

## SYNTHESES OF OXIDIZED METABOLITES IMPLICATED AS ACTIVE FORMS OF THE HIGHLY POTENT CARCINOGENIC HYDROCARBON DIBENZO[*def,p*]CHRYSENE

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**Abstract:** Polycyclic aromatic hydrocarbons (PAHs) are an important class of environmental carcinogens, and dibenzo[*def,p*]chrysene is the most potent carcinogenic PAH currently known. Syntheses of various oxidized metabolites of dibenzo[*def,p*]chrysene implicated as the biologically active forms that interact directly or indirectly with DNA to induce mutations that lead to tumor induction are reported. These include the 8,9- and 11,12-dihydrodiols (2 and 3), the 8,9,11,12-bis-dihydrodiol (5), and the fjord region *anti*-diol epoxide derivative of 3 (4). © 1998 Elsevier Science Ltd. All rights reserved.

**Key words:** dibenzo[*def,p*]chrysene, polycyclic aromatic hydrocarbons, carcinogenesis, photocyclization.

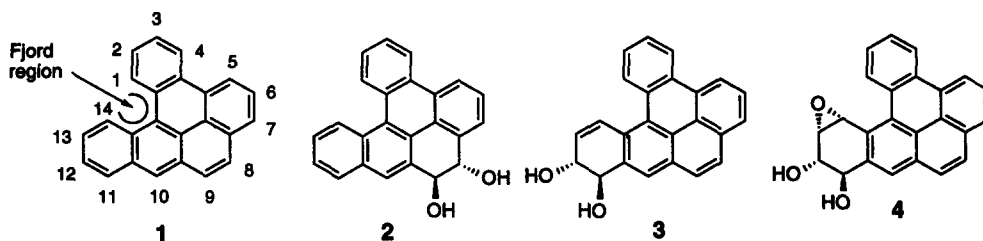
### INTRODUCTION

Polycyclic aromatic hydrocarbons (PAHs) are an important class of environmental pollutants, some of which are potent carcinogens.<sup>1,2</sup> PAHs occur in cigarette smoke, automobile exhaust, and many common foods. They are activated by P-450 microsomal enzymes to reactive forms, principally diol epoxides in which the epoxide ring resides in a bay or fjord molecular region. These active metabolites react with DNA, resulting in mutations that lead to induction of tumors.<sup>1,3</sup>

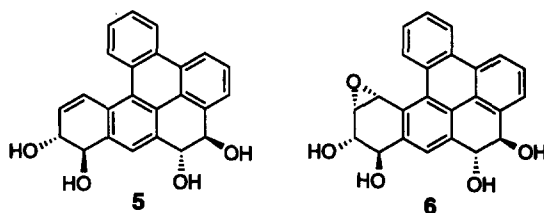
The *peri*-condensed, hexacyclic PAH dibenzo[*def,p*]chrysene (1) (obsolete name dibenzo[*a,l*]pyrene)<sup>2</sup> is the most potent carcinogenic hydrocarbon known.<sup>4</sup> Metabolism of 1 by rat liver microsomes affords mainly the *trans*-8,9- and 11,12-dihydrodiols (2 and 3) and 7-hydroxydibenzo[*def,p*]chrysene.<sup>5</sup> This accords with the concept that metabolic activation of 1 proceeds via formation of 3 which undergoes further oxidation to *trans*-11,12-dihydroxy-*anti*-(or *syn*)-13,14-epoxy-11,12,13,14-tetrahydrodibenzo[*def,p*]chrysene (4), in which the epoxide ring is in a fjord region.<sup>1-3</sup>

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However, the finding that **1** is more carcinogenic than **3** in mice<sup>4b</sup> suggests that other activation paths may also be involved.<sup>6–8</sup> Thus, further metabolism of the 8,9-dihydrodiol (**2**) in the presence of calf thymus DNA generates a major DNA-bound adduct tentatively suggested to be formed via reaction of its 8,9,11,12-tetraol-13,14-epoxide metabolite (**6**).<sup>9</sup> The latter may arise metabolically via oxidation of either **2** or **3**, to a *bis*-dihydrodiol, *trans*-8,9-*trans*-11,12-tetrahydroxy-8,9,11,12-tetrahydrodibenzo[*def,p*]chrysene (**5**), followed by epoxidation. The possibility that **5** and **6** may play a



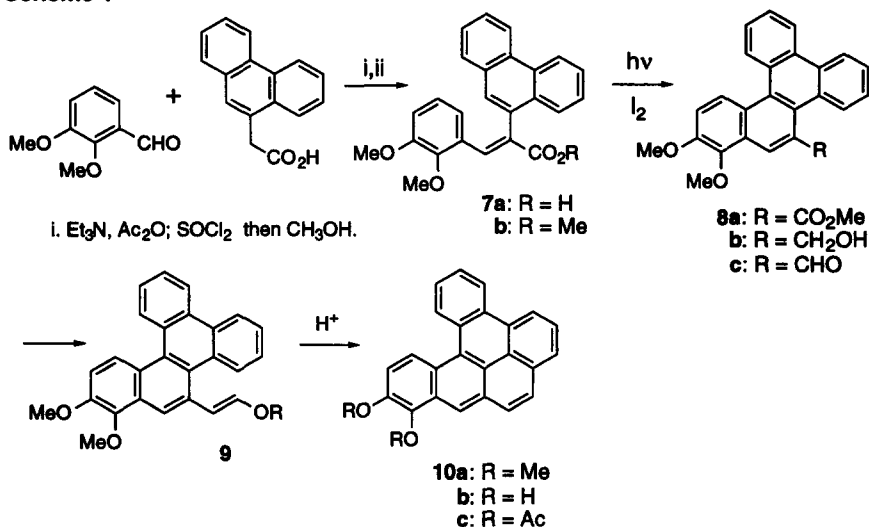
role in carcinogenesis accords with recent findings that higher oxidized metabolites, particularly *bis*-dihydrodiols and *bis*-dihydrodiol epoxides, contribute to the carcinogenic activity of dibenz[*a,h*]anthracene, dibenz[*a,j*]anthracene, dibenzo[*b,def*]chrysene, and other PAHs.<sup>10–16</sup> An alternative path of activation of the PAH *trans*-dihydrodiols involves oxidation to catechols catalyzed by dihydrodiol dehydrogenase.<sup>17</sup> The catechols undergo air oxidation to quinones that in turn enter into a redox cycle with O<sub>2</sub> to generate reactive oxygen species that cause extensive DNA damage. For this reason, the 11,12-quinone of **1** must also be considered a potential carcinogenic metabolite.

