A new efficient route to the phenolic derivatives of chrysene and 5-methylchrysene, precursors to dihydrodiol and diol epoxide metabolites of chrysene and 5-methylchrysene, through Suzuki cross-coupling reaction

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A new, abbreviated synthesis of 5-methylchrysene (**17**), 2-hydroxychrysene (**16**), 8-hydroxy-5-methylchrysene (**23**), and 2-hydroxy-5-methylchrysene (**24**) is reported. The phenolic derivatives **16**, **23**, and **24** can easily be converted to carcinogenic dihydrodiol and diol epoxide metabolites of chrysene and 5-methylchrysene. The method entails the initial Suzuki cross-coupling reaction of naphthalene-2-boronic acid (**1**) and/or 6-methoxynaphthalene-2-boronic acid (**2**) with 2-bromo-5-methoxybenzaldehyde (**3**), methyl 2-bromophenylacetate (**4**), 2-bromophenylacetone (**5**), and/or 2-iodo-5-methoxyphenylacetone (**6**) to produce 2-(2-naphthyl)-5-methoxybenzaldehyde (**7**), methyl 2-(6-methoxy-2-naphthyl)phenylacetate (**8**), 2-(2-naphthyl)phenylacetone (**9**), 2-(2-naphthyl)-5-methoxyphenylacetone (**10**), and 2-(6-methoxy-2-naphthyl)phenylacetone (**11**) in 55–98% yields. 2-Methoxychrysene (**15**) was obtained with high regioselectivity by two different procedures. In the first procedure, the aldehyde function of **7** was elongated with trimethylsulfonium iodide under phase transfer conditions to generate the ethylene oxide **12** which after methanesulfonic acid treatment produced **15**. The second procedure involved modification of ester **8** to its aldehyde analogue **14** which was subsequently treated with methanesulfonic acid to produce **15**. Phenylacetone **10** was converted by methanesulfonic acid treatment into 8-methoxy-5-methylchrysene (**18**) with 90% regioselectivity. However, the similar cyclization of phenylacetones **9** and **11** to 5-methylchrysene (**17**) and 2-methoxy-5-methylchrysene (**19**) occurred with only 33–50% regioselectivity. The separation of **17** and **19** from their chromatographically similar 6-methylbenz[*a*]anthracene byproducts **20** and **22** was readily achieved by a chemical method. The methoxy derivatives of chrysene were finally demethylated with boron tribromide to the corresponding phenolic compounds in 90–98% yields.

