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Synthesis of Phenol and Quinone Metabolites of Benzo[*a*]pyrene, a Carcinogenic Component of Tobacco Smoke Implicated in Lung Cancer

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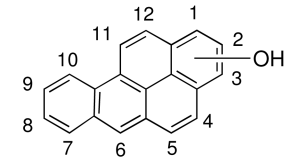
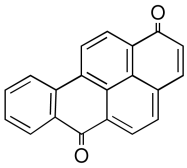
Abstract

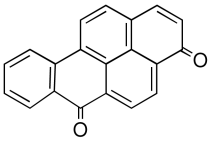


BP phenols

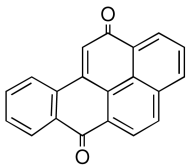
1-, 3-, 6-, 9-, and 12-isomers



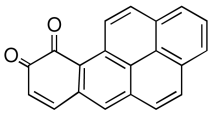
BP 1,6-dione



BP 3,6-dione



BP 6,12-dione



BP 9,10-dione

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants produced in the combustion of organic matter. PAHs are present in automobile exhaust and tobacco smoke, and they have recently been designated as human carcinogens. Current evidence indicates that PAHs are activated enzymatically to mutagenic metabolites that interact with DNA. There is evidence for three pathways of activation, the *diol epoxide* path, the *radical-cation* path, and the *quinone* path. The relative importance of these paths for human lung cancer has not been established. We now report syntheses of the principal phenol and quinone isomers of the prototype PAH carcinogen benzo[*a*]pyrene (BP) that are known or are suspected to be formed as metabolites of BP in human bronchoalveolar cells. The methods of synthesis were designed to be adaptable to preparation of the ^{13}C-labelled analogues of the BP metabolites. These compounds are needed as standards for sensitive LC-MS/MS methods for analysis of BP metabolites formed in lung cells. Efficient novel syntheses of the 1-, 3-, 6-, 9-, and 12-BP phenols, and the BP 1,6-, 3,6-, 6,12-, and 9,10-quinones are now reported. The syntheses of the BP phenols (except 6-HO-BP) involve in the key steps Pd-catalyzed Suzuki-Miyaura cross-coupling of a naphthalene boronate ester with a substituted aryl bromide or triflate ester. The BP quinones were synthesized from the corresponding BP phenols by direct oxidation with the hypervalent iodine reagents IBX or TBI. These reagents exhibited different regiospecificities. IBX oxidation of the 7- and 9- BP phenols provided the *ortho*-quinone isomers (BP 7,8-, and 9.10-dione), whereas TBI oxidation of the 1-, 3-, and 12-BP phenols furnished BP quinone isomers with carbonyl functions in separate rings (BP 1,6-, 3,6-, and 6,12-dione).

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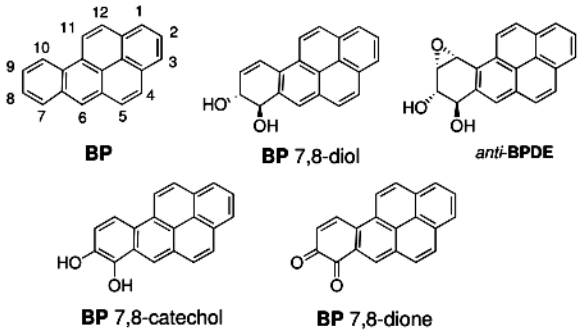
Introduction

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants that are produced in the combustion of organic matter.1–3 PAHs are components of automobile and diesel engine exhaust4 and tobacco smoke,5–7 and they are implicated as causative agents for lung cancer,2,5–10 the principal category of adult cancer death in the U.S. population.11

For PAHs to exert their carcinogenic effects, metabolic activation is required.3 Benzo-[*a*]pyrene (BP) is the prototype PAH carcinogen that has been most intensively investigated. Three activation pathways have been proposed. The most studied path involves cytochrome P-450 [CYP]-mediated formation of BP *trans*-7,8-dihydrodiol (**BP** 7,8-diol) and its oxidation to the highly mutagenic BP *trans*-7,8-diol-*anti*-9,10-epoxide (*anti*-**BPDE**).3,12 A second path entails aldo-keto reductase [AKR]-mediated oxidation of **BP** 7,8-diol to BP 7,8-catechol that enters into a redox cycle with O_2 to form a quinone (BP 7,8-dione) along with reactive oxygen species (ROS) that attack DNA.13–16 The third path entails peroxidase-mediated oxidation of BP to form a radical-cation that reacts with DNA, leading to formation of depurinated adducts.17,18 The relative importance of these activation routes for human cancer has not been established.



Numerous studies of the metabolism of BP by rodent liver microsomes and other model cell systems have been conducted.3,19,20 However, most of these investigation were carried out without an appreciation of all the participating pathways or sufficiently sensitive analytical methods or standards to adequately characterize all the metabolites formed. More recently, human bronchoalveolar H358 cells were introduced as a model to study the metabolic profile of BP in normal human lung epithelial cells.21,22 Development of a stable isotope dilution liquid chromatography tandem mass spectrometric analytical method to quantify the adducts formed with DNA by the metabolites of BP was also reported.23

Enhancement of the scope and sensitivity of the LC-MS analytical methodology requires ^{13}C-labelled analogues of BP and its metabolites as authentic standards. In this connection, we recently reported syntheses of $^{13}C_2$-BP, $^{13}C_2$-BP 7,8-diol, $^{13}C_2$-BP 7,8-dione, and $^{13}C_2$-8-HO-BP.24 We now report improved new syntheses of the principal phenol and quinone isomers of BP formed in its metabolism in human bronchoalveolar H358 cells.21 The synthetic approaches were designed to be adaptable to syntheses of the corresponding ^{13}C-labelled analogues of these BP metabolites with two or more ^{13}C-atoms in the PAH ring system.

Results

The phenol and quinone isomers of BP chosen as synthetic targets for this investigation include the 1-, 3-, 6-, 9-, and 12-phenol isomers (1-HO-BP, 3-HO-BP, 6-HO-BP, 9-HO-BP, and 12-HO-BP) and the 1,6-, 3,6-, 6,12-, and 9,10-quinone isomers (BP 1,6-dione, BP 3,6-

dione, BP 6,12-dione, and BP 9,10-dione). Although not all of these isomers have been identified as metabolites of BP in H358 cells,21 the evidence suggests that some phenol isomers may not have survived sufficiently long to be detected due to the facility of their oxidation to quinones or higher oxidized products. For example, 6-HO-BP was not found as a metabolite, yet BP 1,6-dione and BP 3,6-dione were identified as the principal BP quinone metabolites.21 The fact that 6-HO-BP is a metabolic precursor of the BP 1,6-, 3,6- and 6,12-diones20 suggests that 6-HO-BP is formed but fails to persist due to its further oxidation to the BP 1,6-, 3,6- and 6,12-diones. Other unidentified BP phenol or quinone isomers for which standards were not available may also have been formed but escaped detection because they happen to coelute on chromatography with an isomer for which a standard was available. Satisfactory resolution of these questions requires that the isomeric BP phenol and quinone metabolites that were not available for the initial metabolism studies should be synthesized to serve as additional analytical standards.

Synthesis of all twelve BP phenol isomers by classical synthetic methods have been described in the literature.25,26 However, these syntheses involve relatively large numbers of steps and they were not designed to serve as the basis of methods for efficient syntheses of the ^{13}C-labelled analogues of the BP phenol isomers.

