Published in final edited form as:
Tetrahedron. 2012 September 1; 68(35): . doi:10.1016/j.tet.2012.05.130.

Synthesis of $^{13}C_4$-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 (B*a*P), are ubiquitous environmental contaminants that are implicated in causing lung cancer. B*a*P 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 B*a*P metabolites. We now report efficient syntheses of $^{13}C_4$-B*a*P and the complete set of its $^{13}C_4$-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 $PtCl_2$-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 $^{13}C_4$-B*a*P and $^{13}C_4$-B*a*P-8-ol each require only four steps, and the ^{13}C-atoms are all introduced in a single step. $^{13}C_4$-B*a*P-8-ol serves as the synthetic precursor of all the oxidized metabolites of ^{13}C-B*a*P implicated in initiation of cancer. The isotopic purities of the synthetic $^{13}C_4$-B*a*P metabolites were estimated to be ≥99.9%.

Keywords

Benzo[*a*]pyrene (B*a*P); Carcinogenic polycyclic aromatic; hydrocarbons (PAHs); Synthesis of $^{13}C_4$-labelled B*a*P; $^{13}C_4$-Labelled oxidized metabolites of B*a*P; Enzymatic activation of PAH carcinogens; Synthesis of PAHs via Pd-catalyzed cross-coupling reactions

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]

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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.

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

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

The *diol epoxide path* entails cytochrome P450 catalyzed oxidation of B*a*P to form metastable arene oxide metabolites that rearrange to phenols and/or undergo hydration to dihydrodiols.[1] The (±)-*trans*-7,8-dihydrodiol of B*a*P (B*a*P 7,8-diol) (**1**) undergoes further enzyme-catalyzed oxidation to form highly mutagenic (±)-*anti*- and (±)-*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 B*a*P 7,8-catechol (**3**). This enters into a redox cycle with O_2 to form B*a*P 7,8-dione (**2**) and reactive oxygen species (ROS) that attack DNA to form 8′-hydroxy-2′-deoxyguanosine (8′-HO-2′-*d*Gua) and cause DNA strand breaks.[1,7c,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 *radicalcation path* entails one-electron oxidation of B*a*P catalyzed by P450 monooxygenase or peroxidase to form a B*a*P radicalcation that attacks DNA to yield depurinating adducts.[11a] The signature metabolites formed via this pathway are B*a*P 1,6-dione (**6**) and B*a*P 3,6-dione (**7**). However, the involvement of the radicalcation pathway in carcinogenesis is disputed.[1a,11b]

Human bronchoalveolar H358 cells were examined recently as a model for study of the metabolism of B*a*P 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 $^{13}C_4$-B*a*P metabolites whose syntheses are reported herein were employed as internal standards. In other studies, the syntheses of $^{13}C_2$-B*a*P, $^{13}C_2$-**1**, and $^{13}C_2$-**2** were also reported.[16]

2. Results

The aim of this investigation was to develop methods for efficient synthesis of the $^{13}C_4$-labelled analogues of the complete set of oxidized metabolites of B*a*P. The B*a*P metabolites may be divided into two groups on the basis of their involvement in carcinogenesis. *Group A* includes the oxidized metabolites of B*a*P that current evidence indicates do not play a role in carcinogenesis [the 1-, 2-, 3-, 9-, and 12-phenol isomers of B*a*P, B*a*P-1,6-dione (**6**) and B*a*P-3,6-dione (**7**)] (Fig. 1). *Group B* includes the oxidized metabolites of B*a*P implicated in carcinogenesis [BaP 7,8-diol (**1**), B*a*P 7,8-dione (**2**), B*a*P 7,8-catechol diacetate (**3**), (±)-*anti*-BPDE (**4**), and (±)-*syn*-BPDE (**5**)] (Fig. 1) plus 8-HO-B*a*P and 9-HO-B*a*P. The $^{13}C_4$-labelled B*a*P metabolites are needed as internal standards for LC/MS analysis of the B*a*P 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 $^{13}C_4$-labelled B*a*P metabolites involve the use of Pd-catalyzed cross-coupling reactions (Suzuki, Sonogashira, and/or Hartwig) in combination with $PtCl_2$-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 ^{13}C-labelled precursors are available from commercial sources.

2.1. Part I. B*a*P metabolites not implicated in carcinogenesis (*Group A*)

The initial synthetic targets were the ^{13}C-labelled 1-, 2-, 3-, 9-, and 12-phenols of B*a*P. 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 B*a*P 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 regiospecifically to furnish 2-(2-bromophenyl)-7-methoxynaphthalene (**10c**). Pd-catalyzed cross-coupling of **10c** with $BrZnCH_2CO_2R$ was carried out by a procedure based on Hartwig's method.[17] The choice of this route was dictated by the commercial availability of $^{13}C_2$-$BrCH_2CO_2Et$. 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 $BrZnCH_2CO_2Et$ 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%).

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 $BrZnCH_2CO_2Et$ 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 ^{13}C-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 $MeSO_3H$ at 50 °C to furnish 3-methoxychrysen-5-ol (**12e**) (77%). This was converted to the triflate ester (**12f**), by treatment with trifluoromethanesulfonic anhydride, and Sonogashira coupling[18] of **12f** with (trimethylsilyl) acetylene (TMSA) in the presence of $Pd(PPh_3)_2Cl_2$, CuI, and TEA in DMF gave (3-methoxychrysen-5-ylethynyl)-trimethylsilane (**13e**) (89%). Desilylation of **13e** with K_2CO_3 in MeOH/THF furnished 5-ethynyl-3-methoxychrysene (**13f**) (90%), and $PtCl_2$-catalyzed cyclization[19] of **13f** afforded 3-methoxybenzo[*a*]pyrene (**14e**) (60%). Demethylation of **13f** with BBr_3 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 $Pd(OAc)_2/PPh_3$ provided 2-(2-bromophenyl)-5-methoxynaphthalene (**10a**). Hartwig coupling[17] of **10a** with $BrZnCH_2CO_2Et$ 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 $PtCl_2$-catalyzed cyclization[18] 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 $BrZnCH_2CO_2Et$ provided ethyl 2-(napththalen-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-methoxychrysene (**20b**). Finally, $PtCl_2$-catalyzed cyclization of **20b** furnished 9-methoxy-B*a*P (**21a**), and demethylation gave **21b**.

In principle, benzo[*a*]pyren-8-ol and its $^{13}C_4$-labelled analogue are accessible via an analogous sequence employing 1-bromo-2-iodo-5-methoxybenzene in place of **15**. However, 8-HO-B*a*P 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-boronate ester (**22**) was synthesized from 2-bromo-4-methoxynapthalene[22] 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 $BrZnCH_2CO_2Et$ provided ethyl 2-(4-methoxynapththalen-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 $PtCl_2$-catalyzed cyclization of the latter gave 12-methoxy-B*a*P (**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 B*a*P-1,6- and 3,6-diones (**6** and **7**) were prepared by oxidation of B*a*P-1-ol (**14b**) and B*a*P-3-ol (**14f**) with bis(trifluoroacetoxy)iodobenzene (BTI) by the method reported.[20,23]

2.1.5. Synthesis of $^{13}C_4$-labelled BaP and its Group A metabolites—B*a*P and $^{13}C_4$-B*a*P were synthesized by two methods. *Method A* was modelled on the synthesis of the 1-, 2-, and 3-phenols of B*a*P (Scheme 1). Initial studies were conducted with unlabelled precursors (Scheme 4). Pd-catalyzed Suzuki coupling of **8** with naphthalene-2-boronate ester (**28**) gave 2-(2-bromophenyl) naphthalene (**29**), and cross-coupling of **29** with $BrCH_2CO_2Et$ 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 K_2CO_3 in MeOH/THF afforded **32b**, and $PtCl_2$-catalyzed cyclization gave B*a*P.

Synthesis of $^{13}C_4$-B*a*P was accomplished in seven steps from **29** (Scheme 4). The ^{13}C-atoms were incorporated in pairs, the first pair in the cross-coupling of the Reformatsky ester $^{13}C_2$-$BrZnCH_2CO_2R$ with **29**, and the second pair in the Sonogashira cross-coupling[24] of $^{13}C_2$-TMSA with the triflate ester of $^{13}C_2$-chrysen-5-ol (**31b**). The ^{13}C-atoms in $^{13}C_4$-B*a*Pare located at the *C*-4,-5,-5a, and -6 aromatic ring positions.

The $^{13}C_4$-B*a*P phenol isomers (Fig. 2) were synthesized by methods analogous to those used for synthesis of the unlabelled B*a*P phenols. The ^{13}C-atoms were at the 4,5,5a, and 6-positions of B*a*P, the same as those of the ^{13}C-atoms in $^{13}C_4$-B*a*P. The methods for syntheses of $^{13}C_4$-1-HO-B*a*P, $^{13}C_4$-2-HO-B*a*P, and $^{13}C_4$-3-HO-B*a*P were analogous to those used for preparation of $^{13}C_4$-B*a*P (Scheme 4), using the appropriate methoxy-substituted derivatives (**9a**, **9b**, and **9c**) of the boronate ester in place of **28**. Similarly, the syntheses of $^{13}C_4$-HO-9-B*a*P and $^{13}C_4$-12-HO-B*a*P were carried out by appropriate modification of the procedures for synthesis of unlabelled 9-HO-B*a*P (Scheme 2) and 12-HO-B*a*P (Scheme 3).