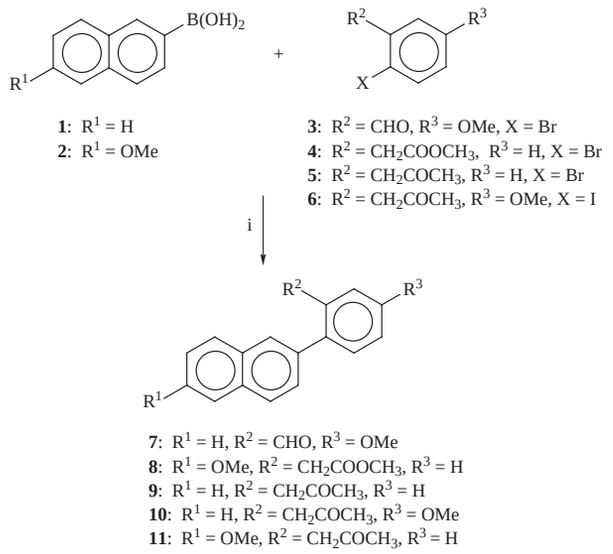
Introduction

Dihydrodiols and diol epoxides are implicated as the active forms of carcinogenic polynuclear aromatic hydrocarbons (PAHs).[1–3] These electrophilic metabolites interact covalently with cellular DNA, leading initially to mutation, and ultimately to tumor induction.[3] Methyl substitution in the bay-region of PAHs often results in significantly more potent carcinogens.[4] For example, the substitution of weakly carcinogenic chrysene at the bay-region position 5 resulted in the potent carcinogen 5-methylchrysene, whereas the substitution of the methyl group at any other position of chrysene produced monomethylchrysenes with carcinogenic potencies far less than that of 5-methylchrysene. In order to investigate the molecular basis for the enhancing effect of the methyl substitution at position 5 of chrysene, the diol epoxides of chrysene and 5-methylchrysene are needed in large quantities as starting materials for the synthesis of site-specifically adducted oligonucleotides. These site-specifically adducted oligonucleotides have been proved to be excellent probes for understanding the mechanism of carcinogenesis at the molecular genetic level.[3,5,6] Although the diol epoxides of chrysene and 5-methylchrysene have been prepared previously,[7–9] the synthetic approaches require a large number of steps, complex or potentially carcinogenic starting materials, and afford the diol epoxides in overall low yields. These drawbacks not only make the synthesis time consuming but also restrict the synthesis of these compounds to small quantities. Consequently, a new approach is needed by which these chrysene derivatives can be synthesized efficiently in a timely manner from readily available starting reactants. Recently, we reported[10] an application of palladium-catalyzed cross coupling reaction (Suzuki reaction[11]) to developing a highly efficient synthesis of the phenolic derivatives of benzo[*c*]phenanthrene and benzo[*g*]chrysene which are convenient intermediates for the preparation of their dihydrodiols and bay-region diol epoxides.[12,13] This prompted us to explore the potential of the Suzuki cross-coupling reaction to develop a novel, abbreviated method for the synthesis of 2-hydroxychrysene, 2-hydroxy-5-methylchrysene and 8-hydroxy-5-methylchrysene from easily accessible reactants. These phenolic compounds are the precursors for the synthesis of dihydrodiol and bay-region diol epoxide derivatives of chrysene and 5-methylchrysene.[9,14]

Results and discussion

The appropriately substituted 2-phenylnaphthalenes required for the synthesis of the phenolic derivatives of chrysene and 5-methylchrysene were envisioned to be obtainable by the Suzuki cross-coupling reaction of naphthaleneboronic acids with appropriately substituted aryl halides. Naphthaleneboronic acids **1**[15] and **2**,[16] and aryl halides **3**,[17] **4**[18] and **5**[19] required in the present studies were readily obtained in large quantities according to the literature procedures. Coupling of the appropriate naphthaleneboronic acid with the aryl halide was carried out following the modified version[20] of the Suzuki cross-coupling reaction in order to avoid any complication due

to the presence of ester, aldehyde or ketone functionality in the reactants. In this modified version, the coupling reaction was performed in the presence of anhydrous caesium fluoride and a catalytic amount of tetrakis(triphenylphosphine)palladium(0) to produce the corresponding 2-arylnaphthalenes **7**–**11** in 55–98% yield (Scheme 1). The biaryl intermediates **7** and **8** were



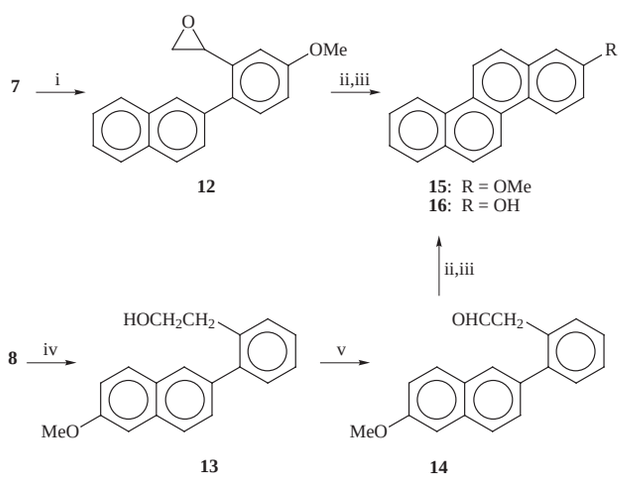
1: R^1 = H
2: R^1 = OMe

3: R^2 = CHO, R^3 = OMe, X = Br
4: R^2 = CH_2COOCH_3, R^3 = H, X = Br
5: R^2 = CH_2COCH_3, R^3 = H, X = Br
6: R^2 = CH_2COCH_3, R^3 = OMe, X = I