We now report convenient syntheses of several oxidized derivatives of dibenzo[*def,p*]chrysene, including **3**, **4**, and **5**, suspected to be active carcinogenic metabolites.

## RESULTS AND DISCUSSION

The key intermediate in these syntheses is 11,12-dimethoxydibenzo[*def,p*]chrysene (**10a**). Compound **10a** was conveniently accessible from simple precursors via the synthetic route in Scheme 1. Condensation of 2,3-dimethoxybenzaldehyde with 9-phenanthrylacetic acid with Et<sub>3</sub>N and HOAc furnished 3-(2,3-dimethoxyphenyl)-2-(9-phenanthryl)-2-propenoic acid (**7a**) as a mixture of *E*- and *Z*-isomers (the *E*-isomer in which the aryl functions are *cis* is shown in Scheme 1). 2D-NMR spectra (NOESY) show NOE effects between the ortho proton of the dimethoxyphenyl group and the peri proton in the 8-position of the phenanthrene ring, indicating that the *E*- isomer is the

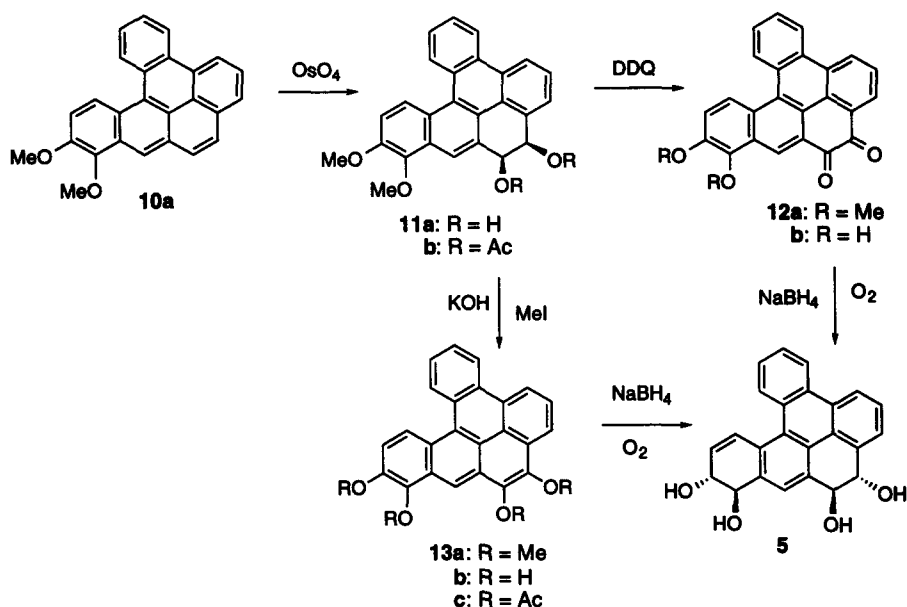
Scheme 1



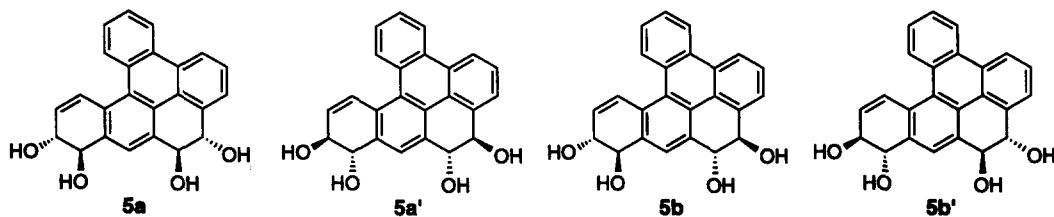
major product ( $\text{E}/\text{Z} > 12:1$ ). Treatment of **7a** with  $\text{SOCl}_2$  followed by reaction of the acid chloride product with  $\text{MeOH}$  in refluxing benzene gave the corresponding methyl ester (**7b**). Oxidative photocyclization of **7b** in the presence of  $\text{I}_2$  and epoxybutane<sup>18</sup> provided 9-carbomethoxy-11,12-dimethoxybenzo[*g*]chrysene (**8a**) as the principal product. The mixture of *E*- and *Z*-isomers of **7b** was used, since facile interconversion of isomers is known to take place in these reactions.<sup>19</sup> It was necessary to use the ester **7b** rather than the free acid **7a** to prevent secondary photocyclization to the lactone.<sup>20</sup> Enlargement of the pentacyclic benzo[*g*]chrysene ring system of **8a** to the hexacyclic ring system of dibenzo[*def,p*]chrysene required introduction of an additional carbon atom. This was accomplished by conversion of **8a** to the enol ether **9**. Reduction of ester **8a** to the alcohol **8b** with  $\text{LiAlH}_4$  followed by oxidation of **8b** with pyridinium chlorochromate (PCC) gave 9-formyl-11,12-dimethoxybenzo[*g*]chrysene (**8c**). Wittig reaction of **8c** with (methoxymethyl)triphenylphosphonium chloride and phenyllithium at  $-65^\circ\text{C}$  gave the enol ether **9** as a mixture of isomers ( $\text{E}/\text{Z} \approx 4:1$ ). Treatment of **9** with methanesulfonic acid provided 11,12-dimethoxydibenzo[*def,p*]chrysene (**10a**).

Conversion of **10a** to the tetrahydrotetraol (**5**) was accomplished via initial oxidation with osmium tetroxide to the *K*-region *cis*-dihydrodiol, *cis*-8,9-dihydroxy-11,12-dimethoxy-8,9-dihydrodibenzo[*def,p*]chrysene (**11a**) (Scheme 2).<sup>21</sup> In view of its probable air sensitivity, **11a** was isolated and characterized as its diacetate (**11b**).<sup>22</sup> Oxidation of **11a** with DDQ gave the dimethoxyquinone, 11,12-dimethoxydibenzo[*def,p*]chrysene-8,9-dione (**12a**). This compound was converted to **5** via demethylation with  $\text{BBr}_3$  to 11,12-dihydroxydibenzo[*def,p*]chrysene-8,9-dione (**12b**) followed by reduction with  $\text{NaBH}_4$  with  $\text{O}_2$  bubbling through the solution. Reduction took place in both rings to provide *trans*-8,9-*trans*-11,12-tetrahydroxy-8,9,11,12-tetrahydrodibenzo[*def,p*]chrysene (**5**). Since reductions of this type are known to take place with high *trans*-stereoselectivity,<sup>23,24</sup> both dihydrodiol functions are presumed have the *trans* configuration.