The $^{13}C_4$-labelled 1,6- and 3,6-quinones of B*a*P (Fig. 2) were prepared by oxidation of $^{13}C_4$-1-HO-B*a*P and $^{13}C_4$-3-HO-B*a*P 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 $^{13}C_4$-labelled oxidized metabolites of B*a*P in *Group B*. They include the B*a*P metabolites implicated in initiation of cancer [Fig. 1: B*a*P 7,8-diol (**1**), B*a*P 7,8-dione (**2**), B*a*P 7,8-catechol diacetate (**3**), (±)-*anti*-BPDE (**4**), and (±)-*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 B*a*P metabolites **1**–**5** were shown previously to be accessible via a synthetic route based on benzo[*a*]pyren-8-ol (**37c**).[20] Synthesis of B*a*P 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 $Pd(OAc)_2Cl_2$, 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 coupling[24] of **35c** with TMSA in the presence of $Pd(Ph_3)_2Cl_2$, 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 cyclization[18] of **36b** gave B*a*P (**37a**). This synthetic route to B*a*P 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 $^{13}C_4$-B*a*P isotopomers.

Benzo[*a*]pyren-8-ol (**37c**) was synthesized by an analogous sequence (Scheme 5). 1-Bromo-2,6-dibenzyoxybenzene (**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-methoxynaphthy lboronic acid (**33b**) furnished 2-(2,6-dibenzyloxyphenyl)-6-methoxynaphthalene (**35d**), and removal of the benzyl groups (by hydrogenation over a Pd/C catalyst) afforded 2-(2,6-dihydroxy phenyl)-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-B*a*P (**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 $Pd(PPh_3)_4$ 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 B*a*P (**37a**). Synthesis of B*a*P 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-B*a*P (**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 B*a*P 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 B*a*P metabolites **1**–**5** and their $^{13}C_4$-labelled analogues. Oxidation of **37c** with *o*-iodoxybenzoic acid (IBX) gave B*a*P 7,8-dione (**2**),[19,20,23] and reduction of **2** with $NaBH_4/O_2$ furnished (±)-B*a*P 7,8-diol (**1**). Although B*a*P 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 B*a*P 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 the same face (Fig. 1).[1b] (±)-*anti*-BPDE was synthesized by epoxidation of **1** with *m*-chloroperbenzoic acid,[1b,27,28] and (±)-*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. $^{13}C_4$-Labelled metabolites of BaP—Syntheses of $^{13}C_4$-BaP and its 1-, 2-, 3-, 9-, and 12-phenol isomers (with ^{13}C at C-4, -5, -5a, and -6) ((Scheme 4 and Fig. 2) via *Method B* were described in Part I. Syntheses of $^{13}C_2$-B*a*P and its key oxidized metabolites $^{13}C_2$-B*a*P *trans*-7,8-diol ($^{13}C_2$-**1**) and $^{13}C_2$-B*a*P-7,8-dione ($^{13}C_2$-**2**) with ^{13}C at C-5,11) (Fig. 2) were reported previously.[16]

The structures of the $^{13}C_4$-labelled B*a*P derivatives synthesized in Part II via *Method B* are shown in Fig. 3. They include $^{13}C_4$-B*a*P, $^{13}C_4$-8-HO-B*a*P ($^{13}C_4$-**37c**), and $^{13}C_4$-9-HO-B*a*P ($^{13}C_4$-**37e**) (with ^{13}C at C-4, -5, -11, and -12). Also included are the $^{13}C_4$-labelled metabolites of B*a*P implicated in carcinogenesis [$^{13}C_4$-B*a*P *trans*-7,8-diol ($^{13}C_4$-**1**), $^{13}C_4$-B*a*P 7,8-dione ($^{13}C_4$-**2**), B*a*P 7,8-catechol ($^{13}C_4$-**3**) and $^{13}C_4$-(±)-*anti*-BPDE ($^{13}C_4$-**4**) with ^{13}C at C-4, -5, -11, and -12] (Fig. 3). B*a*P 7,8-catechol (**3**) was previously shown to undergo decomposition in air.[26] For this reason the $^{13}C_4$-B*a*P 7,8-catechol was isolated as its stable diacetate ($^{13}C_4$-**3** diacetate). And finally, the mixed $^{13}C_4$-B*a*P tetraol isomers were prepared by hydrolysis of $^{13}C_4$-(±)-*anti*-BPDE.

$^{13}C_4$-B*a*P (^{13}C at C-4, -5, -11, and -12) was synthesized by a sequence similar to that for synthesis of unlabelled B*a*P (Scheme 8). Use of this method allowed incorporation of both pairs of $^{13}C_4$-atoms to take place in a single step. Thus, Pd-catalyzed double Sonogashira

coupling of $^{13}C_2$-TMSA with **39a** furnished $^{13}C_4$-**40a**. Removal of the TMS groups by treatment of $^{13}C_4$-**40a** with K_2CO_3 in MeOH/THF converted it to $^{13}C_4$-**40b**, and $PtCl_2$-catalyzed cyclization[18] of the latter afforded $^{13}C_4$-B*a*P ($^{13}C_4$-**37a**).

The 8- and 9-phenols of $^{13}C_4$-B*a*P ($^{13}C_4$-**37c** and $^{13}C_4$-**37e** with ^{13}C at C-4, -5, -11, and -12) were synthesized from **39b** and **39c** via analogous sequences (Scheme 8). The $^{13}C_4$-labelled carcinogenic metabolites [$^{13}C_4$-**1**, $^{13}C_4$-**2**, $^{13}C_4$-**4**, and $^{13}C_4$-**3** diacetate] were prepared from $^{13}C_4$-**37c** (Scheme 9) by methods analogous to those for synthesis of the unlabelled B*a*P metabolites (Scheme 7). Since the $^{13}C_4$-B*a*P metabolites derive from a common synthetic precursor ($^{13}C_4$-**37c**), their ^{13}C-atoms are at the same sites (C-4, -5, -11, and -12).

The isotopic purity of the synthetic $^{13}C_4$-labelled B*a*P 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 B*a*P-tetrol-1 and 6 fmol for all other B*a*P metabolites, and the injection of 10 pmol of each $^{13}C_4$-labelled compound on column, it is estimated that B*a*P-tetrol-1 has an isotopic purity >99.9 % and for all other compounds the isotopic purity is >99.94 %.

3. Discussion

The principal aim of this investigation was to synthesize the complete set of $^{13}C_4$-labelled oxidized metabolites of B*a*P needed as internal standards for a stable isotope dilution LC/MS method for their analysis.[15] The B*a*P metabolites were divided into two groups (*A* and *B*) on the basis of their role in carcinogenesis. *Group A* includes the B*a*P metabolites that have no role in carcinogenesis [1-HO-, 2- HO-, 3- HO-, 9- HO-, and 12-HO-B*a*P, B*a*P-1,6-dione (**6**) and B*a*P-3,6-dione (**7**)] (Fig. 1), and the B*a*P metabolites in *Group B* are those implicated in initiation of cancer [B*a*P 7,8-diol (**1**), B*a*P 7,8-dione (**2**), B*a*P 7,8-catechol (diacetate) (**3**), (±)-*anti*-BPDE (**4**), and (±)-*syn*-BPDE (**5**)] (Fig. 1), plus 8- and 9-HO-B*a*P.

3.1. Synthesis of $^{13}C_4$-labelled oxidized metabolites of B*a*P

This paper reports efficient syntheses of B*a*P and its oxidized metabolites in *Groups A and B* and their $^{13}C_4$-labelled analogues. The synthetic design was influenced by: (1) the cost of the available ^{13}C-labelled precursors; (2) the advantage of introducing the ^{13}C-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 $PtCl_2$-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 $PtCl_2$-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 B*a*P, 8-HO-B*a*P (**37c**), and their $^{13}C_4$-labelled analogues ($^{13}C_4$-B*a*P and $^{13}C_4$-**37c**). The synthesis of B*a*P by *Method A* requires eight steps (Scheme 1), whilst its synthesis by *Method B* requires only four steps

(Scheme 6). Synthesis of the $^{13}C_4$-labelled analogues of B*a*P and **37c** by *Method A* affords $^{13}C_4$-B*a*P and $^{13}C_4$-**37c** (with ^{13}C at C-4, -5, -5a, and -6) (Scheme 4), whilst their synthesis by *Method B* affords the 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 $^{13}C_4$-**37c** via this route combined with the fact that $^{13}C_4$-**37c** is a convenient synthetic precursor of all the $^{13}C_4$-labelled active metabolites ($^{13}C_4$-**1**, $^{13}C_4$-**2**, $^{13}C_4$-**3**, $^{13}C_4$-**4**, and $^{13}C_4$-**5**) (Scheme 9) makes these compounds now all of them readily available for research in carcinogenesis.

3.2. Comparison with the syntheses of the $^{13}C_6$-labelled B*a*P metabolites

Synthesis of $^{13}C_6$-labelled analogues of several *Group B* B*a*P metabolites (**1**, **4**, **5**, and B*a*P tetraols) was reported by Diel et al.[35] Their synthetic approach entailed multistep synthesis of $^{13}C_6$-pyrene from $^{13}C_6$-benzene followed by its use asstarting compound for synthesis of $^{13}C_6$-9,10-dihydro-B*a*P (**42**) (Fig. 4) by Friedel–Crafts chemistry.[1b,33,34]

As a consequence of the symmetry of $^{13}C_6$-pyrene, **42** was obtained as a pair of isotopomers (**42A** and **42B**) each possessing six ^{13}C-atoms, but in different aromatic rings (Fig. 4). This mixture was converted into the mixed $^{13}C_6$-B*a*P 7,8-diol isotopomers ($^{13}C_6$-**1A** and $^{13}C_6$-**1B**), and this was further transformed into the mixed $^{13}C_6$-(±)-*anti*-BPDEs ($^{13}C_6$-**4A** and $^{13}C_6$-**4B**) by the established methods. The $^{13}C_6$-(±)-*syn*-BPDEs (structures not shown) and the mixed $^{13}C_6$-tetraols (from hydrolysis of the *anti*- and *syn*-BPDEs) were also prepared. The principal drawbacks to the use of these $^{13}C_6$-labelled B*a*P analogues in biological studies are the large number of synthetic steps required, the $^{13}C_6$-B*a*P metabolites are mixtures of isotopomers, and many of the likely $^{13}C_6$-B*a*P 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 B*a*P (*Group A and Group B* metabolites) and their $^{13}C_4$-labelled analogues. The synthetic $^{13}C_4$-B*a*P metabolites were required as standards for quantitation of the metabolic profiles of B*a*P 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 (B*a*P) 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 B*a*P 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-B*a*P (14b, 14d, and 14f) and their $^{13}C_4$ 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 $Pd(OAc)_2$ (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%): ^{1}H 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 $C_{17}H_{14}BrO$ $[M+H]^+$ 313.0223, found 313.0225.