7: R^1 = H, R^2 = CHO, R^3 = OMe
8: R^1 = OMe, R^2 = CH_2COOCH_3, R^3 = H
9: R^1 = H, R^2 = CH_2COCH_3, R^3 = H
10: R^1 = H, R^2 = CH_2COCH_3, R^3 = OMe
11: R^1 = OMe, R^2 = CH_2COCH_3, R^3 = H

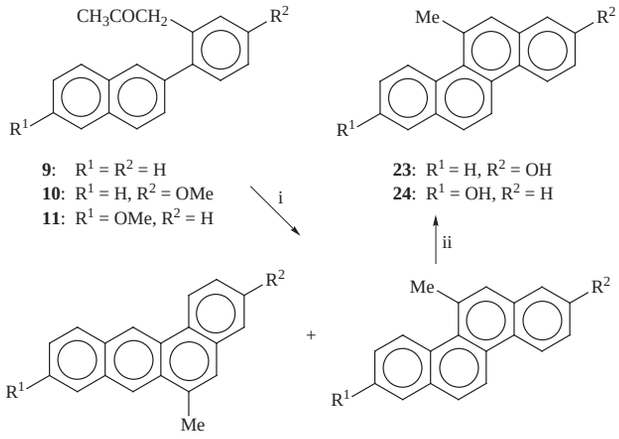
Scheme 1 *Reagents*: i, $Pd(PPh_3)_4$, CsF, DME.

conveniently converted to 2-methoxychrysene (**15**) in two to three steps (Scheme 2). Conversion of the ester **8** to alcohol **13**



Scheme 2 *Reagents*: i, $Me_2S{=}CH_2$; ii, $MeSO_3H$; iii, BBr_3; iv, LAH; v, PCC.

by LAH reduction followed by oxidation of **13** with pyridinium chlorochromate produced 2-(6-methoxy-2-naphthyl)phenylacetaldehyde (**14**). Without further purification, **14** was cyclodehydrated with 5% methanesulfonic acid in $CHCl_3$ for 2 h at room temperature to produce **15** in 56% yield. 2-Methoxychrysene (**15**) was obtained in similar yield in one less step by refluxing the aldehyde **7** for 96 h under phase transfer conditions (CH_2Cl_2/H_2O) with trimethylsulfonium iodide in the presence of a phase transfer catalyst tetrabutylammonium iodide and 50% aqueous NaOH followed by acid-catalyzed cyclodehydration (CH_3SO_3H) of the resulting epoxide **12**. No evidence for the formation of the benz[*a*]anthracene analogue *via* acid-catalyzed cyclization at the C-3 position of the naphthalene moiety of **12** or **14** was noted. A similar cyclodehydration of 2-(2-acetonylphenyl)naphthalenes (**9**–**11**) with methanesulfonic acid treatment took place quantitatively (Scheme 3). However, the reaction was non-regiospecific, and produced a mixture of



9: R^1 = R^2 = H
10: R^1 = H, R^2 = OMe
11: R^1 = OMe, R^2 = H

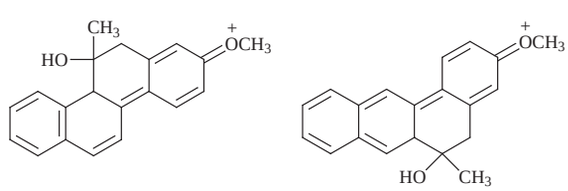
23: R^1 = H, R^2 = OH
24: R^1 = OH, R^2 = H

20: R^1 = R^2 = H
21: R^1 = H, R^2 = OMe
22: R^1 = OMe, R^2 = H

17: R^1 = R^2 = H
18: R^1 = H, R^2 = OMe
19: R^1 = OMe, R^2 = H

Scheme 3 *Reagents*: i, $MeSO_3H$; ii, BBr_3.

