7.20 (m, 1H), 7.85–7.70 (m, 1H), 7.70–7.50 (m, 1H), 7.50–7.20 (m, 3H), 7.00 (dd, *J* = 8.00, 1.15 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 157.61, 136.10 (m), 133.80 (m), 129.63 (m), 128.54 (m), 124.77, 109.91, 56.03. HRMS calculated 296.0144, found 296.0149.

General procedure for the preparation of fluorenones 2 and 5

For 2-iodobenzophenone, a mixture of 2-iodobenzophenone **1** (3.023, 9.600 mmol) and palladium acetate (0.211 g, 0.940 mmol) in N-methylimidazole (9.6 mL) was heated to reflux overnight. For 2-bromobenzophenone, a mixture of methoxy 2-bromobenzophenone (3.340 g, 11.26 mmol), palladium acetate (0.3800 g, 1.689 mmol) and sodium carbonate (2.148 g, 20.27 mmol) in N,N-dimethylacetamide (20 mL) was heated to reflux overnight. The mixture was cooled to room temperature, and water was added. The mixture was extracted with ethyl acetate, and the organic extracts were washed with 2 M HCl, dried over sodium sulfate and concentrated. The residue was purified on silica gel with 2% EtOAc/hexanes to provide the desired compound.

9-Fluorenone 2 (73%)

^{1}H NMR ($CDCl_3$) δ 8.00–7.90 and 7.46–7.36 (m, 1H), 7.87–7.73 (m, 1H), 7.70 and 7.28 (br d, *J* = Hz, 1H), 7.66–7.48 (m, 3H), 7.35–7.28 (m, 1H), 7.30–7.18 and 7.14–6.98 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 144.38 (m), 134.76 (m), 129.09 (m), 124.21 (m), 120.23 (m). HRMS calculated 186.0776, found 186.0773.

4-Methoxy-9-fluorenone 5a (76%)

^{1}H NMR ($CDCl_3$) δ 8.20–8.05 and 7.80–7.65 (m, 1H), 8.00–7.85 and 7.05–6.90 (m, 1H), 7.65–7.45 (m 1H), 7.45–7.15 (m 3H), 7.15–7.05 (m, 1H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 144.06 (m), 134.94 (m), 133.73 (m), 128.21 (m), 124.91 (m), 123.71 (m), 117.99, 116.74, 55.83. HRMS calculated 216.0882, found 216.0882.

3-Methoxy-9-fluorenone 5b (57%)

^{1}H NMR ($CDCl_3$) δ 7.99–7.83 and 7.45–7.33 (m, 1H), 7.83–7.70 (m, 1H), 7.69–7.50 and 7.13–6.95 (m, 1H), 7.65 (d, *J* = 8.23 Hz, 1H), 7.29–7.13 (m, 1H), 7.10–7.00 (m, 1H), 6.77 (dd, *J* = 8.22, 2.09 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 165.53 (d, *J* = 4.93 Hz), 143.48 (m), 135.45 (m), 134.350 (m), 129.40 (dtm), 123.96 (m), 120.22 (m), 113.68, 113.09, 107.23, 55.93.

2-Methoxy-9-fluorenone 5c (92%)

^{1}H NMR ($CDCl_3$) δ 7.94–7.80 and 7.56–7.44 (m, 1H), 7.78–7.63 (m, 1H), 7.41 (dd, *J* = 8.19, 3.15 Hz, 1H), 7.41–7.30 and 7.03–6.89 (m, 1H), 7.21 (d, *J* = 2.46 Hz, 1H), 7.00 (dd, *J* = 8.16, 2.52 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 193.82 (br d, *J* = 54.10 Hz), 160.76, 158.68, 144.81 (m), 134.48 (m), 127.76 (m), 124.17 (m), 119.47 (m), 109.29, 5.67. HRMS calculated 216.0882, found 216.0886.