Scheme 2

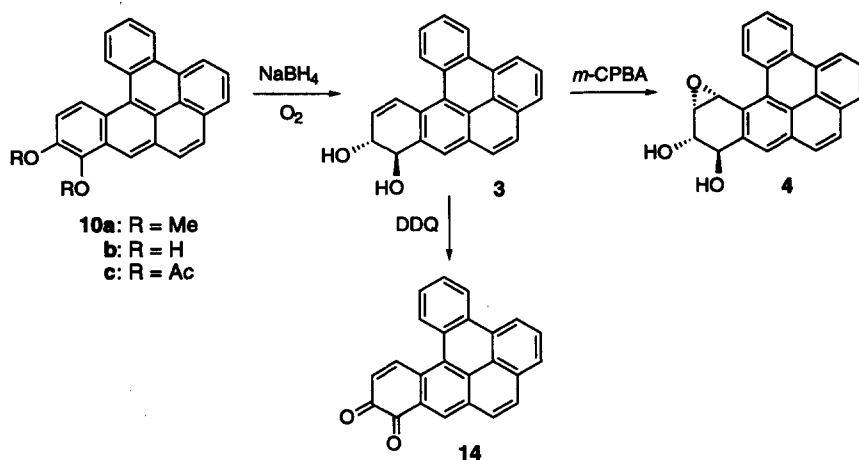


Since the mode of reduction is achiral, the product must consist of an equal mixture of two pairs of enantiomers (5a, 5a' and 5b, 5b'). The coupling constants for the benzylic and allylic protons are in the range of 7.0–9.2 Hz, consistent with the *trans* configurations with the hydroxyl groups oriented predominantly in the diequatorial conformations.<sup>25</sup>



An alternative route for conversion of the *cis*-dihydrodiol (11a) to the *trans,trans*-tetrahydrotetraol (5) was also examined (Scheme 2). Reaction of 11a with KOH and MeI in DMSO failed to provide the expected dimethyl ether derivative, but gave instead 8,9,11,12-tetramethoxydibenzo-*[def,p]*chrysene (13a). Formation of the *bis*-catechol tetramethyl ether (13a) was evidenced by the absence of benzylic signals in its <sup>1</sup>H NMR spectrum, consistent with the fully aromatic structure of 13a. This compound was further characterized by conversion to its diacetate (13c). Treatment of 13a with excess BBr<sub>3</sub> followed by reduction of the *bis*-catechol product (13b) with excess NaBH<sub>4</sub> and O<sub>2</sub> furnished the tetrahydrotetraol 5. Compound 5 was obtained as a pair of diastereomers separable by HPLC on a reverse phase ZORBAX ODS column.

Scheme 3



11,12-Dimethoxydibenzo[*def,p*]chrysene (10a) also served as a convenient synthetic precursor for the terminal ring dihydrodiol and diol epoxide metabolites of dibenzo[*def,p*]chrysene (3 and 4) as well as the terminal ring quinone (14) (Scheme 3). Demethylation of 10a by treatment with  $\text{BBr}_3$  gave 11,12-dihydroxydibenzo[*def,p*]chrysene (10b) which was converted to its diacetate (10c) in order to protect the air-sensitive catechol from autooxidation. Reduction of 10c with  $\text{NaBH}_4$  and  $\text{O}_2$  provided the *trans*-dihydrodiol, *trans*-11,12-dihydroxy-11,12-dihydrodibenzo[*def,p*]chrysene (3). Epoxidation of 3 with *m*-chloroperbenzoic acid by the usual method furnished the corresponding *anti*-diol epoxide, *trans*-11,12-dihydroxy-*anti*-13,14-epoxy-11,12,13,14-tetrahydrodibenzo[*def,p*]chrysene (4). Oxidation of the dihydrodiol 3 with DDQ in moist THF afforded smoothly the corresponding *o*-quinone, dibenzo[*def,p*]chrysene-11,12-dione (14).

The foregoing syntheses of the *trans*-11,12-dihydrodiol (3), *trans*-11,12-diol-*anti*-13,14-epoxide (4), *bis*-dihydrodiol (5), and other known or suspected oxidized metabolites of dibenzo[*def,p*]chrysene (10b, 12b, 13b, and 14) are relatively efficient, providing good overall yields of all compounds. Therefore, these compounds are now readily available for metabolism, tumorigenicity and other biological studies to determine their role in the mechanism of carcinogenesis of the parent PAH. Although syntheses of 3 and 4 have been reported previously,<sup>26</sup> the method described herein is more convenient and provides them in higher overall yield (20% versus 3–8%). Compound 5 is a new compound. The principle limitation of the method for large scale preparations is in the photocyclization steps. While photoreactions of this type usually require dilute conditions, this proved not to be a serious limitation. Good yields of photocyclized products were obtained from photoreactions conducted on 1–2 gram scale. Since the amounts of the oxidized metabolites of dibenzo[*def,p*]chrysene required for most biological studies are in the microgram to milligram range, the quantities of these compounds obtainable are more than sufficient to meet the need.

## EXPERIMENTAL

**Materials and Methods.** Methoxymethyltriphenylphosphonium chloride was prepared by heating an equimolar solution of methoxymethyl chloride and  $\text{PPh}_3$  in a minimum volume of benzene at reflux for 5 h. *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.4 phosphate buffer and drying under reduced pressure. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was purified by recrystallization from benzene. THF was distilled from sodium benzophenone ketyl. The  $^1\text{H}$ -NMR spectra were recorded on 400 or 500 MHz spectrometers in  $\text{CDCl}_3$  with tetramethylsilane as internal standard unless stated otherwise. Integration was consistent with all structural assignments.  $^{13}\text{C}$  NMR were recorded on a 125 MHz spectrometer. Mass spectra (MS) and HRMS were performed by the University of Illinois at Urbana-Champaign, School of Chemical Sciences. All melting points are uncorrected. **Caution:** *Dibenzo[def,p]chrysene is a potent carcinogen in animal assays. It and its dihydrodiol, diol epoxide, and higher oxidized metabolites are all potentially hazardous and should be handled with care in accordance with "NIH Guidelines for the Laboratory Use of Chemical Carcinogens."*