5.2.2. 2-(2-Bromophenyl)-5-methoxynaphthalene (10a)—Reaction of **9a** with **8** gave **10a** (70%): ^{1}H 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 $C_{17}H_{14}BrO$ $[M+H]^+$ 313.0223, found 313.0253.

5.2.3. 2-(2-Bromophenyl)-6-methoxynaphthalene (10b)—Reaction of **9b** with **8** gave **10b**. Yield: 68%: ^{1}H 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 $C_{17}H_{14}BrO$ $[M+H]^+$ 313.0223, found 313.0248.

5.2.4. Ethyl 2-(7-methoxynaphthalenyl)phenylacetate (11b)—To a solution of **10c** (156 mg, 0.5 mmol), $Pd(dba)_2$ (14.5 mg, 0.025 mmol), and Q-phos (18 mg, 0.025 mmol) in THF (0.5 mL) was added $ZnBrCH_2CO_2Et$ (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%): ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485, found 321.1483.

5.2.5. Ethyl $^{13}C_2$-2-(7-methoxynaphthalenyl)phenylacetate ($^{13}C_2$-11b)—^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 172.0 (d, J=228.0 Hz), 39.0 (d, J=228.0 Hz); HRMS calcd for $^{13}C_2$-$C_{21}H_{20}NaO_3$ $[M+Na]^+$ 345.1372, found 345.1349.

5.2.6. Ethyl 2-(5-methoxynaphthalenyl)phenylacetate (11d)—Reaction of **10a** with $ZnBrCH_2CO_2Et$ gave **11d** (93%): ^{1}H NMR (500 MHz, $CDCl_3$) 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); ^{13}C NMR (125.8 MHz, $CDCl_3$) 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 $C_{21}H_{20}NaO_3$ $[M+Na]^+$ 343.1305, found 343.1330.

5.2.7. Ethyl 2-(6-methoxynaphthalenyl)phenylacetate (11f)—Reaction of **10b** with $ZnBrCH_2CO_2Et$ afforded **11f** (90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ7.90–7.70 (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); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ172.0, 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 $C_{21}H_{21}O_3$ $[M+H]^+$ 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 H_2O (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%): ^{1}H NMR (500 MHz, acetone-d_6) δ8.02–7.83 (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); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ173.3, 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 $C_{19}H_{16}O_3$ $[M]^+$ 292.1094, found 292.1061.

5.2.9. 2-(5-Methoxynaphthalenyl)phenylacetic acid (11e)—Hydrolysis of **11d** gave **11e** (92%): ^{1}H NMR (500 MHz, DMSO-d_6) δ8.18 (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); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ173.2, 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 $C_{19}H_{17}O_3$ $[M+H]^+$ 293.1172, found 293.1143.

5.2.10. 2-(6-Methoxynaphthalenyl)phenylacetic acid (11g)—Hydrolysis of **11f** gave **11g** (90%): ^{1}H NMR (500 MHz, DMSO-d_6) δ7.87 (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); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ173.3, 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 $C_{19}H_{17}O_3$ $[M+H]^+$ 293.1172, found 293.1143.

5.2.11. $^{13}C_2$-2-(7-Methoxynaphthalenyl)phenylacetic acid ($^{13}C_2$-11c)—^{1}H NMR (500 MHz, DMSO-d_6) δ12.23 (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, DMSO-d_6) δ173.2 (d, J=218.0 Hz), 39.0 (d, J=218.0 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{17}O_3$ $[M+H]^+$ 295.1239, found 295.1211.

5.2.12. 3-Methoxychrysen-5-ol (12e)—A suspension of **11c** (292 mg, 1 mmol) in $MeSO_3H$ 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 Na_2SO_4. 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%): ^{1}H NMR (500 MHz, acetone-d_6) δ9.79 (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); ^{13}C NMR (125.8 MHz, acetone-d_6) δ158.1, 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 $C_{19}H_{15}O_2$ $[M+H]^+$ 275.1067, found 275.1062.

5.2.13. $^{13}C_2$-3-Methoxychrysen-5-ol ($^{13}C_2$-12e)—^{1}H 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); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ154.9 (d, *J*=277.5 Hz), 108.7 (d, *J*=277.5 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{14}O_2$ $[M]^+$ 276.1055, found 276.1056.

5.2.14. 1-Methoxychrysen-5-ol (12a)—Similar acid-catalyzed cyclization of **11e** gave **12a** (80%): ^{1}H NMR (500 MHz, acetone-d_6) δ9.66 (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); ^{13}C 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 $C_{19}H_{15}O_2$ $[M+H]^+$ 275.1067, found 275.1091.

5.2.15. $^{13}C_2$-1-Methoxychrysen-5-ol ($^{13}C_2$-12a)—^{1}H 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); ^{13}C NMR (125.8 MHz, acetone-d_6) δ154.8 (d, *J*=277.5 Hz), 109.1 (d, *J*=277.5 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{15}O_2$ $[M+H]^+$ 277.1134, found 277.1093.

5.2.16. 2-Methoxychrysen-5-ol (12c)—Acid-catalyzed cyclization of **11g** gave **12c** (87%): ^{1}H NMR (500 MHz, acetone-d_6) δ9.98 (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); ^{13}C NMR (125.8 MHz, acetone-d_6) δ157.7, 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 $C_{19}H_{15}O_2$ $[M+H]^+$ 275.1067, found 275.1085.

5.2.17. $^{13}C_2$-2-Methoxychrysen-5-ol ($^{13}C_2$-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 CH_2Cl_2 (10 mL) was added pyridine (103 mg, 1.3 mmol), and the mixture was stirred for 10 min at room temperature. Then Tf_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%): ^{1}H NMR (500 MHz, $CDCl_3$) δ8.67 (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, $CDCl_3$) δ158.6, 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*=1277.5 Hz), 118.2; HRMS calcd for $C_{20}H_{13}F_3NaO_4S$ $[M+Na]^+$ 429.0379, found 429.0365.

5.2.19. $^{13}C_2$-3-Methoxychrysen-5-ol trifluoromethanesulfonate ($^{13}C_2$-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%): ^{1}H 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=1277.0 Hz), 106.0, 55.8; HRMS calcd for $C_{20}H_{14}F_3O_4S$ $[M+H]^+$ 407.0559, found 407.0575.

5.2.21. $^{13}C_2$-1-Methoxychrysen-5-ol trifluoromethanesulfonate ($^{13}C_2$-12b)—^{1}H 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 $^{13}C_2$-labelled $C_{20}H_{13}F_3O_4S$ (M^+) 408.0553, found 408.0536.

5.2.22. 2-Methoxychrysen-5-ol trifluoromethanesulfonate (12d)—Esterification of **12c** gave **12d** (76%): ^{1}H 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=1276.0 Hz), 118.0, 108.2, 55.4; HRMS calcd for $C_{20}H_{14}F_3O_4S$ $[M+H]^+$ 407.0559, found 407.0588.

5.2.23. 3-Methoxy-5-(trimethylsilylethynyl)chrysene (13e)—To a solution of **12f** (406 mg, 1.0 mmol) in DMF (15 mL) were added $Pd(Ph_3)_2Cl_2$ (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%): ^{1}H 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 $C_{24}H_{22}OSi$ (M^+) 354.1440, found 354.1454.

5.2.24. $^{13}C_4$-3-Methoxy-5-(trimethylsilylethynyl)chrysene ($^{13}C_4$-13e)—^{1}H 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 $^{13}C_4$-$C_{24}H_{22}OSi$ (M^+): 358.1575, found 358.1580.

5.2.25. 1-Methoxy-5-(trimethylsilylethynyl)chrysene (13a)—Synthesis from **12b** by the foregoing procedure gave **13a** (90%): ^{1}H 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, 121.8, 120.4, 119.4, 117.9, 108.6, 105.5, 99.6, 55.8, −0.11; HRMS calcd for $C_{24}H_{22}OSi$ (M^+) 354.1440, found 354.1460.

5.2.26. $^{13}C_4$-1-Methoxy-5-(trimethylsilylethynyl)chrysene ($^{13}C_4$-13a)—^{1}H 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 $^{13}C_4$-$C_{24}H_{22}OSi$ (M^+) 358.1575, found 358.1560.

5.2.27. 2-Methoxy-5-(trimethylsilylethynyl)chrysene (13c)—Synthesis from **12d** by the foregoing procedure gave **13c** (92%): ^{1}H 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 $C_{24}H_{22}OSi$ (M^+) 354.1440, found 354.1426.

5.2.28. 3-Methoxy-5-ethynylchrysene (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%): ^{1}H 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), 8.00–7.7.82 (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 $C_{21}H_{14}O$ (M^+) 282.1045, found 282.1056.

5.2.29. $^{13}C_4$-3-Methoxy-5-ethynylchrysene ($^{13}C_4$-13f)—^{1}H 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 $^{13}C_4$-$C_{21}H_{14}O$ (M^+): 286.1178, found 286.1190.