chromatographically similar 5-methoxychrysene and the corresponding 6-methylbenz[*a*]anthracene derivatives as evident from the presence of two downfield singlets (~δ 8.5 and 9.4) corresponding to H-7 and H-12 of the benz[*a*]anthracene nucleus. The relative amounts of 5-methylchrysene and 6-methylbenz[*a*]anthracene derivatives in the product depended upon the starting ketone. Thus, the product obtained by the decyclodehydration of **10** contained nearly 90% of 8-methoxy-5-methylchrysene (**18**) and 10% of the corresponding 3-methoxy-6-methylbenz[*a*]anthracene (**21**). In contrast, the product obtained from the cyclodehydration of the ketones **9** and **11** contained only 33–50% of chrysene derivatives **17** and **19** and 50–67% of the corresponding benz[*a*]anthracene derivatives **20** and **22** as byproducts. The formation of **18** with relatively high regioselectivity appears to be due to electronic effects and can be rationalized on the basis that the delocalization of the positive charge of the transient carbocation at the methoxy oxygen causes less perturbation in the aromaticity when the transient carbocation is produced through cyclization at C-1 rather than at C-3 of the naphthalene moiety (see structures **25** and **26**). Since similar energetically favorable delocalization



25 **26**

of the positive charge of transient carbocation formed during the cyclodehydration of the ketone **9** or **11** is not possible, it is most likely that the non-regiospecific cyclodehydration of **9** and **11** can be predominantly attributed to the steric effects caused by the ketone functionality during the cyclodehydration reaction. This hypothesis is further supported by the evidence that the similar cyclodehydration of 2-(6-methoxy-2-naphthyl)-phenylacetaldehyde (**14**) produced the expected 2-methoxychrysene (**15**) with no evidence for the formation of 9-methoxybenz[*a*]anthracene (^{1}H-NMR).

The purification of **18** was readily achieved by fractional recrystallization. 5-Methylchrysene (**17**) or 2-methoxy-5-methylchrysene (**19**) which could not be easily purified by fractional recrystallization were also non-separable by chromatography from the corresponding benz[*a*]anthracene derivatives **20** or **22**. Therefore, a chemical strategy was utilized in the purification of the chrysene derivatives **17** or **19** from the corresponding benz-

[*a*]anthracene derivatives **20** or **22**. This strategy was based on the previous observation[21] that in general benz[*a*]anthracene derivatives were oxidized to relatively polar benz[*a*]anthra-7,12-quinones by chromic acid under mild conditions, due to high electron density in the *meso*-anthracenic region (L-region) of these molecules. In contrast, chrysene derivatives which lack a *meso*-anthracenic region were found to be sufficiently stable to similar chromic acid oxidation. Thus, a brief treatment of the mixture of **17** and **20** or **19** and **22** in acetic acid with potassium dichromate resulted in a yellow product which was chromatographed on dry column grade silica gel. The elution of the column with hexane produced pure **17** or **19** in 30–45% yield based on the ketones **9** or **11**. The mps of these chrysene derivatives were not depressed when mixed with the chrysene derivatives prepared according to the literature procedures.

Demethylation of methoxychrysenes **15**, **21**, and **22** was effected as described earlier[22] except that 50% molar excess of boron tribromide was used in order to obtain 84–98% yield of the corresponding phenols **16**, **23**, and **24**. Conversion of these phenols to the corresponding dihydrodiol and diol epoxides was easily achieved by the published procedures.[9,14]

Conclusions

The present study has demonstrated that the Suzuki cross-coupling reaction of naphthaleneboronic acid with appropriately substituted aryl halides provides a convenient and a highly abbreviated route to the phenolic derivatives of chrysene and 5-methylchrysene which are suitable intermediates for the synthesis of bay-region diol epoxides. Steps involved in the synthesis of phenolic chrysenes can easily be carried out in preparative scale due to the simplicity of the reaction conditions, and easy accessibility of the reactants, thus, in principle, allowing the production of their biologically active diol epoxides in gram quantities for biological studies or for the synthesis of site-specifically adducted oligonucleotides to elucidate the mechanism of carcinogenesis. The present study in combination with our previous study[10] have also shown that the present synthetic strategy holds promise as a general synthetic route to ring-substituted PAHs and their metabolites. Work is in progress in our laboratory in order to explore the application of the Suzuki cross-coupling approach in the synthesis of heterocyclic analogues of PAHs and their potentially carcinogenic metabolites.

