



Synthesis of $^{13}\text{C}_4$ -labelled oxidized metabolites of the carcinogenic polycyclic aromatic hydrocarbon benzo[*a*]pyrene

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ABSTRACT

Polycyclic aromatic hydrocarbons (PAHs), such as benzo[*a*]pyrene (BaP), are ubiquitous environmental contaminants that are implicated in causing lung cancer. BaP is a component of tobacco smoke that is transformed enzymatically to active forms that interact with DNA. We reported previously development of a sensitive stable isotope dilution LC/MS method for analysis of BaP metabolites. We now report efficient syntheses of $^{13}\text{C}_4$ -BaP and the complete set of its $^{13}\text{C}_4$ -labelled oxidized metabolites needed as internal standards. They include the metabolites not involved in carcinogenesis (*Group A*) and the metabolites implicated in initiation of cancer (*Group B*). The synthetic approach is novel, entailing use of Pd-catalyzed Suzuki, Sonogashira, and Hartwig cross-coupling reactions combined with PtCl₂-catalyzed cyclization of acetylenic compounds. This synthetic method requires fewer steps, employs milder conditions, and product isolation is simpler than conventional methods of PAH synthesis. The syntheses of $^{13}\text{C}_4$ -BaP and $^{13}\text{C}_4$ -BaP-8-ol each require only four steps, and the ^{13}C -atoms are all introduced in a single step. $^{13}\text{C}_4$ -BaP-8-ol serves as the synthetic precursor of all the oxidized metabolites of ^{13}C -BaP implicated in initiation of cancer. The isotopic purities of the synthetic $^{13}\text{C}_4$ -BaP metabolites were estimated to be $\geq 99.9\%$.

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1. Introduction

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants that are implicated in initiation of lung cancer.^{1–3} PAHs are produced in the combustion of fossil fuels and other organic matter,^{1,3,4} and significant levels of PAHs are present

in tobacco smoke,⁵ auto and diesel engine emissions,⁶ and in fried, smoked, and charbroiled meats.^{1,3}

Metabolic activation of PAHs is required for expression of their carcinogenic activity.^{1,7,8} Benzo[*a*]pyrene (BaP)* has been most intensively investigated, and current evidence indicates that BaP is activated via three pathways, the *diol epoxide* path, the *quinone* path, and the *radical-cation* path (Fig. 1).^{1,3,7}

The *diol epoxide path* entails cytochrome P450 catalyzed oxidation of BaP to form metastable arene oxide metabolites that rearrange to phenols and/or undergo oxidation to dihydrodiols.¹ The (\pm)-*trans*-7,8-dihydrodiol of BaP (BaP 7,8-diol) (**1**) undergoes further enzyme-catalyzed oxidation to form highly mutagenic (\pm)-*anti*- and (\pm)-*syn*-diol epoxide metabolites (**4** and **5**) that react with DNA to form adducts.^{1,8} The *quinone path* entails aldo-keto reductase (AKR)-mediated oxidation of **1** to BaP 7,8-catechol (**3**). This enters into a redox cycle with O₂ to form BaP 7,8-dione (**2**) and reactive oxygen species (ROS) that attack DNA to form 8'-hydroxy-2'-deoxyguanosine (8'-HO-2'-dGua) and cause DNA strand breaks.^{1,7,9} The quinone **2** also combines with DNA to furnish stable and depurinating adducts. Collectively these events result in initiation of cancer. An analogous pathway involving quinone metabolites of steroids is involved in oestrogen-related carcinogenesis leading to breast cancer.¹⁰ The *radical-cation path* entails one-electron oxidation of BaP catalyzed by P450 monooxygenase or peroxidase to form

Abbreviations: AKR1A1, aldo-keto reductase 1A1 enzyme; BaP, benzo[*a*]pyrene; BaP 7,8-diol, *trans*-7,8-dihydro-7,8-dihydroxy-BaP; BaP 1,6-dione, benzo[*a*]pyren-1,6-dione; BaP 3,6-dione, benzo[*a*]pyren-3,6-dione; BaP 7,8-dione, benzo[*a*]pyren-7,8-dione; BTI, bis-(trifluoroacetoxy)iodobenzene; IBX, *o*-iodoxybenzoic acid; *anti*-BPDE, *trans*-7,8-dihydroxy-7,8-dihydro-*anti*-9,10-epoxy-BaP; *syn*-BPDE, *trans*-7,8-dihydroxy-7,8-dihydro-*syn*-9,10-epoxy-BaP; 8'-HO-2'-dGua, 8'-hydroxy-2'-deoxyguanosine; 1-HO-BaP, benzo[*a*]pyren-1-ol; 2-HO-BaP, benzo[*a*]pyren-2-ol; 3-HO-BaP, benzo[*a*]pyren-3-ol; 9-HO-BaP, benzo[*a*]pyren-9-ol; 12-HO-BaP, benzo[*a*]pyren-12-ol; $^{13}\text{C}_4$ -BaP, $^{13}\text{C}_4$ -labelled-BaP (^{13}C at C-4, -5, -5a, and -6 or at C-4, -5, -11, and -12, as specified); $^{13}\text{C}_4$ -1-HO-BaP, $^{13}\text{C}_4$ -labelled-1-HO-BaP (^{13}C at C-4, -5, -5a, and -6); $^{13}\text{C}_4$ -2-HO-BaP, $^{13}\text{C}_4$ -labelled-2-HO-BaP (^{13}C at C-4, -5, -5a, and -6); $^{13}\text{C}_4$ -3-HO-BaP, $^{13}\text{C}_4$ -labelled-3-HO-BaP (^{13}C at C-4, -5, -5a, and -6); $^{13}\text{C}_4$ -9-HO-BaP, $^{13}\text{C}_4$ -labelled-9-HO-BaP (^{13}C at C-4, -5, -5a, and -6); $^{13}\text{C}_4$ -12-HO-BaP, $^{13}\text{C}_4$ -labelled-12-HO-BaP (^{13}C at C-4, -5, -5a, and -6); PAH, polycyclic aromatic hydrocarbon; ROS, reactive oxygen species; TMSA, (trimethylsilyl)acetylene.

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† Dr. Wu and Dr. Xu were primarily responsible for development of the synthetic methods. Their contributions were of essentially equal importance.

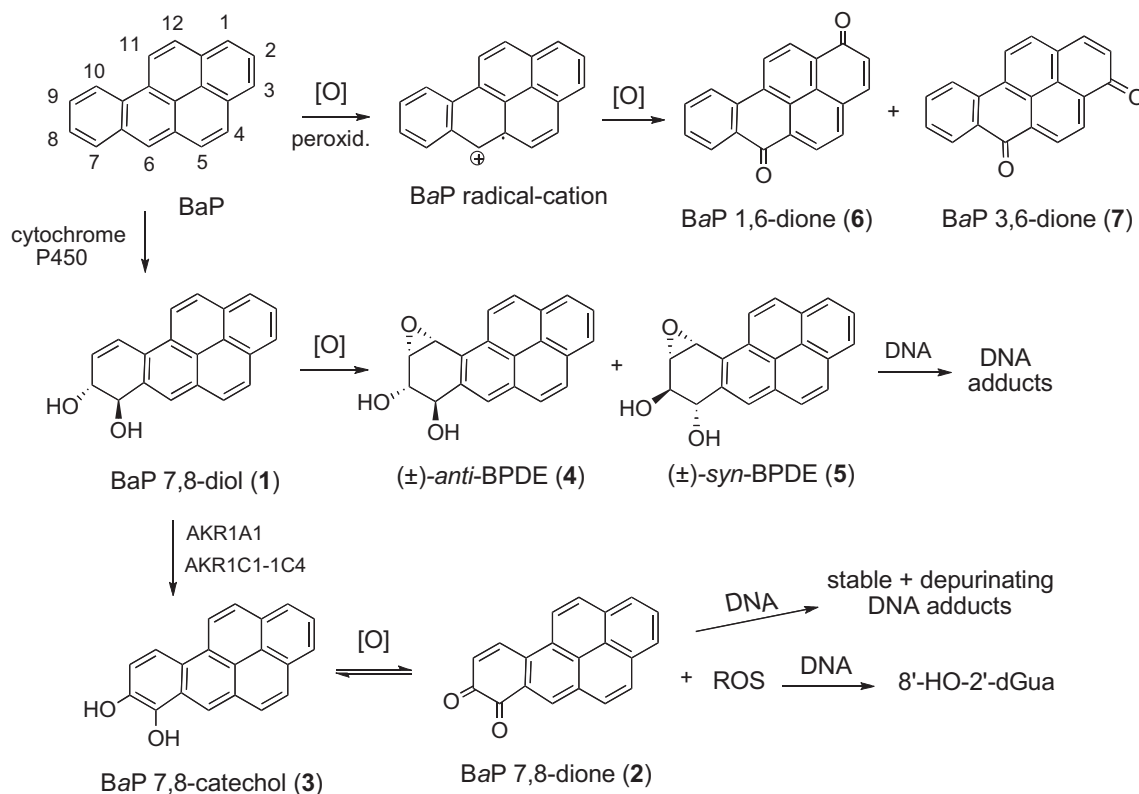


Fig. 1. Pathways of enzymatic activation of benzo[a]pyrene (BaP).

a BaP radical-cation that attacks DNA to yield depurinating adducts.^{11a} The signature metabolites formed via this pathway are BaP 1,6-dione (**6**) and BaP 3,6-dione (**7**). However, the involvement of the radical-cation pathway in carcinogenesis is disputed.^{1a,11b}

Human bronchoalveolar H358 cells were examined recently as a model for study of the metabolism of BaP in normal human lung cells.^{12,13} The findings indicated that activation of **1** in these cells involves the AKR-mediated quinone pathway.¹⁴ More recently, we developed a stable isotope dilution atmospheric pressure chemical ionization tandem mass spectrometric method to assay quantitatively the metabolites formed by all three metabolic pathways.¹⁵ The ¹³C₄-BaP metabolites whose syntheses are reported herein were employed as internal standards. In other studies, the syntheses of ¹³C₂-BaP, ¹³C₂-**1**, and ¹³C₂-**2** were also reported.¹⁶

2. Results

The aim of this investigation was to develop methods for efficient synthesis of the ¹³C₄-labelled analogues of the complete set of oxidized metabolites of BaP. The BaP metabolites may be divided into two groups on the basis of their involvement in carcinogenesis. *Group A* includes the oxidized metabolites of BaP that current evidence indicates do not play a role in carcinogenesis [the 1-, 2-, 3-, 9-, and 12-phenol isomers of BaP, BaP-1,6-dione (**6**) and BaP-3,6-dione (**7**)] (Fig. 1). *Group B* includes the oxidized metabolites of BaP implicated in carcinogenesis [BaP 7,8-diol (**1**), BaP 7,8-dione (**2**), BaP 7,8-catechol diacetate (**3**), (±)-*anti*-BPDE (**4**), and (±)-*syn*-BPDE (**5**)] (Fig. 1) plus 8-HO-BaP and 9-HO-BaP. The ¹³C₄-labelled BaP metabolites are needed as internal standards for LC/MS analysis of the BaP metabolites formed in human cells. This methodology is expected to provide a tool to assess the relative contributions of the three metabolic pathways to induction of cancer.

The methods of synthesis of the ¹³C₄-labelled BaP metabolites involve the use of Pd-catalyzed cross-coupling reactions (Suzuki, Sonogashira, and/or Hartwig) in combination with PtCl₂-catalyzed

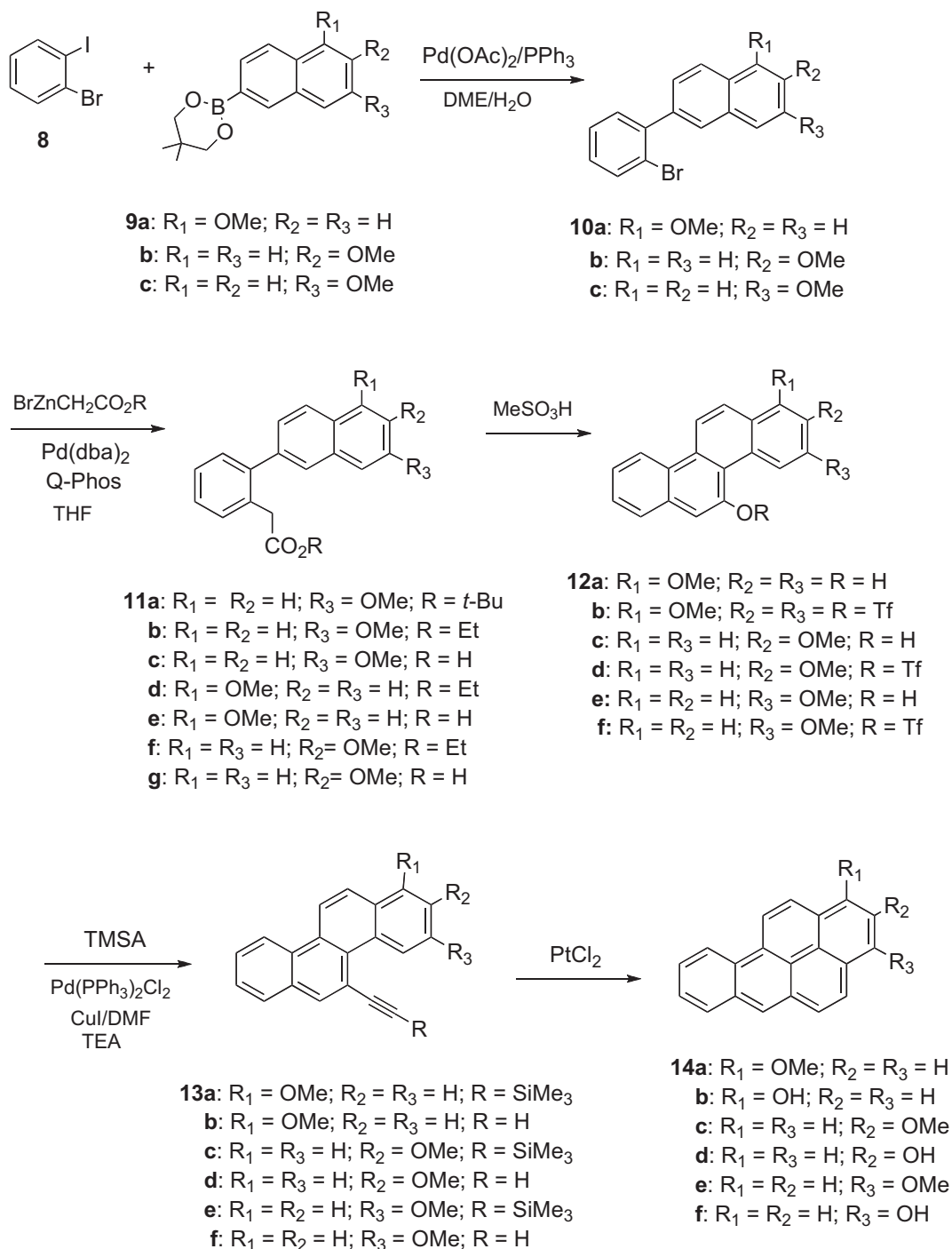
cyclization of acetylenic intermediates. This novel synthetic approach requires fewer steps and employs milder reaction conditions than the conventional methods for construction of PAH ring systems based on Friedel–Crafts chemistry. This synthetic method also has the advantage that the requisite ¹³C-labelled precursors are available from commercial sources.

2.1. Part I. BaP metabolites not implicated in carcinogenesis (Group A)

The initial synthetic targets were the ¹³C-labelled 1-, 2-, 3-, 9-, and 12-phenols of BaP. Exploratory studies to establish the feasibility of the planned synthetic approach were carried out with unlabelled precursors.

2.1.1. Synthesis of benzo[a]pyren-1-ol, -2-ol, and -3-ol.

2.1.1.1. *Benzo[a]pyren-3-ol (14f)*. It was shown previously that **14f** is the principal phenol metabolite of BaP formed in H358 human cells.¹³ Synthesis of **14f** was carried out by the sequence in Scheme 1. Palladium-catalyzed Suzuki–Miyaura cross-coupling of 1-bromo-2-iodobenzene (**8**) with the 2-boronate ester of 7-methoxynaphthalene (**9c**) took place at the iodo position regioselectively to furnish 2-(2-bromophenyl)-7-methoxynaphthalene (**10c**). Pd-catalyzed cross-coupling of **10c** with BrZnCH₂CO₂R was carried out by a procedure based on Hartwig's method.¹⁷ The choice of this route was dictated by the commercial availability of ¹³C₂-BrCH₂CO₂Et. However, only *tert*-butyl esters were employed in the published examples of this reaction. Direct reaction of **10c** with the zinc enolate of *tert*-butyl acetate afforded the expected *tert*-butyl ester adduct (**11a**) in moderate yield, but similar reaction of **10c** with the zinc enolate of ethyl acetate failed to furnish the adduct of the ethyl ester (**11b**). However, cross-coupling of **10c** with BrZnCH₂CO₂Et took place smoothly in the presence of Pd(dba)₂ and Q-phos to yield ethyl 2-(7-methoxynaphthalenyl)phenylacetate (**11b**) in moderate yield (40%).



Scheme 1.

A brief study of this reaction was undertaken with the intent of improving the yield of **11b** (Table 1). The yield was significantly improved by: (1) increasing the ratio of BrZnCH₂CO₂Et from 1.1 equiv to 2.0–3.0 equiv and (2) increasing the catalyst ratio from 1.0 mol % to 5.0 mol %. On the other hand, decreasing reaction time from 12 h to 1.5 h had minimal effect. The syntheses of the ¹³C-labelled compounds were carried out using the conditions in entry 5.