1-Methoxy-9-fluorenone 5d (58%)

^{1}H NMR ($CDCl_3$) δ 8.25–8.02 and 7.35–7.15 (m, 1H), 7.90–7.67 (m, 1H), 7.67–7.46 (m, 1H), 7.56–7.47 (m 1H), 7.47–7.35 (m, 1H), 7.12–7.05 (m, 1H), 6.92 (dd, *J* = 68.6, 8.5 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 157.61, 134.65 (m), 132.97 (m), 129.77 (m), 128.10 (m), 124.01, 120.98, 55.61.

9-Fluorenol 3 (76%)

To a solution of 9-fluorenone **2** (1.391 g, 7.470 mmol) in methanol (35 mL) was added sodium borohydride (0.311 g, 8.22 mmol) in one portion at 0 °C. The mixture was allowed to warm to room temperature and stirred for 0.5 h until TLC analysis showed a complete reaction. The solvent was removed by rotary evaporation, and the residue was partitioned between water and ethyl acetate. The organic extracts were dried over sodium sulfate and concentrated. The residue was purified on silica gel with 5% EtOAC/hexanes to provide 1.068 g (76%) of the title product as a white solid. ^{1}H NMR ($CDCl_3$) δ 8.05–7.65 (m, 1H), 7.65–7.55 (m, 2H), 7.55–7.25 (m, 3H), 7.25–6.90 (m, 1H), 5.60 (s, 1H), 1.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 145.66 (m), 139.95 (m), 129.14 (m), 127.72 (m), 125.00 (m), 119.90 (m), 75.0 (bd, *J* = 46.45 Hz). HRMS calculated 188.0933, found 188.0927. Anal. Calcd for $^{13}C_6^{12}C_7H_{10}O$: C, 86.14; H, 5.36. Found: C, 86.24; H, 5.38.

General procedure for the preparation of methoxyfluorene 6

In a 100 mL Parr hydrogenation reaction, bottle was charged with fluorenone **5** (0.497 g, 2.30 mmol) and absolute ethanol (25 mL). One drop of concentrated sulfuric acid was added followed by addition of 10% Pd/C (0.113 g). The mixture was heated with a heating tape and hydrogenated at 55 psi at 65 °C (wall temperature) for 2.5 h and at room temperature for 1 h. TLC showed a complete reaction. The mixture was filtered to remove the catalyst, and the filtrate was concentrated. The residue was partitioned between ethyl acetate and water, washed with 5% sodium bicarbonate and brine. The organic layers were combined and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 1–2% ethyl acetate/hexanes to provide the title product.

4-Methoxyfluorene 6a (88%)

^{1}H NMR ($CDCl_3$) δ 8.54–8.40 and 7.87–7.76 (m, 1H), 8.0–7.87 (m, 1H), 7.74–7.48 (m, 1H), 7.40–7.23 (m, 1H), 7.20 (d, *J* = 7.51 Hz, 1H), 7.16–7.00 (m, 1H), 6.93 (d, *J* = 8.16 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 141.48 (m), 134.11 (m), 126.26 (m), 124.22 (m), 117.32, 110.51, 108.63, 55.32, 29.70. HRMS calculated 202.1089, found 202.1091.

3-Methoxyfluorene 6b (93%)

^{1}H NMR ($CDCl_3$) δ 8.10–7.77 (m, 1H), 7.77–7.50 (m, 1H), 7.47 (d, *J* = 8.28 Hz, 1H), 7.35 (t, *J* = 2.66Hz, 1H), 7.18–7.02 (m, 1H), 6.91 (dd, *J* = 8.28, 2.49 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 144.48 (m), 141.71 (m), 127.19 (m), 126.50 (m), 125.02 (m), 119.89 (m), 113.98, 113.36, 111.05, 104.98, 55.71, 42.32 (td, *J* = 296.48, 32.73 Hz).