Experimental

Naphthalene-2-boronic acid (**1**),[15] 6-methoxynaphthalene-2-boronic acid (**2**),[16] 2-bromo-5-methoxybenzaldehyde (**3**),[17] 2-bromophenylacetone (**5**),[18] and 2-iodo-5-methoxyphenylacetone (**6**)[19] were obtained as described in the literature. Methyl 2-bromophenylacetate (**4**) was prepared by esterification of 2-bromophenylacetic acid with methanol in the presence of toluene-*p*-sulfonic acid. All the reagents and solvents (anhydrous or otherwise) were used as received without additional purification. The phrase 'usual work-up' refers to treatment of the reaction mixture with water, extraction with EtOAc or CH_2Cl_2, drying (Na_2SO_4) of the organic extract, and evaporation to dryness under reduced pressure. Dry column grade silica gel and preparative TLC plates were purchased from E. Merck and Analtech, respectively. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 400 MHz NMR and 500 MHz spectrometers, respectively, with tetramethylsilane (TMS) or $CDCl_3$ as internal standards. Chemical shifts were measured in ppm from internal standard. All melting points are uncorrected.

2-(2-Naphthyl)-5-methoxybenzaldehyde (7)

A mixture of 1.9 g (11 mmol) of **1**, 2.15 g (10 mmol) of 2-bromo-5-methoxybenzaldehyde (**3**), caesium fluoride (3.4 g, 22 mmol), and tetrakis(triphenylphosphine)palladium(0) (0.39 g, 0.34 mmol) in 50 mL of anhydrous 1,2-dimethoxyethane (DME) was refluxed under argon for 20 h. The usual work-up of the reaction mixture gave a solid which was recrystallized from CH_2Cl_2–hexane to produce 92–100% of **7**, mp 141–143 °C, ^{1}H-NMR (400 MHz, d_6-acetone): δ 3.97 (s, 3 H), 7.35 (dd, 1 H, J = 2.4, 8.6 Hz), 7.5 (d, 1 H, J = 2.4 Hz), 7.55–8.07 (m, 8 H), 10.0 (s, 1 H). ^{13}C-NMR ($CDCl_3$): δ 192.4 (CHO), 159.2, 139.0, 134.9, 134.7, 133.0, 132.5, 132.3, 129.4, 128.1, 128.0, 127.9, 127.7, 126.7, 126.5, 121.4, 109.9, 55.6 (OMe). Anal. Calc for $C_{18}H_{14}O_2 \cdot 1/20\ CH_2Cl_2$: C, 81.3; H, 5.3. Found C, 81.2; H, 5.4%.

Methyl 2-(6-methoxy-2-naphthyl)phenylacetate (8)

6-Methoxynaphthalene-2-boronic acid (**2**) (1.76 g, 8.8 mmol), methyl 2-bromophenylacetate (**4**) (1.84 g, 8.03 mmol), caesium fluoride (2.7 g, 17.5 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.31 g, 0.27 mmol), and 40 mL of anhydrous 1,2-dimethoxyethane (DME) were refluxed under argon for 5 h. The usual work-up of the reaction mixture gave a solid which was recrystallized from EtOAc–hexane to produce 2.17 g (89%) of **8** as a light yellow crystalline solid, mp 85–87 °C, ^{1}H-NMR (400 MHz, d_6-acetone): δ 3.58 (s, 3 H), 3.65 (s, 2 H), 3.87 (s, 3 H), 7.19 (dd, 1 H, J = 2.3, 8.6 Hz), 7.32–7.46 (m, 6 H), 7.74 (m, 1 H), 7.81–7.89 (m, 2 H). ^{13}C-NMR ($CDCl_3$): δ 172.4, 157.8, 142.4, 136.3, 133.5, 132.0, 130.4, 130.3, 129.5, 128.6, 128.0, 127.8, 127.5, 127.2, 126.6, 119.2, 105.4, 55.3 (OMe), 51.9 (OMe), 38.8 (CH_2). Anal. Calc for $C_{20}H_{16}O_3$: C, 78.9; H, 5.2. Found C, 78.6; H, 6.0%.