Treatment of **11b** with NaOH in EtOH gave 2-(7-methoxynaphthalen-2-yl)phenylacetic acid (**11c**) (90%) (Scheme 1), and **11c** underwent cyclization in the presence of MeSO₃H at 50 °C to furnish 3-methoxychrysen-5-ol (**12e**) (77%). This was

Table 1
Effect of conditions on reaction of **10c** with BrZnCH₂CO₂Et^a

Entry	Time (h)	Pd(dba) ₂ / Q-phos (mol %)	BrZnCH ₂ CO ₂ Et (equiv)	Yield 11b (%)
1	12	1	1.1	40
2	12	5	1.1	52
3	12	1	3.0	62
4	1.5	1	3.0	92
5 ^b	1.5	5	2.0	85
6	1.5	10	3.0	90
7	1.5	20	3.0	95

^a Reactions were carried out by the method reported.¹⁷

^b Syntheses of ¹³C-labelled analogues were carried out under these conditions.

converted to the triflate ester (**12f**), by treatment with trifluoromethanesulfonic anhydride, and Sonogashira coupling¹⁸ of **12f** with (trimethylsilyl) acetylene (TMSA) in the presence of Pd(PPh₃)₂Cl₂, CuI, and TEA in DMF gave (3-methoxychrysen-5-ylethynyl)-trimethylsilane (**13e**) (89%). Desilylation of **13e** with K₂CO₃ in MeOH/THF furnished 5-ethynyl-3-methoxychrysen-5-yl (**13f**) (90%), and PtCl₂-catalyzed cyclization¹⁹ of **13f** afforded 3-methoxybenzo[*a*]pyrene (**14e**) (60%). Demethylation of **13f** with BBr₃ gave benzo[*a*]pyren-3-ol (**14f**).

2.1.1.2. Benzo[*a*]pyren-1-ol (14b) and benzo[*a*]pyren-2-ol (14d). Syntheses of **14b** and **14d** were carried out by the method in Scheme 1. The 2-boronate ester of 5-methoxynaphthalene (**9a**) was prepared from 5-methoxy-2-naphthol,^{19,20} and Suzuki cross-coupling of **8** with **9a** in the presence of Pd(OAc)₂/PPh₃ provided 2-(2-bromophenyl)-5-methoxynaphthalene (**10a**). Hartwig coupling¹⁷ of **10a** with BrZnCH₂CO₂Et in the presence of Pd(dba)₂ and Q-phos afforded ethyl 2-(5-methoxynaphthalenyl)phenylacetate (**11b**). Ethanolysis of **11b** gave **11e**, and acid-catalyzed cyclization of **11e** furnished 1-methoxychrysen-5-ol (**12a**). Sonogashira coupling of the triflate ester (**12b**) with TMSA yielded (1-methoxychrysen-5-ylethynyl)trimethylsilane (**13a**). Removal of the TMS group followed by PtCl₂-catalyzed cyclization¹⁸ afforded 1-methoxybenzo[*a*]pyrene (**14a**), and demethylation gave **14b**. Synthesis of benzo[*a*]pyren-2-ol (**14d**) was carried out via an analogous sequence based on reaction of **8** with the 2-boronate ester of 6-methoxynaphthalene (**9b**) (Scheme 1).

2.1.2. Synthesis of benzo[*a*]pyren-9-ol (21b). Synthesis of **21b** was accomplished via an analogous sequence employing consecutive Suzuki, Hartwig, and Sonogashira cross-coupling reactions (Scheme 2). Pd-catalyzed Suzuki cross-coupling of 1-bromo-2-iodo-4-methoxybenzene (**15**)²¹ with naphthalene 2-boronic acid ester (**16**) furnished 2-(2-bromo-5-methoxyphenyl)naphthalene (**17**). Pd-catalyzed Hartwig coupling of **17** with BrZnCH₂CO₂Et provided ethyl 2-(naphthalen-2-yl)-5-methoxyphenyl acetate

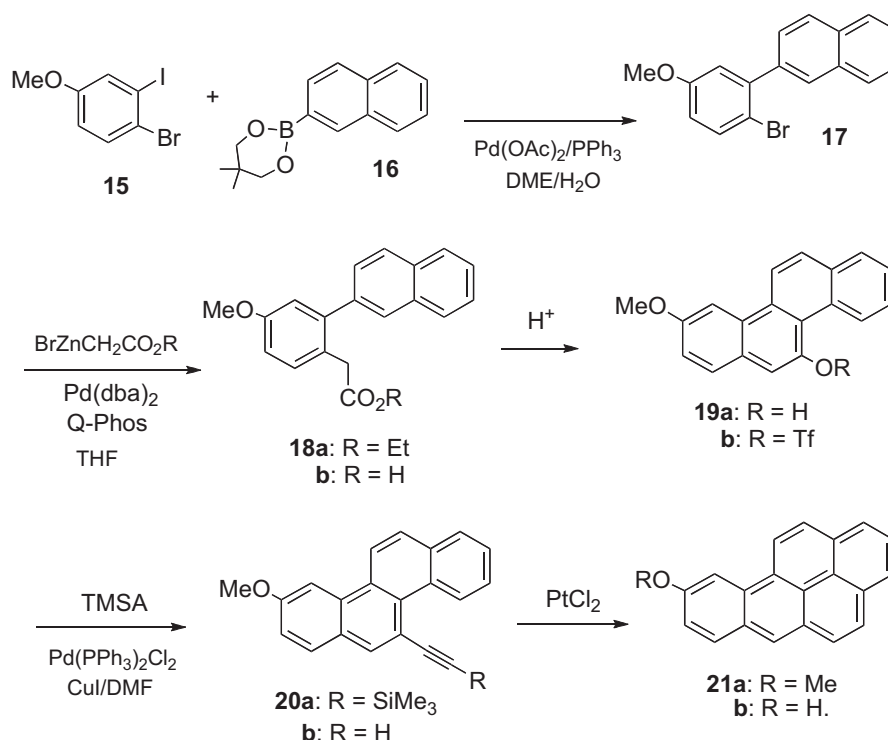
(**18a**). Ethanolysis of **18a** gave **18b**, which underwent acid-catalyzed cyclization to 3-methoxychrysen-11-ol (**19a**) and esterification to the triflate ester **19b**. Sonogashira coupling of **19b** with TMSA furnished ((9-methoxychrysen-5-yl)ethynyl) trimethylsilane (**20a**), and removal of the trimethylsilyl group gave 5-ethynyl-9-methoxychrysen-5-yl (**20b**). Finally, PtCl₂-catalyzed cyclization of **20b** furnished 9-methoxy-BaP (**21a**), and demethylation gave **21b**.

In principle, benzo[*a*]pyren-8-ol and its ¹³C₄-labelled analogue are accessible via an analogous sequence employing 1-bromo-2-iodo-5-methoxybenzene in place of **15**. However, 8-HO-BaP was synthesized by the alternative method described in Part II.

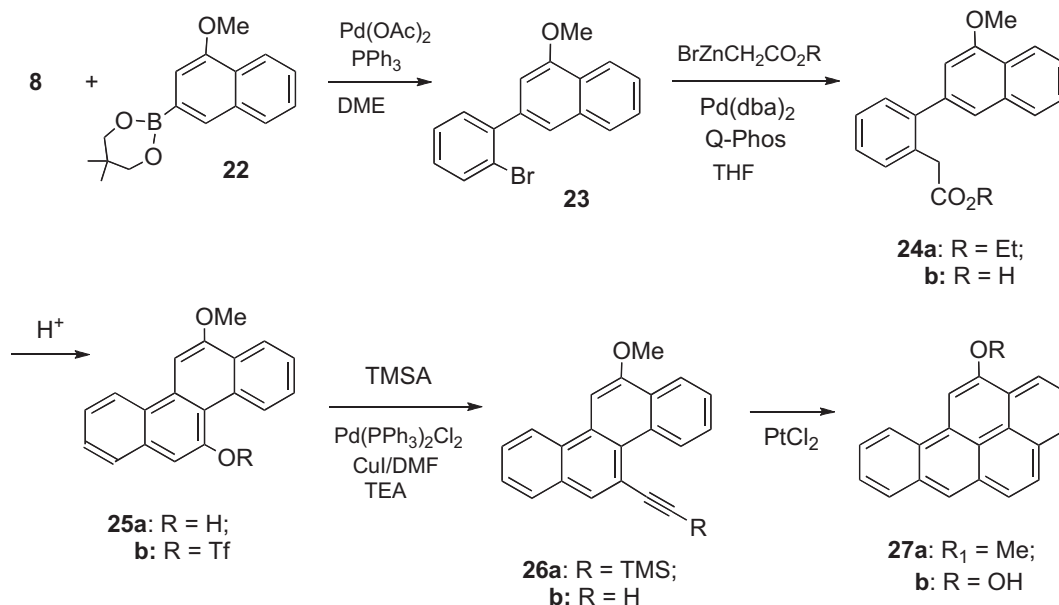
2.1.3. Synthesis of benzo[*a*]pyren-12-ol (27b). Synthesis of **27b** was accomplished by consecutive application of the Suzuki, Hartwig, and Sonogashira cross-coupling methods (Scheme 3). 4-Methoxynaphthalene-2-boronic acid ester (**22**) was synthesized from 2-bromo-4-methoxynaphthalene²² by modification of the method for preparation of **9c**. Pd-catalyzed Suzuki cross-coupling of **22** with **8** gave 2-(2-bromophenyl)-4-methoxynaphthalene (**23**), and Pd-catalyzed cross-coupling of **23** with BrZnCH₂CO₂Et provided ethyl 2-(4-methoxynaphthalen-2-yl)phenyl acetate (**24a**). Ethanolysis of **24a** afforded the carboxylic acid (**24b**), which underwent acid-catalyzed cyclization to 12-methoxychrysen-5-ol (**25a**). This phenol was converted to the triflate ester (**25b**), and Sonogashira coupling of **25b** with TMSA afforded **26a**. Desilylation of **26a** gave **26b**, and PtCl₂-catalyzed cyclization of the latter gave 12-methoxy-BaP (**27a**), which underwent demethylation to furnish **27b**.

2.1.4. Synthesis of benzo[*a*]pyren-1,6-dione (6) and -3,6-dione (7). The BaP-1,6- and 3,6-diones (**6** and **7**) were prepared by oxidation of BaP-1-ol (**14b**) and BaP-3-ol (**14f**) with bis(trifluoroacetoxy)iodobenzene (BTI) by the method reported.^{20,23}

2.1.5. Synthesis of ¹³C₄-labelled BaP and its Group A metabolites. BaP and ¹³C₄-BaP were synthesized by two methods. Method A was modelled on the synthesis of the 1-, 2-, and 3-phenols of BaP



Scheme 2.



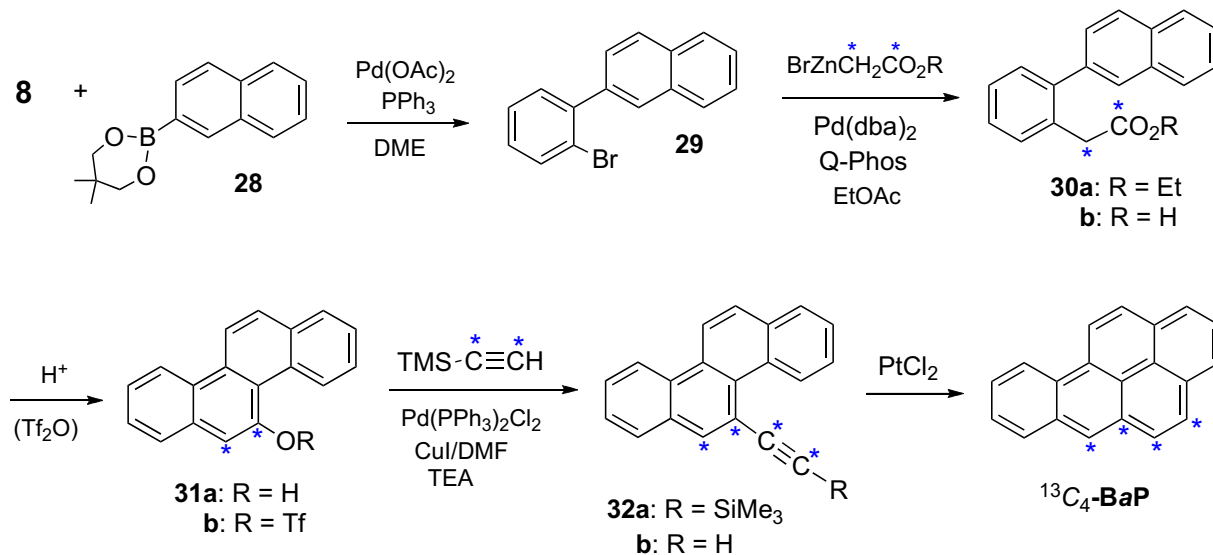
Scheme 3.

(Scheme 1). Initial studies were conducted with unlabelled precursors (Scheme 4). Pd-catalyzed Suzuki coupling of **8** with naphthalene-2-boronic acid ester (**28**) gave 2-(2-bromophenyl)naphthalene (**29**), and cross-coupling of **29** with BrCH₂CO₂Et by the modified Hartwig method gave ethyl 2-(2-naphthalenyl)phenylacetate (**30a**). Conversion of **30a** to the carboxylic acid (**30b**) and acid-catalyzed cyclization of **30b** gave chrysen-5-ol (**31a**). Sonogashira cross-coupling of the triflate ester (**31b**) with TMSA yielded (chrysen-5-ylethynyl)trimethyl silane (**32a**). Removal of the TMS group by treatment of **32a** with K₂CO₃ in MeOH/THF afforded **32b**, and PtCl₂-catalyzed cyclization gave BaP.

Synthesis of ¹³C₄-BaP was accomplished in seven steps from **29** (Scheme 4). The ¹³C-atoms were incorporated in pairs, the first pair in

the cross-coupling of the Reformatsky ester ¹³C₂-BrZnCH₂CO₂R with **29**, and the second pair in the Sonogashira cross-coupling²⁴ of ¹³C₂-TMSA with the triflate ester of ¹³C₂-chrysen-5-ol (**31b**). The ¹³C-atoms in ¹³C₄-BaP are located at the C-4, -5, -5a, and -6 aromatic ring positions.

The ¹³C₄-BaP phenol isomers (Fig. 2) were synthesized by methods analogous to those used for synthesis of the unlabelled BaP phenols. The ¹³C-atoms were at the 4,5,5a, and 6-positions of BaP, the same as those of the ¹³C-atoms in ¹³C₄-BaP. The methods for syntheses of ¹³C₄-1-HO-BaP, ¹³C₄-2-HO-BaP, and ¹³C₄-3-HO-BaP were analogous to those used for preparation of ¹³C₄-BaP (Scheme 4), using the appropriate methoxy-substituted derivatives (**9a**, **9b**, and **9c**) of the boronic acid in place of **28**. Similarly, the syntheses of ¹³C₄-HO-9-BaP and ¹³C₄-12-HO-BaP were carried out by



* Sites of the ¹³C-atoms.

Scheme 4.

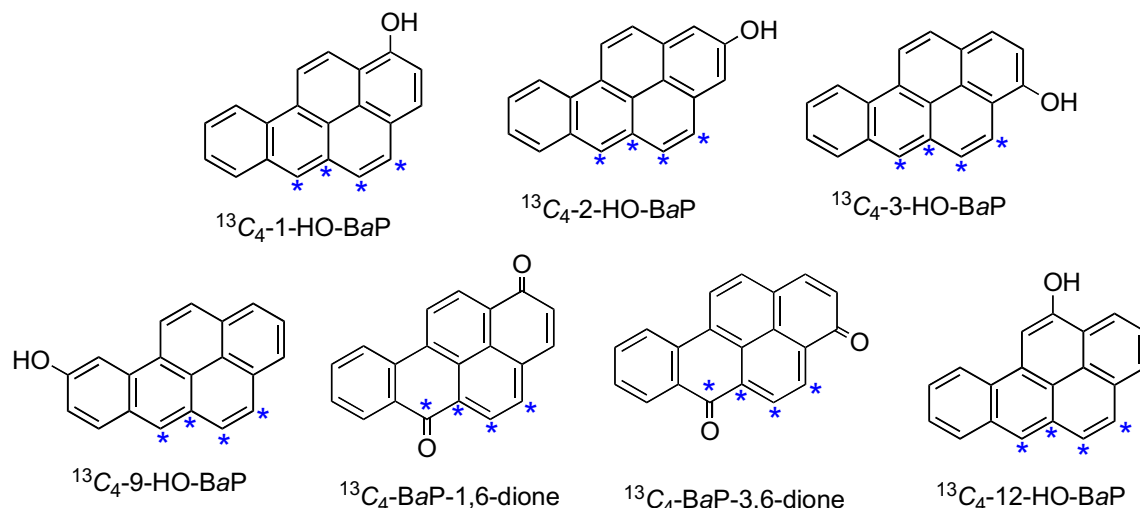


Fig. 2. $^{13}\text{C}_4$ -Labelled BaP phenols and quinones (* sites of ^{13}C -atoms).

appropriate modification of the procedures for synthesis of unlabelled 9-HO-BaP (Scheme 2) and 12-HO-BaP (Scheme 3).

The $^{13}\text{C}_4$ -labelled 1,6- and 3,6-quinones of BaP (Fig. 2) were prepared by oxidation of $^{13}\text{C}_4$ -1-HO-BaP and $^{13}\text{C}_4$ -3-HO-BaP with bis-(trifluoroacetoxy)iodobenzene (TBI).^{20,23}

2.2. Part II. BaP metabolites implicated in carcinogenesis (Group B)

The synthetic targets in this phase were the $^{13}\text{C}_4$ -labelled oxidized metabolites of BaP in Group B. They include the BaP metabolites implicated in initiation of cancer [Fig. 1: BaP 7,8-diol (**1**), BaP 7,8-dione (**2**), BaP 7,8-catechol diacetate (**3**), (\pm)-*anti*-BPDE (**4**), and (\pm)-*syn*-BPDE (**5**)] plus the 8- and 9-phenol isomers (**37c** and **37e**).