2-Methoxyfluorene 6c (89%)

^{1}H NMR ($CDCl_3$) 8.05–7.76 (m, 1H), 7.72 (dd, *J* = 8.36, 2.27 Hz, 1 H) and 7.70–7.38 (m, 1H), 7.38–7.17 (m, 1H), 7.17–7.02 and 6.94–6.75 (m, 1H), 6.98 (dd, *J* = 8.36, 2.27 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.00, 142.71 (m), 141.47 (m), 128.32 (m), 126.82 (m), 125.30 (m), 119.03 (m), 115.00, 113.00, 111.40, 110.60, 56.49, 41.5 (td, *J* = 230.05, 32.56 Hz). HRMS calculated 202.1089, found 202.1088.

1-Methoxyfluorene 6d (80%)

^{1}H NMR ($CDCl_3$) δ 8.11–7.98 and 7.89–7.78 (m, 1H), 7.70–7.27 (m, 4 H) and 7.21–6.93 (m, 1H), 6.84 (dd, *J* = 7.89, 0.82 Hz, 1H), 3.93 (s, 3H), 3.83 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 142.6 (m), 126.7 (m), 125.0 (m), 120.1 (m), 112.7, 108.5, 55.3, 34.2 (d, *J* = 44.9 Hz). HRMS calculated 216.0882, found 216.0882.

General procedure for the preparation of fluorenol 7

To a solution of 3-methoxyfluorene **6c** (0.433 g, 2.14 mmol) in dichloromethane (10.0 mL) was added dropwise 1.0-M boron tribromide in dichloromethane (2.36 mL, 2.36 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1 h or until the

TLC showed a complete reaction. Methanol was added to decompose excess boron tribromide while cooled at 0 °C. The solvent was removed under reduced pressure, and the residue was adsorbed on silica gel and purified by flash chromatography with 10% ethyl acetate in hexanes to provide the title product **7c** (0.334 g, 83%).

4-Fluorenol 7a (80%)

^{1}H NMR ($CDCl_3$) δ 8.47–8.35 and 7.50–7.40 (m, 1H), 7.95–7.76 (m, 1H), 7.76–7.50 (m, 1H), 7.40–6.90 (m, 3H), 6.90–6.77 (m, 1H), 4.00 (br, s, 2H). ^{13}C NMR ($CDCl_3$) δ 141.54 (m), 135.01 (m), 128.38 (m), 126.38 (m), 124.28 (m), 117.61, 113.66, 37.24 (br d, J = 43.47 Hz). Anal. Calcd for $^{13}C_6^{12}C_7H_{10}O$: C, 86.14; H, 5.36. Found: C, 85.71; H, 5.60.

3-Fluorenol 7b (83%)

^{1}H NMR ($CDCl_3$) δ 8.08–7.78 (m, 1H), 7.78–7.54 (m, 1H), 7.54–7.46 and 7.38–7.25 (m, 1H), 7.25–6.90 (m, 1H), 7.44 (d, J = 8.08 Hz, 1H), 7.30 (t, J = 3.03 Hz, 1 H), 6.84 (dd, J = 8.08, 2.37 Hz, 1H). ^{13}C NMR ($CDCl_3$) 144.36 (m), 141.25 (m), 126.46 (m), 124.87 (m), 119.80 (m), 114.06 (m), 36.13 (br d, J = 38.15 Hz). HRMS calculated 188.0933, found 188.0929.

2-Fluorenol 7c (91%)

^{1}H NMR ($CDCl_3$). δ 8.00–7.89 and 7.84–7.70 (m, 1H), 7.64 (dd, J = 8.17, 2.25 Hz, 1H), 7.60–6.92 (m, 3H), 7.05 (s, 1H), 6.85 (dd, J = 8.17, 2.25 Hz, 1H), 3.85 (s). ^{13}C NMR ($CDCl_3$) δ 142.3 (m, 1C), 125.9 (m, 3C), 119.2 (m, 1C), 37.1 (br d, J = 41.7 Hz). HRMS calculated 188.0933, found 188.0930.

1-Fluorenol 7d (88%)

^{1}H NMR ($CDCl_3$) δ 8.09–7.99 and 7.90–7.78 (m, 1H), 7.73–7.24 (m, 4H), 7.24–6.92 (m, 1H), 6.77 (d, J = 7.89, 0.77 Hz, 1H), 3.85 (d, J = 3.34 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 142.2 (m), 126.8 (m), 125.1 (m), 120.1 (m), 33.3 (br d, J = 40.7 Hz).