**3-(2,3-Dimethoxyphenyl)-2-(9-phenanthryl)-2-propenoic acid (7a).** A mixture of 9-phenanthrylacetic acid (8.5 g, 36.0 mmol), 2,3-dimethoxybenzaldehyde (6.0 g, 36.1 mmol),  $\text{Et}_3\text{N}$  (8.5 mL), and  $\text{Ac}_2\text{O}$  (8.5 mL) was heated at 160 °C for 16 h. Then the solution was cooled to room temperature, water and dilute hydrochloric acid were added, and the resulting solution was extracted with ether. The combined ether extracts were washed with dilute HCl, brine, and dried over  $\text{Na}_2\text{SO}_4$ . Chromatography of the product on a Florisil column eluted with ether afforded **7a** (8.6 g, 62%) as a yellow solid, mp 197–199 °C:  $^1\text{H}$  NMR  $\delta$  8.74 (d, 1,  $J$  = 8.2 Hz), 8.70 (d, 1,  $J$  = 8.3 Hz), 8.60 (s, 1), 7.88 (d, 1,  $J$  = 8.1 Hz), 7.78 (d, 1,  $J$  = 7.8 Hz), 7.60–7.70 (m, 2), 7.57 (s, 1), 7.55 (dd, 1,  $J$  = 8.0, 1.0 Hz), 3.96 (s, 3);  $^{13}\text{C}$  NMR (acetone- $d_6$ )  $\delta$  56.0, 61.3, 114.4, 121.7, 123.5, 124.1, 126.7, 127.6, 127.6, 127.8, 128.8, 129.5, 131.1, 131.3, 132.1, 132.6, 132.9, 134.3, 137.3, 149.5, 153.6, 168.7. Anal. Calcd for  $\text{C}_{25}\text{H}_{20}\text{O}_4$ : C, 78.11; H, 5.24. Found: C, 77.85; H, 5.28.

**Methyl 3-(2,3-dimethoxyphenyl)-2-(9-phenanthryl)-2-propenoate (7b).** A solution of **7a** (1.32 g, 3.43 mmol) and  $\text{SOCl}_2$  (1.0 mL, 13.7 mmol) in 20 mL of dry benzene was heated at reflux for 2 h. The solvent was removed under vacuum, then 20 mL of dry benzene and 3 mL of anhydrous MeOH were added, and the solution was heated at reflux for 6 h. The usual workup gave **7b** (1.26 g, 92%) as a white solid: mp 153–155 °C (EtOAc-hexane) (lit.<sup>25b</sup> 138 °C):  $^1\text{H}$  NMR  $\delta$  8.76 (d, 1,  $J$  = 8.3 Hz), 8.72 (d, 1,  $J$  = 8.3 Hz), 8.50 (s, 1), 7.85 (d, 1,  $J$  = 8.1 Hz), 7.78 (d, 1,  $J$  = 7.8 Hz), 7.65–7.69 (m, 2), 7.55–7.59 (m, 3), 6.68 (d, 1,  $J$  = 8.1 Hz), 6.40 (dd, 1,  $J$  = 8.1 Hz), 6.22 (d, 1,  $J$  = 8.0 Hz), 3.98 (s, 3), 3.80 (s, 3), 3.71 (s, 3). Anal. Calcd for  $\text{C}_{26}\text{H}_{22}\text{O}_4$ : C, 78.37; H, 5.57. Found: C, 78.34; H, 5.63.

**9-Carbomethoxy-11,12-dimethoxybenzo[*g*]chrysene (8a).** Argon was bubbled through a stirred solution of **7b** (2.0 g, 5.0 mmol) and  $\text{I}_2$  (1.30 g, 5.1 mmol) in 700 mL of benzene for 30 min, and then 10 mL of epoxybutane was added. The solution was irradiated by UV light from a 450-W Hanovia medium pressure lamp with a Pyrex filter, and the argon flow was maintained throughout the procedure. When NMR analysis showed reaction to be complete (8 h), the solvent was removed under vacuum, and ~200 mL of  $\text{CH}_2\text{Cl}_2$  was added. The organic layer was washed with an aqueous

solution of  $\text{Na}_2\text{S}_2\text{O}_3$  and brine and dried over  $\text{MgSO}_4$ . Chromatography of the crude product on a silica gel column eluted with hexane-EtOAc (96:4) gave **8a** (1.8 g, 90%) as a yellow solid, mp 172–173 °C (EtOAc-hexane) (lit.<sup>25b</sup> 167–168 °C):  $^1\text{H}$  NMR  $\delta$  8.73 (d, 1,  $J$  = 8.2 Hz), 8.69 (d, 1,  $J$  = 8.1 Hz), 8.63 (d, 1,  $J$  = 8.0 Hz), 8.60 (s, 1), 8.56 (d, 1,  $J$  = 9.3 Hz), 7.94 (dd, 1,  $J$  = 8.2, 1.0 Hz), 7.70 (dd, 1,  $J$  = 7.5 Hz), 7.62 (dd, 2,  $J$  = 7.0, 7.9 Hz), 7.56 (dd, 1,  $J$  = 7.1, 8.1 Hz), 7.43 (d, 1,  $J$  = 9.3 Hz), 4.11 (s, 3), 4.07 (s, 3), 3.91 (s, 3). Anal. Calcd for  $\text{C}_{26}\text{H}_{20}\text{O}_4$ : C, 78.77; H, 5.19. Found: C, 78.78; H, 5.11.