2.2.1. Synthesis of BaP, benzo[a]pyren-8-ol (37c**), and BaP-9-ol (**37e**) via Method B.** The BaP metabolites **1–5** were shown previously to be accessible via a synthetic route based on benzo[a]pyren-8-ol (**37c**).²⁰ Synthesis of BaP via an analogous route (designated Method B) was initially investigated. This method (Scheme 5) entailed Pd-catalyzed Suzuki–Miyaura cross-coupling of naphthylboronic acid (**33a**) with 1-bromo-2,6-dimethoxy benzene (**34a**). Reaction took place in the presence of $\text{Pd}(\text{OAc})_2\text{Cl}_2$, biphenyl(di-*tert*-butylphosphine), and K_3PO_4 in THF at 40 °C to yield 2-(2,6-dimethoxyphenyl)naphthalene (**35a**). Demethylation of **35a** with BBr_3 yielded 2-(2,6-dihydroxyphenyl)naphthalene (**35b**), and treatment of the latter with triflic anhydride and pyridine afforded the triflate diester (**35c**). Sonogashira coupling²⁴ of **35c** with TMSA in the presence of $\text{Pd}(\text{Ph}_3)_2\text{Cl}_2$, CuI, and TEA in DMF furnished **36a**. Reaction of **36a** with K_2CO_3 in MeOH/THF provided 2-(2,6-diethynylphenyl)naphthalene (**36b**), and PtCl_2 -catalyzed cyclization¹⁸ of **36b** gave BaP (**37a**). This synthetic route to BaP is shorter than Method A (Scheme 4), and the availability of these two synthetic approaches provides the basis for the synthesis of two different pure $^{13}\text{C}_4$ -BaP isotopomers.

Benzo[a]pyren-8-ol (**37c**) was synthesized by an analogous sequence (Scheme 5). 1-Bromo-2,6-dibenzoyloxybenzene (**34c**) was prepared by demethylation of **34a** with BBr_3 and base-catalyzed reaction of 1-bromo-2,6-dihydroxybenzene (**34b**) with benzyl bromide. Pd-catalyzed Suzuki cross-coupling of **34c** with 6-methoxynaphthylboronic acid (**33b**) furnished 2-(2,6-dibenzoyloxyphenyl)-6-methoxynaphthalene (**35d**), and removal of the benzyl groups (by hydrogenation over a Pd/C catalyst) afforded 2-(2,6-dihydroxyphenyl)-6-methoxynaphthalene (**35e**). Treatment of **35e** with triflic anhydride and pyridine provided the triflate diester (**35f**), and Pd-

catalyzed Sonogashira coupling of **35e** with TMSA furnished **36c**. Reaction of **36c** with K_2CO_3 in MeOH/THF afforded 2-(2,6-diethynylphenyl)naphthalene (**36d**), and PtCl_2 -catalyzed cyclization of **36d** furnished 8-MeO-BaP (**37b**). Demethylation of **37b** with BBr_3 afforded **37c**.

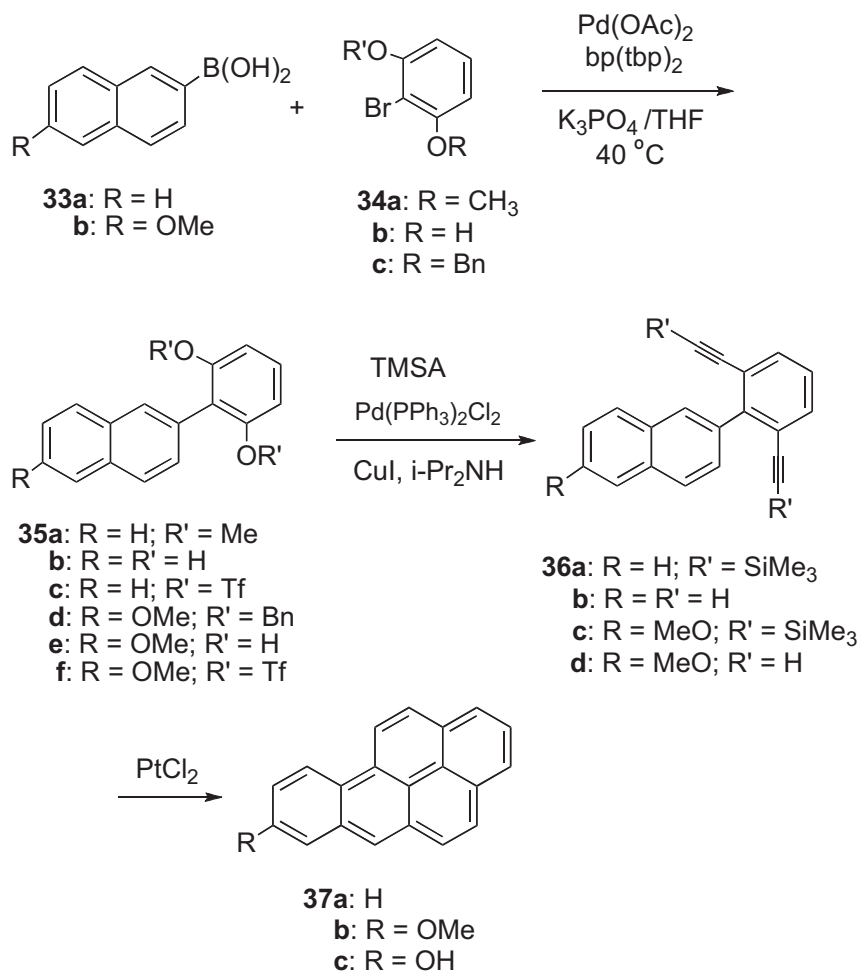
The synthetic approach in Scheme 5 was improved by use of 2,6-dibromo-1-iodobenzene (**38**)²⁵ in place of **34a** as the aryl halide reactant (Scheme 6). Compound **38** was prepared from 2,6-dibromoaniline by a modification of the literature method.²⁵ Suzuki cross-coupling of **33a** with **38** took place smoothly in the presence of $\text{Pd}(\text{PPh}_3)_4$ and KF in refluxing dioxane to provide 2-(2,6-dibromophenyl)naphthalene (**39a**). Double Sonogashira coupling of **39a** with TMSA followed by removal of the TMS groups and PtCl_2 -catalyzed cyclization gave BaP (**37a**). Synthesis of BaP via this route requires only four steps.

Benzo[a]pyren-8-ol (**37c**) was synthesized by a similar sequence (Scheme 6). Pd-catalyzed Suzuki coupling of **33b** with **38** provided 2-(2,6-dibromophenyl)-6-methoxynaphthalene (**39b**), and Pd-catalyzed double Sonogashira coupling of **39b** with TMSA furnished **40c**. This was transformed to **37c** by removal of the TMS groups to give **40d**, PtCl_2 -catalyzed cyclization to yield **37b**, and demethylation to **37c**.

Benzo[a]pyren-9-ol (**37e**) was synthesized by an analogous sequence (Scheme 6). Pd-catalyzed Suzuki–Miyaura cross-coupling of **33c** with **38** furnished **39c**, and this was converted to 9-HO-BaP (**37e**) via double Sonogashira coupling with TMSA, removal of the TMS groups, PtCl_2 -catalyzed cyclization, and demethylation. The boronate ester 2-(7-methoxynaphthalen-2-yl)-5,5-dimethyl-[1,3,2]dioxaborinane may be used in place of **33c**.

2.2.2. Synthesis of BaP metabolites (1–5) implicated in carcinogenesis. The BaP metabolites (**1–5**) implicated in initiation of cancer were shown previously to be synthetically accessible via a sequence based on **37c** (Scheme 7).^{20,23} This approach was employed for the synthesis of the BaP metabolites **1–5** and their $^{13}\text{C}_4$ -labelled analogues. Oxidation of **37c** with *o*-iodoxybenzoic acid (IBX) gave BaP 7,8-dione (**2**),^{19,20,23} and reduction of **2** with NaBH_4/O_2 furnished (\pm)-BaP 7,8-diol (**1**). Although BaP 7,8-catechol (**3a**) decomposes in air, it may be obtained pure as its diacetate derivative (**3b**) by reduction of **2** with NaBH_4 in DMF and diacetylation with Ac_2O /pyridine.^{20,23,26}

anti-BPDE (**4**) is by definition the BaP diol epoxide isomer with the epoxide oxygen atom on the molecular face opposite the benzylic hydroxyl group, whereas *syn*-BPDE (**5**) bears these groups on



Scheme 5.

the same face (Fig. 1).^{1b} (\pm)-*anti*-BPDE was synthesized by epoxidation of **1** with *m*-chloroperbenzoic acid,^{1b,27,28} and (\pm)-*syn*-BPDE was prepared by conversion of **1** to the *trans*-bromohydrin (**41**) and base-catalyzed cyclization by established methods.^{27,28} The pure enantiomers of **1** are readily accessible by chromatographic separation of the diastereomeric (–)-menthoxyacetate or MTPA esters of **1**.²⁹ Small amounts of the (+) and (–)-enantiomers of **1** may be obtained by chromatography of the racemates on chiral HPLC columns.³⁰

2.2.3. ¹³C₄-Labelled metabolites of BaP. Syntheses of ¹³C₄-BaP and its 1-, 2-, 3-, 9-, and 12-phenol isomers (with ¹³C at C-4, -5, -5a, and -6) ((Scheme 4 and Fig. 2) via *Method B* were described in Part I. Syntheses of ¹³C₂-BaP and its key oxidized metabolites ¹³C₂-BaP *trans*-7,8-diol (¹³C₂-**1**) and ¹³C₂-BaP-7,8-dione (¹³C₂-**2**) with ¹³C at C-5,11) (Fig. 2) were reported previously.¹⁶

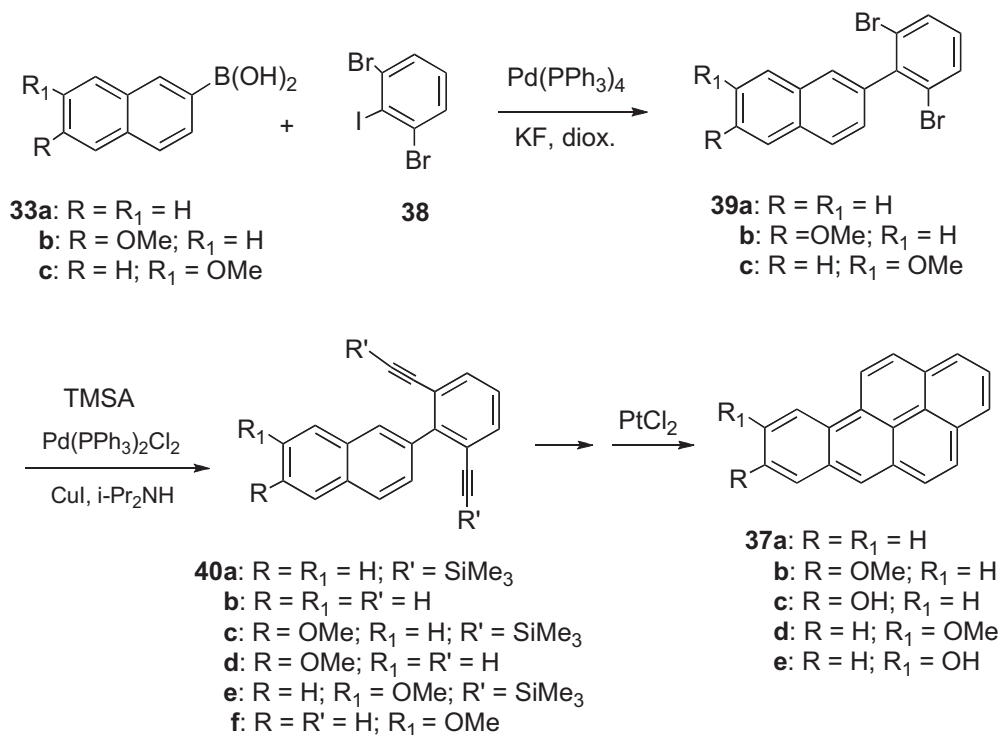
The structures of the ¹³C₄-labelled BaP derivatives synthesized in Part II via *Method B* are shown in Fig. 3. They include ¹³C₄-BaP, ¹³C₄-8-HO-BaP (¹³C₄-**37c**), and ¹³C₄-9-HO-BaP (¹³C₄-**37e**) (with ¹³C at C-4, -5, -11, and -12). Also included are the ¹³C₄-labelled metabolites of BaP implicated in carcinogenesis [¹³C₄-BaP *trans*-7,8-diol (¹³C₄-**1**), ¹³C₄-BaP 7,8-dione (¹³C₄-**2**), BaP 7,8-catechol (¹³C₄-**3**) and ¹³C₄-(\pm)-*anti*-BPDE (¹³C₄-**4**) with ¹³C at C-4, -5, -11, and -12] (Fig. 3). BaP 7,8-catechol (**3**) was previously shown to undergo decomposition in air.²⁶ For this reason the ¹³C₄-BaP 7,8-catechol was isolated as its stable diacetate (¹³C₄-**3** diacetate). And finally,

the mixed ¹³C₄-BaP tetraol isomers were prepared by hydrolysis of ¹³C₄-(\pm)-*anti*-BPDE.

¹³C₄-BaP (¹³C at C-4, -5, -11, and -12) was synthesized by a sequence similar to that for synthesis of unlabelled BaP (Scheme 8). Use of this method allowed incorporation of both pairs of ¹³C₄-atoms to take place in a single step. Thus, Pd-catalyzed double Sonogashira coupling of ¹³C₂-TMSA with **39a** furnished ¹³C₄-**40a**. Removal of the TMS groups by treatment of ¹³C₄-**40a** with K₂CO₃ in MeOH/THF converted it to ¹³C₄-**40b**, and PtCl₂-catalyzed cyclization¹⁸ of the latter afforded ¹³C₄-BaP (¹³C₄-**37a**).

The 8- and 9-phenols of ¹³C₄-BaP (¹³C₄-**37c** and ¹³C₄-**37e** with ¹³C at C-4, -5, -11, and -12) were synthesized from **39b** and **39c** via analogous sequences (Scheme 8). The ¹³C₄-labelled carcinogenic metabolites [¹³C₄-**1**, ¹³C₄-**2**, ¹³C₄-**4**, and ¹³C₄-**3** diacetate] were prepared from ¹³C₄-**37c** (Scheme 9) by methods analogous to those for synthesis of the unlabelled BaP metabolites (Scheme 7). Since the ¹³C₄-BaP metabolites derive from a common synthetic precursor (¹³C₄-**37c**), their ¹³C-atoms are at the same sites (C-4, -5, -11, and -12).

The isotopic purity of the synthetic ¹³C₄-labelled BaP metabolites was estimated by measurement of their product precursor ion transitions in the [12C] and [13C] channels (Supplemental Fig. 1). Based on a limit-of-detection (100), which is 10 fmol for the BaP-tetrol-1 and 6 fmol for all other BaP metabolites, and the injection of 10 pmol of each ¹³C₄-labelled compound on column, it is estimated that BaP-tetrol-1 has an isotopic purity >99.9% and for all other compounds the isotopic purity is >99.94%.



Scheme 6.

3. Discussion

The principal aim of this investigation was to synthesize the complete set of ¹³C₄-labelled oxidized metabolites of BaP needed as internal standards for a stable isotope dilution LC/MS method for their analysis.¹⁵ The BaP metabolites were divided into two groups (A and B) on the basis of their role in carcinogenesis. *Group A* includes the BaP metabolites that have no role in carcinogenesis [1-HO-, 2-HO-, 3-HO-, 9-HO-, and 12-HO-BaP, BaP-1,6-dione (**6**) and BaP-3,6-dione (**7**)] (Fig. 1), and the BaP metabolites in *Group B*

are those implicated in initiation of cancer [BaP 7,8-diol (**1**), BaP 7,8-dione (**2**), BaP 7,8-catechol (diacetate) (**3**), (±)-*anti*-BPDE (**4**), and (±)-*syn*-BPDE (**5**)] (Fig. 1), plus 8- and 9-HO-BaP.

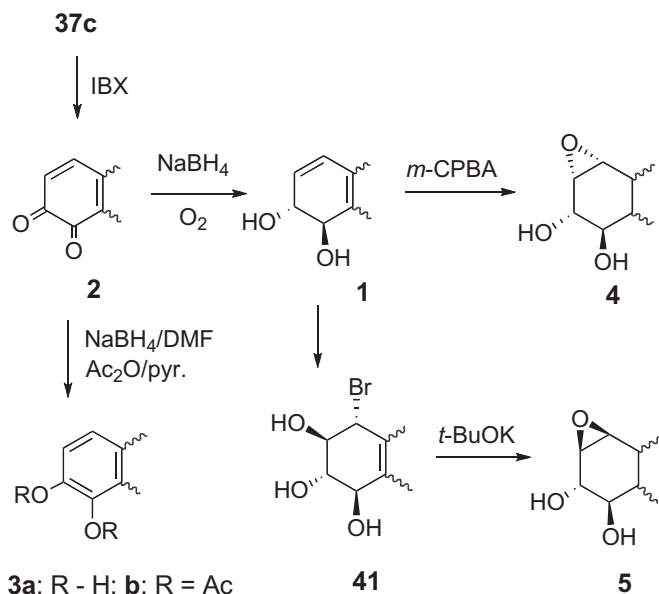
3.1. Synthesis of ¹³C₄-labelled oxidized metabolites of BaP

This paper reports efficient syntheses of BaP and its oxidized metabolites in *Groups A and B* and their ¹³C₄-labelled analogues. The synthetic design was influenced by: (1) the cost of the available ¹³C-labelled precursors; (2) the advantage of introducing the ¹³C-atoms late in the sequence; (3) the need to minimize the number of synthetic steps; and (4) the need for operational simplicity.

The *Group A* metabolites were synthesized via *Method A* (Suzuki, Sonogashira, and Hartwig cross-coupling reactions in combination with PtCl₂-catalyzed cyclization of an acetylenic intermediate) (Scheme 1). The *Group B* metabolites were synthesized via *Method B* (Suzuki and Sonogashira cross-coupling reactions combined with PtCl₂-catalyzed cyclization of a diacetylenic intermediate) (Scheme 8). The use of Suzuki cross-coupling for synthesis of biphenyls and other PAHs has been described,^{16,31} and the use of Sonogashira cross-coupling for synthesis of substituted phenanthrenes and terphenyls was reported.^{18,32}

Synthesis of PAHs by transition metal-catalyzed cross-coupling chemistry has advantages over their synthesis via conventional Friedel–Crafts chemistry.^{1b,33,34} This approach requires fewer steps, employs milder reaction conditions (no Lewis acid catalysts), isomeric coproducts are not formed, and purification of products is relatively simple and straightforward.