Benzo[*a*]pyren-3-ol (3-HO-BP)

3-HO-BP was the principal phenol isomer detected as a metabolite of BP in H358 cells.21 Synthesis of 3-HO-BP was accomplished via the reaction sequence in Scheme 1. The key step entailed Pd-catalyzed Suzuki-Miyaura cross-coupling of the 2-boronate ester of 7-methoxy-naphthalene (**3**) with 2-bromophenylacetone (**4**). The boronate ester **3** was prepared from 7-methoxy-2-naphthol (**1a**) via initial conversion to its triflate ester (**1b**) by the procedure reported.27 Reaction of **1b** (1 mmol) with bis(neopentylglycolato)diboron (**2**) (1.2 mmol) in the presence of $Pd(dppf)Cl_2$ (0.03 mmol) as catalyst and KOAc as base took place in DMSO at 80 °C to afford the boronate ester **3** in moderate yield (40%). A brief study of this reaction was undertaken with the aim of improving the yield of **3** (Table 1). It was not significantly enhanced by the use of $Pd(PPh_3)_4$ as catalyst, increase in reaction time, or use of CH_3CN as solvent. On the other hand, the yield of **3** was significantly improved and reaction time was decreased with the use of THF or dioxane as solvent. The optimum yield (82%) was obtained with dioxane as solvent.

Cross-coupling of **3** with **4** took place in the presence of $Pd(PPh_3)_4$ and Na_2CO_3 in DME to furnish 2-(7-methoxynaphthyl)phenylacetone (**5**) as principal product (62%). It was recently shown28 that acid-catalyzed cyclization of an analogue of **5** lacking a methoxy group was acccompanied by secondary rearrangement of the bay region methyl group of the product to the adjacent ring position due to steric crowding. Rearrangement was diminished by the use of $TiCl_4$ as catalyst. $TiCl_4$-catalyzed cyclization of **5** furnished 3-methoxy-5-methylchrysene (**6**) as major product (74%). Conversion of the methyl group of **6** to an aldehyde function was accomplished via bromination with NBS to give 5-bromomethyl-3-methoxychrysene (**7a**), and reaction of **7a** with DMSO and $NaHCO_3$ yielded 5-formyl-3-methoxychrysene (**7b**). Although **7a** was unstable, satisfactory yields of **7b** could be obtained by the direct use of **7a** without isolation. Wittig reaction of **7b** with methoxymethylenetriphenylphosphine furnished 3-methoxy-5-(2-methoxy-vinyl)chrysene (**8**) as a mixture of *E*- and *Z*-isomers. Acid-catalyzed cyclization of **8** gave 3-methoxybenzo[*a*]pyrene (76% from **7b**), and demethylation by treatment with BBr_3 provided 3-HO-BP.

Benzo[*a*]pyren-1-ol (1-HO-BP)

Synthesis of 1-HO-BP was carried out by a procedure analogous to that for preparation of 3-HO-BP (Scheme 2). The 2-boronate ester of 5-methoxynaphthalene (**10**) was prepared from

5-methoxy-2-naphthol (**9a**) via conversion to the triflate ester (**9b**) followed by reaction of **9b** with **2** in the presence of Pd(dppf)Cl_2 by the procedure for preparation of **3**. Cross-coupling of **10** with **4** with Pd(PPh_3)$_4$ and Na_2CO_3 in DME gave 2-(5-methoxynaphthyl)phenylacetone (**11**) (77%). $TiCl_4$-catalyzed cyclodehydration of **11** afforded 1-methoxy-5-methylchrysene (**12**) (68%), and reaction of **12** with NBS gave **13a** which was converted to 5-formyl-1-methoxychrysene (**13b**) (74%) by reaction with DMSO and $NaHCO_3$. 28,30

Wittig reaction of **13b** with methoxymethylenetriphenylphosphine yielded 1-methoxy-5-(2-methoxyvinyl)chrysene (**14**) (90%) as a mixture of *E*- and *Z*-isomers. Acid-catalyzed cyclization of **14** afforded 1-methoxybenzo[*a*]pyrene. Attempted demethylation by treatment with BBr_3 was unsuccessful, but conversion of 1-MeO-BP to 1-HO-BP was accomplished by treatment with HI/HOAc. The usefulness of HI/HOAc for demethylation of aryl ethers was noted in an earlier study,32 but the scope of the method was not explored. It appears that HI/HOAc may be a superior to BBr_3 as a reagent for demethylation of PAH methyl ethers.

Benzo[*a*]pyren-9-ol (9-HO-BP)

Synthesis of 9-HO-BP was carried out by a procedure analogous to that reported for preparation of 7-benzo[*a*]pyren-7-ol (Scheme 3).31,32 2-Bromobenzene-1,3-dialdehyde (**15**) was synthesized by the reported method,31 and Suzuki-Miyaura coupling of **15** with the boronate ester (**3**) catalyzed by Pd(PPh_3)$_4$ furnished the dialdehyde adduct (**16**). Double Wittig reaction of **16** with (methoxymethylene)triphenylphosphine ($CH_3OCH{=}PPh_3$)24 provided the di(methoxyvinyl) derivative (**17**) as a mixture of *E*- and *Z*-isomers. Acid-catalyzed cyclization of **17** furnished 9-methoxybenzo[a]pyrene, and demethylation with BBr_3 gave 9-HO-BP.

Benzo[*a*]pyren-12-ol (12-HO-BP)

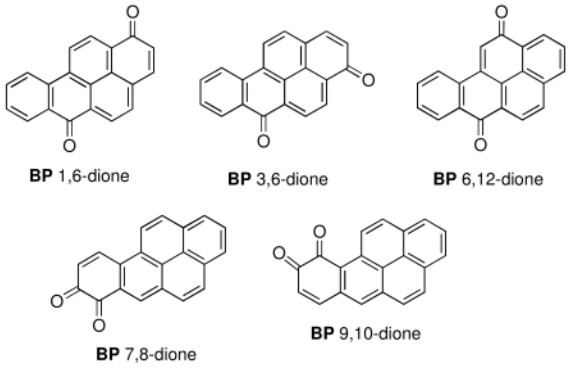
Synthesis of 12-HO-BP is outlined in Scheme 4. The 2-boronate ester of 1-methyl-naphthalene (**19**) was prepared from 1-methyl-2-naphthol (**18a**) via conversion to the triflate ester (**18b**) followed by reaction of **18b** with **6** in the presence of Pd(dppf)Cl_2. Reaction of **19** with 2-bromobenzaldehyde in the presence of Pd(PPh_3)$_4$ and Na_2CO_3 in DME gave 2-(5-methyl-naphthalen-2-yl)phenylacetone (**20**) (74%), and reaction of **20** with methoxymethylenetriphenyl-phosphine furnished **21** as a mixture of *E*- and *Z*-isomers. Acid-catalyzed cyclization of **21** afforded 12-methylbenz[*a*]anthracene (**22a**). This was converted to 12-HO-BP via bromination with NBS to yield **22b**, reaction of **22b** with KCN to provide **22c**, hydrolysis of **22c** with KOH in ethylene glycol to yield **22d**, and acid-catalyzed cyclization of **22d** to furnish 12-HO-BP.26g

Benzo[*a*]pyren-6-ol (6-HO-BP)

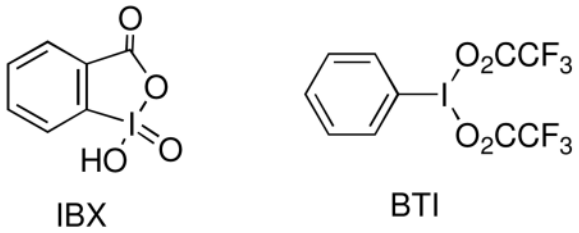
The most convenient synthetic precursors of 6-HO-BP and $^{13}C_2$-6-HO-BP are BP and $^{13}C_2$-BP themselves. An efficient synthesis of $^{13}C_2$-BP from was recently reported.24 Direct synthesis of 6-HO-BP from BP was accomplished via initial Vilsmeier-Haack reaction of BP with $POCl_3$ and DMF to furnish 8-formylbenzo[*a*]pyrene (**23**) (Scheme 4).33 Baeyer-Villager oxidation of **23** with *m*-chloroperbenzoic acid provides 8-formyloxybenzo[*a*]pyrene (**24**). The formate ester derivative was relatively stable in contrast to 6-HO-BP which exhibited a strong tendency to undergo oxidative decomposition on exposure to air. The ease of auto-oxidation of 6-HO-BP accords with the earlier findings of Lorentzen et al20c who showed the principal products of auto-oxidation of 6-HO-BP to be the the BP 1,6-, 3,6-, and 6,12-diones.