5.2.30. 1-Methoxy-5-ethynylchrysene (13b)—Similar reaction of **13a** gave **13b** (95%): ^{1}H 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 $C_{21}H_{14}O$ (M^+) 282.1045, found 282.1069.

5.2.31. $^{13}C_4$-1-Methoxy-5-ethynylchrysene ($^{13}C_4$-13b)—^{1}H 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, $CDCl_3$) δ137.5 (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 $^{13}C_4$-$C_{21}H_{14}O$ (M^+) 286.1178, found 286.1167.

5.2.32. 2-Methoxy-5-ethynylchrysene (13d)—Similar reaction of **13c** gave **13d** (90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ10.34 (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, $CDCl_3$) δ158.0, 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 $C_{21}H_{15}O$ $[M+H]^+$ 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 ^{1}H NMR spectrum of **7e** matched that of an authentic sample.

5.2.34. $^{13}C_4$-3-Methoxybenzo[a]pyrene ($^{13}C_4$-14e)—^{1}H 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, $CDCl_3$) δ130.3 (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 $^{13}C_4$-labelled $C_{21}H_{24}O$ (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. $^{13}C_4$-1-Methoxybenzo[a]pyrene ($^{13}C_4$-14b)—^{1}H 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, $CDCl_3$) δ130.3 (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 $^{13}C_4$-$C_{21}H_{14}O$ (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%): ^{1}H NMR (500 MHz, $CDCl_3$) δ7.98–7.89 (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, $CDCl_3$) δ158.9, 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 $C_{17}H_{14}BrO$ $[M+H]^+$ 313.0223, found 313.0205.

5.3.2. Ethyl 2-(napththalen-2-yl)-5-methoxyphenyl acetate (18a)—Pd-catalyzed coupling of **17** with $BrZnCH_2CO_2Et$ with **16** gave **18a** (90%): ^{1}H NMR (500 MHz, $CDCl_3$) δ7.98–7.89 (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, $CDCl_3$) δ172.3, 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 $C_{21}H_{21}O_3$ $[M+H]^+$ 321.1485, found 321.1472.

5.3.3. Ethyl $^{13}C_2$-2-(napththalen-2-yl)-5-methoxyphenyl acetate ($^{13}C_2$-18a)—^{1}H 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 $^{13}C_2$-$C_{21}H_{21}O_3$ $[M]^+$ 322.1477, found 322.1514.

5.3.4. 2-(Napththalen-2-yl)-5-methoxyphenylacetic acid (18b)—Hydr olysis of **18a** by the procedure for preparation of **11c** gave **18b** (91%): ^{1}H 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 $C_{19}H_{16}NaO_3$ $[M+Na]^+$ 315.0992, found 315.0966.

5.3.5. $^{13}C_2$-2-(Napththalen-2-yl)-5-methoxyphenylacetic acid ($^{13}C_2$-18b)—^{1}H 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 $^{13}C_2$-$C_{19}H_{17}O_3$ $[M+H]^+$ 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%): ^{1}H 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 $C_{19}H_{14}O_2$ (M^+) 274.0994, found 274.0976.

5.3.7. $^{13}C_2$-3-Methoxychrysen-11-ol ($^{13}C_2$-19a)—^{1}H 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 $^{13}C_2$-$C_{19}H_{15}O_2$ $[M+H]^+$ 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%): ^{1}H 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 $C_{20}H_{14}F_3O_4S$ $[M+H]^+$ 407.0559, found 407.0542.

5.3.9. $^{13}C_2$-3-Methoxychrysen-11-ol triflate ($^{13}C_2$-3-19b)—^{1}H 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=8.5and 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 $^{13}C_2$-labelled $C_{20}H_{13}F_3O_4S$ (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%): ^{1}H 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 $C_{24}H_{22}OSi$ (M^+) 354.1440, found 354.1446.

5.3.11. $^{13}C_4$-((9-Methoxychrysen-5-yl)ethynyl)trimethylsilane ($^{13}C_4$-20a)—^{1}H 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 $^{13}C_4$-$C_{24}H_{22}OSi$ (M^+) 358.1575, found 358.1583.

5.3.12. 5-Ethynyl-9-methoxychrysene (20b)—Removal of the trimethylsilyl group of **20a** gave **20b** (92%): ^{1}H 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 $C_{21}H_{15}O$ $[M+H]^+$ 283.1117, found 283.1105.

5.3.13. $^{13}C_4$-5-Ethynyl-9-methoxychrysene ($^{13}C_4$-20b)—^{1}H 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 $^{13}C_4$-$C_{21}H_{14}O$ (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 ^{1}H and ^{13}C NMR spectra matched those of an authentic standard.

5.3.15. $^{13}C_4$-9-Methoxybenzo[a]pyrene ($^{13}C_4$-21a)—^{1}H 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 $^{13}C_4$-$C_{21}H_{14}O$ (M^+): 286.1178, found 286.1190.

5.4. Synthesis of 12-HO-B*a*P (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%): ^{1}H 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 $C_{17}H_{14}BrO$ $[M+H]^+$ 313.0223, found 313.0250.

5.4.2. Ethyl 2-(4-methoxynaphthalen-2-yl)phenyl acetate (24a)—Pd-catalyzed coupling of **23** with $BrZnCH_2CO_2Et$ provided **24a** (85%): ^{1}H 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, $CDCl_3$) δ171.9, 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 $C_{21}H_{20}NaO_3$ $[M+Na]^+$ 343.1305, found 343.1307.

5.4.3. Ethyl $^{13}C_2$-2-(4-methoxynaphthalen-2-yl)phenyl acetate ($^{13}C_2$-24a)—^{1}H NMR (500 MHz, DMSO-d_6) δ12.23 (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, DMSO-d_6) δ173.2 (d, *J*=218.0 Hz), 39.0 (d, *J*=218.0 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{17}O_3$ $[M+H]^+$ 295.1239, found 295.1211.

5.4.4. 2-(4-Methoxynaphthalen-2-yl)phenylacetic acid (24b)—Ethan olysis of **24a** provided **24b** (91%): ^{1}H NMR (500 MHz, acetone-d_6) δ9.30 (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) δ173.3, 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 $C_{19}H_{16}NaO_3$ $[M+Na]^+$ 315.0992, found 315.0966.

5.4.5. $^{13}C_2$-2-(4-Methoxynaphthalen-2-yl)phenylacetic acid ($^{13}C_2$-24b)—^{1}H NMR (500 MHz, DMSO-d_6) δ12.33(brs, 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, DMSO-d_6) δ173.5 (d, *J*=218.5 Hz), 39.2 (d, *J*=218.5 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{17}O_3$ $[M+H]^+$ 295.1239, found 295.1219.

5.4.6. 12-Methoxychrysen-5-ol (25a)—Acid-catalyzed cyclization of **24b** afforded **25a** (82%): ^{1}H NMR (500 MHz, acetone-d_6) δ10.06 (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) δ154.6, 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 $C_{19}H_{15}O_2$ $[M+H]^+$ 275.1067, found 275.1094.

5.4.7. $^{13}C_2$-12-Methoxychrysen-5-ol ($^{13}C_2$-25a)—^{1}H NMR (500 MHz, $CDCl_3$) δ9.83 (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, $CDCl_3$) δ150.9 (d, *J*=286.5 Hz), 109.7 (d, *J*=286.5 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{15}O_2$ $[M+H]^+$ 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%): ^{1}H NMR (500 MHz, $CDCl_3$) δ9.15 (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, $CDCl_3$) δ155.6, 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 $C_{20}H_{13}O_4F_3S$ (M^+) 406.0485, found 406.0458.

5.4.9. $^{13}C_2$-12-Methoxychrysen-5-ol triflate ($^{13}C_2$-25b)—^{1}H NMR (500 MHz, DMSO-d_6) δ10.77 (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, DMSO-d_6) δ154.6 (d, *J*=277.5 Hz), 107.0 (d, *J*=277.5 Hz); HRMS calcd for $^{13}C_2$-$C_{19}H_{15}O_2$ $[M+H]^+$ 277.1134, found 277.1155.

5.4.10. ((Chrysen-5-yl)ethynyl)trimethylsilane (26a)—Sonogashira coupling of **25b** with (trimethylsilyl)acetylene afforded **26a** (95%): ^{1}H NMR (500 MHz, $CDCl_3$) δ10.48 (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, $CDCl_3$) δ154.5, 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 $C_{24}H_{22}OSi$ (M^+) 354.1440, found 354.1417.

5.4.11. $^{13}C_4$-((Chrysen-5-yl)ethynyl)trimethylsilane ($^{13}C_4$-26a)—^{1}H NMR (500 MHz, $CDCl_3$) δ10.48 (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, $CDCl_3$) δ134.4 (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 $^{13}C_4$-$C_{24}H_{22}OSi$ (M^+) 358.1575, found 358.1545.

5.4.12. 5-Ethynyl-12-methoxychrysene (26b)—Treatment of **26a** with K_2CO_3 in MeOH/THF provided **26b** (91%): ^{1}H NMR (500 MHz, $CDCl_3$) δ10.37 (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, $CDCl_3$) δ154.6, 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 $C_{21}H_{14}O$ (M^+), 282.1045, found 282.1053.

5.4.13. $^{13}C_4$-5-Ethynyl-12-methoxychrysene ($^{13}C_4$-26b)—^{1}H NMR (500 MHz, $CDCl_3$) δ10.37 (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, $CDCl_3$) δ135.3 (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 $^{13}C_4$-$C_{21}H_{14}O$ (M^+) 286.1178, found 286.1167.