2-Methoxychrysene (15)

Method A. To the two phase system containing aldehyde **7** (2.0 g) in 50 mL CH_2Cl_2 and 23 mL of 50% aqueous NaOH was added trimethylsulfonium iodide (1.7 g) and tetrabutylammonium iodide (30 mg). The mixture was stirred vigorously under reflux for 96 h, and the mixture was poured into ice-cold water. The product was isolated by extraction to afford 2.02 g (96%) of the epoxide **12** as a light yellow syrupy oil. ^{1}H-NMR (400 MHz, d_6-acetone): δ 2.84 (dd, 1 H, J = 2.6, 5.6 Hz), 3.09 (dd, 1 H, J = 4.2, 5.6 Hz), 3.81 (dd, 1 H, J = 2.6, 4.2 Hz), 3.86 (s, 3 H), 6.88 (d, 1 H, J = 2.6 Hz), 6.99 (dd, 1 H, J = 2.6, 8.2 Hz), 7.37 (d, 1 H, J = 8.2 Hz), 7.49–8.01 (m, 7 H).

To a stirred solution of the epoxide **12** (2.5 g) in anhydrous $CHCl_3$ (75 mL) under argon was added dropwise methanesulfonic acid (2.5 mL) in 2–3 min. The reaction mixture was stirred at room temperature for 2 h. After usual work-up of the reaction mixture, a solid was obtained which was recrystallized from benzene to produce 1.3 g (56%) of 2-methoxychrysene (**15**) as colorless crystals, mp 246–247 °C [lit.,[23] mp 245–247 °C].

Method B. A 1 M solution of LAH in THF (3 mL, 3 mmol) was added dropwise at room temperature to a stirred solution of **8** (0.49 g, 1.6 mmol) in 20 mL of dry THF (LAH) under an argon atmosphere. The mixture was stirred at room temperature for 3 h, and then poured onto ice-cooled 5% aqueous HCl (20 mL). The usual work-up of the reaction mixture gave TLC pure **13** (0.47 g, 100%) as an oil [^{1}H-NMR (400 MHz, d_6-acetone): δ 2.86 (t, 1 H, J = 7.5 Hz), 2.95 (s, 1 H, exchangeable with D_2O), 3.61 (t, 1 H, J = 7.5 Hz), 7.10–7.95 (m, 10 H)]. The aforementioned alcohol **13** (0.43 mg, 1.55 mmol) was dissolved in dry CH_2Cl_2 (15 mL), and then pyridinium chlorochromate (0.64 g) was added in one lot to the solution. The mixture was stirred at room temperature for 3 h at which time TLC (15% EtOAc–hexane) indicated the completion of the reaction, and the formation of a single product. The mixture was treated with ice-cold 6 M aqueous HCl, and then extracted with EtOAc (2 × 50 mL). The combined organic phase was washed with water (2 × 25 mL), dried

(Na_2SO_4), and concentrated to yield an oil. This oil was passed through a small column of dry column grade silica gel with the aid of CH_2Cl_2. Concentration of the CH_2Cl_2 solution gave 350 mg (81%) of **14** as a nearly colorless oil [^{1}H-NMR (400 MHz, d_6-acetone): δ 3.78 (d, 2 H, J = 1.83 Hz), 3.94 (s, 3 H), 7.15–7.90 (m, 10 H), 9.65 (t, 1 H, J = 1.83 Hz)]. To a stirred solution of **14** (350 mg) in $CHCl_3$ (15 mL) was added methanesulfonic acid (2 mL), and the mixture was stirred for 2 h. The usual work-up of the reaction mixture produced a solid. The NMR spectrum of this solid indicated the formation of 2-methoxychrysene (**15**) as the sole product of cyclodehydration reaction. The recrystallization of the product from benzene produced 0.24 g (73%) of **15** as colorless leaflets, mp 246–247 °C.

2-Hydroxychrysene (16)

To a stirred solution of **15** (1.3 g) in dry CH_2Cl_2 (70 mL), a 1 M solution of BBr_3 (8.0 mL) in CH_2Cl_2 was added at 0 °C under argon over a period of 2–3 min. After 12 h of stirring at room temperature, the reaction mixture was hydrolyzed with ice-cold water, and the product was isolated by usual work-up of the mixture to produce a solid which was triturated with hexane, and filtered to produce 1.2 g (98%) of pure **16**, mp 274–276 °C [lit.,[9] mp 273–275 °C].