9-Phenanthrenol 8 (63%)

To a solution of 9-fluorenone **2** (0.372 g, 2.00 mmol) in dichloromethane (20.0 mL) was added dropwise boron trifluoride (0.38 mL, 1.12 mmol) at −78 °C followed by dropwise addition of 2.0 M trimethylsilyl diazomethane in hexanes (41.5 mL, 3.0 mmol). The mixture was stirred at −78 °C for 1 h or until TLC showed a complete reaction. Water was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with dichloromethane. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 30% ethyl acetate in hexanes to provide the title product **8** (0.254 g, 63%). ^{1}H NMR ($CDCl_3$) δ 9.05–8.55 (m, 2H), 8.55–8.30 (m, 1H), 8.30–7.90 (m, 1H), 7.90–7.65 (m, 2H), 7.65–7.50 (m, 1H), 7.50–7.20 (m, 1H), 7.10–6.95 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 136.02 (m), 131.53 (m), 126.68 (m), 122.46 (m). HRMS calculated 200.0933, found 200.0937.

General procedure for the preparation of methoxyphenanthrenols 9

To a solution of 2-methoxyfluorenone **5c** (1.211 g, 5.600 mmol) in dichloromethane (56 mL) was added dropwise boron trifluoride (1.192 g, 8.400 mmol) at −20 °C. A solution of 2.0 M trimethylsilyl diazomethane (4.2 mL, 8.4 mmol) in hexanes was diluted with dichloromethane (40 mL) and then added dropwise via cannula to the previous reaction mixture. The reaction mixture was stirred at this temperature for 2 h or until the TLC showed a complete reaction. Water was added and the layers were separated. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 5% ethyl acetate in hexanes to provide the title product (1.084 g, 84%).

4-Methoxyphenanthrenols 9a (88%)

^{1}H NMR ($CDCl_3$) δ 10.10–9.10 (m, 1H), 9.10–7.90 (m, 2H), 7.90–7.30 (m, 3H), 7.30–7.10 (m, 2H), 4.18, 4.16 (two s, 3H). ^{13}C NMR ($CDCl_3$) δ 140.33 (m), 135.79 (m), 132.81 (m), 130.04 (m), 128.42 (m), 56.20.

3-Methoxyphenanthrenols 9b (89%)

^{1}H NMR ($CDCl_3$) δ 8.90–7.70 (m, 4H), 7.70–7.50 (m, 1H), 7.50–7.25 (m, 1H), 7.25–6.90 (m, 1H), 4.09, 4.03 (two s, 3H). ^{13}C NMR ($CDCl_3$) δ 136.14 (m), 130.78 (m), 126.74 (m), 124.18 (m), 122.14 (m), 55.45, 55.33 (two s).

2-Methoxyphenanthrenols 9c (84%)

^{1}H NMR ($CDCl_3$) δ 9.20–8.35 (m, 1H), 8.35–7.70 (m, 3H), 7.70–7.35 (m 2H), 7.30–7.20 (m, 1H), 7.20–6.90 (m, 1H), 4.07, 4.04 (two s, 3H). ^{13}C NMR ($CDCl_3$) δ 135.78 (m), 133.43 (m), 130.99 (m), 126.68 (m), 124.66(m), 122.73 (m).

1-Methoxyphenanthrenols 9d (75%)

^{1}H NMR ($CDCl_3$) δ 9.58 and 9.02–8.54 (m, 1H), 8.49–7.69(m, 3H), 7.69–7.42 (m, 2H), 7.20–6.90 (m, 2H), 4.16, 4.06 (two s, 3H). ^{13}C NMR ($CDCl_3$) δ 133.4 (m), 130.9 (m), 126.6 (m), 125.0 (m), 124.1 (m), 122.9 (m), 116.7 (s), 106.6 (s), 56.1 (s).