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

5.4.15. $^{13}C_4$-12-Methoxybenzo[a]pyrene ($^{13}C_4$-27a)—^{1}H 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, $CDCl_3$) δ132.0–127.1 (m, 3C), 122.4 (ddd, J=219.0, 25.0, and 16.0 Hz); HRMS calcd for $^{13}C_4$-$C_{21}H_{14}O$ (M^+) 286.1178, found 286.1192.

5.5. Syntheses of BaP, $^{13}C_4$-BaP, and the $^{13}C_4$-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%): ^{1}H NMR (500 MHz, $CDCl_3$) δ8.05–7.95 (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, $CDCl_3$) δ142.5, 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 $C_{16}H_{11}Br$ $(M)^+$: 282.0044, found 282.0040.

5.5.2. Ethyl 2-(2-naphthalenyl)phenylacetate (30a)—Coupling of **29** with $ZnBrCH_2CO_2Et$ by the method for preparation of **11b** gave **30a** (93 %): ^{1}H 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 $C_{20}H_{19}O_2$ $[M+H]^+$: 291.1380, found 291.1373.

5.5.3. Ethyl $^{13}C_2$-2-(2-naphthalenyl)phenylacetate ($^{13}C_2$-30a)—^{1}H 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 $^{13}C_2$-$C_{20}H_{18}O_2$ $[M]^+$ 292.1375, found 292.1374.

5.5.4. 2-(2-Naphthalenyl)phenylacetic acid (30b)—Hydrolysis of **30a** by the usual method gave **30b** (91%): ^{1}H NMR (500 MHz, 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, 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 $C_{18}H_{15}O_2$ $[M+H]^+$ 263.1063, found 263.1012.

5.5.5. $^{13}C_2$-2-(2-Naphthalenyl)phenylacetic acid ($^{13}C_2$-30b)—^{1}H 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, DMSO-d_6) δ 173.2 (d, J=223.5 Hz), 39.1 (d, J=223.5 Hz); HRMS calcd for $^{13}C_2$-$C_{18}H_{14}NaO_2$ $[M+Na]^+$ 287.0953, found 287.0933.

5.5.6. Chrysen-5-ol (31a)—Acid-catalyzed cyclization of **30b** by the usual method gave **31a** (87%): ^{1}H 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 $C_{18}H_{13}O$ $[M+H]^+$ 245.0961, found 245.0970.

5.5.7. $^{13}C_2$-Chrysen-5-ol ($^{13}C_2$-31a)—^{1}H NMR (500 MHz, 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, DMSO-d_6) δ 154.8 (d, J=277.5 Hz), 109.2 (d, J=277.5 Hz); HRMS calcd for $^{13}C_2$-$C_{18}H_{13}O$ $[M+H]^+$ 247.1032, found 247.1019.

5.5.8. Chrysen-5-ol triflate (31b)—Esterification of **31a** gave **31b** (80%): ^{1}H 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 $C_9H_{11}F_3O_3S$ (M^+) 376.0381, found 376.0385.

5.5.9. $^{13}C_2$-Chrysen-5-ol triflate ($^{13}C_2$-31b)—^{1}H 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 $^{13}C_2$-$C_{19}H_{11}F_3O_3S$ (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%): ^{1}H 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 $C_{23}H_{20}Si$ (M^+) 324.1334, found 324.1322.

5.5.11. $^{13}C_4$-(Chrysen-5-ylethynyl)trimethylsilane ($^{13}C_4$-32a)—^{1}H 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 $^{13}C_4$-$C_{23}H_{20}Si$ (M^+) 328.1468, found 328.1469.

5.5.12. 5-Ethynylchrysene (32b)—Removal of the TMS group of **32a** gave **32b** (85%): ^{1}H 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 $C_{20}H_{13}$ $[M+H]^+$ 253.1012, found 253.1006.

5.5.13. $^{13}C_4$-5-Ethynylchrysene ($^{13}C_4$-32b)—^{1}H 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 $^{13}C_4$-$C_{20}H_{12}$ (M^+) 256.1073, found 256.1046.

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

5.5.15. $^{13}C_4$-Benzo[a]pyrene ($^{13}C_4$-BaP)—^{1}H 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 $^{13}C_4$-$C_{20}H_{14}$ (M^+): 256.1073, found 256.1079.

5.6. B*a*P-1,6- and 3,6-dione (5 and 6) and their $^{13}C_4$-labelled analogues ($^{13}C_4$-B*a*P-1,6-dione and $^{13}C_4$-B*a*P-3,6-dione) (Fig. 1)

These quinones were synthesized by oxidation of B*a*P-1-ol (**7b**) and B*a*P-3-ol (**7f**) with BTI by the methods reported.[20,24] *Check refs!!*

5.6.1. $^{13}C_4$-BaP-1,6-dione and $^{13}C_4$-BaP-3,6-dione—These quinones were synthesized by oxidation of $^{13}C_4$-B*a*P-1-ol and $^{13}C_4$-B*a*P-3-ol with BTI by methods analogous to those for oxidation of the unlabelled analogues.

$^{13}C_4$-BaP-1,6-dione: ^{1}H 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.

$^{13}C_4$-BaP-3,6-dione: ^{1}H 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This investigation was supported by NIH grants R01-ES015857 and P30-ES013508 (awarded to T.M.P.) and R01-CA130038 (awarded to I.A.B.).

Abbreviations

AKR1A1	aldo-keto reductase 1A1 enzyme
B*a*P	benzo[*a*]pyrene
B*a*P 7	8-diol, *trans*-7,8-dihydro-7,8-dihydroxy-B*a*P
B*a*P 1	6-dione, benzo[*a*]pyren-1,6-dione
B*a*P 3	6-dione, benzo[*a*]pyren-3,6-dione
B*a*P 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-B*a*P
***syn*-BPDE**	*trans*-7,8-dihydroxy-7,8-dihydro-*syn*-9,10-epoxy-B*a*P
8′-HO-2′-*d*Gua	8′-hydroxy-2′-deoxyguanosine
1-HO-B*a*P	benzo[*a*]pyren-1-ol
2-HO-B*a*P	benzo[*a*]pyren-2-ol
3-HOB*a*P	benzo[*a*]pyren-3-ol
9-HO-B*a*P	benzo[*a*]pyren-9-ol
12-HO-B*a*P	benzo[*a*]py-ren-12-ol
$^{13}C_4$-B*a*P	$^{13}C_4$-labelled-B*a*P (^{13}C *at C*-4,-5,-5a, and -6 or *at C*-4,-5,-11, and -12, as specified)
$^{13}C_4$-1-HO-B*a*P	$^{13}C_4$-labelled-1-HO-B*a*P (^{13}C *at C*-4,-5,-5a, and -6)
$^{13}C_4$-2-HO-B*a*P	$^{13}C_4$-labelled-2-HO-B*a*P (^{13}C *at C*-4,-5,-5a, and -6)
$^{13}C_4$-3-HO-B*a*P	$^{13}C_4$-labelled-3-HO-B*a*P (^{13}C *at C*-4,-5,-5a, and -6)
$^{13}C_4$-9-HO-B*a*P	$^{13}C_4$-labelled-9-HO-B*a*P (^{13}C *at C*-4,-5,-5a, and -6)
$^{13}C_4$-12-HO-B*a*P	$^{13}C_4$-labelled-12-HO-B*a*P (^{13}C *at C*-4,-5,-5a, and -6)
PAH	polycyclic aromatic hydrocarbon
ROS	reactive oxygen species

TMSA (trimethylsilyl)acetylene

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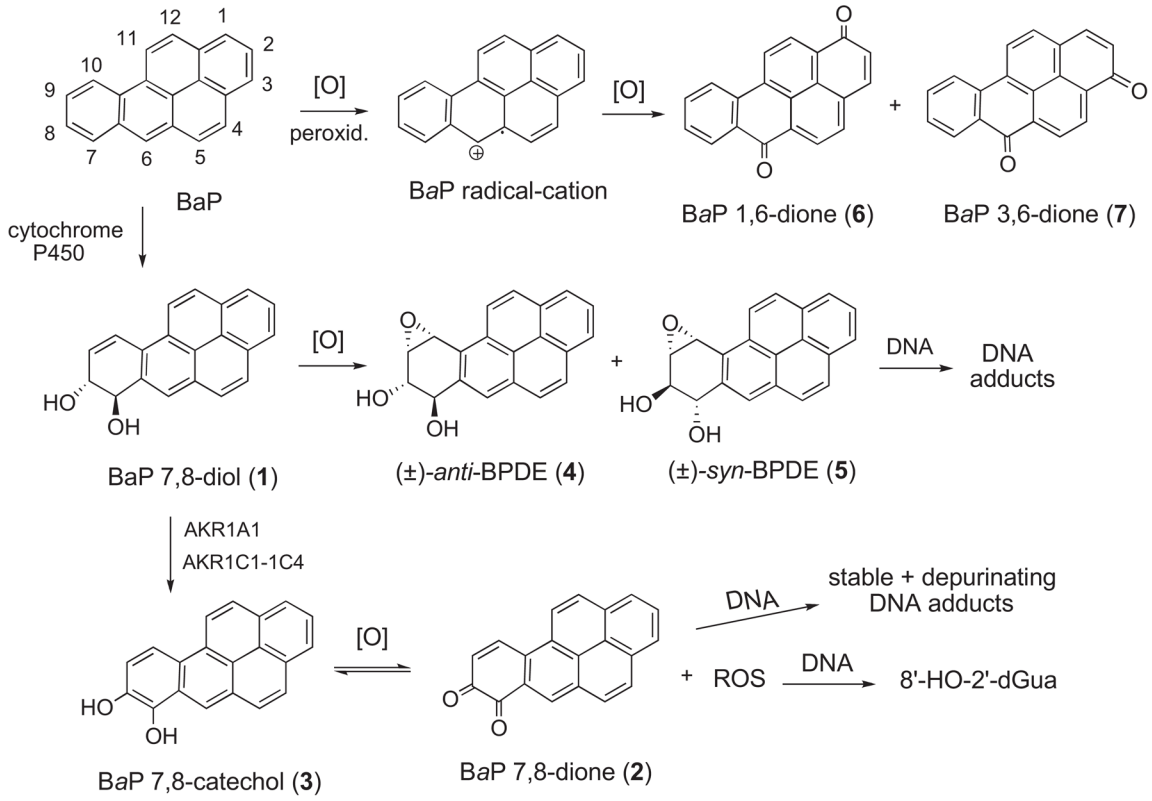


Fig. 1.
Pathways of enzymatic activation of benzo[*a*]pyrene (B*a*P).