Synthesis of BP Quinones

Direct oxidation of BP with chromium reagents, ceric ammonium nitrate, and other oxidants has been shown by various investigators to furnish mixtures of BP quinones that are difficult to separate.34 This problem was reinvestigated by Cho and Harvey35 who used careful chromatographic techniques to isolate and identify the pure BP 1,6-, 3,6-, and 6,12-dione isomers. They were obtained in yields of 40, 20, and 7 %, respectively. However, this approach is impractical for synthesis of the individual pure ^{13}C-labelled BP 1,6-, 3,6-, and 6,12-diones.



A more promising synthetic route to the BP quinones of interest is via oxidation of the individual BP phenol isomers. In a prior study we showed that oxidation of 8-HO-BP with the hypervalent iodine reagent *o*-iodoxybenzoic acid (IBX) provided convenient synthetic access to BP 7,8-dione.24,32 We now report that oxidation of 9-HO-BP with IBX by a similar procedure furnished BP 9,10-dione in good yield (82%).



Attempts to oxidize 1-HO-BP or 3-HO-BP by IBX were not successful, failing to provide either the unknown *ortho*-quinone isomers (BP 1,2- or 2,3-dione) or the BP 1,6- or 3,6-quinone isomers. Transformation of 1-HO-BP and 3-HO-BP to the desired BP quinone isomers (BP 1,6-dione and BP 3,6-dione) was accomplished by direct oxidation with another hypervalent iodine reagent, [bis(trifluoroacetoxy)iodo]benzene (BTI). BP 1,6-dione and BP 3,6-dione were obtained in yields of 82% and 85%, respectively. Similarly, oxidation of 12-HO-BP by BTI provided BP 6,12-dione. BTI was shown previously to oxidize substituted 1-naphthols to 1,4-naphtho-quinones,37 but no examples of its use for oxidation of PAH phenols with larger ring systems have been reported. BTI holds promise as a reagent for regioselective oxidation of PAH phenols to quinones with carbonyl functions in separate rings, such as the BP 1,6- and 3,6-diones.

Discussion

Oxidative metabolism of BP and other PAHs in mammalian cells is part of the normal process of enzymatic detoxification of xenobiotic substances.3,16,19 Metabolism of BP by P-450 microsomal enzymes affords initially arene oxides that may either (i) rearrange to

phenols or (ii) undergo epoxide hydrolase-catalyzed hydration to furnish *trans*-dihydrodiols, such as the BP *trans*-7,8- or *trans*-9,10-dihydrodiols. These primary metabolites are converted to glucuronides or other water-soluble conjugates that are eventually excreted. However, some of the primary metabolites are able to survive and undergo further oxidative metabolism to quinones, diol epoxides, and other potentially carcinogenic species.

This paper reports efficient syntheses of the principal phenol and quinone isomers of BP that have been identified or are suspected to be formed as metabolites of BP in normal human bronchoalveolar cells.21 The BP phenols include the 1-, 3-, 6-, 9-, and 12-phenol isomers (1-HO-BP, 3-HO-BP, 6-HO-BP, 9-HO-BP, and 12-HO-BP). The BP quinone isomers are the BP 1,6-, 3,6-, 6,12-, and 9,10-diones.

The syntheses of the BP phenols involve in the key steps Pd-catalyzed Suzuki cross-coupling of a naphthalene boronate ester derivative with an aryl bromide or a triflate ester. The BP quinones were synthesized from the BP phenols by oxidation with the hypervalent iodine reagents IBX and TBI. These reagents exhibited different regiospecificities of oxidation. Reaction of IBX with 7-HO- and 9-HO-BP yielded the *ortho*-quinone isomers (BP 7,8- and 9,10-dione), whereas reaction of TBI with 1-HO-, 3-HO-, and 12-HO-BP furnished exclusively quinone isomers with carbonyl functions in separate rings (BP 1,6-, 3,6-, and 6,12-dione). The remarkable regioselectivities of these oxidations are consistent with the mechanisms. Oxidations with IBX are thought to proceed via initial reaction of the reagent with the phenol to form an intermediate complex.38 This is followed by intramolecular transfer of an oxygen atom from the IBX component of the complex to the carbon atom adjacent to the hydroxyl group of the phenolic component, leading to formation of an *ortho*-quinone product. Oxidations with BTI also entail initial reaction of the reagent with the phenol to form an intermediate complex.37 This reacts with water, generally at a less sterically restricted *para* position, thereby generating a *para*-catechol intermediate that undergoes further oxidation to yield a quinone product. The BP 1-, 3-, and 12-phenols lack a *para* position, so that the reactions of their intermediate complexes with water take place at the most reactive alternative site, the 6-position, to generate the BP 1,6-, 3,6-, and 6,12-diones.39 These are the first examples of oxidation of PAH phenols with TBI to afford PAH quinones with carbonyl functions in separate rings.

The synthetic approaches to the BP phenol and quinone metabolites outlined above were designed to be adaptable to preparation of ^{13}C-labelled analogues of these compounds. The isotopically-labelled compounds are needed as substrates and/or standards for metabolism and other studies in normal human lung cells. Syntheses of the ^{13}C-labelled analogues are in progress. This work is virtually complete and the findings will be reported shortly.

The methods reported herein for synthesis of BP phenol derivatives via Suzuki cross-coupling are potentially broad in scope, providing convenient synthetic access to many other PAHs and their substituted derivatives.

Experimental Section

Caution

Benzo[*a*]pyrene (BP) has been designated a human carcinogen by the World Health Organization.2 BP should be handled with appropriate caution following the procedures recommended in the publication *NIH Guidelines for the Laboratory Use of Chemical Carcinogens*. The phenol and quinone isomers of BP have not been designated as carcinogenic hazards, but prudence suggests that they also be handled with caution.

2-(7-Methoxynaphthyl)phenylacetone (5)

To a solution of 2-bromophenylacetone (**4**) (0.852 g, 4.0 mmol) in DME (10 mL) under argon was added $Pd(PPh_3)_4$ (46 mg, 0.40 mmol), and the resulting solution was stirred for 20 min. Then the boronic ester **3** (1.30 g, 4.8 mmol) and EtOH (15 mL) were added. Stirring was continued for 20 min, then $NaCO_3$ (4 mL of a 2M solution) was added and the solution was heated at reflux for 4 h, then cooled to room temp. The precipitate was filtered off, washed with EtOAc (50 mL), and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (80 mL), washed with water (3 × 15 mL), dried over Na_2SO_4, and evaporated to dryness. Chromatography of the residue on a column of silica gel eluted with hexane/EtOAc (20:1) afforded **5** (0.72 g, 62%): ^{1}H NMR (500MHz, $CDCl_3$) δ 7.85-7.78 (m, 2 H), 7.42 (s, 1 H), 7.45-7.30 (m, 3 H), 7.30-7.20 (m, 3 H), 7.17 (s, 1 H), 3.96 (s, 3 H), 3.77 (s, 2 H), 2.02 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 206.3, 157.8, 142.2, 139.1, 134.2, 132.1, 130.4, 130.0, 129.0, 127.6, 127.38, 127.35, 126.8, 126.5, 124.8, 118.8, 105.6, 55.0, 48.1, 29.4; HRMS (M^+) calcd for $C_{20}H_{18}O_2$ (M^+): 290.1307, found 290.1309.