The only compounds synthesized by both methods were BaP, 8-HO-BaP (**37c**), and their ¹³C₄-labelled analogues (¹³C₄-BaP and ¹³C₄-**37c**). The synthesis of BaP by *Method A* requires eight steps (Scheme 1), whilst its synthesis by *Method B* requires only four steps (Scheme 6). Synthesis of the ¹³C₄-labelled analogues of BaP and **37c** by *Method A* affords ¹³C₄-BaP and ¹³C₄-**37c** (with ¹³C at C-4, -5, -5a, and -6) (Scheme 4), whilst their synthesis by *Method B* affords the



Scheme 7.

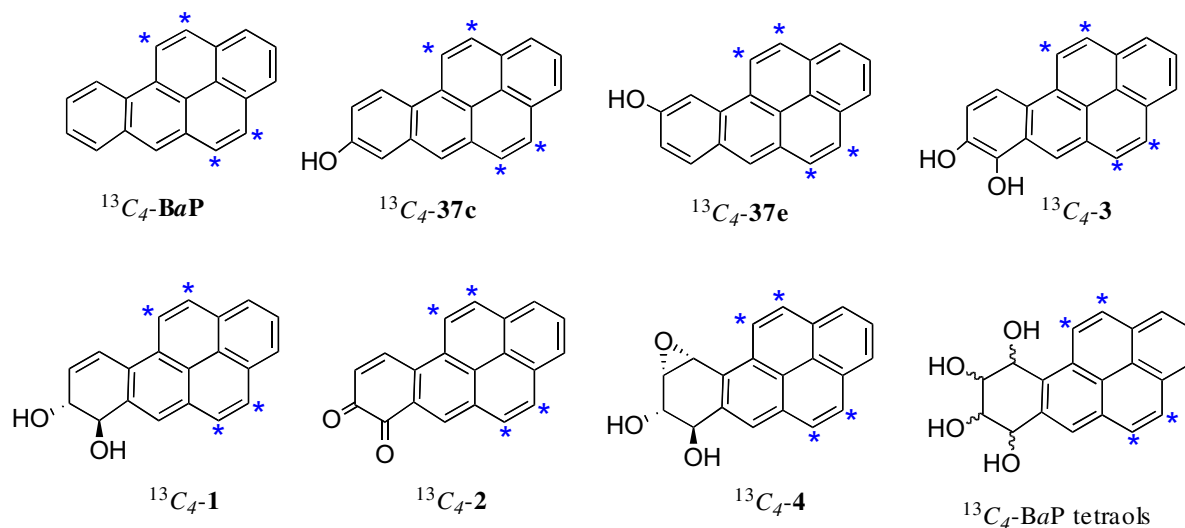
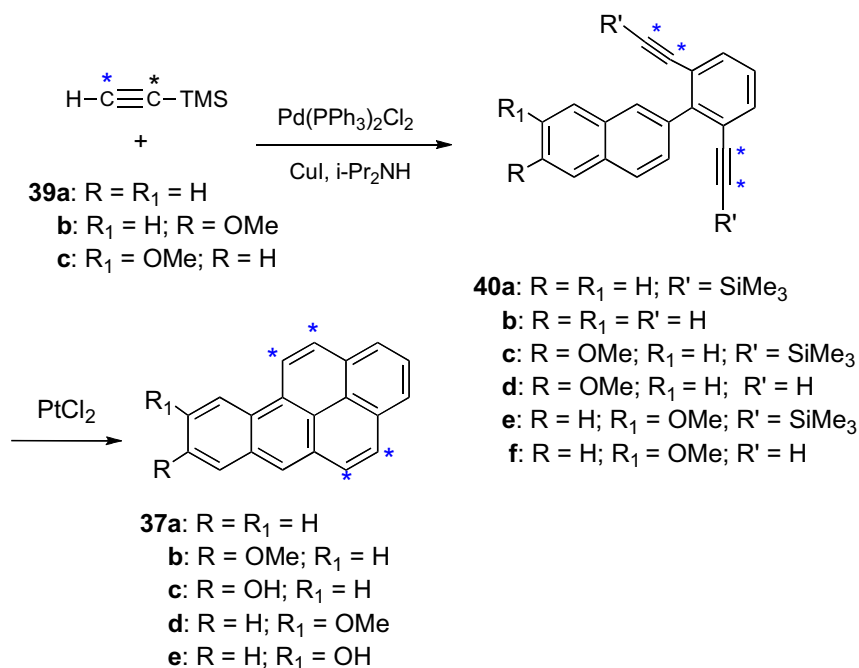
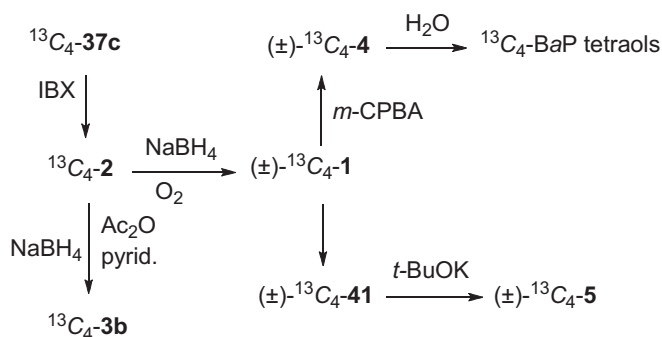


Fig. 3. $^{13}\text{C}_4$ -labelled BaP metabolites synthesized by Method B (* sites of ^{13}C -atoms).



Scheme 8.



Scheme 9.

isotopomers (with ^{13}C at C-4, -5, -11, and -12) (Fig. 3). Method B has the major advantage that all four ^{13}C -atoms are introduced simultaneously in a single step. The ease of synthesis of $^{13}\text{C}_4\text{-37c}$ via this route combined with the fact that $^{13}\text{C}_4\text{-37c}$ is a convenient synthetic precursor of all the $^{13}\text{C}_4$ -labelled active metabolites ($^{13}\text{C}_4\text{-1}$, $^{13}\text{C}_4\text{-2}$, $^{13}\text{C}_4\text{-3}$, $^{13}\text{C}_4\text{-4}$, and $^{13}\text{C}_4\text{-5}$) (Scheme 9) makes these compounds now all of them readily available for research in carcinogenesis.

3.2. Comparison with the syntheses of the $^{13}\text{C}_6$ -labelled BaP metabolites

Synthesis of $^{13}\text{C}_6$ -labelled analogues of several Group B BaP metabolites (1, 4, 5, and BaP tetraols) was reported by Diel et al.³⁵ Their synthetic approach entailed multistep synthesis of $^{13}\text{C}_6$ -pyrene from $^{13}\text{C}_6$ -benzene followed by its use as starting compound for synthesis of $^{13}\text{C}_6$ -9,10-dihydro-BaP (42) (Fig. 4) by Friedel–Crafts chemistry.^{1b,33,34}

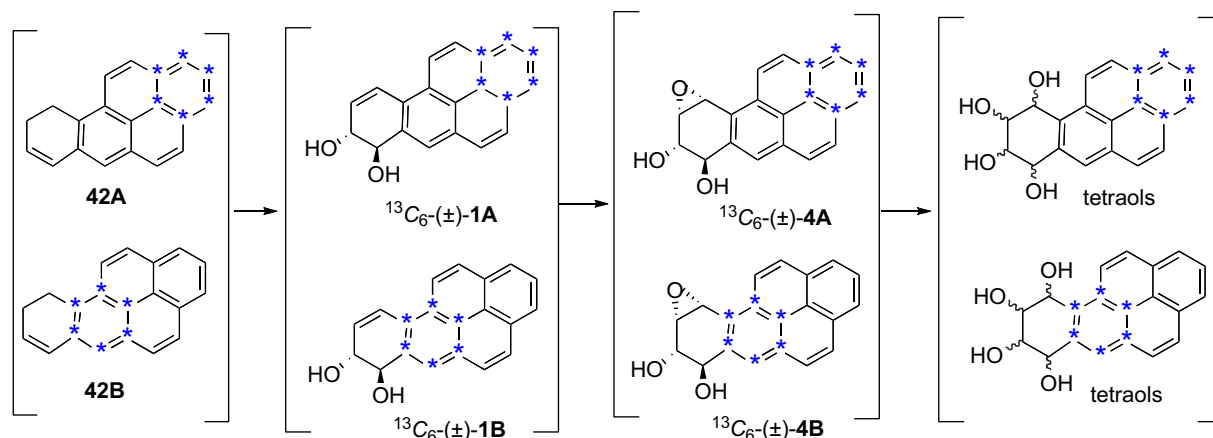


Fig. 4. $^{13}\text{C}_6$ -9,10-Dihydro-BaP was obtained as a mixture of isotomers (**42A** and **42B**) that were transformed into the (±)-dihydrodiols ($^{13}\text{C}_6$ -**1A** and $^{13}\text{C}_6$ -**1B**), and they were converted into the anti- and syn-(±)-diol epoxides (only the anti-isomers, $^{13}\text{C}_6$ -**4A** and $^{13}\text{C}_6$ -**4B**, are shown). Sites of ^{13}C -atoms are indicated by asterisks '*'.

As a consequence of the symmetry of $^{13}\text{C}_6$ -pyrene, **42** was obtained as a pair of isotomers (**42A** and **42B**) each possessing six ^{13}C -atoms, but in different aromatic rings (Fig. 4). This mixture was converted into the mixed $^{13}\text{C}_6$ -BaP 7,8-diol isotomers ($^{13}\text{C}_6$ -**1A** and $^{13}\text{C}_6$ -**1B**), and this was further transformed into the mixed $^{13}\text{C}_6$ -(±)-anti-BPDEs ($^{13}\text{C}_6$ -**4A** and $^{13}\text{C}_6$ -**4B**) by the established methods. The $^{13}\text{C}_6$ -(±)-syn-BPDEs (structures not shown) and the mixed $^{13}\text{C}_6$ -tetraols (from hydrolysis of the anti- and syn-BPDEs) were also prepared. The principal drawbacks to the use of these $^{13}\text{C}_6$ -labelled BaP analogues in biological studies are the large number of synthetic steps required, the $^{13}\text{C}_6$ -BaP metabolites are mixtures of isotomers, and many of the likely $^{13}\text{C}_6$ -BaP metabolites (e.g., those in Group A) are not obtainable by this approach.

4. Conclusions

This paper reports efficient syntheses of the complete set of oxidized metabolites of the prototypical carcinogenic PAH BaP (Group A and Group B metabolites) and their $^{13}\text{C}_4$ -labelled analogues. The synthetic $^{13}\text{C}_4$ -BaP metabolites were required as standards for quantitation of the metabolic profiles of BaP in human bronchoalveolar (H358) cells by stable isotope dilution liquid chromatography.¹⁵ The syntheses of these polycyclic aromatic molecules were accomplished by a novel approach based on use of Pd-catalyzed Suzuki, Sonogashira, and Hartwig cross-coupling reactions in combination with PtCl_2 -catalyzed cyclization of acetylenic intermediates. This method requires fewer steps, employs milder conditions, and product isolation is simpler than the conventional methods of PAH synthesis based on Friedel–Crafts chemistry. It is also potentially applicable to the synthesis of a broad range of other PAH compounds and their ^{13}C -labelled analogues.

5. Experimental section

5.1. Caution

Benzo[a]pyrene (BaP) has been designated a human carcinogen by the World Health Organization.² It should be handled with caution following procedures recommended in the *NIH Guidelines for the Laboratory Use of Chemical Carcinogens*. Although the oxidized metabolites of BaP are not included in the official list of carcinogens, prudence suggests that they should also be handled with caution.

5.2. Synthesis of 1-, 2-, and 3-HO-BaP (**14b**, **14d**, and **14f**) and their $^{13}\text{C}_4$ analogues

These phenols were synthesized by Pd-catalyzed Suzuki–Miyaura cross-coupling of **8** with the 2-boronate esters of 5-, 6-, and 7-methoxynaphthalene (**9a**, **9b**, or **9c**) (Scheme 1).

5.2.1. 2-(2-Bromophenyl)-7-methoxynaphthalene (10c**).** To a solution of $\text{Pd}(\text{OAc})_2$ (101 mg, 0.45 mmol), PPh_3 (354 mg, 1.35 mmol), K_2CO_3 (2.76 g, 20.0 mmol) in DME (30 mL) and H_2O (10 mL) at room temperature under argon was added **9c** (3.0 g, 11 mol). The resulting solution was stirred for 10 min, then **8** (2.83 g, 10.0 mmol) was added, and the solution was heated at reflux for 23 h and monitored by TLC. The resulting solution was cooled to room temperature, EtOAc (100 mL) was added, and the solution was washed with a saturated brine solution and water, and dried over anhydrous Na_2SO_4 . Following evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (150:1) to yield **10c** (2.84 g, 91%): ^1H NMR (500 MHz, CDCl_3) δ 7.87 (d, $J=8.5$ Hz, 1H), 7.82 (d, $J=8.5$ Hz, 1H), 7.81 (s, 1H), 7.76 (dd, $J=8.0$ and 1.0 Hz, 1H), 7.45–7.50 (m, 2H), 7.43 (dt, $J=7.0$ and 1.0 Hz, 1H), 7.22–7.30 (m, 3H), 3.97 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 157.9, 142.7, 139.1, 134.2, 133.1, 131.4, 129.2, 128.7, 128.1, 127.3, 127.1, 125.3, 122.7, 119.1, 106.0, 55.3; HRMS calcd for $\text{C}_{17}\text{H}_{14}\text{BrO}$ $[\text{M}+\text{H}]^+$ 313.0223, found 313.0225.

5.2.2. 2-(2-Bromophenyl)-5-methoxynaphthalene (10a**).** Reaction of **9a** with **8** gave **10a** (70%): ^1H NMR (500 MHz, CDCl_3) δ 8.43 (d, $J=8.5$ Hz, 1H), 7.91 (d, $J=1.5$ Hz, 1H), 7.79 (dd, $J=8.5$ and 1.0 Hz, 1H), 7.66 (dd, $J=8.5$ and 1.5 Hz, 1H), 7.42–7.57 (m, 4H), 7.66 (td, $J=7.5$ and 1.5 Hz, 1H), 6.91 (d, $J=7.5$ Hz, 1H), 4.08 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 155.5, 142.6, 139.1, 134.1, 133.1, 131.5, 128.8, 127.8, 127.4, 126.9, 126.4, 124.7, 122.8, 121.7, 120.4, 104.2, 55.5; HRMS calcd for $\text{C}_{17}\text{H}_{14}\text{BrO}$ $[\text{M}+\text{H}]^+$ 313.0223, found 313.0253.

5.2.3. 2-(2-Bromophenyl)-6-methoxynaphthalene (10b**).** Reaction of **9b** with **8** gave **10b**. Yield: 68%: ^1H NMR (500 MHz, CDCl_3) δ 7.80–7.90 (m, 3H), 7.75 (d, $J=8.0$ Hz, 1H), 7.59 (d, $J=8.5$ Hz, 1H), 7.39–7.50 (m, 2H), 7.20–7.30 (m, 3H), 3.98 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 158.0, 142.6, 136.4, 133.8, 133.1, 131.5, 129.6, 128.6, 128.5, 128.05, 128.02, 127.4, 126.2, 122.9, 119.1, 105.6, 55.3; HRMS calcd for $\text{C}_{17}\text{H}_{14}\text{BrO}$ $[\text{M}+\text{H}]^+$ 313.0223, found 313.0248.

5.2.4. Ethyl 2-(7-methoxynaphthalenyl)phenylacetate (11b**).** To a solution of **10c** (156 mg, 0.5 mmol), $\text{Pd}(\text{dba})_2$ (14.5 mg, 0.025 mmol),

and Q-phos (18 mg, 0.025 mmol) in THF (0.5 mL) was added ZnBrCH₂CO₂Et (1M in THF, 1.5 mL) dropwise at room temperature under argon. The resulting mixture was stirred for 2 h, monitored by TLC, and diluted with EtOAc (20 mL). After evaporation of the solvent, the residue was purified by chromatography on a silica gel column. Elution with hexane/EtOAc (40:1 to 20:1) gave **11b** (147 mg, 92%): ¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J*=8.0 Hz, 1H), 7.82 (d, *J*=9.0 Hz, 1H), 7.73 (s, 1H), 7.39–7.48 (m, 4H), 7.35 (dd, *J*=8.0 and 1.5 Hz, 1H), 7.21 (dd, *J*=8.5 and 2.5 Hz, 1H), 7.18 (d, *J*=2.5 Hz, 1H), 4.11 (q, *J*=7.0 Hz, 2H), 3.96 (s, 3H), 3.68 (s, 2H), 1.20 (t, *J*=7.0 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.9, 157.9, 142.5, 138.1, 134.3, 132.0, 130.29, 130.25, 129.1, 127.8, 127.5, 127.4, 127.1, 126.9, 125.3, 118.8, 105.8, 60.6, 55.2, 39.0, 14.0; HRMS calcd for C₂₁H₂₁O₃ [M+H]⁺ 321.1485, found 321.1483.

5.2.5. Ethyl ¹³C₂-2-(7-methoxynaphthalenyl)phenylacetate (**11b**). ¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J*=8.0 Hz, 1H), 7.82 (d, *J*=9.0 Hz, 1H), 7.73 (s, 1H), 7.48–7.39 (m, 4H), 7.35 (dd, *J*=8.0 and 1.5 Hz, 1H), 7.21 (dd, *J*=8.5 and 2.5 Hz, 1H), 7.18 (d, *J*=2.5 Hz, 1H), 4.11 (q, *J*=7.0 Hz, 2H), 3.96 (s, 3H), 3.68 (dd, *J*=129.0 and 8.0 Hz, 2H), 1.20 (t, *J*=7.0 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.0 (d, *J*=228.0 Hz), 39.0 (d, *J*=228.0 Hz); HRMS calcd for ¹³C₂-C₂₁H₂₀NaO₃ [M+Na]⁺ 345.1372, found 345.1349.