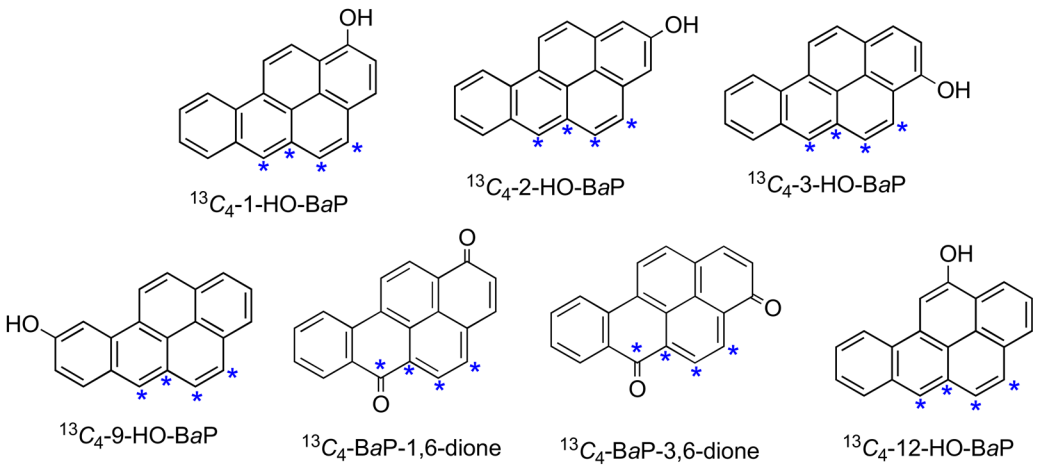


Fig. 2.
$^{13}C_4$-Labelled B*a*P phenols and quinones (*sites of ^{13}C-atoms).

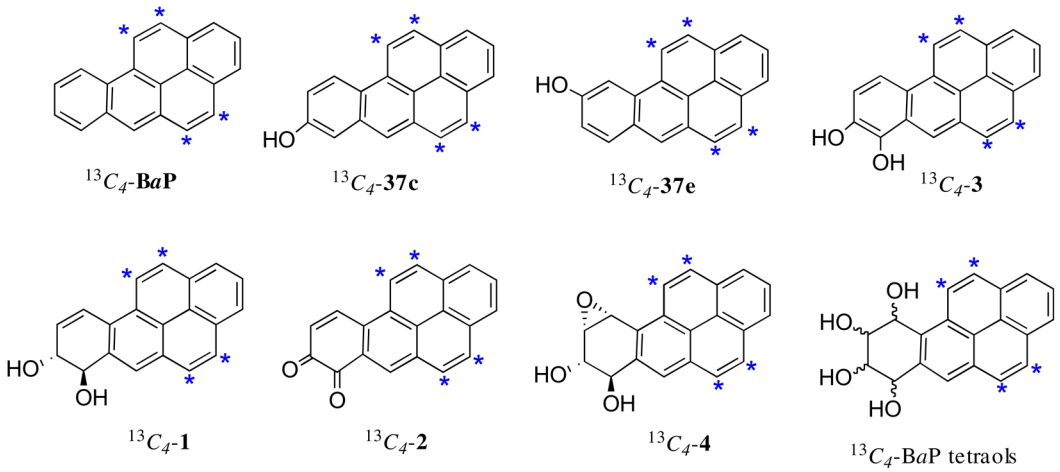


Fig. 3.
$^{13}C_4$-labelled B*a*P metabolites synthesized by *Method B* (*sites of ^{13}C-atoms).

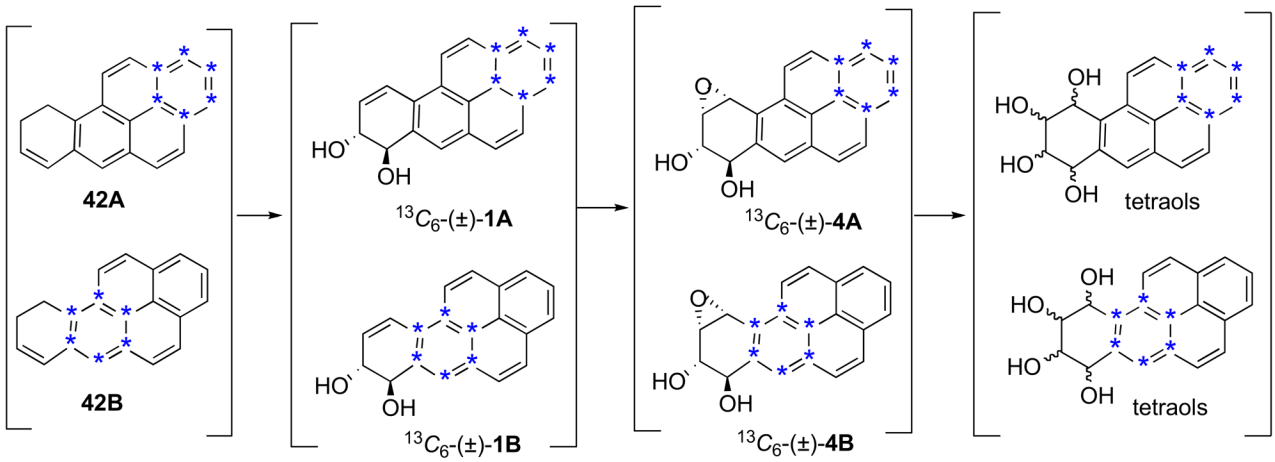
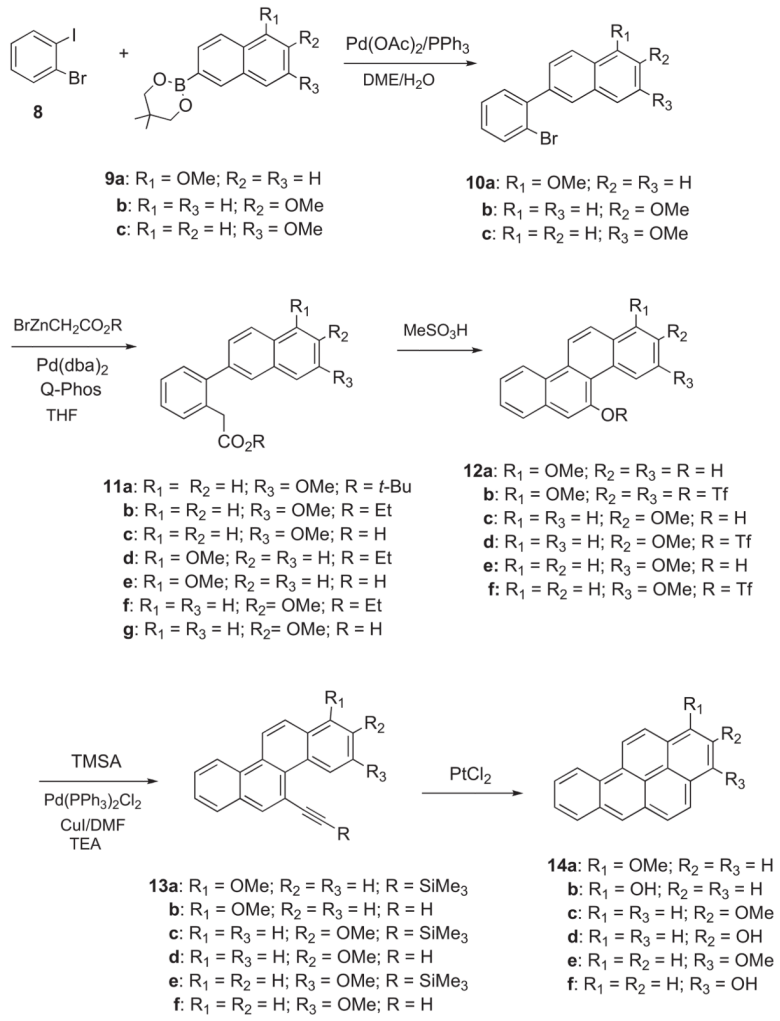
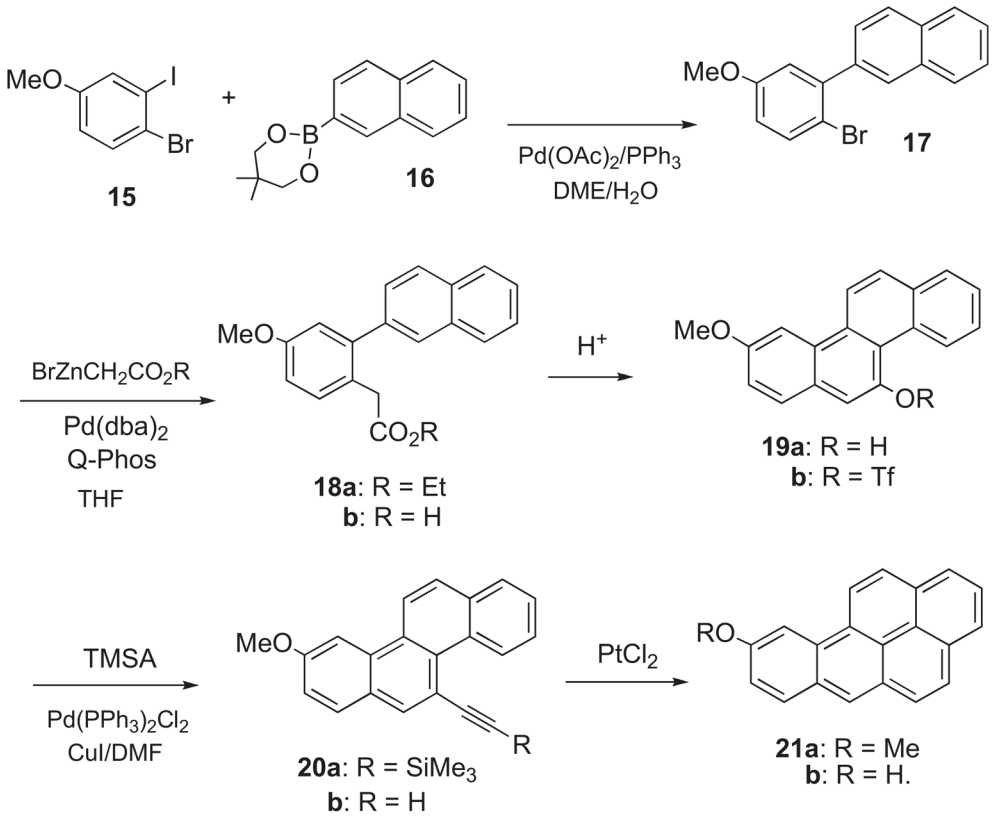