**9-Hydroxymethyl-11,12-dimethoxybenzo[g]chrysene (8b).** A solution of **8a** (230 mg, 0.58 mmol) in 5 mL of  $\text{Et}_2\text{O}$ -THF (1:1) was added dropwise to a stirred solution of  $\text{LiAlH}_4$  (0.70 mL of a 1.0 M solution) in 4 mL of dry  $\text{Et}_2\text{O}$ , and the resulting solution was heated at reflux for 1.5 h. The usual workup and chromatography on a silica gel column eluted with hexane-EtOAc (80:20) gave **8b** (196 mg, 92%) as a white solid, mp 152–154 °C (lit.<sup>25b</sup> 148–150 °C):  $^1\text{H}$  NMR  $\delta$  8.70 (d, 1,  $J$  = 9.3 Hz), 8.68 (d, 2,  $J$  = 9.2 Hz), 8.57 (d, 1,  $J$  = 9.5 Hz), 8.50 (d, 1,  $J$  = 9.3 Hz), 8.41 (s, 1), 7.65–7.69 (m, 3), 7.60 (dd, 1,  $J$  = 7.5 Hz), 7.37 (d, 1,  $J$  = 9.3 Hz), 5.34 (d, 2,  $J$  = 5.9 Hz), 4.11 (s, 3), 4.07 (s, 3). Anal. Calcd for  $\text{C}_{25}\text{H}_{20}\text{O}_3$ : C, 81.50; H, 5.47. Found: C, 81.35; H, 5.63.

**9-Formyl-11,12-dimethoxybenzo[g]chrysene (8c).** A solution of alcohol **8b** (330 mg, 0.90 mmol) in 9 mL of  $\text{CH}_2\text{Cl}_2$  was added dropwise to a stirred suspension of pyridinium chlorochromate (386 mg, 1.79 mmol) in 180 mL of  $\text{CH}_2\text{Cl}_2$ . The mixture was stirred overnight at room temperature, then passed through a short Florisil column. Chromatography of the product on a silica gel column eluted with hexane-EtOAc (4:1) provided **8c** (249 mg, 76%) as a yellow solid, mp 199–201 °C (EtOAc-hexane) (lit.<sup>25b</sup> 193–194 °C):  $^1\text{H}$  NMR  $\delta$  10.54 (s, 1), 8.87 (s, 1), 8.78 (d, 1,  $J$  = 8.0 Hz), 8.74 (d, 1,  $J$  = 9.6 Hz), 8.72 (d, 1,  $J$  = 7.1 Hz), 8.60 (d, 1,  $J$  = 9.3 Hz), 7.86 (d, 1,  $J$  = 7.7 Hz), 7.65–7.75 (m, 4), 7.51 (d, 1,  $J$  = 9.4 Hz), 4.14 (s, 3), 4.09 (s, 3). Anal. Calcd for  $\text{C}_{25}\text{H}_{18}\text{O}_3$ : C, 81.95; H, 4.95. Found: C, 81.85; H, 5.00.

**(Z)- and (E)-1-[9-(11,12-dimethoxybenzo[g]chrysenyl)-2-methoxyethene (9).** Methoxymethyltriphenylphosphonium chloride (660 mg, 1.93 mmol) was dried under vacuum for 4 h prior to use. Then 20 mL of dry ether was added under argon at -65 °C and 1.10 mL of a 1.8 M solution of phenyllithium (2.0 mmol) in ether was added dropwise. The mixture was stirred at -65 °C for 0.5 h, then allowed to warm to -15 °C for 0.5 h, and then cooled back to -65 °C. The aldehyde **8c** (106 mg, 0.29 mmol) was added and stirring was continued for an additional h at -65 °C overnight. Then the solution was allowed to warm to ambient temperature, and stirring was continued overnight. The solvent was removed under vacuum, and the crude product was purified by chromatography on a silica gel column eluted with hexane- $\text{CH}_2\text{Cl}_2$  (3:2) afforded **9** (102 mg, 89%) as a mixture of E- and Z-isomers as a semisolid:  $^1\text{H}$  NMR (E-isomer)  $\delta$  8.95 (d, 1,  $J$  = 8.3 Hz), 8.71 (d, 1,  $J$  = 8.3 Hz), 8.67 (d, 1,  $J$  = 8.0 Hz), 8.64 (d, 1,  $J$  = 8.2 Hz), 8.45 (d, 1,  $J$  = 9.3 Hz), 8.07 (s, 1), 7.66 (dd, 1,  $J$  = 8.0, 7.1 Hz), 7.62 (dd, 1,  $J$  = 8.3, 7.1 Hz), 7.55 (dd, 1,  $J$  = 8.3, 7.0 Hz), 7.35 (d, 1,  $J$  = 13.0 Hz), 7.29 (d, 1,  $J$  = 9.3 Hz), 6.50 (d, 1,  $J$  = 13.0 Hz), 4.10 (s, 3), 4.05 (s, 3), 3.82 (s, 3).  $^1\text{H}$  NMR (Z-isomer)  $\delta$  8.90 (d, 1,  $J$  = 8.1 Hz), 8.61–8.71 (m, 3), 8.45 (d, 1,  $J$  = 9.3 Hz), 7.52–7.65 (m, 3), 7.31–7.34 (m, 2), 7.29 (d, 1,  $J$  = 9.3 Hz), 6.42 (d, 1,  $J$  = 7.0 Hz), 5.92 (d, 1,  $J$  = 7.0 Hz), 4.09 (s, 3), 4.05 (s, 3), 3.90 (s, 3); MS (mixed isomers),  $m/e$ , 394 ( $\text{M}^+$  100); HRMS Calcd for  $\text{C}_{27}\text{H}_{22}\text{O}_3$ : 394.1569. Found: 394.1570. Anal. (mixed isomers) Calcd for  $\text{C}_{27}\text{H}_{22}\text{O}_3$ : C, 82.21; H, 5.62. Found: C, 81.69; H, 5.87.

**11, 12-Dimethoxydibenzo[def,p]chrysene (10a).**  $\text{CH}_3\text{SO}_3\text{H}$  (1.0 mL, 1.54 mmol) was added dropwise to a stirred solution of **9** (95 mg, 0.241 mmol) in 10 mL of  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$  under argon. The mixture was stirred at  $0^\circ\text{C}$  for 3 h. The usual workup gave **10a** (77 mg, 88%) as a yellow solid, mp  $157\text{--}158^\circ\text{C}$  (lit.<sup>25b</sup>  $154\text{--}155^\circ\text{C}$ ):  $^1\text{H}$  NMR  $\delta$  9.08 (d, 1,  $J = 8.3$  Hz), 9.00 (d, 1,  $J = 9.5$  Hz), 8.93 (d, 1,  $J = 8.3$  Hz), 8.91 (d, 1,  $J = 8.0$  Hz), 8.84 (s, 1), 8.08 (d, 1,  $J = 7.5$  Hz), 8.02 (d, 1,  $J = 9.0$  Hz), 8.00 (dd, 1,  $J = 7.60$  Hz), 7.86 (d, 1,  $J = 9.1$  Hz), 7.78 (dd, 1,  $J = 7.0, 8.0$  Hz), 7.73 (dd, 1,  $J = 7.6, 7.0$  Hz), 7.55 (d, 1,  $J = 9.5$  Hz), 4.20 (s, 3), 4.14 (s, 3). Anal. Calcd for  $\text{C}_{26}\text{H}_{18}\text{O}_2$ : C, 86.16; H, 4.93; Found: C, 85.91; H, 5.08.