5.2.6. Ethyl 2-(5-methoxynaphthalenyl)phenylacetate (**11d**). Reaction of **10a** with ZnBrCH₂CO₂Et gave **11d** (93%): ¹H NMR (500 MHz, CDCl₃) δ 8.36 (d, *J*=8.5 Hz, 1H), 7.80 (d, *J*=1.5 Hz, 1H), 7.55–7.35 (m, 7H), 6.89 (dd, *J*=6.5 and 2.0 Hz, 1H), 4.12 (q, *J*=7.0 Hz, 2H), 4.07 (s, 3H), 3.68 (s, 2H), 1.22 (t, *J*=7.0 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.9, 155.4, 142.4, 139.1, 134.2, 132.0, 130.31, 130.26, 127.6, 127.5, 127.1, 126.8, 126.3, 124.5, 121.9, 120.2, 103.9, 60.6, 55.5, 38.9, 14.0; HRMS calcd for C₂₁H₂₀NaO₃ [M+Na]⁺ 343.1305, found 343.1330.

5.2.7. Ethyl 2-(6-methoxynaphthalenyl)phenylacetate (**11f**). Reaction of **10b** with ZnBrCH₂CO₂Et afforded **11f** (90%): ¹H NMR (500 MHz, CDCl₃) δ 7.90–7.70 (m, 3H), 7.50–7.30 (m, 5H), 7.25–7.15 (m, 2H), 4.10 (q, *J*=7.0 Hz, 2H), 3.98 (s, 3H), 3.67 (s, 2H), 1.20 (t, *J*=7.0 Hz, 3H); ¹³C NMR (125.8 MHz, CDCl₃) δ 172.0, 157.9, 142.5, 136.4, 133.6, 132.2, 130.5, 130.4, 129.6, 128.7, 128.1, 127.9, 127.5, 127.2, 126.6, 119.2, 105.6, 60.8, 55.4, 39.1, 14.2; HRMS Calcd for C₂₁H₂₁O₃ [M+H]⁺ 321.1485, found 321.1517.

5.2.8. 2-(7-Methoxynaphthalenyl)phenylacetic acid (**11c**). To a solution of **11b** (467 mg, 1.46 mmol) in EtOH (18 mL) and H₂O (6 mL) was added NaOH (175 mg, 4.38 mmol). The resulting mixture was heated at reflux for 1 h, and reaction was monitored by TLC. This was evaporated to dryness, and the residue was diluted with water (50 mL), and acidified with 37% HCl. The solid was filtered off, and dried to provide **11c** (385 mg, 90%): ¹H NMR (500 MHz, acetone-*d*₆) δ 8.02–7.83 (m, 2H), 7.76 (s, 1H), 7.50–7.44 (m, 1H), 7.44–7.29 (m, 5H), 7.19 (dd, *J*=9.0 and 2.5 Hz, 1H), 3.94 (s, 3H), 3.67 (s, 2H); ¹³C NMR (125.8 MHz, DMSO-*d*₆) δ 173.3, 158.1, 142.4, 139.4, 134.6, 133.2, 131.3, 130.3, 129.6, 127.9, 127.4, 127.0, 125.4, 119.2, 106.7, 55.7; HRMS calcd for C₁₉H₁₆O₃ [M]⁺ 292.1094, found 292.1061.

5.2.9. 2-(5-Methoxynaphthalenyl)phenylacetic acid (**11e**). Hydrolysis of **11d** gave **11e** (92%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.18 (d, *J*=9.0 Hz, 1H), 7.77 (s, 1H), 7.60–7.35 (m, 7H), 6.99 (dd, *J*=5.5 and 3.0 Hz, 1H), 3.99 (s, 3H), 3.60 (s, 2H); ¹³C NMR (125.8 MHz, DMSO-*d*₆) δ 173.2, 155.3, 142.1, 139.3, 134.3, 133.1, 131.4, 130.3, 128.0, 127.7, 127.5, 127.2, 127.0, 124.2, 121.9, 120.6, 105.1, 56.1, 39.1; HRMS calcd for C₁₉H₁₇O₃ [M+H]⁺ 293.1172, found 293.1143.

5.2.10. 2-(6-Methoxynaphthalenyl)phenylacetic acid (**11g**). Hydrolysis of **11f** gave **11g** (90%): ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.87 (d, *J*=8.0 Hz, 1H), 7.75 (s, 1H), 7.45–7.29 (m, 6H), 7.20 (d, *J*=8.0 Hz, 1H), 3.89 (s, 3H), 3.57 (s, 2H); ¹³C NMR (125.8 MHz,

DMSO-*d*₆) δ 173.3, 157.9, 142.3, 136.5, 133.7, 133.1, 131.3, 130.5, 129.9, 128.7, 128.2, 127.83, 127.75, 127.4, 127.0, 119.5, 106.2, 55.7, 39.1; HRMS calcd for C₁₉H₁₇O₃ [M+H]⁺ 293.1172, found 293.1143.

5.2.11. ¹³C₂-2-(7-Methoxynaphthalenyl)phenylacetic acid (**11c**). ¹H NMR (500 MHz, DMSO-*d*₆) δ 12.23 (br s, 1H), 8.00–7.83 (m, 2H), 7.87 (s, 1H), 7.50–7.29 (m, 6H), 7.19 (dd, *J*=9.0 and 2.5 Hz, 1H), 3.89 (s, 3H), 3.57 (dd, *J*=128.5 and 8.0 Hz, 2H); ¹³C NMR (125.8 MHz, DMSO-*d*₆) δ 173.2 (d, *J*=218.0 Hz), 39.0 (d, *J*=218.0 Hz); HRMS calcd for ¹³C₂-C₁₉H₁₇O₃ [M+H]⁺ 295.1239, found 295.1211.

5.2.12. 3-Methoxychrysen-5-ol (**12e**). A suspension of **11c** (292 mg, 1 mmol) in MeSO₃H was heated at 50 °C for 1 h and monitored by TLC, then cooled to room temperature, and poured onto crushed ice (50 g). The solid was filtered off, and dissolved in EtOAc (50 mL). The solution was washed with brine and water, and dried over anhydrous Na₂SO₄. After evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column. Elution with hexane/EtOAc (10:1 to 5:1) gave **12e** (221 mg, 77%): ¹H NMR (500 MHz, acetone-*d*₆) δ 9.79 (s, 1H), 9.62 (d, *J*=3.0 Hz, 1H), 8.78 (d, *J*=11.0 Hz, 1H), 8.72 (d, *J*=11.0 Hz, 1H), 8.04 (d, *J*=11.5 Hz, 1H), 7.99 (d, *J*=11.0 Hz, 1H), 7.82 (d, *J*=11.0 Hz, 1H), 7.65–7.45 (m, 3H), 7.33 (dd, *J*=8.5 and 2.5 Hz, 1H), 4.00 (s, 3H); ¹³C NMR (125.8 MHz, acetone-*d*₆) δ 158.1, 154.4, 133.3, 132.2, 131.5, 129.3, 128.1, 127.9, 126.8, 126.1, 126.0, 123.7, 123.4, 119.0, 116.6, 110.2, 108.6, 54.7; HRMS calcd for C₁₉H₁₅O₂ [M+H]⁺ 275.1067, found 275.1062.

5.2.13. ¹³C₂-3-Methoxychrysen-5-ol (**12e**). ¹H NMR (500 MHz, DMSO-*d*₆) δ 10.87 (s, 1H), 9.51 (d, *J*=2.5 Hz, 1H), 8.78 (d, *J*=8.5 Hz, 1H), 8.72 (d, *J*=9.0 Hz, 1H), 8.04 (d, *J*=9.0 Hz, 1H), 8.01 (d, *J*=9.0 Hz, 1H), 7.88–7.78 (m, 1H), 7.62–7.42 (m, 3H), 7.33 (dd, *J*=9.0 and 2.5 Hz, 1H), 3.96 (s, 3H); ¹³C NMR (125.8 MHz, DMSO-*d*₆) δ 154.9 (d, *J*=277.5 Hz), 108.7 (d, *J*=277.5 Hz); HRMS calcd for ¹³C₂-C₁₉H₁₄O₂ [M]⁺ 276.1055, found 276.1056.

5.2.14. 1-Methoxychrysen-5-ol (**12a**). Similar acid-catalyzed cyclization of **11e** gave **12a** (80%): ¹H NMR (500 MHz, acetone-*d*₆) δ 9.66 (s, 1H), 9.65 (d, *J*=8.5 Hz, 1H), 8.86 (d, *J*=9.0 Hz, 1H), 8.81 (d, *J*=8.5 Hz, 1H), 8.40 (d, *J*=9.0 Hz, 1H), 7.82 (d, *J*=9.0 Hz, 1H), 7.65–7.49 (m, 4H), 7.17 (d, *J*=7.5 Hz, 1H), 4.09 (s, 3H); ¹³C NMR (125.8 MHz, acetone-*d*₆) δ 155.2, 154.3, 133.2, 131.9, 131.3, 126.8, 126.2, 126.01, 125.96, 124.3, 123.8, 123.4, 121.5, 121.4, 120.5, 109.0, 108.9, 105.2, 55.2; HRMS calcd for C₁₉H₁₅O₂ [M+H]⁺ 275.1067, found 275.1091.

5.2.15. ¹³C₂-1-Methoxychrysen-5-ol (**12a**). ¹H NMR (500 MHz, acetone-*d*₆) δ 10.87 (s, 1H), 9.55 (d, *J*=9.0 Hz, 1H), 8.86 (d, *J*=9.0 Hz, 1H), 8.80 (d, *J*=8.5 Hz, 1H), 8.44 (d, *J*=9.5 Hz, 1H), 7.82–7.75 (m, 1H), 7.65–7.27 (m, 4H), 7.20 (d, *J*=7.5 Hz, 1H), 4.05 (s, 3H); ¹³C NMR (125.8 MHz, acetone-*d*₆) δ 154.8 (d, *J*=277.5 Hz), 109.1 (d, *J*=277.5 Hz); HRMS calcd for ¹³C₂-C₁₉H₁₅O₂ [M+H]⁺ 277.1134, found 277.1093.

5.2.16. 2-Methoxychrysen-5-ol (**12c**). Acid-catalyzed cyclization of **11g** gave **12c** (87%): ¹H NMR (500 MHz, acetone-*d*₆) δ 9.98 (d, *J*=9.5 Hz, 1H), 9.66 (s, 1H), 8.82 (d, *J*=9.0 Hz, 1H), 8.76 (d, *J*=8.0 Hz, 1H), 8.02 (d, *J*=9.0 Hz, 1H), 7.82 (d, *J*=7.5 Hz, 1H), 7.60–7.40 (m, 4H), 7.32 (dd, *J*=9.5 and 2.5 Hz, 1H), 3.99 (s, 3H); ¹³C NMR (125.8 MHz, acetone-*d*₆) δ 157.7, 153.9, 134.9, 132.7, 130.8, 129.6, 127.9, 126.3, 126.2, 126.0, 125.4, 123.8, 123.0, 121.8, 121.4, 117.0, 109.0, 107.6, 54.7; HRMS calcd for C₁₉H₁₅O₂ [M+H]⁺ 275.1067, found 275.1085.

5.2.17. ¹³C₂-2-Methoxychrysen-5-ol (**12c**). This unstable compound was used directly.

5.2.18. 3-Methoxychrysen-5-ol trifluoromethanesulfonate (**12f**). To a solution of **12e** (180 mg, 0.65 mmol) in CH₂Cl₂ (10 mL) was added pyridine (103 mg, 1.3 mmol), and the mixture was stirred for

10 min at room temperature. Then Ti_2O (275 mg, 0.98 mmol) was added dropwise at -78°C , and the mixture was warmed to room temperature, and stirred overnight. Then it was diluted with diethyl ether (50 mL), filtered, and the filtrate was washed with brine and water and dried over anhydrous Na_2SO_4 . The solvent was evaporated, and the residue was purified by chromatography on a silica gel column eluted with hexane/EtOAc (40:1) to yield **12f** (188 mg, 70%): ^1H NMR (500 MHz, CDCl_3) δ 8.67 (d, $J=8.5$ Hz, 1H), 8.59 (d, $J=2.0$ Hz, 1H), 8.55 (d, $J=9.0$ Hz, 1H), 7.96 (s, 1H), 7.94 (s, 1H), 7.92–7.85 (m, 2H), 7.78–7.65 (m, 2H), 7.34 (dd, $J=8.5$ and 2.5 Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 158.6, 145.8, 132.1, 130.7, 130.0, 129.8, 129.35, 129.28, 128.4, 128.0, 127.7, 127.6, 123.5, 120.7, 119.2, 118.72, 118.67 (q, $J=127.5$ Hz), 118.2; HRMS calcd for $\text{C}_{20}\text{H}_{13}\text{F}_3\text{NaO}_4\text{S} [\text{M}+\text{Na}]^+$ 429.0379, found 429.0365.

5.2.19. $^{13}\text{C}_2$ -3-Methoxychrysen-5-ol trifluoromethanesulfonate ($^{13}\text{C}_2$ -**12f**). This unstable compound was used directly in the next step.

5.2.20. 1-Methoxychrysen-5-ol trifluoromethanesulfonate (**12b**). Esterification of **12a** by a similar procedure gave **12b** (75%): ^1H NMR (500 MHz, CDCl_3) δ 8.80–8.75 (m, 2H), 8.69 (d, $J=9.0$ Hz, 1H), 8.61 (d, $J=9.5$ Hz, 1H), 7.98 (d, $J=7.5$ Hz, 1H), 7.95 (s, 1H), 7.80–7.62 (m, 3H), 7.10 (d, $J=9.0$ Hz, 1H), 4.09 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 155.5, 145.6, 131.9, 130.8, 129.7, 129.2, 128.4, 127.9, 127.7, 127.3, 124.7, 123.6, 123.1, 121.3, 120.0, 119.8, 119.4, 118.7 (q, $J=127.0$ Hz), 106.0, 55.8; HRMS calcd for $\text{C}_{20}\text{H}_{14}\text{F}_3\text{O}_4\text{S} [\text{M}+\text{H}]^+$ 407.0559, found 407.0575.

5.2.21. $^{13}\text{C}_2$ -1-Methoxychrysen-5-ol trifluoromethanesulfonate ($^{13}\text{C}_2$ -**12b**). ^1H NMR (500 MHz, CDCl_3) δ 8.80 (d, $J=8.5$ Hz, 1H), 8.77 (d, $J=8.5$ Hz, 1H), 8.73 (d, $J=9.5$ and 1.5 Hz, 1H), 8.63 (d, $J=9.5$ Hz, 1H), 8.18–7.78 (m, 3H), 7.78–7.62 (m, 2H), 7.10 (d, $J=8.0$ Hz, 1H), 4.11 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 145.6 (d, $J=308.0$ Hz), 120.1 (d, $J=308.0$ Hz); HRMS calcd for $^{13}\text{C}_2$ -labelled $\text{C}_{20}\text{H}_{13}\text{F}_3\text{O}_4\text{S} (\text{M}^+)$ 408.0553, found 408.0536.

5.2.22. 2-Methoxychrysen-5-ol trifluoromethanesulfonate (**12d**). Esterification of **12c** gave **12d** (76%): ^1H NMR (500 MHz, CDCl_3) δ 9.10 (d, $J=9.5$ Hz, 1H), 8.68 (d, $J=8.5$ Hz, 1H), 8.62 (d, $J=9.0$ Hz, 1H), 8.00–7.80 (m, 3H), 7.74 (t, $J=7.0$ Hz, 1H), 7.67 (t, $J=7.0$ Hz, 1H), 7.38 (dd, $J=9.5$ and 3.0 Hz, 1H), 7.32 (d, $J=2.5$ Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 158.2, 145.3, 134.9, 130.3, 130.2, 129.8, 128.9, 128.7, 128.5, 127.9, 127.2, 123.2, 122.6, 121.7, 121.2, 120.1, 118.7 (q, $J=127.6$ Hz), 118.0, 108.2, 55.4; HRMS calcd for $\text{C}_{20}\text{H}_{14}\text{F}_3\text{O}_4\text{S} [\text{M}+\text{H}]^+$ 407.0559, found 407.0588.

5.2.23. 3-Methoxy-5-(trimethylsilylethynyl)chrysen (**13e**). To a solution of **12f** (406 mg, 1.0 mmol) in DMF (15 mL) were added Pd(Ph_3) $_2\text{Cl}_2$ (35 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), TEA (1.3 mL), (trimethylsilyl)acetylene (120 mg, 1.2 mmol) under argon. The mixture was stirred for 2 h at room temperature and monitored by TLC. It was then diluted with EtOAc (100 mL), washed with brine and water, and dried over anhydrous Na_2SO_4 . Following evaporation of the solvent under vacuum, the residue was chromatographed on a silica gel column. Elution with hexane/EtOAc (120:1) gave **13e** (334 mg, 95%): ^1H NMR (500 MHz, CDCl_3) δ 9.96 (d, $J=2.0$ Hz, 1H), 8.80 (d, $J=8.5$ Hz, 1H), 8.55 (d, $J=9.0$ Hz, 1H), 8.34 (s, 1H), 8.00–7.92 (m, 2H), 7.90 (d, $J=8.5$ Hz, 1H), 7.76–7.62 (m, 2H), 7.34 (dd, $J=8.5$ and 2.0 Hz, 1H), 4.08 (s, 3H), 0.42 (s, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 157.8, 137.5, 132.2, 130.9, 130.5, 129.7, 129.4, 127.94, 127.88, 127.7, 127.6, 126.8, 126.1, 123.3, 118.8, 117.5, 117.4, 108.7, 108.1, 99.7, 55.9, 0.12; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{OSi} (\text{M}^+)$ 354.1440, found 354.1454.

5.2.24. $^{13}\text{C}_4$ -3-Methoxy-5-(trimethylsilylethynyl)chrysen ($^{13}\text{C}_4$ -**13e**). ^1H NMR (500 MHz, CDCl_3) δ 9.95 (s, 1H), 8.73 (d, $J=8.5$ Hz,

1H), 8.60 (d, $J=9.0$ Hz, 1H), 8.33 (dd, $J=99.5$ and 7.5 Hz, 1H), 7.97 (d, $J=8.0$ Hz, 1H), 7.95–7.93 (m, 1H), 7.91 (d, $J=9.0$ Hz, 1H), 7.76–7.62 (m, 2H), 7.34 (dd, $J=9.0$ and 2.5 Hz, 1H), 4.07 (s, 3H), 0.38 (d, $J=2.5$ Hz, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 137.5 (dd, $J=251.0$ and 9.5 Hz), 117.5 (ddd, $J=331.5$, 251.0, and 36.0 Hz), 108.6 (dd, $J=542.0$ and 331.5 Hz), 99.7 (ddd, $J=542.0$, 36.0, and 9.5 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{24}\text{H}_{22}\text{OSi} (\text{M}^+)$: 358.1575, found 358.1580.