2-(2-Naphthyl)phenylacetone (9)

A mixture of naphthalene-2-boronic acid (**1**) (2.14 g, 10.0 mmol), 2-bromophenylacetone (**5**) (2.36 g, 9.0 mmol), anhydrous CsF (3.66 g, 2.0 mmol), and $Pd(PPh_3)_4$ (0.36 g, 0.30 mmol) in anhydrous DME (50 mL) was heated under reflux for 4 h under argon. The reaction was monitored by TLC (15% EtOAc–hexane) until no more bromide was detected. The reaction mixture was then cooled and extracted with a mixture of EtOAc (100 mL) and water (100 mL). The EtOAc layer was separated, dried (Na_2SO_4), and concentrated to yield an oil which was chromatographed over dry column grade silica gel using 11% EtOAc–hexane as an eluant to provide 2.50 g (87%) of **9** as a colorless liquid. ^{1}H-NMR (d_6-acetone): δ 1.95 (s, 3 H), 3.80 (s, 2 H), 7.29–7.44 (m, 5 H), 7.51–7.58 (m, 2 H), 7.76 (s, 1 H), 7.89–7.99 (m, 3 H). ^{13}C-NMR ($CDCl_3$): δ 206.6 (CO), 142.3, 138.8, 133.2, 132.4, 132.3, 130.6, 130.4, 128.0, 127.9, 127.8, 127.7, 127.7, 127.3, 127.2, 126.4, 126.1, 48.4 (CH_2), 29.7 (CH_3). Anal. Calcd for $C_{19}H_{16}O$: C, 87.7; H, 6.1. Found: C, 87.3; H, 6.5%.

5-Methylchrysene (17)

To a stirred solution of **9** (2.0 g) in anhydrous $CHCl_3$ (200 mL) under argon was added dropwise methanesulfonic acid (14 mL) in 2–3 min. The mixture was stirred at room temperature for 1 h. The reaction mixture was partitioned between ice-cold water (100 mL) and EtOAc (250 mL). After washing the organic phase with 5% aqueous NaOH (200 mL), and water (200 mL), successively, it was dried over anhydrous Na_2SO_4 and concentrated to produce 1.80 g of a solid as a 1 : 1 mixture of 5-methylchrysene (**17**) and 6-methylbenz[*a*]anthracene (**20**). This mixture was dissolved in warm AcOH (100 mL), and then 2.0 g of chromium trioxide was added to the solution with stirring. After an additional stirring for 10 min at the ambient temperature, the mixture was diluted with water (200 mL), and then extracted with EtOAc (2 × 150 mL). The combined EtOAc solution was washed with ice-cold 10% aqueous NaOH (3 × 75 mL) and water (1 × 75 mL), and then dried over anhydrous Na_2SO_4. Evaporation of the EtOAc solution produced a yellow solid which was chromatographed on dry column grade silica gel using hexane as an eluant to provide 0.90 g of crystalline solid. Recrystallization of the solid afforded 0.78 g (42% based on ketone **9**) of pure **17** as colorless needles, mp 116–117 °C (lit.,[14] mp 115–117 °C).

2-(2-Naphthyl)-5–methoxyphenylacetone (10)

Naphthalene-2-boronic acid (**1**) (1.34 g, 7.9 mmol), 2-iodo-5-methoxyphenylacetone (**6**) (2.06 g, 7.1 mmol), anhydrous CsF (2.4 g, 15.8 mmol), and $Pd(PPh_3)_4$ (0.27 g, 0.23 mmol) in anhydrous DME (50 mL) were heated under reflux for 7 h under argon. The reaction was monitored by TLC (15% EtOAc–hexane) until no more iodide was detected. The mixture was then cooled and extracted with a mixture of EtOAc (100 mL) and water (75 mL). The EtOAc layer was separated, dried (Na_2SO_4), and concentrated to yield a dark red solid. The crude product was chromatographed over dry column grade silica gel. The column was eluted with 10% EtOAc–hexane to produce 2.0 g (97%) of **10** as a light yellow crystalline solid, mp 62–63 °C, ^{1}H-NMR (d_6-acetone): δ 1.97 (s, 3 H), 3.80 (s, 2 H), 3.86 (s, 3 H), 6.86 (d, 1 H, J = 0.5 Hz), 6.95 (dd, 1 H, J = 0.5, 16.6 Hz), 7.28 (d, 1 H, J = 16.6 Hz), 7.39 (dd, 1 H, J = 3.3, 16.6 Hz), 7.48–7.57 (m, 2 H), 7.73 (s, 1 H), 7.86–7.97 (m, 3 H). ^{13}C-NMR ($CDCl_3$): δ 206.6 (CO), 159.0, 138.5, 134.9, 133.5, 133.2, 132.2, 131.5, 128.0, 127.9, 127.8, 127.7, 127.7, 126.3, 126.0, 115.8, 112.8, 55.3 (OMe), 48.6 (CH_2), 29.7 (CH_3). Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.7; H, 6.2. Found: C, 82.5; H, 6.1%.