**cis-8,9-Dihydroxy- and cis-8,9-Diacetoxy-8,9-dihydro-11, 12-dimethoxydibenzo[def,p]-chrysene (11a and 11b).** A solution of  $\text{OsO}_4$  (250 mg, 0.98 mmol) in 1.3 mL of dry pyridine was added to a stirred solution of **10a** (339 mg, 0.94 mmol) in 4.5 mL of pyridine. The reaction mixture was stirred at room temperature under argon for 5 days. Then an aqueous solution of  $\text{Na}_2\text{SO}_3$  (1.7 g in 12 mL of  $\text{H}_2\text{O}$ ) was added, and stirring was continued for another 3 h.  $\text{EtOAc}$  was added, and the organic phase was washed with water and dried over  $\text{Na}_2\text{SO}_4$ . Removal of the solvent under vacuum afforded crude **11a** as a black residue. In view of its air sensitivity, **11a** was isolated and characterized as its diacetate (**11b**) obtained as a white solid (31% from **10a**), mp  $194\text{--}196^\circ\text{C}$ :  $^1\text{H}$  NMR  $\delta$  8.93 (d, 1,  $J = 8.2$  Hz), 8.77 (d, 1,  $J = 7.9$  Hz), 8.69–8.73 (m, 2), 8.83 (s, 1), 7.66–7.75 (m, 4), 7.43 (d, 1,  $J = 9.4$  Hz), 6.67 (d, 1,  $J = 3.5$  Hz), 6.59 (d, 1,  $J = 3.5$  Hz), 4.11 (s, 3), 4.09 (s, 3), 2.12 (s, 6);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.0, 21.1, 56.5, 61.3, 70.7, 71.3, 114.2, 123.1, 123.7, 124.6, 125.5, 125.7, 126.2, 126.4, 126.9, 127.0, 127.1, 127.2, 127.4, 128.3, 128.5, 129.0, 129.1, 129.2, 129.4, 130.6, 130.7, 149.0, 170.6, 170.7; MS  $m/e$  480 ( $\text{M}^+$ , 30); HRMS, Calcd for  $\text{C}_{30}\text{H}_{24}\text{O}_6$ : 480.1573. Found: 480.1560.

**11, 12-Dimethoxydibenzo[def,p]chrysene-8,9-dione (12a).** Reaction of **10a** (95 mg, 0.26 mmol) with  $\text{OsO}_4$  (68 mg, 0.28 mmol) by the procedure described above gave crude **11a** which was dissolved in 45 mL of wet THF (1%  $\text{H}_2\text{O}$ ). To this was added DDQ (295 mg, 1.30 mmol), and the mixture was stirred at room temperature for 2 days, then ~50% of the solvent was removed under vacuum and water was added. The black solid precipitate was filtered, washed with water, and dried. Chromatography on a Florisil column eluted with hexane-THF (3:7) furnished **12a** (74 mg, 72%), mp  $261\text{--}263^\circ\text{C}$ :  $^1\text{H}$  NMR  $\delta$  9.32 (s, 1), 8.99 (d, 1,  $J = 8.3$  Hz), 8.84 (d, 1,  $J = 8.3$  Hz), 8.76 (d, 1,  $J = 8.1$  Hz), 8.67 (d, 1,  $J = 9.4$  Hz), 8.58 (d, 1,  $J = 7.5$  Hz), 7.83 (dd, 1,  $J = 7.6, 8.1$  Hz), 7.79 (dd, 1,  $J = 7.1, 8.2$  Hz), 7.73 (dd, 1,  $J = 7.1, 8.2$  Hz), 7.56 (d, 1,  $J = 9.4$  Hz), 4.16 (s, 3), 4.10 (s, 3);  $^{13}\text{C}$  NMR ( $\text{THF}-d_8$ )  $\delta$  56.8, 61.7, 118.6, 124.3, 124.7, 125.6, 127.0, 127.7, 128.4, 128.5, 128.6, 129.3, 129.7, 129.8, 130.0, 130.2, 130.2, 130.3, 130.7, 131.5, 132.1, 146.1, 150.6, 180.2, 180.4; MS,  $m/e$ , 392 ( $\text{M}^+$ , 100); HRMS Calcd for  $\text{C}_{26}\text{H}_{16}\text{O}_4$ : 392.1049. Found: 392.1054.

**8,9,11,12-Tetramethoxydibenzo[def,p]chrysene (13a).** Reaction of **10a** (82 mg, 0.23 mmol) with  $\text{OsO}_4$  (64 mg, 0.25 mmol) by the procedure described for preparation of **11b** gave crude **11a** which was dissolved in a stirred suspension of KOH (253 mg, 4.5 mmol) in 4.5 mL of dry DMSO. To this was added MeI (0.3 mL, 4.8 mmol), and the mixture was stirred overnight at room temperature. The usual workup and chromatography on a Florisil column eluted with hexane-THF (95:5) furnished **13a** (81 mg, 85%), mp  $143\text{--}145^\circ\text{C}$ :  $^1\text{H}$  NMR  $\delta$  9.13 (s, 1), 9.07 (d, 1,  $J = 7.9$  Hz), 8.98 (d, 1,  $J = 9.5$  Hz), 8.92 (d, 1,  $J = 8.1$  Hz), 8.89 (d, 1,  $J = 7.6$  Hz), 8.44 (d, 1,  $J = 6.8$  Hz), 8.03 (dd, 1,  $J = 7.9$  Hz), 7.78 (dd, 1,  $J = 6.8$  Hz), 7.72 (dd, 1,  $J = 6.9$  Hz), 7.54 (d, 1,  $J = 9.5$  Hz), 4.26 (s, 3), 4.22 (s, 3), 4.21 (s, 3), 4.14



(s, 3);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  56.9, 61.0, 61.1, 61.5, 113.2, 114.3, 120.0, 120.3, 121.4, 123.0, 123.7, 123.8, 124.7, 126.2, 126.4, 126.7, 126.9, 127.1, 128.3, 128.8, 128.9, 129.0, 129.9, 131.2, 142.6, 143.8, 143.9, 147.9. Anal. Calcd for  $\text{C}_{28}\text{H}_{22}\text{O}_4$ : C, 79.60; H, 5.25; Found: C, 79.61; H, 5.30.