3-Methoxy-5-methylchrysene (6)

To a dry flask was added a solution of **5** (460 mg, 1.6 mmol) in CH_2Cl_2 (15 mL) under argon. Then a solution of $TiCl_4$ (1.6 mL, 1 M in CH_2Cl_2) was added dropwise at -78 °C. The resulting mixture was stirred for 3.5 h at 0 °C, and reaction was monitored by TLC. Reaction was quenched by pouring on crushed ice (15 g), extracted with EtOAc (3 × 50 mL), and the combined organic layer was washed with water and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column. Elution with hexane/EtOAc (10:1) afforded **6** and a small amount of an unidentified isomer. Crystallization from EtOH gave pure **6** (321 mg, 74%): ^{1}H NMR (500MHz, $CDCl_3$) δ 8.73 (d, J = 8.5 Hz, 1 H), 8.64 (d, J = 9.0 Hz, 1 H), 8.41 (d, J = 2.0 Hz, 1 H), 7.94-7.90 (m, 3 H), 7.83 (s, 1 H), 7.70-7.55 (m, 2 H), 7.32 (dd, J = 8.5 and 2.0 Hz, 1 H), 4.04 (s, 3 H), 3.28 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 157.2, 133.0, 132.9, 131.7, 130.4, 130.2, 129.8, 129.7, 128.8, 128.4, 127.4, 127.2, 126.5, 126.0, 123.3, 119.5, 116.1, 109.4, 55.5, 27.7; MS (APCI): m/z = 273 (100%).

3-Methoxy-5-formylchrysene (7b)

To a dry flask containing a solution of **6** (272 mg, 1 mmol) in CCl_4 (10 mL) under argon were added NBS (196 mg, 1.1 mmol) and benzoylperoxide (6 mg), and the mixture was heated at reflux for 3 h and reaction was monitored by TLC. Then the mixture was cooled to room temp., the precipitate of was filtered off and was washed with CCl_4 (2 mL). To the solution were added DMSO (2.8 mL) and $NaHCO_3$ (168 mg, 2 mmol), and the mixture was heated at 80-90 °C for 3.0 h (reaction was monitored by TLC). The mixture was diluted with EtOAc (100 mL), washed with water (3 × 30 mL), and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column. Elution with hexane/EtOAc (40: 1) furnished **7b** (170 mg, 60%): ^{1}H NMR (500MHz, $CDCl_3$) δ 10.69 (s, 1 H), 8.73 (d, J = 9.5 Hz, 1 H), 8.56 (d, J = 9.0 Hz, 1 H), 8.40 (s, 1 H), 8.11 (d, J = 7.5 Hz, 1 H), 8.01 (d, J = 8.5 Hz, 1 H), 7.96 (d, J = 8.5 Hz, 1 H), 7.82 (t, J = 8.5 Hz, 1 H), 7.72 (t, J = 7.5 Hz, 1 H), 7.46 (d, J = 2.0 Hz, 1 H), 7.35 (dd, J = 9.0 and 2.0 Hz, 1 H), 4.00 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 193.2, 158.4, 133.8, 132.3, 130.6, 130.5, 130.4, 130.3, 130.2, 129.9, 129.2, 128.1, 128.0, 127.3, 126.0, 123.3, 118.8, 117.9, 109.2, 55.6; HRMS (M^+) calcd for $C_{20}H_{14}O_2$ 286.0994, found 286.0984.

3-Methoxybenzo[*a*]pyrene

To a suspension of methoxymethyltriphenylphosphonium chloride (222 mg, 0.65 mmol) in anhydrous THF (1.0 mL) under argon at room temp. was added *t*-BuOK (0.65 mL, 1 M in

THF) dropwise. The resulting mixture was stirred at room temperature for 1.5 h and a solution of **7b** (160 mg, 0.54 mmol) in THF (2 mL) was added. Stirring was continued for 1.5 h and reaction was monitored by TLC. Diethyl ether (50 mL) was added, and the precipitate was filtered off and washed with Et_2O (30 mL). Following removal of the solvent under pressure, the residue was purified by quick chromatography on a silica gel column. Elution with hexane/EtOAc (10:1) provided **8** (156 mg, 92%) as an oil shown by ^{1}H NMR analysis to consist of 1:1 mixture of (*E*)- and (*Z*)-isomers used directly in the next step.

To this solution of **8** (156 mg, 0.50 mmoL) in CH_2Cl_2 (5 mL) was added CH_3SO_3H (50 μL) at 0 °C, and the mixture was stirred at room temp. for 3 h as reaction was monitored by TLC. EtOAc (50 mL) was added, and the solution was washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column. Elution with hexane/ Et_2O (20: 1) gave 3-methoxybenzo[*a*]pyrene (115 mg, 83%): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.02 (d, *J* = 8.5 Hz, 1 H), 8.90 (d, *J* = 8.0 Hz, 1 H), 8.47 (s, 1 H), 8.34 (d, *J* = 9.5 Hz, 1 H), 8.30-8.15 (m, 3 H), 8.00 (d, *J* = 9.5 Hz, 1 H), 7.86-7.75 (m, 2 H), 7.65 (d, *J* = 8.0 Hz, 1 H), 4.21 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 153.5, 131.6, 130.3, 128.8, 128.0, 127.9, 127.4, 127.0, 126.5, 126.3, 126.0, 125.9, 125.5, 123.9, 123.6, 123.1, 121.4, 119.9, 119.6, 109.9, 56.3; MS (APCI): *m/z* = 283 (100%).

Benzo[*a*]pyren-3-ol (3-HO-BP)

To a suspension of 3-methoxybenzo[*a*]pyrene (56 mg, 0.2 mmol) in HOAc (7 mL) was added HI (7 mL of a 57% solution) under argon. The mixture was stirred for 1.5 h at 140 °C (reaction monitored by TLC). The mixture was cooled to ambient temp. and poured onto crushed ice (50 g). The solid precipitate was filtered off, washed with water, and then dissolved in EtOAc. The solution was washed with brine and dried over Na_2SO_4. Evaporation of the solvent under vacuum gave a residue that was purified by chromatography on a silica gel column. Elution with hexane/EtOAc (4:1) gave **3-HO-BP** (40 mg, 75%): ^{1}H NMR (500MHz, acetone-d_6) δ 9.53 (bs, 1H), 9.08 (d, *J* = 8.0 Hz, 1 H), 8.94 (d, *J* = 9.0 Hz, 1 H), 8.49 (s, 1 H), 8.35-8.20 (m, 3 H), 8.19 (d, *J* = 8.5 Hz, 1 H), 7.99 (d, *J* = 9.5 Hz, 1 H), 7.85-7.70 (m, 2 H), 7.69 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, acetone-d^6): δ 151.8, 131.7, 130.5, 128.6, 128.1, 127.8, 127.7, 126.73, 126.70, 126.3, 126.1, 125.6, 125.5, 123.9, 123.1, 123.0, 121.7, 119.3, 117.6, 115.0; MS (APCI): *m/z* = 269 (70%), 283 (100%).

2-(5-Methoxynaphthalen-2-yl)phenylacetone (11)

To a solution of 2-bromophenyl-acetone **4** (1.214 g, 5.7 mmol) in DME (16 mL) under argon was added $Pd(PPh_3)_4$ (66 mg, 0.057 mmol), The resulting solution was stirred for 20 min, then boronic ester **10** (1.85 g, 6.84 mmol) and EtOH (23 mL) were added. After 20 min, a solution of Na_2CO_3 (2 M, 5.7 mL) was added, and the mixture was heated at reflux for 4 h, and reaction was monitored by TLC. The solution was cooled to room temp., and the precipitate was filtered off and washed with EtOAc (50 mL). The filtrate was evaporated to dryness, and the residue was dissolved in EtOAc (100 mL), washed with water (3 × 20 mL) and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (20:1) to afford **11** (1.27 g, 77%): ^{1}H NMR (500MHz, $CDCl_3$): δ 8.33 (d, *J* = 8.5 Hz, 1 H), 7.70 (d, *J* = 1.5 Hz, 1 H), 7.50-7.35 (m, 6 H), 7.32-7.28 (m, 1 H), 6.91-6.87 (m, 1 H), 4.06 (s, 3 H), 3.75 (s, 2 H), 2.01 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 206.6, 155.5, 142.4, 139.4, 134.3, 132.3, 130.7, 130.4, 127.8, 127.4, 127.2, 126.7, 126.6, 124.5, 122.1, 120.3, 104.0, 55.6, 48.4, 29.7; HRMS Calcd for $C_{20}H_{18}O_2$ (M^+): 290.1307, found 290.1309.