5.2.25. 1-Methoxy-5-(trimethylsilylethynyl)chrysen (**13a**). Synthesis from **12b** by the foregoing procedure gave **13a** (90%): ^1H NMR (500 MHz, CDCl_3) δ 10.11 (d, $J=9.0$ Hz, 1H), 8.80–8.60 (m, 2H), 8.55 (d, $J=9.0$ Hz, 1H), 8.36 (s, 1H), 7.93 (d, $J=9.0$ Hz, 1H), 7.71 (t, $J=1.5$ Hz, 1H), 7.66 (t, $J=3.0$ Hz, 1H), 7.59 (t, $J=7.5$ Hz, 1H), 7.07 (d, $J=7.5$ Hz, 1H), 4.09 (s, 3H), 0.45 (s, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 155.4, 136.8, 132.1, 130.9, 130.5, 129.6, 128.0, 127.7, 126.9, 126.8, 125.3, 124.5, 123.4, 123.4, 121.8, 120.4, 119.4, 117.9, 108.6, 105.5, 99.6, 55.8, -0.11 ; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{OSi} (\text{M}^+)$ 354.1440, found 354.1460.

5.2.26. $^{13}\text{C}_4$ -1-Methoxy-5-(trimethylsilylethynyl)chrysen ($^{13}\text{C}_4$ -**13a**). ^1H NMR (500 MHz, CDCl_3) δ 10.08 (d, $J=9.0$ Hz, 1H), 8.76 (d, $J=8.5$ Hz, 1H), 8.73 (d, $J=8.5$ Hz, 1H), 8.55 (d, $J=9.5$ Hz, 1H), 8.36 (dd, $J=162.5$ and 7.0 Hz, 1H), 7.95–7.90 (m, 1H), 7.71 (t, $J=7.5$ Hz, 1H), 7.65 (t, $J=7.5$ Hz, 1H), 7.57 (t, $J=7.5$ Hz, 1H), 7.07 (d, $J=7.5$ Hz, 1H), 4.10 (s, 3H), 0.40 (d, $J=2.5$ Hz, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 136.8 (dd, $J=252.5$ and 10.0 Hz), 117.8 (ddd, $J=332.5$, 252.5, and 36.0 Hz), 108.5 (dd, $J=543.0$ and 332.5 Hz), 99.6 (ddd, $J=543.0$, 36.0, and 10.0 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{24}\text{H}_{22}\text{OSi} (\text{M}^+)$ 358.1575, found 358.1560.

5.2.27. 2-Methoxy-5-(trimethylsilylethynyl)chrysen (**13c**). Synthesis from **12d** by the foregoing procedure gave **13c** (92%): ^1H NMR (500 MHz, CDCl_3) δ 10.46 (d, $J=9.5$ Hz, 1H), 8.64 (d, $J=9.0$ Hz, 1H), 8.62 (d, $J=9.0$ Hz, 1H), 8.35 (s, 1H), 7.91 (d, $J=7.5$ Hz, 1H), 7.88 (d, $J=9.0$ Hz, 1H), 7.68 (t, $J=7.5$ Hz, 1H), 7.61 (t, $J=7.5$ Hz, 1H), 7.38–7.20 (m, 2H), 4.01 (s, 3H), 0.48 (s, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 158.0, 136.8, 134.7, 130.7, 130.5, 128.7, 128.0, 127.8, 127.70, 127.68, 127.3, 126.4, 125.7, 123.0, 121.7, 117.3, 116.3, 108.6, 107.4, 99.5, 55.4, -0.07 ; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{OSi} (\text{M}^+)$ 354.1440, found 354.1426.

5.2.28. 3-Methoxy-5-ethynylchrysen (**13f**). To a solution of **13e** (124 mg, 0.35 mmol) in THF (3.6 mL) and MeOH (3.6 mL) was added K_2CO_3 (75 mg, 0.54 mmol). The resulting mixture was stirred for 1 h at room temperature and monitored by TLC. Evaporation of the solvent under reduced pressure and chromatography of the residue on a silica gel column eluted with hexane/EtOAc (40:1) gave **13f** (94 mg, 92%): ^1H NMR (500 MHz, CDCl_3) δ 9.87 (d, $J=2.5$ Hz, 1H), 8.69 (d, $J=8.5$ Hz, 1H), 8.54 (d, $J=9.0$ Hz, 1H), 8.33 (s, 1H), 8.00–7.782 (m, 3H), 7.75–7.66 (m, 1H), 7.63 (t, $J=7.0$ Hz, 1H), 7.33 (dd, $J=9.0$ and 2.5 Hz, 1H), 4.04 (s, 3H), 3.72 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 157.8, 137.3, 132.0, 130.7, 130.6, 129.7, 129.5, 128.0, 127.9, 127.74, 127.70, 126.8, 126.4, 123.3, 118.7, 117.9, 116.3, 107.2, 87.1, 82.1, 55.6; HRMS calcd for $\text{C}_{21}\text{H}_{14}\text{O} (\text{M}^+)$ 282.1045, found 282.1056.

5.2.29. $^{13}\text{C}_4$ -3-Methoxy-5-ethynylchrysen ($^{13}\text{C}_4$ -**13f**). ^1H NMR (500 MHz, CDCl_3) δ 9.89 (d, $J=2.5$ Hz, H), 8.74 (d, $J=8.5$ Hz, 1H), 8.60 (d, $J=9.0$ Hz, 1H), 8.36 (dd, $J=162.5$ and 7.0 Hz, 1H), 8.00–7.85 (m, 3H), 7.75–7.55 (m, 2H), 7.33 (dd, $J=8.5$ and 2.5 Hz, 1H), 4.05 (s, 3H), 4.00–3.30 (m, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 137.3 (dd, $J=253.0$ and 11.5 Hz), 116.3 (ddd, $J=347.0$, 253.0, and 53.5 Hz), 87.2 (dd, $J=704.5$ and 347.0 Hz), 82.0 (ddd, $J=704.5$, 53.5, and 11.5 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{21}\text{H}_{14}\text{O} (\text{M}^+)$: 286.1178, found 286.1190.

5.2.30. 1-Methoxy-5-ethynylchrysen (**13b**). Similar reaction of **13a** gave **13b** (95%): ^1H NMR (500 MHz, CDCl_3) δ 10.02 (d, $J=9.0$ Hz, 1H),

8.73 (d, $J=8.0$ Hz, 1H), 8.70 (d, $J=9.0$ Hz, 1H), 8.55 (d, $J=9.5$ Hz, 1H), 8.37 (s, 1H), 7.92 (d, $J=8.0$ Hz, 1H), 7.71 (t, $J=7.5$ Hz, 1H), 7.70–7.55 (m, 2H), 7.06 (d, $J=7.5$ Hz, 1H), 4.08 (s, 3H), 3.70 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 155.4, 137.6, 132.0, 130.9, 130.6, 129.6, 127.9, 127.8, 126.9, 126.8, 125.7, 124.5, 123.4, 121.9, 120.4, 119.1, 116.8, 105.5, 86.9, 82.5, 55.8; HRMS calcd for $\text{C}_{21}\text{H}_{14}\text{O}$ (M^+) 282.1045, found 282.1069.

5.2.31. $^{13}\text{C}_4$ -1-Methoxy-5-ethynylchrysene ($^{13}\text{C}_4$ -**13b**). ^1H NMR (500 MHz, CDCl_3) δ 10.00 (d, $J=9.0$ Hz, 1H), 8.78 (d, $J=8.5$ Hz, 1H), 8.73 (d, $J=9.0$ Hz, 1H), 8.56 (d, $J=9.5$ Hz, 1H), 8.37 (dd, $J=162.5$ and 7.0 Hz, 1H), 7.96–7.90 (m, 1H), 7.74 (t, $J=7.5$ Hz, 1H), 7.70–7.55 (m, 2H), 7.08 (d, $J=8.0$ Hz, 1H), 4.10 (s, 3H), 3.98–3.30 (m, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 137.5 (dd, $J=253.0$ and 11.5 Hz), 116.8 (ddd, $J=346.5$, 253.0 , and 55.5 Hz), 86.8 (dd, $J=706.0$ and 346.5 Hz), 82.3 (ddd, $J=706.0$, 55.5 , and 11.5 Hz); HRMS calcd for $^{13}\text{C}_4$ - $\text{C}_{21}\text{H}_{14}\text{O}$ (M^+) 286.1178, found 286.1167.

5.2.32. 2-Methoxy-5-ethynylchrysene (**13d**). Similar reaction of **13c** gave **13d** (90%): ^1H NMR (500 MHz, CDCl_3) δ 10.34 (d, $J=9.5$ Hz, 1H), 8.67 (d, $J=8.5$ Hz, 1H), 8.64 (d, $J=9.5$ Hz, 1H), 8.35 (s, 1H), 7.95–7.88 (m, 2H), 7.70 (t, $J=7.5$ Hz, 1H), 7.61 (t, $J=7.5$ Hz, 1H), 7.38–7.29 (m, 2H), 4.00 (s, 3H), 3.68 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 158.0, 137.6, 134.6, 130.8, 130.4, 128.3, 128.0, 127.83, 127.81, 127.78, 127.3, 126.5, 125.6, 123.0, 121.7, 116.6, 116.2, 107.7, 86.8, 82.4, 55.4; HRMS calcd for $\text{C}_{21}\text{H}_{15}\text{O}$ [$\text{M}+\text{H}$] $^+$ 283.1117, found 283.1116.

5.2.33. 3-Methoxybenzo[*a*]pyrene (**14e**). To a solution of **13f** (100 mg, 0.35 mmol) in toluene (5.2 mL) was added PtCl_2 (9 mg, 0.035 mmol). The resulting mixture was heated overnight at 80°C . After evaporation of the solvent under reduced pressure, the residue was purified by chromatography on a column of silica gel. Elution with hexane/EtOAc (40:1) gave **14e** (70 mg, 70%). The ^1H NMR spectrum of **7e** matched that of an authentic sample.

5.2.34. $^{13}\text{C}_4$ -3-Methoxybenzo[*a*]pyrene ($^{13}\text{C}_4$ -**14e**). ^1H NMR (500 MHz, CDCl_3) δ 9.01 (d, $J=8.0$ Hz, 1H), 8.88 (d, $J=9.0$ Hz, 1H), 8.65–7.72 (m, 8H), 7.62 (d, $J=8.5$ Hz, 1H), 4.19 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 130.3 (dd, $J=247.0$ and 219.0 Hz), 127.0 (ddd, $J=255.0$, 219.0 , and 8.0 Hz), 123.5 (ddd, $J=247.0$, 26.0 and 8.0 Hz), 121.3 (ddd, $J=255.0$, 26.0 , and 8.0 Hz); HRMS calcd for $^{13}\text{C}_4$ -labelled $\text{C}_{21}\text{H}_{24}\text{O}$ (M^+) 286.1178, found 286.1198.

5.2.35. 1-Methoxybenzo[*a*]pyrene (**14b**). Analogous PtCl_2 -catalyzed reaction of **13b** gave **14b** (65%). The NMR spectral data matched that of an authentic sample.

5.2.36. $^{13}\text{C}_4$ -1-Methoxybenzo[*a*]pyrene ($^{13}\text{C}_4$ -**14b**). ^1H NMR (500 MHz, CDCl_3) δ 9.05–8.95 (m, 2H), 8.69 (d, $J=9.5$ Hz, 1H), 8.59–8.22 (m, 2H), 8.04–7.92 (m, 2H), 7.82–7.75 (m, 2H), 7.68–7.62 (m, 1H), 7.42 (d, $J=8.0$ Hz, 1H), 4.19 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 130.3 (ddd, $J=249.0$, 212.5 and 3.5 Hz), 127.0 (ddd, $J=256.0$, 26.0 , and 3.5 Hz), 125.5 (ddd, $J=256.0$, 212.5 and 8.0 Hz), 123.8 (ddd, $J=249.0$, 26.0 , and 8.0 Hz); HRMS calcd for $^{13}\text{C}_4$ - $\text{C}_{21}\text{H}_{14}\text{O}$ (M^+) 286.1178, found 286.1167.

5.3. Synthesis of 9-HO-BaP (**21b**) (Scheme 2)

5.3.1. 2-(2-Bromo-4-methoxyphenyl)naphthalene (**18**). Pd-catalyzed coupling of **15** with **16** by the method for preparation of **10c** gave 2-(2-bromo-5-methoxyphenyl)naphthalene (**17**) (78%): ^1H NMR (500 MHz, CDCl_3) δ 7.98–7.89 (m, 4H), 7.69–7.60 (m, 2H), 7.57 (q, $J=3.0$ Hz, 2H), 7.55 (d, $J=3.5$ Hz, 1H), 7.03 (d, $J=3.0$ Hz, 1H), 6.86 (dd, $J=8.5$ and 3.0 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 158.9, 143.4, 138.7, 133.8, 133.1, 132.7, 128.23, 128.21, 127.8, 127.6,

127.5, 126.3, 117.0, 114.9, 113.3, 55.6; HRMS calcd for $\text{C}_{17}\text{H}_{14}\text{BrO}$ [$\text{M}+\text{H}$] $^+$ 313.0223, found 313.0205.

5.3.2. Ethyl-2-(naphthalen-2-yl)-5-methoxyphenyl acetate (**18a**). Pd-catalyzed coupling of **17** with $\text{BrZnCH}_2\text{CO}_2\text{Et}$ with **16** gave **18a** (90%): ^1H NMR (500 MHz, CDCl_3) δ 7.98–7.89 (m, 4H), 7.60–7.50 (m, 3H), 7.41 (d, $J=9.0$ Hz, 1H), 7.10–7.00 (m, 2H), 4.15 (q, $J=7.0$ Hz, 2H), 3.89 (s, 3H), 3.65 (s, 2H), 1.23 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 172.3, 158.6, 143.6, 138.8, 133.3, 132.6, 131.6, 128.14, 128.05, 127.9, 127.8, 127.6, 126.4, 126.2, 124.5, 115.7, 113.5, 60.7, 55.4, 38.3, 14.2; HRMS calcd for $\text{C}_{21}\text{H}_{21}\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 321.1485, found 321.1472.

5.3.3. Ethyl $^{13}\text{C}_2$ -2-(naphthalen-2-yl)-5-methoxyphenyl acetate ($^{13}\text{C}_2$ -**18a**). ^1H NMR (500 MHz, CDCl_3) δ 7.98–7.89 (m, 4H), 7.60–7.50 (m, 3H), 7.41 (d, $J=9.0$ Hz, 1H), 7.10–7.00 (m, 2H), 4.09 (qd, $J=7.0$ and 4.0 Hz, 2H), 3.85 (s, 3H), 3.56 (dd, $J=127.0$ and 8.0 Hz, 2H), 1.16 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 172.2 (d, $J=229.0$ Hz), 38.2 (d, $J=229.0$ Hz); HRMS calcd for $^{13}\text{C}_2$ - $\text{C}_{21}\text{H}_{21}\text{O}_3$ [M] $^+$ 322.1477, found 322.1514.

5.3.4. 2-(Naphthalen-2-yl)-5-methoxyphenylacetic acid (**18b**). Hydrolysis of **18a** by the procedure for preparation of **11c** gave **18b** (91%): ^1H NMR (500 MHz, acetone- d_6) δ 9.30 (br s, 1H), 7.98–7.80 (m, 4H), 7.60–7.50 (m, 3H), 7.42 (d, $J=8.0$ Hz, 1H), 7.10–6.95 (m, 2H), 3.83 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (125.8 MHz, acetone- d_6) δ 173.3, 158.7, 143.5, 139.0, 133.4, 132.6, 132.0, 128.1, 127.9, 127.8, 127.7, 127.5, 126.4, 126.2, 124.7, 115.4, 113.3, 54.5, 37.5; HRMS calcd for $\text{C}_{19}\text{H}_{16}\text{NaO}_3$ [$\text{M}+\text{Na}$] $^+$ 315.0992, found 315.0966.

5.3.5. $^{13}\text{C}_2$ -2-(Naphthalen-2-yl)-5-methoxyphenylacetic acid ($^{13}\text{C}_2$ -**18b**). ^1H NMR (500 MHz, acetone- d_6) δ 10.62 (br s, 1H), 8.10–7.90 (m, 3H), 7.88 (s, 1H), 7.60–7.50 (m, 3H), 7.38 (dd, $J=8.0$ and 4.0 Hz, 1H), 6.98 (dd, $J=8.5$ and 3.0 Hz, 1H), 6.82 (d, $J=1.5$ Hz, 1H), 3.83 (s, 3H), 3.57 (dd, $J=128.0$ and 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, DMSO- d_6) δ 173.5 (d, $J=218.5$ Hz), 38.2 (d, $J=218.5$ Hz); HRMS calcd for $^{13}\text{C}_2$ - $\text{C}_{19}\text{H}_{17}\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 295.1239, found 295.1220.

5.3.6. 3-Methoxychrysen-11-ol (**19a**). Acid-catalyzed cyclization of **18b** by the method for preparation of **12e** gave **19a** (52%): ^1H NMR (500 MHz, acetone- d_6) δ 10.10 (d, $J=8.5$ Hz, 1H), 9.52 (s, 1H), 8.84 (d, $J=9.0$ Hz, 1H), 8.22 (s, 1H), 8.10–8.00 (m, 2H), 7.77 (d, $J=9.0$ Hz, 1H), 7.70–7.55 (m, 2H), 7.52 (s, 1H), 7.28 (dd, $J=8.5$ and 2.0 Hz, 1H), 4.04 (s, 3H); ^{13}C NMR (125.8 MHz, acetone- d_6) δ 156.8, 152.5, 133.1, 131.0, 130.2, 129.3, 128.1, 127.95, 127.92, 127.5, 127.1, 126.1, 126.0, 121.7, 121.4, 118.3, 109.2, 103.7, 54.9; HRMS calcd for $\text{C}_{19}\text{H}_{14}\text{O}_2$ (M^+) 274.0994, found 274.0976.