General procedure for the preparation of methoxyphenanthrenyl tosylate 10

To a solution of methoxyphenanthrenol **9b** (1.084 g, 4.710 mmol) in dichloromethane (80.0 mL) was added triethylamine (1.43 g, 14.1 mmol) followed by triflic anhydride (3.99 g, 14.1 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 2–3 h or until TLC showed a complete reaction. The reaction mixture was washed with 5% sodium bicarbonate, brine and extracted with dichloromethane. The combined organic extracts were dried with sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 5% ethyl acetate in hexanes to provide the title product (1.35 g, 79%).

4-Methoxyphenanthrenyl triflate 10a (72%)

^{1}H NMR ($CDCl_3$) δ 10.0–6.80 (m, 8H), 4.07 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 135.36 (m), 132.37 (m), 129.61 (m), 127.61 (m), 55.80.

3-Methoxyphenanthrenyl triflate 10b (71%)

^{1}H NMR ($CDCl_3$) δ 9.00–7.80 (m, 4H), 7.80–7.30 (m, 4H), 4.03, 4.02 (two s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.00 (d, J = 16.1 Hz), 131.99 (m), 129.53 (m), 128.22 (m), 126.83 (m), 124.42 (m), 122.59 (m), 109.00 (d, 3.0 Hz), 101.83, 55.68, 55.62 (two s). HRMS calculated 362.0531, found 362.0526.

2-Methoxyphenanthrenyl triflate 10c (79%)

^{1}H NMR ($CDCl_3$) δ 9.00–7.80 (m, 5H), 7.80–7.45 (m, 2H), 7.41, 7.35 (two dd, J = 9.08, 2.50 Hz, 1H), 4.07, 4.08 (two s, 3H). ^{13}C NMR ($CDCl_3$) δ 160.00 (dd, J = 13.5, 4.7 Hz), 131.11 (m), 127.97 (m), 127.41 (m), 125.70 (m), 122.93 (m), 121.59 (m), 55.57, 55.55(two s), 42.56. HRMS calculated 362.0531, found 362.0528.

1-Methoxyphenanthrenyl triflate 10d (59%)

^{1}H NMR ($CDCl_3$) δ 9.06–8.87 and 8.54–8.40 (m, 1H), 8.40–7.86 (m, 3H), 7.76–7.38 (m, 3H), 7.21–7.08 (m, 1H), 4.09 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 131.3 (m), 129.7 (m), 127.7 (m), 127.3 (m), 123.1 (m), 121.1 (m), 115.1, 114.5, 112.0, 108.0, 106.2, 55.4, 55.0.

General procedure for the preparation of methoxyphenanthrene 11

A stirred mixture of 4-methoxyphenanthrenyl triflate **10a** (1.258 g, 3.470 mmol), palladium acetate (0.030 g, 0.13 mmol), triphenylphosphine (0.0703 g, 0.266 mmol), triethylamine (2.107 g, 20.82 mmol) and formic acid (0.55 mL, 85% in water) in dimethyl formamide (12.0 mL) was heated

to 80–85 °C overnight, cooled to room temperature, and water was added. The layers were separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified on silica gel with 5% ethyl acetate hexanes, v/v, using 60 A silica gel, to provide the title product **11d** (0.655 g, 88%).

4-Methoxyphenanthrene 11a (88%)

^{1}H NMR ($CDCl_3$) δ 10.10–9.30 (m, 1H), 8.40–7.30 (m, 7H), 7.30–7.10 (m, 1H), 4.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 131.16, 129.24, 128.17, 127.12, 126.05, 125.60, 121.13 (d, J = 2.3 Hz), 107.89 (d, J = 0.13 Hz), 55.30.

3-Methoxyphenanthrene 11b (90%)

^{1}H NMR ($CDCl_3$) δ 9.00–8.00 (m, 3H), 8.00–7.50 (m, 4H), 7.50–7.10 (m, 2H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.23, 130.70, 128.45, 126.04, 122.08, 117.06 (d, J = 3.9 Hz), 108.47 (d, J = 1.8 Hz), 55.39. HRMS calculated 200.0933, found 200.0927.