1-Methoxy-5-methylchrysene (12)

To a dry flask was added a solution of **11** (670 mg, 2.3 mmol) in CH_2Cl_2 (21 mL) under argon. Then a solution of $TiCl_4$ (2.3 mL, 1 M in CH_2Cl_2) was added dropwise at -78 °C, and the resulting mixture was stirred for 3.5 h at 0 °C. The reaction was monitored by TLC, and then quenched by pouring onto crushed ice (20 g). The mixture was extracted with EtOAc (3 × 50 mL), and the combined extracts were washed with water and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the residue was purified by chromatography on a silica gel column. Elution with hexane/EtOAc (10:1) afforded **12** along with a minor unidentified compound. Recrystallization from EtOH gave pure **12** (425 mg, 68%): ^{1}H NMR (500MHz, $CDCl_3$) δ 8.80-8.72 (m, 2 H), 8.56 (d, *J* = 8.5 Hz, 1 H), 8.53 (d, *J* = 9.5 Hz, 1 H), 7.90 (dd, *J* = 9.0 and 1.5 Hz, 1 H), 7.85 (s, 1 H), 7.70-7.55 (m, 3 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 4.11 (s, 3 H), 3.23 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.4, 133.2, 132.6, 131.6, 130.3, 130.0, 129.4, 129.1, 127.2, 126.3, 125.7, 125.1, 124.7, 123.1, 120.9, 120.7, 120.0, 104.6, 55.5, 27.8; MS (APCI): *m/z* = 273 (100%).

1-Methoxy-5-formylchrysene (13b)

Bromination of **12** (272 mg, 1 mmol) with NBS (196 mg, 1.1 mmol) was carried out by the procedure employed for preparation of **7a**. The product **13a** was reacted with DMSO (2.83 mL) and $NaHCO_3$ (168 mg, 2 mmol) according to the procedure employed for synthesis of **7b**. Purification of the product by chromatography on silica gel gave **13b** (213 mg, 74%): ^{1}H NMR (500MHz, $CDCl_3$) δ 10.60 (s, 1 H), 8.72 (d, *J* = 8.5 Hz, 1 H), 8.64 (d, *J* = 9.0 Hz, 1 H), 8.52 (d, *J* = 9.5 Hz, 1 H), 8.41 (s, 1 H), 8.09 (d, *J* = 8.0 Hz, 1 H), 7.78 (t, *J* = 7.5 Hz, 1 H), 7.75-7.50 (m, 3 H), 7.05 (d, *J* = 7.5 Hz, 1 H), 4.09 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 193.2, 155.8, 133.7, 132.0, 130.6, 130.41, 130.40, 130.0, 129.9, 129.1, 127.2, 126.7, 126.3, 124.6, 123.3, 122.1, 120.9, 120.2, 105.6, 55.8; HRMS Calcd for $C_{20}H_{14}O_2$ (M^+): 286.0994, found 286.0999.

1-Methoxybenzo[*α*]pyrene (1-MeO-BP)

The conversion of **13b** (162 mg, 0.566 mmol) to 1-MeO-BP was carried out by a procedure analogous to that employed for the synthesis of 3-MeO-BP from **7b**. There was obtained 1-MeO-BP (117 mg, 73%): ^{1}H NMR (500MHz, $CDCl_3$): δ 9.05-8.95 (m, 2 H), 8.67 (d, *J* = 9.5 Hz, 1 H), 8.38 (s, 1 H), 8.24 (dd, *J* = 9.5 and 2.0 Hz, 1 H), 7.96 (d, *J* = 8.5 Hz, 1 H), 7.83-7.75 (m, 3 H), 7.42-7.37 (m, 2 H), 4.17 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 154.1, 131.6, 130.3, 128.7, 128.0, 127.8, 127.7, 126.4, 126.1, 125.6, 125.5, 125.23, 125.19, 124.0, 123.8, 123.1, 121.6, 121.4, 121.3, 106.5, 56.0; MS (APCI): *m/z* = 283 (100%).

Benzo[*α*]pyrene-1-ol (1-HO-BP)

To a suspension of 1-MeO-BP (74 mg, 0.262 mmol) in HOAc (9 mL) was added HI solution (57%, 9 mL) under argon. The mixture was stirred for 1.5 h at 140 °C and reaction was monitored by TLC. Then the mixture was cooled to room temp. and poured onto crushed ice (50 g). The resulting precipitate was filtered off, washed with water. Then it was dissolved in EtOAc, washed with brine and dried over Na_2SO_4. After evaporation the solvent under vacuum, the residue was purified by chromatography on a silica gel column Elution with hexane/EtOAc (4/1) provided **1-HO-BP** (56 mg, 80%): ^{1}H NMR (500MHz, DMSO-d_6) δ 10.80 (bs, 1 H), 9.20-9.10 (m, 2 H), 8.60 (d, *J* = 9.0 Hz, 1 H), 8.54 (s, 1 H), 8.32 (d, *J* = 8.0 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.92-7.75 (m, 4 H), 7.52 (d, *J* = 8.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, DMSO-d^6): δ 153.1, 131.6, 130.4, 129.0, 128.4, 128.1, 127.5, 126.8, 126.6, 126.5, 126.2, 124.9, 124.0, 123.9, 123.8, 123.6, 122.4, 121.4, 120.5, 112.1; MS (APCI): *m/z* = 269 (70%), 283 (100%).

2-(7-Methoxynaphthalene-6-yl)benzene-1,3-dialdehyde (16)

2-Bromobenzene-1,3-dialdehyde (**15**) was synthesized by the reported method.31 To a solution of **15** (104 mg, 0.49 mmol) in DME (1 mL) under argon was added $Pd(PPh_3)_4$ (6 mg, 0.005 mmol). The resulting solution was stirred for 20 min, then boronic ester **3** (175 mg, 0.65 mmol) and EtOH (1.6 mL) were added. After 20 min, a solution of Na_2CO_3 (2 M, 0.5 mL) was added, and the mixture was heated at reflux for 4 h and reaction was monitored by TLC. Then it was cooled to room temp., and the precipitate was filtered off and washed with EtOAc (20 mL). The filtrate was evaporated to dryness. The residue was dissolved in EtOAc (30 mL), washed with water (3 × 10 mL), and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column. Elution with hexane/EtOAc (10:1) afforded **16** (124 mg, 88%): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.85 (s, 2 H), 8.27 (d, *J* = 8.0 Hz, 2 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 7.84 (d, *J* = 8.0 Hz, 1 H), 7.74 (s, 1 H), 7.68 (t, *J* = 8.0 Hz, 1 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.26 (d, *J* = 8.0 Hz, 1 H), 7.17 (s, 1 H), 3.94 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 190.9, 158.7, 148.2, 134.8, 133.8, 132.6, 130.2, 129.34, 129.31, 128.4, 128.3, 127.9, 125.8, 120.2, 105.7, 55.3; HRMS Calcd for $C_{19}H_{14}O_3$ (M^+): 290.0943, found 290.0948.

9-Methoxybenzo[*α*]pyrene

To a suspension of methoxylmethyltriphenylphosphonium chloride (324 mg, 0.95 mmol) in anhydrous THF (1.5 mL) under argon at room temp. was added *t*-BuOK (0.95 mL, 1 M in THF) dropwise. The resulting mixture was stirred at room temp. for 1.5 h and a solution of **15** (120 mg, 0.395 mmol) in THF (2 mL) was added. The resulting mixture was stirred for 1.5 h, monitored by TLC, and quenched by dilution with Et_2O (50 mL). The precipitate was filtered off, washed with Et_2O (30 mL), and the solvent was removed under pressure. The residue was chromatographed on a silica gel column eluted with hexane: EtOAc (10:1) to provide **17** as an oil (123 mg, 90%) used directly in the next step.