Fig. 4.

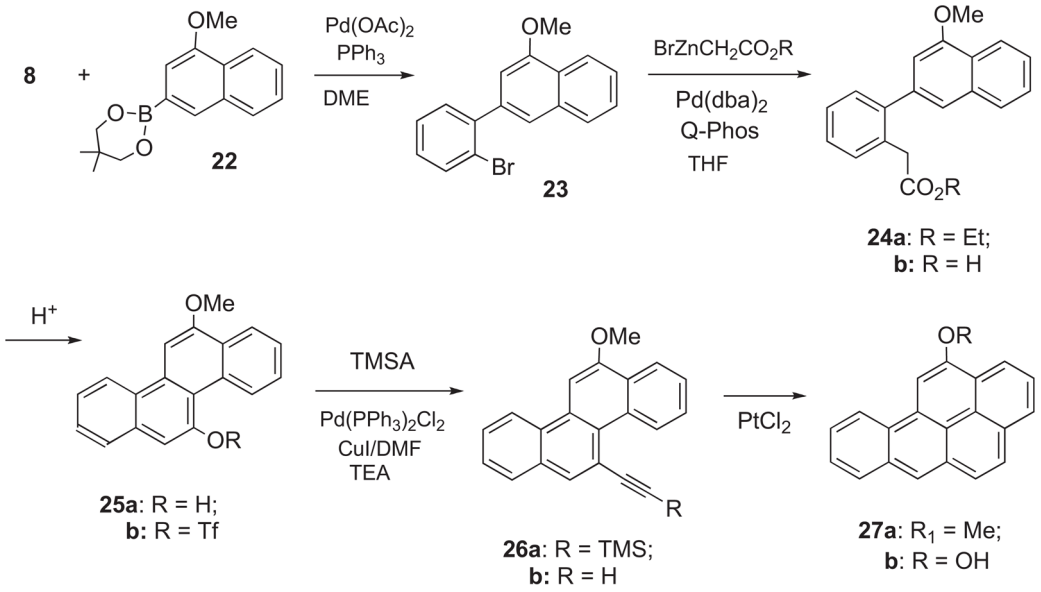
$^{13}C_6$-9,10-Dihydro-B*a*P was obtained as a mixture of isotopomers (**42A** and **42B**) that were transformed into the (±)-dihydrodiols ($^{13}C_6$-**1A** and $^{13}C_6$-**1B**), and they were converted into the *anti*- and *syn*-(±)-diol epoxides (only the *anti*-isomers, $^{13}C_6$-**4A** and $^{13}C_6$-**4B**, are shown). Sites of ^{13}C-atoms are indicated by asterisks '*'.



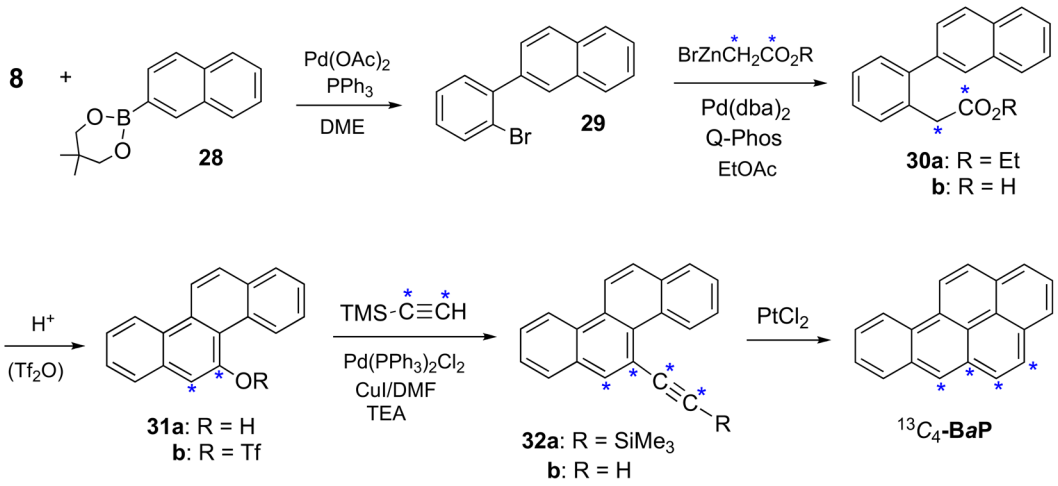
Scheme 1.



Scheme 2.

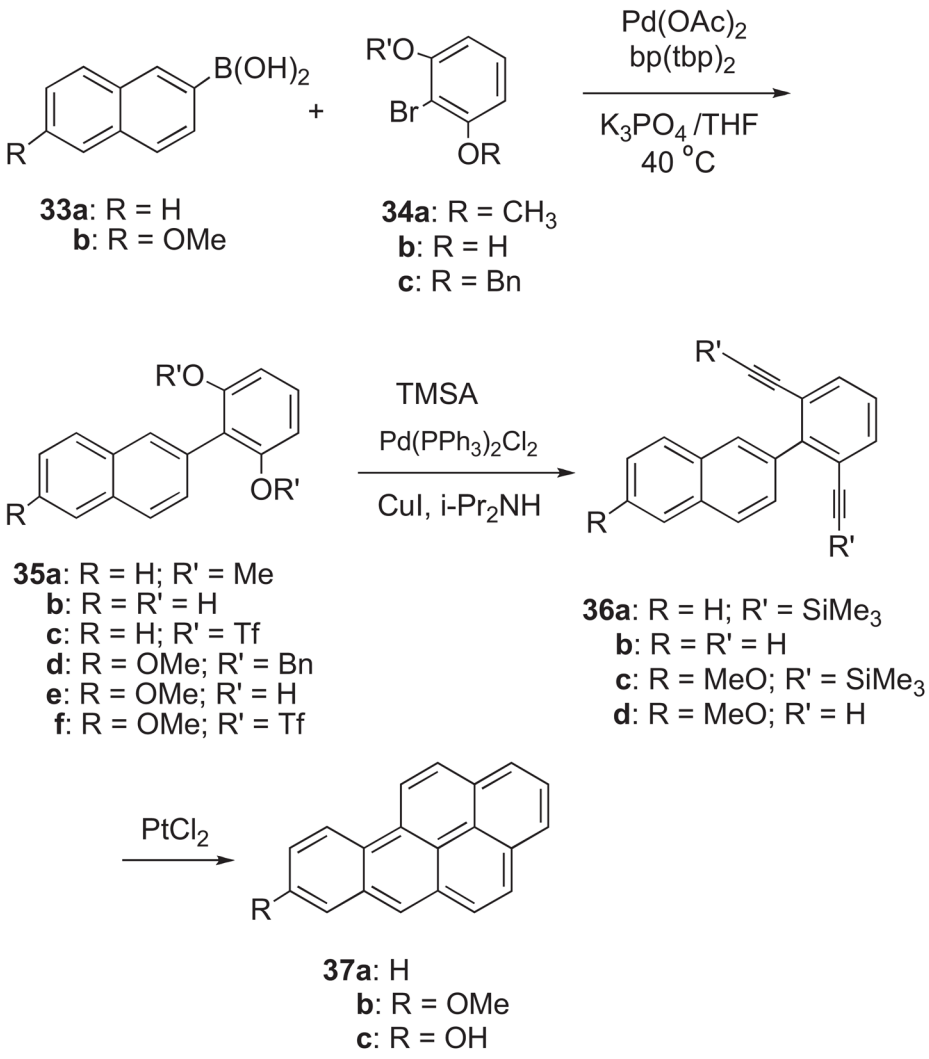


Scheme 3.