8-Methoxy-5-methylchrysene (18)

To a stirred solution of **10** (1.9 g) in anhydrous $CHCl_3$ (50 mL) under argon was added dropwise methanesulfonic acid (5 mL) in 2–3 min. The mixture was stirred at room temperature for 2 h. The mixture was poured on to ice-cold 10% aqueous NaOH (50 mL). The reaction mixture was worked-up as described for the synthesis of **17** to produce a solid. Recrystallization of the solid from ethanol afforded 1.50 g (84%) of **18** as colorless needles, mp 149–151 °C (lit.,[22] mp 150–151 °C).

8-Hydroxy-5-methylchrysene (23)

This compound was prepared by stirring a solution of **18** (0.50 g, 1.84 mmol) in dry CH_2Cl_2 (20 mL) and a 1 M solution of BBr_3 (3.0 mL, 3.0 mmol) at 0 °C under argon for 5 h at room temperature. The product was isolated as described above for **16**, and triturated with hexane to give 0.45 g (96%) of **23** as a crystalline solid, mp 191–193 °C (lit.,[9] mp 196.5–197 °C).

2-(6-methoxy-2-naphthyl)phenylacetone (11)

A mixture of 6-methoxynaphthalene-2-boronic acid (**2**) (1.61 g, 8.05 mmol), 2-bromophenylacetone (**5**) (1.87 g, 8.8 mmol), anhydrous CsF (2.9 g, 19 mmol), and $Pd(PPh_3)_4$ (0.38 g, 0.32 mmol) in anhydrous DME (30 mL) was heated under reflux for 5 h under argon. The reaction mixture was worked up as described for **9** to produce a semi-solid which was chromatographed over dry column grade silica gel using 10% EtOAc–hexane as an eluant to produce 1.3 g (56.5%) of pure **11** crystalline solid, mp 60–62 °C, ^{1}H-NMR (d_6-acetone): δ 1.97 (s, 3 H), 3.80 (s, 2 H), 3.97 (s, 3 H), 7.20 (dd, 1 H, J = 2.4, 9.3 Hz), 7.27–7.41 (m, 6 H), 7.68 (s, 1 H), 7.80–7.88 (m, 2 H). ^{13}C-NMR ($CDCl_3$): δ 206.7 (CO), 157.8, 142.3, 136.5, 133.5, 132.3, 130.6, 130.4, 129.4, 128.6, 127.8, 127.6, 127.5, 127.1, 126.6, 119.2, 105.5, 55.3 (OMe), 48.4 (CH_2), 29.7 (CH_3). Anal. Calcd for $C_{20}H_{18}O_2$: C, 82.7; H, 6.2. Found: C, 83.1; H, 6.4%.

2-Methoxy-5-methylchrysene (19)

Acid-catalyzed cyclization of **11** (2.4 g) in 100 mL of anhydrous $CHCl_3$ containing methanesulfonic acid (10 mL), and the isolation of pure **19** from a 1 : 3 mixture of **19** and 6-methyl-8-methoxybenz[*a*]anthracene (**22**) were conducted as described for **17** to produce 0.70 g (33%) of **19** as colorless crystals, mp 151–152 °C (lit.,[22] mp 147–148 °C).

2-Hydroxy-5-methylchrysene (24)

Demethylation of **19** (0.70 g, 2.6 mmol) in dry CH_2Cl_2 (40 mL) with a 1 M solution of BBr_3 (4.0 mL, 4.0 mmol) in CH_2Cl_2 was effected under argon as described for **16**. The isolated product was triturated with hexane to give 0.58 g (90%) of **24** as colorless flakes, mp 191–192 °C (lit.,[22] mp 186–187 °C).

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