**trans-8,9-trans-11,12-Tetrahydroxy-8,9,11,12-tetrahydrodibenzo[def,p]chrysene (5).** (A) From 12a. Compound 12a (30 mg, 0.076 mmol) was dissolved in 70 mL of  $\text{CH}_2\text{Cl}_2$  and 0.82 mL of a 1M solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  was added dropwise at  $0^\circ\text{C}$ . The solution was stirred at room temperature for 5 h, and then the reaction was quenched by addition of 0.2 mL of water. Following removal of the solvent under vacuum, THF (20 mL) and EtOAc (100 mL) were added, and the organic layer was washed with water, and dried over  $\text{Na}_2\text{SO}_4$ . Evaporation of the solvent afforded crude 11, 12-dihydroxydibenzo[def,p]chrysene-8,9-dione (12b). To this was added 120 mL of EtOH and  $\text{NaBH}_4$  (500 mg, 13.2 mmol), and the suspension was stirred overnight at room temperature with  $\text{O}_2$  bubbling through it. Following removal of the solvent under vacuum with heating, water was added, and the aqueous suspension was extracted with EtOAc-THF. The organic extracts were washed with water, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. Chromatography of the residue on a column of Florisil eluted with hexane-THF (3:7) gave 5 (23 mg, 81%) as a white solid identical in its physical and spectral properties with authentic 5 prepared by method (B).

(B) From 13a. Compound 13a (30 mg, 0.071 mmol) was dissolved in 50 mL of  $\text{CH}_2\text{Cl}_2$  and 1.0 mL of a 1M solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  was added dropwise at  $0^\circ\text{C}$ . The solution was stirred for 1 h at room temperature, and reaction was quenched by addition of 0.2 mL of water. The solvent was removed under vacuum, THF (20 mL) and EtOAc (100 mL) were added, and the organic layer was washed with water, dried over  $\text{Na}_2\text{SO}_4$  and evaporated to dryness to afford 8,9,11, 12-tetrahydroxydibenzo[def,p]chrysene (13b):  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  9.21 (s, 1), 9.12 (d, 1,  $J = 8.0$  Hz), 9.01 (d, 1,  $J = 8.0$  Hz), 8.91 (d, 1,  $J = 8.0$  Hz), 8.68 (s, 0.6, exchangeable with  $\text{D}_2\text{O}$ ), 8.64 (d, 1,  $J = 9.2$  Hz), 8.43 (d, 1,  $J = 7.7$  Hz), 8.30 (s, 0.6, exchangeable with  $\text{D}_2\text{O}$ ), 8.15 (s, 0.6, exchangeable with  $\text{D}_2\text{O}$ ), 8.12 (s, 0.6, exchangeable with  $\text{D}_2\text{O}$ ), 8.02 (t, 1,  $J = 7.9$  Hz), 7.77 (dd, 1,  $J = 7.7$  Hz), 7.73 (dd, 1,  $J = 7.0$  Hz), 7.44 (d, 1,  $J = 9.2$  Hz). Compound 13b was further characterized by conversion to its tetraacetate (13c) with  $\text{Ac}_2\text{O}$ : 13c was obtained as a yellow solid, mp  $202\text{--}205^\circ\text{C}$ :  $^1\text{H}$  NMR  $\delta$  9.10 (d, 1,  $J = 9.5$  Hz), 9.01 (d, 1,  $J = 8.2$  Hz), 8.97 (d, 1,  $J = 7.3$  Hz), 8.89 (d, 1,  $J = 7.6$  Hz), 8.51 (s, 1), 8.13 (dd, 1,  $J = 0.9, 7.7$  Hz), 8.07 (dd, 1,  $J = 7.8$  Hz), 7.81 (dd, 1,  $J = 7.5$  Hz), 7.74 (dd, 1,  $J = 7.6$  Hz), 7.60 (d, 1,  $J = 9.5$  Hz), 2.59 (s, 3), 2.58 (s, 3), 2.57 (s, 3), 2.43 (s, 3); MS,  $m/e$ , 534 ( $\text{M}^+$ , 6), 149 (100); HRMS Calcd for  $\text{C}_{32}\text{H}_{22}\text{O}_8$ : 534.1315. Found: 534.1319.

To 13b in 50 mL of EtOH was added  $\text{NaBH}_4$  (500 mg, 13.2 mmol), and the suspension was stirred overnight at room temperature with  $\text{O}_2$  bubbling through it. The usual workup gave 5 (23 mg, 81%) as a white solid: MS,  $m/e$ , 370 ( $\text{M}^+$ , 15); 309 ( $\text{M}^+$ , 100); HRMS Calcd for  $\text{C}_{28}\text{H}_{22}\text{O}_4$ : 422.1518. Found: 422.1518; HRMS Calcd for  $\text{C}_{24}\text{H}_{18}\text{O}_4$ : 370.1205. Found: 370.1202; UV  $I_{\text{max}}$  (e) 209 ( $7.44 \times 10^4$ ), 277 ( $5.84 \times 10^4$ ) nm;  $^1\text{H}$  NMR analysis showed two isomers of 5;  $^{13}\text{C}$  NMR (THF- $d_8$ )  $\delta$  73.1, 73.4, 74.5, 75.0, 75.1, 75.2, 76.4, 76.8, 121.0, 120.3, 121.3, 122.1, 122.2, 123.5, 124.3, 124.5, 125.2, 125.4, 126.0, 126.4, 126.8, 127.0, 127.4, 127.5, 127.6, 127.6, 127.8, 127.9, 128.0, 128.1, 130.3, 130.6, 131.1, 132.5, 132.7. The isomers were separable by HPLC on a reverse phase ZORBAX ODS column (9.4 x 25 cm) eluted with a linear gradient of 50% MeOH- $\text{H}_2\text{O}$  - 100% MeOH (in 15 min) with a flow rate