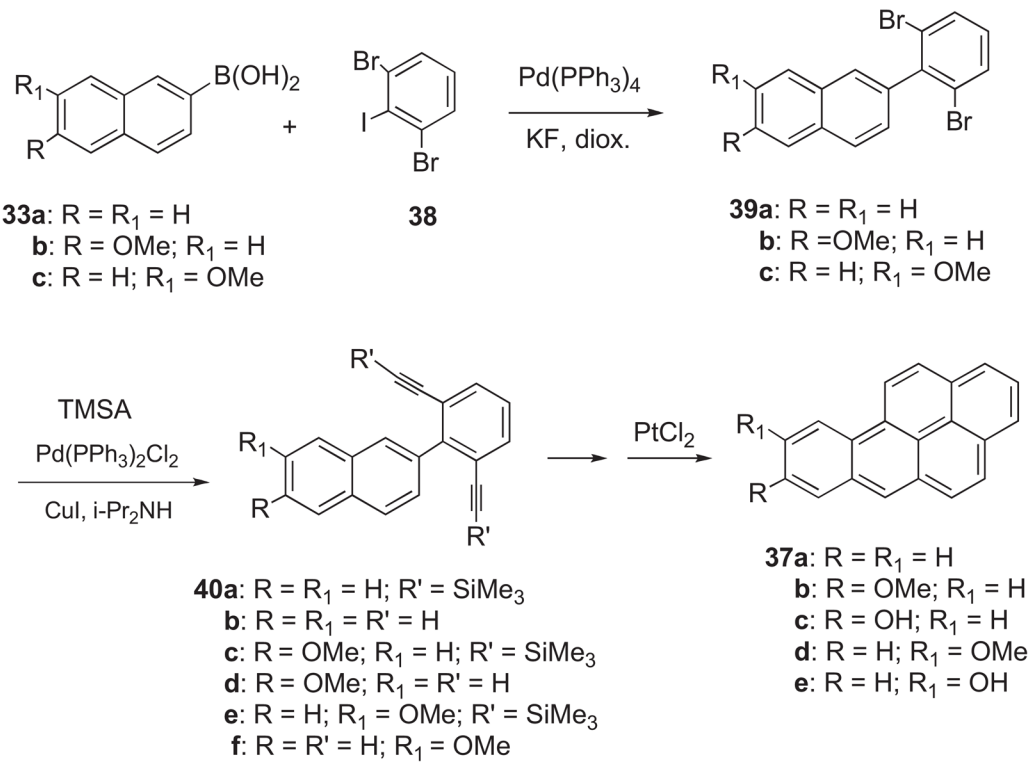


* Sites of the ^{13}C-atoms.

Scheme 4.
*Sites of the ^{13}C-atoms.



Scheme 5.



33a: R = R_1 = H
b: R = OMe; R_1 = H
c: R = H; R_1 = OMe

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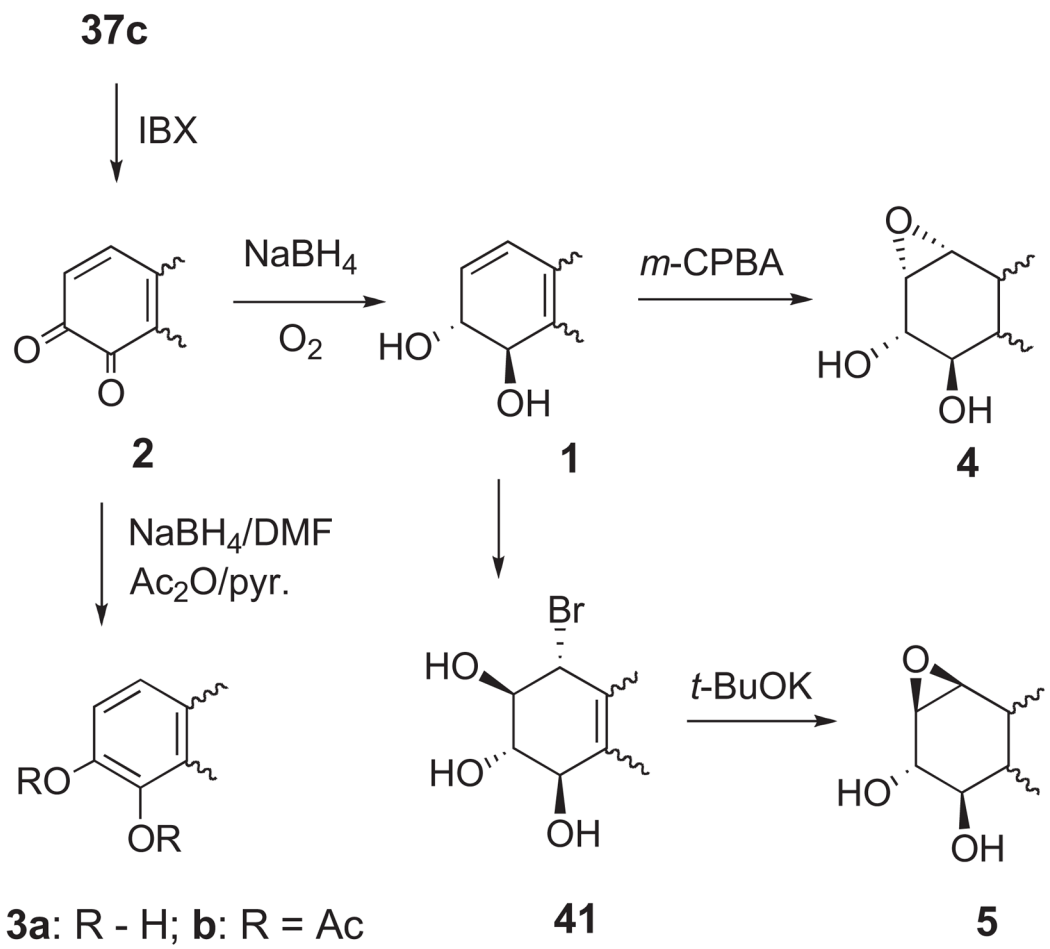
39a: R = R_1 = H
b: R =OMe; R_1 = H
c: R = H; R_1 = OMe

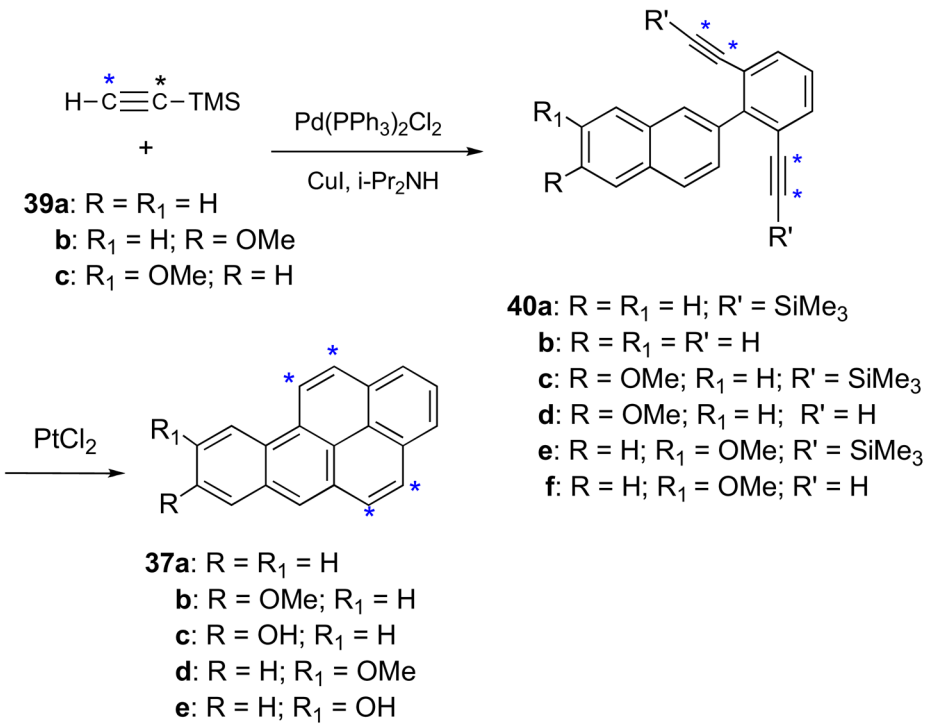
40a: R = R_1 = H; R' = $SiMe_3$
b: R = R_1 = R' = H
c: R = OMe; R_1 = H; R' = $SiMe_3$
d: R = OMe; R_1 = R' = H
e: R = H; R_1 = OMe; R' = $SiMe_3$
f: R = R' = H; R_1 = OMe

37a: R = R_1 = H
b: R = OMe; R_1 = H
c: R = OH; R_1 = H
d: R = H; R_1 = OMe
e: R = H; R_1 = OH

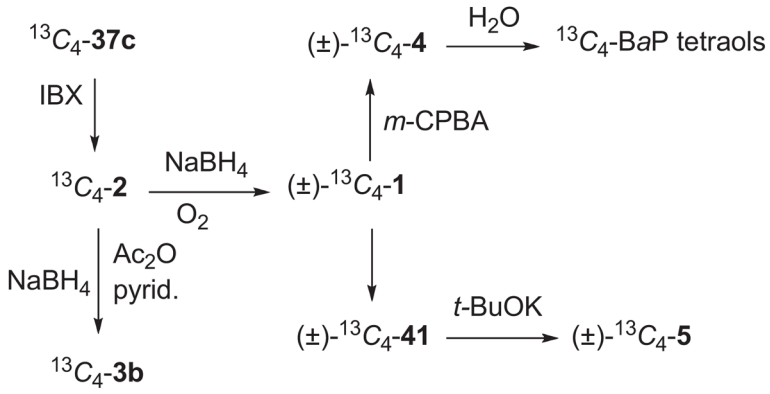
Scheme 6.



Scheme 7.



Scheme 8.



Scheme 9.

Table 1

Effect of conditions on reaction of **10c** with $BrZnCH_2CO_2Et$[a]

Entry	Time (h)	$Pd(dba)_2$/Q-phos (mol %)	$BrZnCH_2CO_2$ 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 ^{13}C-labelled analogues were carried out under these conditions.