5.3.7. $^{13}\text{C}_2$ -3-Methoxychrysen-11-ol ($^{13}\text{C}_2$ -**19a**). ^1H NMR (500 MHz, CDCl_3) δ 9.83 (d, $J=8.5$ Hz, 1H), 8.65 (d, $J=9.0$ Hz, 1H), 8.07 (s, 1H), 8.05–7.98 (m, 2H), 7.77 (d, $J=9.0$ Hz, 1H), 7.75–7.63 (m, 3H), 7.29 (d, $J=2.0$ Hz, 1H), 7.23 (dd, $J=155.0$ and 2.5 Hz, 1H), 5.61 (s, 1H), 4.06 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 150.9 (d, $J=286.5$ Hz), 109.7 (d, $J=286.5$ Hz); HRMS calcd for $^{13}\text{C}_2$ - $\text{C}_{19}\text{H}_{15}\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 277.1134, found 277.1161.

5.3.8. 3-Methoxychrysen-11-ol triflate (**19b**). Esterification of **19a** with triflic anhydride and pyridine gave **19b** (72%): ^1H NMR (500 MHz, CDCl_3) δ 9.18 (d, $J=8.5$ Hz, 1H), 8.41 (d, $J=9.5$ Hz, 1H), 8.00–7.60 (m, 7H), 7.30 (dd, $J=8.5$ and 1.5 Hz, 1H), 4.00 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 159.4, 143.7, 133.1, 131.2, 130.4, 129.8, 129.0, 128.7, 128.1, 127.2, 127.1, 127.0, 125.4, 121.8, 120.5, 119.9, 118.8, 118.7 (q, $J=1276.5$ Hz), 103.8, 55.4; HRMS calcd for $\text{C}_{20}\text{H}_{14}\text{F}_3\text{O}_4\text{S}$ [$\text{M}+\text{H}$] $^+$ 407.0559, found 407.0542.

5.3.9. $^{13}\text{C}_2$ -3-Methoxychrysen-11-ol triflate ($^{13}\text{C}_2$ -**3-19b**). ^1H NMR (500 MHz, CDCl_3) δ 9.18 (d, $J=8.5$ Hz, 1H), 8.57 (d, $J=9.5$ Hz, 1H),

8.10–7.60 (m, 7H), 7.35 (dd, $J=8.5$ and 1.5 Hz, 1H), 4.06 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 143.8 (d, $J=308.0$ Hz), 120.0 (d, $J=308.0$ Hz); HRMS calcd for $^{13}\text{C}_2$ -labelled $\text{C}_{20}\text{H}_{13}\text{F}_3\text{O}_4\text{S}$ (M^+) 408.0553, found 408.0555.

5.3.10. *((9-Methoxychrysen-5-yl)ethynyl)trimethylsilane (20a)*. Sonogashira coupling of **19b** with (trimethylsilyl)acetylene afforded **20a** (90%): ^1H NMR (500 MHz, CDCl_3) δ 10.70–10.55 (m, 1H), 8.54 (d, $J=9.0$ Hz, 1H), 8.29 (s, 1H), 8.00–7.85 (m, 3H), 7.82 (d, $J=8.5$ Hz, 1H), 7.73–7.64 (m, 2H), 7.28 (d, $J=8.5$ Hz, 1H), 4.03 (s, 3H), 0.47 (s, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 159.3, 136.6, 133.0, 132.0, 131.1, 129.6, 128.4, 128.1, 127.9, 127.6, 127.1, 126.6, 126.0, 125.3, 121.2, 118.0, 115.0, 108.8, 103.6, 98.8, 55.5, -0.03 ; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{OSi}$ (M^+) 354.1440, found 354.1446.

5.3.11. $^{13}\text{C}_4$ -*((9-Methoxychrysen-5-yl)ethynyl)trimethylsilane (13C4-20a)*. ^1H NMR (500 MHz, CDCl_3) δ 10.70–10.55 (m, 1H), 8.62 (d, $J=8.5$ Hz, 1H), 8.30 (dd, $J=162.0$ and 6.5 Hz, 1H), 8.08–7.95 (m, 3H), 7.86 (dd, $J=8.5$ and 5.0 Hz, 1H), 7.71–7.62 (m, 2H), 7.30 (d, $J=8.5$ and 2.5 Hz, 1H), 4.07 (s, 3H), 0.41 (d, $J=2.5$ Hz, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 136.6 (dd, $J=251.5$ and 10.0 Hz), 115.0 (ddd, $J=334.0$, 251.5 , and 37.0 Hz), 108.6 (dd, $J=541.0$ and 334.0 Hz), 98.8 (ddd, $J=541.0$, 37.0 , and 10.0 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{24}\text{H}_{22}\text{OSi}$ (M^+) 358.1575, found 358.1583.

5.3.12. *5-Ethynyl-9-methoxychrysen-5-yl (20b)*. Removal of the trimethylsilyl group of **20a** gave **20b** (92%): ^1H NMR (500 MHz, CDCl_3) δ 10.43 (d, $J=8.5$ Hz, 1H), 8.54 (d, $J=9.0$ Hz, 1H), 8.28 (s, 1H), 8.00–7.85 (m, 3H), 7.80 (d, $J=8.5$ Hz, 1H), 7.73–7.60 (m, 2H), 7.27 (dd, $J=8.5$ and 2.0 Hz, 1H), 4.03 (s, 3H), 3.67 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 159.4, 137.3, 132.9, 132.1, 130.9, 129.6, 128.4, 128.2, 127.9, 127.6, 126.8, 126.6, 125.9, 125.7, 121.1, 118.1, 113.9, 103.6, 87.0, 81.9, 55.5; HRMS calcd for $\text{C}_{21}\text{H}_{15}\text{O}$ [$\text{M}+\text{H}$] $^+$ 283.1117, found 283.1105.

5.3.13. $^{13}\text{C}_4$ -*5-Ethynyl-9-methoxychrysen-5-yl (13C4-20b)*. ^1H NMR (500 MHz, CDCl_3) δ 10.42 (d, $J=8.5$ Hz, 1H), 8.62 (d, $J=9.0$ Hz, 1H), 8.32 (dd, $J=162.5$ and 7.0 Hz, 1H), 8.10–7.95 (m, 3H), 7.86 (dd, $J=8.5$ and 5.0 Hz, 1H), 7.75–7.64 (m, 2H), 7.31 (dd, $J=8.5$ and 2.0 Hz, 1H), 4.08 (s, 3H), 3.99–3.30 (m, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 137.3 (dd, $J=252.5$ and 11.5 Hz), 114.0 (ddd, $J=350.0$, 252.5 , and 54.0 Hz), 86.9 (dd, $J=706.0$ and 350.0 Hz), 81.7 (ddd, $J=706.0$, 54.0 , and 11.5 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{21}\text{H}_{14}\text{O}$ (M^+): 286.1178, found 286.1194.

5.3.14. *9-Methoxybenzo[a]pyrene (21a)*. Cyclization of **20b** catalyzed by PtCl_2 gave **21a** (60%) whose ^1H and ^{13}C NMR spectra matched those of an authentic standard.

5.3.15. $^{13}\text{C}_4$ -*9-Methoxybenzo[a]pyrene (13C4-21a)*. ^1H NMR (500 MHz, CDCl_3) δ 8.94 (d, $J=9.0$ Hz, 1H), 8.63–8.27 (m, 3H), 8.25–8.18 (m, 2H), 8.15–7.62 (m, 4H), 7.47 (dd, $J=9.0$ and 2.0 Hz, 1H), 4.15 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 128.4–124.4 (m, 4C); HRMS calcd for $^{13}\text{C}_4\text{-C}_{21}\text{H}_{14}\text{O}$ (M^+): 286.1178, found 286.1190.

5.4. Synthesis of 12-HO-BaP (27b) (Scheme 3)

5.4.1. *2-(2-Bromophenyl)-4-methoxynaphthalene (23)*. Pd-catalyzed Suzuki cross-coupling of **8** with **22** by the usual method furnished **23** (75%): ^1H NMR (500 MHz, CDCl_3) δ 8.47–8.38 (m, 1H), 7.95–7.88 (m, 1H), 7.80 (dd, $J=8.0$ and 0.5 Hz, 1H), 7.65–7.57 (m, 2H), 7.55–7.53 (m, 2H), 7.46 (td, $J=8.0$ and 1.0 Hz, 1H), 7.31 (td, $J=8.0$ and 1.0 Hz, 1H), 7.02 (d, $J=0.5$ Hz, 1H), 4.10 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 154.7, 142.8, 138.8, 134.0, 133.1, 131.4, 128.7, 127.7, 127.3, 126.7, 125.5, 124.8, 122.7, 121.9, 120.6, 106.0,

55.5; HRMS calcd for $\text{C}_{17}\text{H}_{14}\text{BrO}$ [$\text{M}+\text{H}$] $^+$ 313.0223, found 313.0250.

5.4.2. *Ethyl 2-(4-methoxynaphthalen-2-yl)phenyl acetate (24a)*. Pd-catalyzed coupling of **23** with $\text{BrZnCH}_2\text{CO}_2\text{Et}$ provided **24a** (85%): ^1H NMR (500 MHz, CDCl_3) δ 8.32 (d, $J=7.5$ Hz, 1H), 7.83 (d, $J=7.5$ Hz, 1H), 7.60–7.50 (m, 2H), 7.50–7.35 (m, 5H), 6.89 (d, $J=1.0$ Hz, 1H), 4.13 (q, $J=7.0$ Hz, 2H), 4.04 (s, 3H), 3.68 (s, 2H), 1.21 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 171.9, 155.0, 142.7, 138.8, 134.1, 132.0, 130.3, 130.1, 127.53, 127.52, 127.0, 126.7, 125.2, 124.5, 121.8, 120.3, 105.9, 60.7, 55.5, 38.9, 14.0; HRMS calcd for $\text{C}_{21}\text{H}_{20}\text{NaO}_3$ [$\text{M}+\text{Na}$] $^+$ 343.1305, found 343.1307.

5.4.3. *Ethyl $^{13}\text{C}_2$ -2-(4-methoxynaphthalen-2-yl)phenyl acetate ($^{13}\text{C}_2$ -24a)*. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 12.23 (br s, 1H), 8.00–7.83 (m, 2H), 7.87 (s, 1H), 7.50–7.29 (m, 6H), 7.19 (dd, $J=9.0$ and 2.5 Hz, 1H), 3.89 (s, 3H), 3.57 (dd, $J=128.5$ and 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $\text{DMSO-}d_6$) δ 173.2 (d, $J=218.0$ Hz), 39.0 (d, $J=218.0$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{19}\text{H}_{17}\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 295.1239, found 295.1211.

5.4.4. *2-(4-Methoxynaphthalen-2-yl)phenylacetic acid (24b)*. Ethan-olysis of **24a** provided **24b** (91%): ^1H NMR (500 MHz, acetone- d_6) δ 9.30 (br s, 1H), 7.98–7.80 (m, 4H), 7.60–7.50 (m, 3H), 7.42 (d, $J=8.0$ Hz, 1H), 7.10–6.95 (m, 2H), 3.83 (s, 3H), 3.65 (s, 2H); ^{13}C NMR (125.8 MHz, acetone- d_6) δ 173.3, 158.7, 143.5, 139.0, 133.4, 132.6, 132.0, 128.1, 127.9, 127.8, 127.7, 127.5, 126.4, 126.2, 124.7, 115.4, 113.3, 54.5, 37.5; HRMS calcd for $\text{C}_{19}\text{H}_{16}\text{NaO}_3$ [$\text{M}+\text{Na}$] $^+$ 315.0992, found 315.0966.

5.4.5. $^{13}\text{C}_2$ -*2-(4-Methoxynaphthalen-2-yl)phenylacetic acid ($^{13}\text{C}_2$ -24b)*. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 12.33 (br s, 1H), 8.17 (d, $J=8.5$ Hz, 1H), 7.88 (d, $J=8.0$ Hz, 1H), 7.60–7.50 (m, 2H), 7.50–7.30 (m, 5H), 6.91 (s, 1H), 3.97 (s, 3H), 3.57 (dd, $J=128.0$ and 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $\text{DMSO-}d_6$) δ 173.5 (d, $J=218.5$ Hz), 39.2 (d, $J=218.5$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{19}\text{H}_{17}\text{O}_3$ [$\text{M}+\text{H}$] $^+$ 295.1239, found 295.1219.

5.4.6. *12-Methoxychrysen-5-ol (25a)*. Acid-catalyzed cyclization of **24b** afforded **25a** (82%): ^1H NMR (500 MHz, acetone- d_6) δ 10.06 (d, $J=8.5$ Hz, 1H), 9.65 (s, 1H), 8.79 (d, $J=8.5$ Hz, 1H), 8.47 (dd, $J=8.5$ and 1.0 Hz, 1H), 8.20 (s, 1H), 7.79 (d, $J=7.5$ Hz, 1H), 7.70–7.65 (m, 2H), 7.60–7.45 (m, 2H), 7.39 (s, 1H), 4.29 (s, 3H); ^{13}C NMR (125.8 MHz, acetone- d_6) δ 154.6, 154.2, 133.5, 132.1, 132.0, 129.0, 126.71, 126.68, 126.3, 126.0, 125.63, 125.60, 123.5, 123.3, 121.5, 116.2, 106.9, 98.3, 55.2; HRMS calcd for $\text{C}_{19}\text{H}_{15}\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 275.1067, found 275.1094.

5.4.7. $^{13}\text{C}_2$ -*12-Methoxychrysen-5-ol ($^{13}\text{C}_2$ -25a)*. ^1H NMR (500 MHz, CDCl_3) δ 9.83 (d, $J=8.5$ Hz, 1H), 8.65 (d, $J=9.0$ Hz, 1H), 8.07 (s, 1H), 8.05–7.98 (m, 2H), 7.77 (d, $J=9.0$ Hz, 1H), 7.75–7.63 (m, 3H), 7.29 (d, $J=2.0$ Hz, 1H), 7.23 (dd, $J=155.0$ and 2.5 Hz, 1H), 5.61 (s, 1H), 4.06 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 150.9 (d, $J=286.5$ Hz), 109.7 (d, $J=286.5$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{19}\text{H}_{15}\text{O}_2$ [$\text{M}+\text{H}$] $^+$ 277.1134, found 277.1161.

5.4.8. *12-Methoxychrysen-5-ol triflate (25b)*. Esterification of **25a** with triflic anhydride and pyridine provided **25b** (60%): ^1H NMR (500 MHz, CDCl_3) δ 9.15 (d, $J=8.5$ Hz, 1H), 8.65 (d, $J=8.5$ Hz, 1H), 8.51 (d, $J=8.5$ Hz, 1H), 7.98 (d, $J=8.0$ Hz, 1H), 7.92 (s, 1H), 7.82 (s, 1H), 7.80–7.65 (m, 4H), 4.24 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 155.6, 145.5, 132.7, 131.1, 129.2, 129.1, 128.6, 127.7, 127.6, 127.4, 127.0, 126.9, 126.7, 123.4, 122.4, 118.7 (q, $J=1276.0$ Hz), 117.5, 116.7, 97.4, 55.6; HRMS calcd for $\text{C}_{20}\text{H}_{13}\text{O}_4\text{F}_3\text{S}$ (M^+) 406.0485, found 406.0458.

5.4.9. $^{13}\text{C}_2$ -*12-Methoxychrysen-5-ol triflate ($^{13}\text{C}_2$ -25b)*. ^1H NMR (500 MHz, $\text{DMSO-}d_6$) δ 10.77 (s, 1H), 9.96 (d, $J=8.5$ Hz, 1H), 8.82 (d, $J=8.0$ Hz, 1H), 8.38 (d, $J=8.0$ Hz, 1H), 8.15 (s, 1H), 7.80–7.62 (m, 3H), 7.56 (t, $J=7.5$ Hz, 1H), 7.48 (d, $J=8.5$ Hz, 1H), 7.33 (d, $J=176.5$ Hz, 1H), 4.23 (s, 3H); ^{13}C NMR (125.8 MHz, $\text{DMSO-}d_6$) δ 154.6 (d,

$J=277.5$ Hz), 107.0 (d, $J=277.5$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{19}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$ 277.1134, found 277.1155.

5.4.10. ((Chrysen-5-yl)ethynyl)trimethylsilane (**26a**). Sonogashira coupling of **25b** with (trimethylsilyl)acetylene afforded **26a** (95%): ^1H NMR (500 MHz, CDCl_3) δ 10.48 (dd, $J=6.5$ and 3.5 Hz, 1H), 8.63 (d, $J=8.5$ Hz, 1H), 8.28 (dd, $J=6.5$ and 3.5 Hz, 1H), 8.22 (s, 1H), 7.93 (s, 1H), 7.91 (d, $J=8.5$ Hz, 1H), 7.75–7.60 (m, 4H), 4.23 (s, 3H), 0.43 (s, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 154.5, 134.5, 131.9, 131.1, 130.1, 130.0, 128.1, 127.2, 126.8, 126.7, 126.4, 126.3, 126.0, 123.1, 122.3, 121.8, 117.3, 108.5, 99.5, 97.8, 55.5, -0.12 ; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{OSi}$ (M^+) 354.1440, found 354.1417.

5.4.11. $^{13}\text{C}_4$ -((Chrysen-5-yl)ethynyl)trimethylsilane ($^{13}\text{C}_4$ -**26a**). ^1H NMR (500 MHz, CDCl_3) δ 10.48 (dd, $J=6.5$ and 3.5 Hz, 1H), 8.61 (d, $J=8.5$ Hz, 1H), 8.48 (dd, $J=6.5$ and 3.5 Hz, 1H), 8.22 (dd, $J=163.0$ and 7.0 Hz, 1H), 7.93–7.87 (m, 2H), 7.72–7.58 (m, 4H), 4.21 (s, 3H), 0.44 (d, $J=3.0$ Hz, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 134.4 (dd, $J=251.5$ and 10.0 Hz), 117.3 (ddd, $J=331.5$, 251.5 , and 36.0 Hz), 108.5 (ddd, $J=541.5$, 331.5 , and 3.0 Hz), 99.4 (ddd, $J=541.5$, 36.0 , and 10.0 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{24}\text{H}_{22}\text{OSi}$ (M^+) 358.1575, found 358.1545.