To a solution of (123 mg, 0.36 mmoL) in CH_2Cl_2 (4.5 mL) was added CH_3SO_3H (50 μL) at 0 °C. The mixture was stirred for 2.5 h at room temp., and reaction was monitored by TLC. Reaction was quenched by dilution with EtOAc (50 mL), and the solution was washed with saturated $NaHCO_3$ solution and dried over Na_2SO_4. After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column. Elution with hexane/Et_2O (20: 1) afforded 9-methoxybenzo[α]pyrene (71 mg, 70%): ^{1}H NMR (500MHz, $CDCl_3$): δ 8.81 (d, *J* = 9.0 Hz, 1 H), 8.35 (s, 1 H), 8.23-8.15 (m, 3 H), 8.12 (d, *J* = 9.0 Hz, 1 H), 8.05 (d, *J* = 7.5 Hz, 1 H), 7.97 (t, *J* = 7.5 Hz, 1 H), 7.91 (d, *J* = 9.0 Hz, 1 H), 7.84 (d, *J* = 9.0 Hz, 1 H), 7.43 (dd, *J* = 9.0 and 2.0 Hz, 1 H), 4.10 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 158.0, 131.8, 131.5, 130.5, 129.4, 128.2, 127.9, 126.9, 126.73, 126.70, 126.1, 126.0, 125.5, 125.0, 124.6, 124.4, 124.1, 122.1, 118.5, 101.9, 55.5; MS (APCI): *m/z* = 283 (100%).

Benzo[α]pyren-9-ol (9-HO-BP)

To a solution of 9-MeO-BP (64 mg, 0.226 mmol) in dry CH_2Cl_2 (15 mL) at -20 °C was added dropwise a solution of BBr_3 (1 M in CH_2Cl_2, 1.2 mL). The resulting purple solution was stirred at -20 °C for 30 min and then at room temp. overnight. The reaction mixture was then immersed in a dry ice, ice was added, and the organic solvent was removed at room temp. under reduced pressure. The aqueous suspension was extracted with EtOAc, and the combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness. The residue was chromatographed on a silica gel column eluted with 10-25% EtOAc in hexane to give **9-HO-BP** (44 mg, 72%): ^{1}H NMR (500MHz, acetone-d_6): δ 9.11 (bs, 1 H), 8.90 (d, *J* = 9.0 Hz, 1 H), 8.50 (s, 1 H), 8.45 (d, *J* = 2.0 Hz, 1 H), 8.29 (d, *J* = 9.0 Hz, 1 H), 8.22 (t, *J* = 7.5 Hz, 2 H), 8.08 (d, *J* = 7.5 Hz, 1 H), 8.00-7.90 (m, 2 H), 7.87 (d, *J* = 9.0 Hz, 1 H), 7.49 (dd, *J* = 9.0 and 2.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, acetone-d^6): δ 156.3, 131.9,

131.7, 130.8, 130.1, 128.3, 127.4, 126.9, 126.4, 126.3, 126.2, 125.8, 125.4, 125.0, 124.9, 124.3, 124.0, 122.3, 118.7, 105.1; MS (APCI): *m/z* = 269 (85%), 283 (100%).

1-Methyl-2-naphthyl trifluoromethanesulfonate (18b)

To a solution of 1-methyl-naphthalen-2-ol (6.32 g, 40 mmol) and pyridine (60 mmol) in CH_2Cl_2 (200 mL) was added Tf_2O (50 mmol) dropwise at 0 °C under argon. The mixture was stirred at room temp. for 3 h, then reaction was quenched by addition of water (50 mL). The organic layer was washed with water (3 × 50 mL), brine (50 mL), and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (10:1) to afford **18b** (10.67 g, 92%): ^{1}H NMR (500MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 1 H), 7.90 (d, *J* = 8.0 Hz, 1 H), 7.79 (d, *J* = 8.0 Hz, 1 H), 7.70-7.55 (m, 2 H), 7.39 (d, *J* = 9.0 Hz, 1 H), 2.73 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 145.4, 133.2, 132.4, 128.6, 128.4, 127.3, 126.7, 126.5, 124.6, 119.5, 118.7 (q, *J* = 320.1 Hz), 12.2; ^{19}FNMR (470.6 MHz, $CDCl_3$): δ -73.7; HRMS Calcd for $C_{12}H_9O_3F_3S$ (M^+): 290.0225, found 290.0226.

2-(1-Methyl-2-naphthyl)benzaldehyde (20)

Synthesis of **20** was carried out by the procedure for synthesis of **15**. Reaction of **19** (1.219 g, 4.8 mmol) with 2-bromobenzaldehyde (0.74 g, 4.0 mmol) provided **20** (0.728 g, 74%): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.86 (s, 1 H), 8.15 (d, *J* = 7.5 Hz, 2 H), 7.96 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.75-7.55 (m, 4 H), 7.45-7.37 (m, 2 H), 2.53 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 192.0, 146.2, 134.3, 134.0, 133.5, 133.0, 132.4, 132.1, 131.0, 128.5, 127.9, 127.7, 126.9, 126.6, 126.0, 125.9, 124.3, 16.2; HRMS Calcd for $C_{18}H_{14}O$ (M^+): 246.1045, found 246.1064.

12-Methylbenz[*a*]anthracene (22a)

Synthesis of **22a** was carried out by a procedure based on that employed for the synthesis of 3-MeO-BP. Reaction of **20** (738 mg, 3.0 mmol) by this method gave **22a** (363 mg, 50%): ^{1}H NMR (500MHz, $CDCl_3$) δ 8.65 (d, *J* = 9.0 Hz, 1 H), 8.39 (d, *J* = 9.0 Hz, 1 H), 8.23 (s, 1 H), 8.08 (d, *J* = 8.0 Hz, 1 H), 7.89 (d, *J* = 9.0 Hz, 1 H), 7.80-7.55 (m, 6 H), 3.43 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 133.8, 132.6, 131.52, 131.47, 131.4, 131.2, 129.8, 128.8, 128.4, 128.11, 128.06, 126.9, 126.5, 125.8, 125.4, 125.3, 125.2, 125.1, 20.9; MS (APCI): *m/z* = 243 (100%).

6-Formyloxybenzo[*α*]pyrene (24)

6-Formylbenzo[*α*]pyrene (**23**) was synthesized from BP by the procedure described previously.33 To a solution of **23** to (219 mg, 0.782 mmol) in CH_2Cl_2 (60 mL) was added *m*-chloroperbenzoic acid (403 mg, 2.35 mmol), and the mixture was stirred at room temp. for 72 h. Sodium thiosulfate (10 mL of 10% aqueous solution) was added, stirring was continued for 30 min, and the mixture was poured into aqueous $Na_2S_2O_3$ solution (10 mL). The aqueous phase was extracted with CH_2Cl_2 (50 mL) and combined with the organic layer, and the combined organic phase was washed with 10% aqueous sodium thiosulfate and brine, dried, and evaporated to dryness. The residue was purified by chromatography on silica gel. Elution with hexane/EtOAc (10:1) afforded pure **24** (93 mg, 40%): ^{1}H NMR (500MHz, $CDCl_3$) δ 9.07 (d, *J* = 8.5 Hz, 1 H), 9.01 (d, *J* = 9.0 Hz, 1 H), 8.78 (s, 1 H), 8.31 (d, *J* = 8.5 Hz, 2 H), 8.26 (d, *J* = 7.5 Hz, 1 H), 8.11 (d, *J* = 7.5 Hz, 1 H), 8.10-7.90 (m, 3 H), 7.90-7.80 (m, 2 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 160.1, 139.4, 131.4, 130.9, 129.5, 128.6, 127.7, 127.0, 126.53, 126.49, 126.47, 126.4, 125.6, 125.0, 124.5, 123.7, 123.4, 121.93, 121.86, 121.2, 120.4; HRMS Calcd for $C_{21}H_{12}O_2$ (M^+): 296.0837, found 296.0817.