2-Methoxyphenanthrene 11c (100%)

^{1}H NMR ($CDCl_3$) δ 9.05–8.30 (m, 1H), 8.30–7.50 (m, 6H), 7.50–7.20 (m, 2H), 4.05 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 158.41 (d, J = 4.9 Hz), 132.38 (m), 129.60 (m), 128.63 (m), 126.68 (m), 125.91 (m), 122.49 (m), 116.70, 103.89, 55.47. HRMS calculated 214.1089, found 214.1092.

1-Methoxyphenanthrene 11d (93%)

^{1}H NMR ($CDCl_3$) δ 9.04–8.91 and 8.52–8.40 (m, 1H), 8.39–7.32 (m, 7H), 7.06 (d, J = 7.8 Hz), 4.09 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 133.5 (m), 126.6 (m), 124.8 (m), 124.1 (m), 122.9 (m), 116.70, 106.6, 56.1.

General procedure for the preparation of hydroxyphenanthrene 12

To a solution of methoxyphenanthrene **11c** (0.854 g, 3.99 mmol) in dichloromethane (18.0 mL) was added dropwise 1.0-M boron tribromide in dichloromethane (4.39 mL, 4.39 mmol) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 1–2 h or until the TLC showed a complete reaction. Methanol was added to the reaction mixture to decompose excess boron tribromide while cooled at 0 °C. The solvent was removed under reduced pressure. The residue was adsorbed on silica gel and purified using silica gel chromatography using10% ethyl acetate/hexanes, v/v, to provide the title product (0.558 g, 70%).

4-Hydroxyphenanthrene 12a (90%)

^{1}H NMR ($CDCl_3$) δ 10.15–9.20 (m, 1H), 8.40–7.30 (m, 7H), 7.20–6.90 (m, 1H), 6.00–5.30 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 131.46 (m), 129.58 (m), 128.44 (m), 122.72 (m), 126.47 (m), 125.80 (m), 121.74 (d, J = 2.46 Hz), 113.22 (d, J = 2.72 Hz). Anal. Calcd. for $^{13}C_6^{12}C_8H_{10}O$: C, 86.97; H, 5.04. Found: C, 84.51; H, 5.40.

3-Hydroxyphenanthrene 12b (60%)

^{1}H NMR ($CDCl_3$) δ 9.00–8.25 (m, 2H), 8.25–7.50 (m, 4H), 7.50–7.20 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 130.85 (m), 128.76 (m), 126.29 (m), 122.09 (m), 116.72 (d, J = 4.16 Hz), 111.90 (d, J = 2.76 Hz). HRMS calculated 200.0933, found 200.0927. Anal. Calcd. for $^{13}C_6^{12}C_8H_{10}O$: C, 86.97; H, 5.04. Found: C, 85.65; H, 5.26.

2-Hydroxyphenanthrene 12c (70%)

^{1}H NMR ($CDCl_3$) δ 8.93–8.82 and 8.41–8.30 (m, 1H), 8.63 (dd, J = 8.6, 2.6 Hz, 1H), 8.22–7.51 (m, 4H), 7.48–7.22 (m, 3H), 4.99 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 130.3, 128.2, 126.4, 125.1, 121.5. HRMS calculated 200.0933, found 200.0928.

1-Hydroxyphenanthrene 12d (90%)

^{1}H NMR ($CDCl_3$) δ 9.05–8.86 and 8.53–8.39 (m, 1H), 8.38–7.60 (m, 5H), 7.60–7.33 (m, 2H), 7.02 (d, J = 7.7 Hz), 5.37 (br s). ^{13}C NMR ($CDCl_3$) δ 131.1 (m), 128.1 (m), 126.6 (m), 125.8 (m), 123.4 (m), 122.7 (m), 119.5, 115.1, 110.2.

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Conflict of Interest

The authors did not report any conflict of interest.

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