5.4.12. 5-Ethynyl-12-methoxychrysenene (**26b**). Treatment of **26a** with K_2CO_3 in MeOH/THF provided **26b** (91%): ^1H NMR (500 MHz, CDCl_3) δ 10.37 (d, $J=8.0$ Hz, 1H), 8.65 (d, $J=8.5$ Hz, 1H), 8.48 (d, $J=8.0$ Hz, 1H), 8.25 (s, 1H), 7.95 (s, 1H), 7.92 (d, $J=8.0$ Hz, 1H), 7.78–7.60 (m, 4H), 4.24 (s, 3H), 3.67 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 154.6, 135.2, 131.8, 131.1, 130.3, 130.1, 128.1, 127.3, 126.8, 126.5, 126.4, 126.3, 123.2, 122.4, 121.9, 116.3, 97.8, 86.8, 82.3, 55.5; HRMS calcd for $\text{C}_{21}\text{H}_{14}\text{O}$ (M^+), 282.1045, found 282.1053.

5.4.13. $^{13}\text{C}_4$ -5-Ethynyl-12-methoxychrysenene ($^{13}\text{C}_4$ -**26b**). ^1H NMR (500 MHz, CDCl_3) δ 10.37 (d, $J=8.5$ Hz, 1H), 8.66 (d, $J=8.5$ Hz, 1H), 8.48 (dd, $J=8.0$ and 1.5 Hz, 1H), 8.26 (dd, $J=163.0$ and 7.0 Hz, 1H), 7.96 (s, 1H), 7.93 (t, $J=6.5$ Hz, 1H), 7.77–7.60 (m, 4H), 4.25 (s, 3H), 3.90–3.30 (m, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 135.3 (dd, $J=252.5$ and 11.5 Hz), 116.3 (ddd, $J=345.0$, 252.5 , and 55.5 Hz), 86.9 (dd, $J=704.5$ and 345.0 Hz), 82.2 (ddd, $J=704.5$, 55.5 , and 11.5 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{21}\text{H}_{14}\text{O}$ (M^+) 286.1178, found 286.1167.

5.4.14. 12-Methoxybenzo[a]pyrene (**27a**). PtCl_2 -catalyzed cyclization of **26b** gave **27a** (70%); the ^1H and ^{13}C NMR spectra matched those of an authentic sample.

5.4.15. $^{13}\text{C}_4$ -12-Methoxybenzo[a]pyrene ($^{13}\text{C}_4$ -**27a**). ^1H NMR (500 MHz, CDCl_3) δ 8.95 (d, $J=8.5$ Hz, 1H), 8.63 (d, $J=8.0$ Hz, 1H), 8.37 (dd, $J=159.0$ and 5.0 , 1H), 8.32–8.26 (m, 2H), 8.15–7.98 (m, 3H), 7.88–7.70 (m, 3H), 4.35 (s, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 132.0–127.1 (m, 3C), 122.4 (ddd, $J=219.0$, 25.0 , and 16.0 Hz); HRMS calcd for $^{13}\text{C}_4\text{-C}_{21}\text{H}_{14}\text{O}$ (M^+) 286.1178, found 286.1192.

5.5. Syntheses of BaP, $^{13}\text{C}_4$ -BaP, and the $^{13}\text{C}_4$ -BaP phenols

5.5.1. 2-(2-Bromophenyl)naphthalene (**29**). Pd-catalyzed Suzuki cross-coupling of **8** with **28** by the method for preparation of **11c** afforded **29** (87%): ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.95 (m, 4H), 7.83 (dd, $J=8.5$ and 1.0 Hz, 1H), 7.70 (d, $J=8.5$ and 1.5 Hz, 1H), 7.65–7.58 (m, 2H), 7.53 (dd, $J=7.5$ and 1.5 Hz, 1H), 7.47 (td, $J=7.5$ and 1.5 Hz, 1H), 7.35 (td, $J=7.5$ and 1.5 Hz, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 142.5, 138.6, 133.1, 133.0, 132.6, 131.5, 128.8, 128.2, 128.1, 127.7, 127.6, 127.39, 127.36, 126.22, 126.20, 122.8; HRMS calcd for $\text{C}_{16}\text{H}_{11}\text{Br}$ (M^+): 282.0044, found 282.0040.

5.5.2. Ethyl 2-(2-naphthalenyl)phenylacetate (**30a**). Coupling of **29** with $\text{ZnBrCH}_2\text{CO}_2\text{Et}$ by the method for preparation of **11b** gave

30a (93%): ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.87 (m, 3H), 7.86 (s, 1H), 7.60–7.50 (m, 3H), 7.60–7.35 (m, 4H), 4.13 (q, $J=7.0$ Hz, 2H), 3.67 (s, 2H), 1.21 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 171.8, 142.3, 138.6, 133.1, 132.3, 132.1, 130.34, 130.30, 127.99, 127.96, 127.7, 127.62, 127.58, 127.5, 127.1, 126.2, 125.9, 60.7, 39.0, 14.0; HRMS calcd for $\text{C}_{20}\text{H}_{19}\text{O}_2$ $[\text{M}+\text{H}]^+$: 291.1380, found 291.1373.

5.5.3. Ethyl $^{13}\text{C}_2$ -2-(2-naphthalenyl)phenylacetate ($^{13}\text{C}_2$ -**30a**). ^1H NMR (500 MHz, CDCl_3) δ 8.05–7.87 (m, 3H), 7.86 (s, 1H), 7.60–7.50 (m, 3H), 7.60–7.35 (m, 4H), 4.13 (qd, $J=7.0$ and 3.0 Hz, 2H), 3.67 (dd, $J=129.0$ and 8.0 Hz, 2H), 1.21 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 172.0 (d, $J=229.0$ Hz), 39.0 (d, $J=229.0$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{20}\text{H}_{19}\text{O}_2$ $[\text{M}]^+$ 292.1375, found 292.1374.

5.5.4. 2-(2-Naphthalenyl)phenylacetic acid (**30b**). Hydrolysis of **30a** by the usual method gave **30b** (91%): ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 12.25 (br s, 1H), 8.03–7.95 (m, 2H), 7.95–7.90 (m, 1H), 7.84 (s, 1H), 7.60–7.51 (m, 2H), 7.47 (dd, $J=8.5$ and 1.5 Hz, 1H), 7.45–7.30 (m, 4H), 3.59 (s, 2H); ^{13}C NMR (125.8 MHz, $\text{DMSO}-d_6$) δ 173.3, 142.2, 138.8, 133.3, 133.1, 132.4, 131.4, 130.4, 128.4, 128.1, 128.03, 128.02, 127.9, 127.8, 127.4, 126.9, 126.6, 39.1; HRMS Calcd for $\text{C}_{18}\text{H}_{15}\text{O}_2$ $[\text{M}+\text{H}]^+$ 263.1063, found 263.1012.

5.5.5. $^{13}\text{C}_2$ -2-(2-Naphthalenyl)phenylacetic acid ($^{13}\text{C}_2$ -**30b**). ^1H NMR (500 MHz, acetone- d_6) δ 10.68 (br s, 1H), 8.03–7.90 (m, 3H), 7.87–7.82 (m, 1H), 7.60–7.44 (m, 4H), 7.43–7.34 (m, 3H), 3.67 (dd, $J=128.5$ and 8.0 Hz, 2H); ^{13}C NMR (125.8 MHz, $\text{DMSO}-d_6$) δ 173.2 (d, $J=223.5$ Hz), 39.1 (d, $J=223.5$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{18}\text{H}_{14}\text{NaO}_2$ $[\text{M}+\text{Na}]^+$ 287.0953, found 287.0933.

5.5.6. Chrysen-5-ol (**31a**). Acid-catalyzed cyclization of **30b** by the usual method gave **31a** (87%): ^1H NMR (500 MHz, acetone- d_6) δ 10.12 (d, $J=8.5$ Hz, 1H), 9.80 (s, 1H), 8.83 (d, $J=9.0$ Hz, 1H), 8.76 (d, $J=8.5$ Hz, 1H), 8.10–8.00 (m, 2H), 7.85 (d, $J=8.0$ Hz, 1H), 7.75–7.63 (m, 2H), 7.61–7.55 (m, 2H), 7.55–7.50 (m, 1H); ^{13}C NMR (125.8 MHz, acetone- d_6) δ 154.4, 133.2, 133.1, 131.1, 130.9, 129.2, 128.5, 128.2, 126.8, 126.3, 126.09, 126.08, 126.0, 123.9, 123.3, 121.4, 121.1, 109.1; HRMS calcd for $\text{C}_{18}\text{H}_{13}\text{O}$ $[\text{M}+\text{H}]^+$ 245.0961, found 245.0970.

5.5.7. $^{13}\text{C}_2$ -Chrysen-5-ol ($^{13}\text{C}_2$ -**31a**). ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 10.87 (br s, 1H), 9.97 (d, $J=8.5$ Hz, 1H), 8.87 (d, $J=9.0$ Hz, 1H), 8.70 (d, $J=8.5$ Hz, 1H), 8.15–8.00 (m, 2H), 7.85–7.90 (m, 1H), 7.70–7.31 (m, 5H); ^{13}C NMR (125.8 MHz, $\text{DMSO}-d_6$) δ 154.8 (d, $J=277.5$ Hz), 109.2 (d, $J=277.5$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{18}\text{H}_{13}\text{O}$ $[\text{M}+\text{H}]^+$ 247.1032, found 247.1019.

5.5.8. Chrysen-5-ol triflate (**31b**). Esterification of **31a** gave **31b** (80%): ^1H NMR (500 MHz, CDCl_3) δ 9.21 (d, $J=8.5$ Hz, 1H), 8.72 (d, $J=8.5$ Hz, 1H), 8.67 (d, $J=9.0$ Hz, 1H), 8.10–7.92 (m, 4H), 7.80–7.64 (m, 4H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 145.5, 133.0, 131.6, 130.8, 129.73, 129.66, 128.7, 128.5, 128.1, 127.9, 127.7, 127.20, 127.16, 127.1, 123.4, 121.5, 120.6, 120.1, 118.7 (q, $J=1276.5$ Hz); HRMS calcd for $\text{C}_9\text{H}_{11}\text{F}_3\text{O}_3\text{S}$ (M^+) 376.0381, found 376.0385.

5.5.9. $^{13}\text{C}_2$ -Chrysen-5-ol triflate ($^{13}\text{C}_2$ -**31b**). ^1H NMR (500 MHz, CDCl_3) δ 9.22 (d, $J=9.0$ Hz, 1H), 8.76 (d, $J=8.0$ Hz, 1H), 8.71 (d, $J=9.0$ Hz, 1H), 8.08 (d, $J=9.0$ Hz, 1H), 8.06–7.97 (m, 2H), 7.99 (dd, $J=164.0$ and 5.0 Hz, 1H), 7.80–7.64 (m, 4H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 145.5 (d, $J=358.0$ Hz), 120.1 (d, $J=358.0$ Hz); HRMS calcd for $^{13}\text{C}_2\text{-C}_{19}\text{H}_{11}\text{F}_3\text{O}_3\text{S}$ (M^+) 378.0429, found 378.0435.

5.5.10. (Chrysen-5-ylethynyl)trimethylsilane (**32a**). Sonogashira coupling of **31b** with trimethylsilylacetylene by the usual procedure

gave **32a** (91%): ^1H NMR (500 MHz, CDCl_3) δ 10.60–10.55 (m, 1H), 8.70–8.50 (m, 2H), 8.40 (s, 1H), 8.10–7.90 (m, 3H), 7.80–7.50 (m, 4H), 0.51 (s, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 136.7, 132.8, 130.9, 130.8, 130.4, 129.2, 128.3, 128.1, 127.9, 127.6, 127.0, 126.9, 126.7, 126.5, 125.3, 123.2, 121.1, 117.5, 108.4, 99.6, –0.15; HRMS calcd for $\text{C}_{23}\text{H}_{20}\text{Si}$ (M^+) 324.1334, found 324.1322.

5.5.11. $^{13}\text{C}_4$ -(Chrysen-5-ylethynyl)trimethylsilane ($^{13}\text{C}_4$ -**32a**). ^1H NMR (500 MHz, CDCl_3) δ 10.52 (t, $J=5.0$ Hz, 1H), 8.75–8.70 (m, 2H), 8.36 (dd, $J=163.0$ and 7.0 Hz, 1H), 8.10–7.90 (m, 3H), 7.78–7.60 (m, 4H), 0.43 (d, $J=3.0$ Hz, 9H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 136.8 (dd, $J=251.5$ and 10.5 Hz), 117.6 (ddd, $J=332.0$, 251.5, and 36.0 Hz), 108.6 (dd, $J=542.5$ and 332.0 Hz), 99.6 (ddd, $J=542.5$, 36.0, and 10.5 Hz); HRMS calcd for $^{13}\text{C}_4$ - $\text{C}_{23}\text{H}_{20}\text{Si}$ (M^+) 328.1468, found 328.1469.

5.5.12. 5-Ethynylchrysen (**32b**). Removal of the TMS group of **32a** gave **32b** (85%): ^1H NMR (500 MHz, CDCl_3) δ 10.45 (d, $J=8.5$ Hz, 1H), 8.70–8.55 (m, 2H), 8.39 (s, 1H), 8.05–7.80 (m, 3H), 7.80–7.50 (m, 4H), 3.72 (s, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 137.6, 132.9, 130.9, 130.8, 130.6, 129.3, 128.5, 128.3, 128.0, 127.9, 127.1, 126.9, 126.7, 126.6, 125.8, 123.3, 121.1, 116.6, 86.8, 82.6; HRMS calcd for $\text{C}_{20}\text{H}_{13}$ [$\text{M}+\text{H}$] $^+$ 253.1012, found 253.1006.

5.5.13. $^{13}\text{C}_4$ -5-Ethynylchrysen ($^{13}\text{C}_4$ -**32b**). ^1H NMR (500 MHz, CDCl_3) δ 10.42 (d, $J=8.5$ Hz, 1H), 8.80–8.70 (m, 2H), 8.39 (dd, $J=162.5$ and 7.0 Hz, 1H), 8.05–7.80 (m, 3H), 7.80–7.50 (m, 4H), 4.10–3.30 (m, 1H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 137.5 (dd, $J=253.0$ and 11.0 Hz), 116.5 (ddd, $J=346.0$, 253.0, and 56.0 Hz), 86.7 (ddd, $J=706.0$, 346.0, and 4.5 Hz), 82.4 (ddd, $J=706.0$, 56.0, and 11.0 Hz); HRMS calcd for $^{13}\text{C}_4$ - $\text{C}_{20}\text{H}_{12}$ (M^+) 256.1073, found 256.1046.

5.5.14. Benzo[a]pyrene (BaP). PtCl_2 -catalyzed cyclization of **32b** furnished BaP (65%). The ^1H and ^{13}C NMR spectra were in good agreement with those of an authentic sample.

5.5.15. $^{13}\text{C}_4$ -Benzo[a]pyrene ($^{13}\text{C}_4$ -BaP). ^1H NMR (500 MHz, CDCl_3) δ 9.12–9.02 (m, 2H), 8.72–8.22 (m, 4H), 8.20–7.94 (m, 3H), 7.90–7.75 (m, 3H); ^{13}C NMR (125.8 MHz, CDCl_3) δ 130.3–124.5 (m, 4C); HRMS calcd for $^{13}\text{C}_4$ - $\text{C}_{20}\text{H}_{14}$ (M^+): 256.1073, found 256.1079.

5.6. BaP-1,6- and 3,6-dione (**5** and **6**) and their $^{13}\text{C}_4$ -labelled analogues ($^{13}\text{C}_4$ -BaP-1,6-dione and $^{13}\text{C}_4$ -BaP-3,6-dione) (Fig. 1)

These quinones were synthesized by oxidation of BaP-1-ol (**7b**) and BaP-3-ol (**7f**) with BTI by the methods reported.^{20,24} Check refs!!

5.6.1. $^{13}\text{C}_4$ -BaP-1,6-dione and $^{13}\text{C}_4$ -BaP-3,6-dione. These quinones were synthesized by oxidation of $^{13}\text{C}_4$ -BaP-1-ol and $^{13}\text{C}_4$ -BaP-3-ol with BTI by methods analogous to those for oxidation of the unlabelled analogues.

$^{13}\text{C}_4$ -BaP-1,6-dione: ^1H NMR (500 MHz, CDCl_3) δ 8.60 (d, $J=7.5$ Hz, 1H), 8.51 (d, $J=8.0$ Hz, 1H), 8.44 (dd, $J=3.5$, 7 Hz), 8.31 (d, $J=8$ Hz), 8.05–8.00 (m, 1H), 7.99–7.71 (m, 3H), 7.66–7.61 (m, 1H), 6.76 (d, $J=9.5$ Hz); ^{13}C NMR (125.8 MHz, CDCl_3) δ 183.58, 183.55, 183.48, 183.42, 183.30, 183.17, 183.14, 183.10, 131.14, 131.10, 130.95, 130.82, 130.74, 130.70, 130.66, 130.35, 129.97, 129.92, 129.87, 129.80, 129.64, 129.49, 129.41, 129.35.

$^{13}\text{C}_4$ -BaP-3,6-dione: ^1H NMR (500 MHz, CDCl_3) δ 8.70–8.66 (m, 1H), 8.60–8.56 (m, 1H), 8.49–8.46 (m, 1H), 8.39 (d, $J=7.5$ Hz, 1H), 8.29 (d, $J=8$ Hz, 1H), 7.83–7.74 (m, 3H), 7.61 (t, $J=7.5$ Hz, 1H), 6.73 (d, $J=10$ Hz); ^{13}C NMR (125.8 MHz, CDCl_3) δ 183.60, 183.58, 183.56, 183.55, 183.17, 183.16, 183.14, 183.13, 132.53, 132.49, 132.10, 132.08,

132.07, 131.66, 131.62, 129.99, 129.95, 129.92, 129.55, 129.52, 129.48, 129.38, 129.36, 128.93, 128.92, 128.49, 128.48.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2012.05.130.

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