Benzo[*a*]pyren-9,10-dione (BP-9,10-dione)

To a solution of 9-HO-BP (27 mg, 0.1 mmol) in DMSO (2 mL) was added IBX (56 mg, 0.2 mmol). The mixture was stirred at room temp. for 2 h. The purple precipitate was filtered off and purified by chromatography on a column of silica gel. Elution with EtOAc/$CHCl_3$ (1:10) gave BP-9,10-dione (23 mg, 82%) as a purple solid: ^{1}H NMR (500MHz, $CDCl_3$) δ 9.77 (d, *J* = 9.5 Hz, 1 H), 8.40-8.25 (m, 4 H), 8.15-8.10 (m, 2 H), 8.02 (s, 1 H), 7.74 (d, *J* = 10.0 Hz, 1 H), 6.60 (d, *J* = 9.5 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 181.9, 181.6, 147.6, 136.5, 134.8, 133.7, 133.6, 132.2, 131.4, 130.4, 128.5, 128.2, 128.0, 127.6, 127.5, 127.4, 125.6, 125.5, 123.7, 122.2; MS (APCI): *m/z* = 283 (100%).

Benzo[*a*]pyren-1,6-dione (BP-1,6-dione)

To a solution of BTI (63 mg, 0.147 mmol) in CH_3CN-H_2O (v/v = 2/1, 1 mL) was added 1-HO-BP (18 mg, 0.067 mmol) in CH_3CN-acetone-water (v/v/v = 5/2.5/2, 9.5 mL) dropwise under argon, and the mixture was stirred at room temp. for 1.5 h. The orange solid was filtered off and purified by chromatography on a silica gel column. Elution with $CHCl_3$/EtOAc (10/1) afforded BP-1,6-dione (15 mg, 78%) as an orange solid: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.5 Hz, 1 H), 8.64 (d, *J* = 8.0 Hz, 1 H), 8.56 (d, *J* = 8.0 Hz, 1 H), 8.47 (dd, *J* = 8.0 and 1.5 Hz, 1 H), 8.34 (d, *J* = 8.0 Hz, 1 H), 7.91 (d, *J* = 7.5 Hz, 1 H), 7.80 (dt, *J* = 8.0 and 1.5 Hz, 1 H), 7.74 (d, *J* = 10.0 Hz, 1 H), 7.64 (dt, *J* = 7.5 and 0.5 Hz, 1 H), 6.78 (d, *J* = 10.0 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 185.3, 183.4, 141.2, 135.1, 134.1, 133.9, 133.6, 131.1, 130.91, 130.86, 130.5, 130.1, 129.9, 129.6, 129.2, 128.7, 127.7, 127.2, 123.99, 123.97; MS (APCI): *m/z* = 283 (100%).

Benzo[*a*]pyren-3,6-dione (BP-3,6-dione)

Oxidation of 3-HO-BP (30 mg, 0.112 mmol) with BTI (105 mg, 0.244 mmol) by the procedure employed in the preceding example gave BP-3,6-dione (26 mg, 82%) as a red solid: ^{1}H NMR (500MHz, $CDCl_3$) δ 8.84 (d, *J* = 7.5 Hz, 1 H), 8.74 (d, *J* = 7.5 Hz, 1 H), 8.47 (dd, *J* = 8.0 and 1.0 Hz, 1 H), 8.39 (d, *J* = 7.5 Hz, 1 H), 8.29 (d, *J* = 8.0, 1 H), 7.85-7.70 (m, 3 H), 7.61 (t, *J* = 7.5 Hz, 1 H), 6.73 (d, *J* = 9.5 Hz, 1 H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 185.3, 183.6, 141.8, 135.4, 134.1, 132.8, 132.1, 131.4, 131.0, 130.7, 129.7, 129.6, 129.4, 129.1, 129.0, 128.7, 127.98, 127.96, 124.0, 123.5; MS (APCI): *m/z* = 283 (100%).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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29. Compound **10** was accompanied by minor amounts of one or more isomeric products that were separable from **10** by recrystallization.
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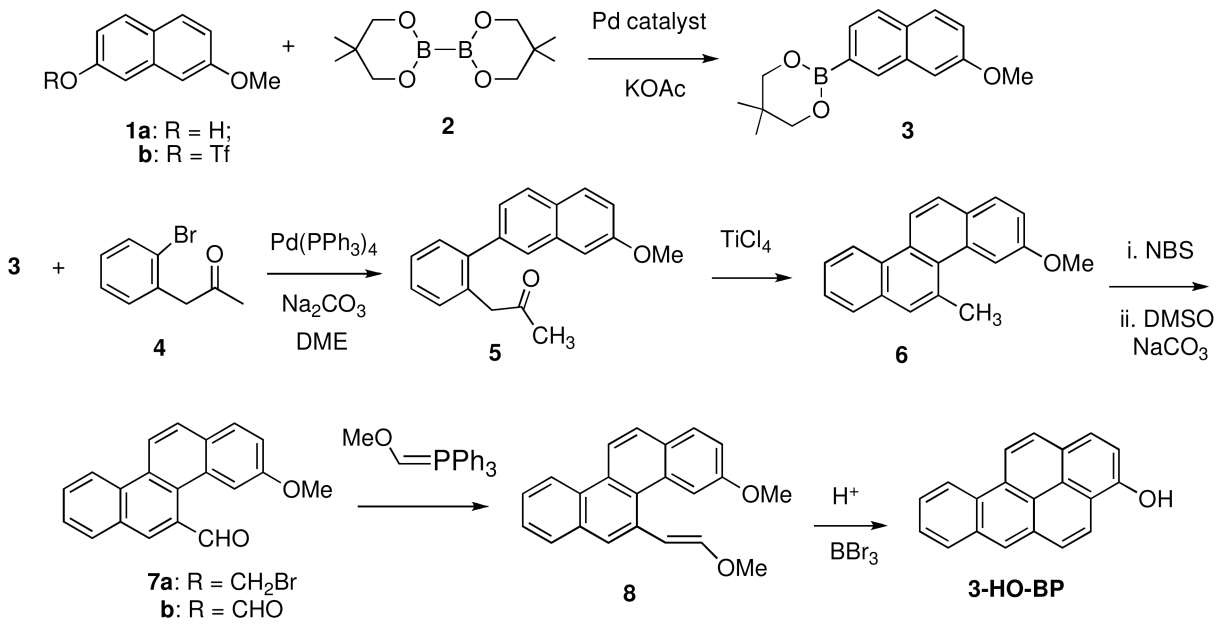
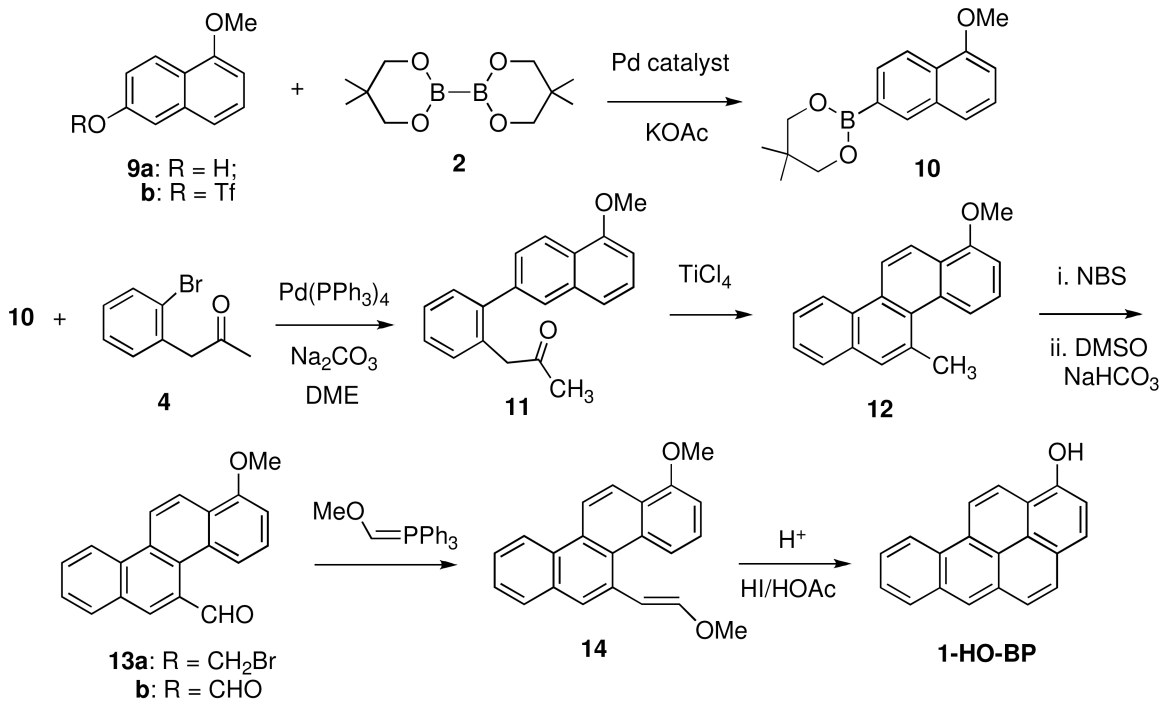
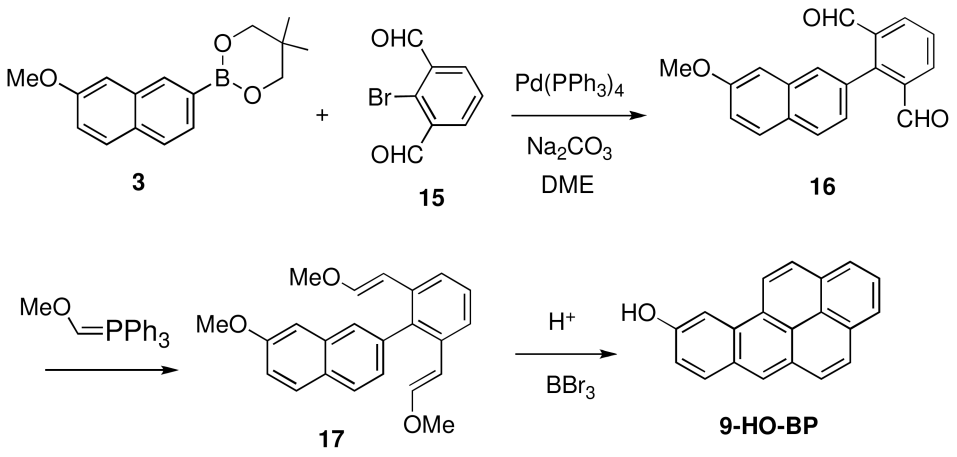
39. Electrophilic reactions of BP are well-known to take place preferentially at the 6-position in accord with of molecular orbital theoretical prediction (ref. 3a). The presence of electron-donating groups, such as methoxy, in the 1-, 3-, or 12-positions would likely increase the likelihood of substitution in the 6-position. A reviewer has pointed out that there are 36 possible BP quinone structures (Dias J. J Chem Inf Comput Sci. 1999; 30:53–61.). and that the BP quinones formed as metabolites are among those with the largest number of Kekulé structures (6).



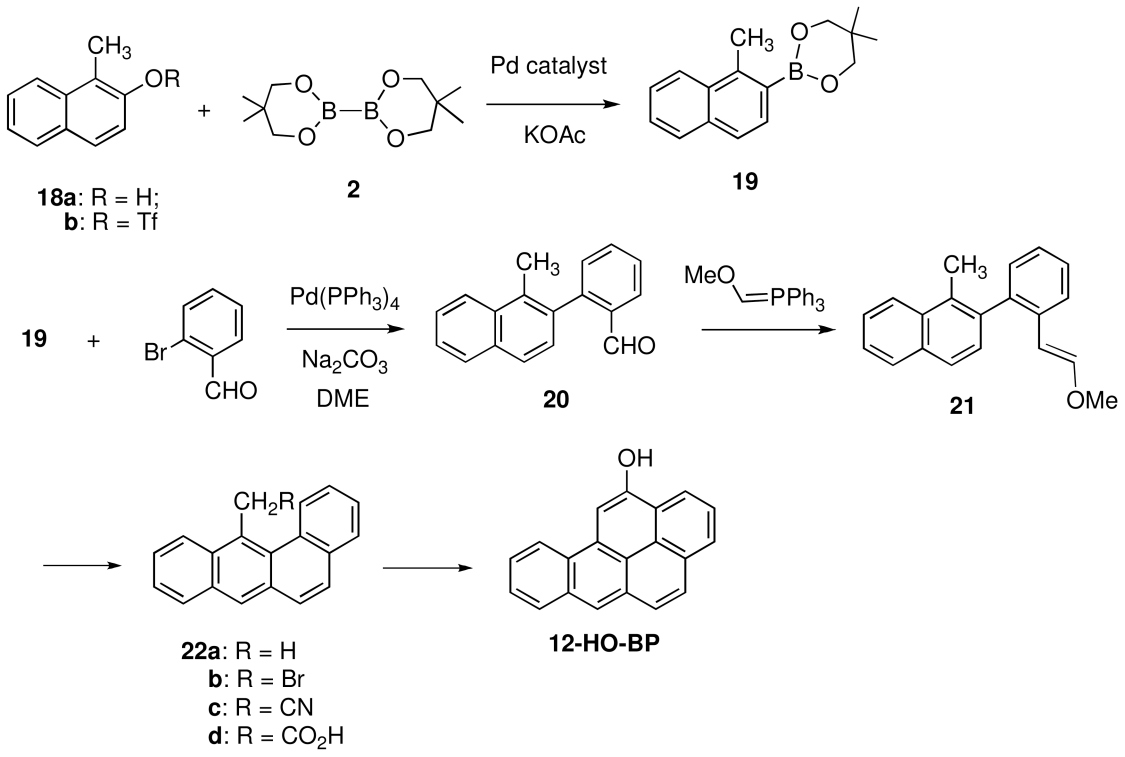
Scheme 1.



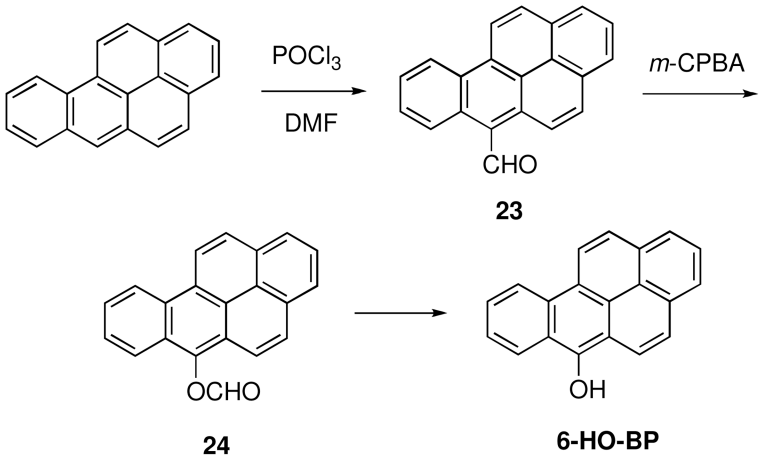
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

Table 1

Optimization of Conditions For Synthesis of 3[a]

entry	catalyst	solvent	time (h)	Yield (%)
1	$Pd(dppf)Cl_2$	DMSO	2	40
2	$Pd(pph_3)_4$	DMSO	3	35
3	$Pd(dppf)\ Cl_2$	CH_3CN	5	40
4	$Pd(dppf)Cl_2$	THF	3	70
5	$Pd(dppf)Cl_2$	dioxane	1.5	82

[a]Experimental: To a 2-neck flask flushed with N_2 were added Pd catalyst (0.03 mmol), **2** (1.2 mmol), and a solution of **1b** (1.0 mmol) in a solvent (8 mL). The mixture was stirred at 80 °C for the time indicated, the solvent was removed under vacuum, and the residue was chromatographed on silica gel.