of 4.0 mL/min. Isomer **5a** was a white solid, mp  $\sim 220^\circ\text{C}$  (darkening):  $^1\text{H}$  NMR (THF- $d_8$ )  $\delta$  8.65 (d, 1,  $J = 8.4$  Hz), 8.50 (d, 1,  $J = 8.3$  Hz), 8.41 (d, 1,  $J = 7.7$  Hz), 8.24 (s, 1), 7.86 (d, 1,  $J = 7.4$  Hz), 7.59–7.61 (m, 2), 7.51 (t, 1,  $J = 8.1$  Hz), 7.12 (d, 1,  $J = 11$  Hz), 6.17 (d, 1,  $J = 10$  Hz), 4.97 (d, 0.6, exchangeable with  $\text{D}_2\text{O}$ ,  $J = 5.0$  Hz), 4.92 (d, 0.6, exchangeable with  $\text{D}_2\text{O}$ ,  $J = 5.0$  Hz), 4.83–4.89 (m, 2, on addition of  $\text{D}_2\text{O}$  changed to two doublets: d 4.89, 1,  $J = 11$  Hz; 4.84, 1,  $J = 10$  Hz), 4.61–4.64 (m, 1, on addition of  $\text{D}_2\text{O}$  changed to doublet,  $J = 11$  Hz), 4.51–4.53 (m, 1, on addition of  $\text{D}_2\text{O}$  changed to doublet,  $J = 12$  Hz). Isomer **5b** was a white solid, mp  $\sim 240^\circ\text{C}$  (darkening):  $^1\text{H}$  NMR (THF- $d_8$ )  $\delta$  8.67 (d, 1,  $J = 8.2$  Hz), 8.52 (d, 1,  $J = 8.2$  Hz), 8.46 (d, 1,  $J = 8.2$  Hz), 8.29 (s, 1), 7.92 (d, 1,  $J = 7.4$  Hz), 7.61 (dd, 1,  $J = 7.7, 7.9$  Hz), 7.59 (dd, 1,  $J = 7.0, 8.0$  Hz), 7.52 (dd, 1,  $J = 7.7, 7.4$  Hz), 7.10 (dd, 1,  $J = 10, 2.3$  Hz), 6.18 (dd, 1,  $J = 10, 2.0$  Hz), 5.13 (d, 0.6, exchangeable with  $\text{D}_2\text{O}$ ,  $J = 5.0$  Hz), 5.03 (d, 0.6, exchangeable with  $\text{D}_2\text{O}$ ,  $J = 5.0$  Hz), 4.90–4.94 (m, 1, on addition of  $\text{D}_2\text{O}$  changed to doublet:  $J = 11$  Hz), 4.79–4.82 (m, 1, on addition of  $\text{D}_2\text{O}$  changed to doublet:  $J = 11$  Hz), 4.61–4.58 (m, 1, on addition of  $\text{D}_2\text{O}$  changed to doublet:  $J = 12$  Hz), 4.49–4.55 (m, 1, on addition of  $\text{D}_2\text{O}$  changed to doublet:  $J = 12$  Hz).

**11,12-Dihydroxy- and 11,12-Diacetoxydibenzo[def,p]chrysene (10b and 10c).** To a stirred solution of **10a** (91 mg, 0.25 mmol) in 240 mL of  $\text{CH}_2\text{Cl}_2$  under argon was added dropwise 2.5 mL of a 1M solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  at  $0^\circ\text{C}$ . The solution was stirred for 1 h at room temperature and worked up in the usual manner to furnish **10b** (77 mg) as a dark solid:  $^1\text{H}$  NMR (acetone- $d_6$ )  $\delta$  9.12 (d, 1,  $J = 8.1$  Hz), 9.00 (d, 1,  $J = 7.1$  Hz), 8.98 (d, 1,  $J = 7.8$  Hz), 8.93 (s, 1), 8.68 (d, 1,  $J = 9.3$  Hz), 8.12 (d, 1,  $J = 7.4$  Hz), 8.06 (d, 1,  $J = 9.0$  Hz), 7.99 (dd, 1,  $J = 7.9, 7.6$  Hz), 7.88 (d, 1,  $J = 9.0$  Hz), 7.78 (dd, 1,  $J = 6.9, 7.3$  Hz), 7.74 (dd, 1,  $J = 8.1, 6.9$  Hz), 7.51 (d, 1,  $J = 9.2$  Hz). In view of its air sensitivity, **10b** was characterized as its diacetate. A solution of **10b** (77 mg) in 3.0 mL of  $\text{Ac}_2\text{O}$  and 5.0 mL of pyridine was stirred overnight at room temperature. The usual workup provided **10c** (91 mg, 87% for 2 steps) as a yellow solid, mp  $212\text{--}214^\circ\text{C}$  (lit.<sup>25b</sup>  $191\text{--}193^\circ\text{C}$ ) (EtOAc):  $^1\text{H}$  NMR  $\delta$  9.13 (d, 1,  $J = 9.4$  Hz), 9.04 (d, 1,  $J = 8.1$  Hz), 8.93 (d, 1,  $J = 7.4$  Hz), 8.92 (d, 1,  $J = 7.9$  Hz), 8.51 (s, 1), 8.11 (d, 1,  $J = 7.3$  Hz), 8.04 (t, 1,  $J = 7.7$  Hz), 7.98 (d, 1,  $J = 9.1$  Hz), 7.91 (d, 1,  $J = 9.0$  Hz), 7.80 (dd, 1,  $J = 7.0, 8.0$  Hz), 7.74 (dd, 1,  $J = 8.1, 7.0$  Hz), 7.58 (d, 1,  $J = 9.4$  Hz), 2.63 (s, 1), 2.44 (s, 1). Anal. Calcd for  $\text{C}_{28}\text{H}_{18}\text{O}_4$ : C, 80.37; H, 4.34; Found: C, 80.12; H, 4.39.

**trans-11,12-dihydroxy-11,12-dihydrodibenzo[def,p]chrysene (3).**  $\text{O}_2$  was bubbled through a stirred suspension of **10c** (42 mg, 0.10 mmol) and  $\text{NaBH}_4$  (150 mg, 4.0 mmol) in 120 mL of EtOH for 2 days at room temperature. The solvent was removed under vacuum without heating, water was added, and the aqueous suspension was extracted with EtOAc. The combined organic extracts were washed with brine, dried over  $\text{Na}_2\text{SO}_4$ , and evaporated to dryness. Chromatography of the product on a column of Florisil eluted with hexane-THF (4:1) afforded **3** (28 mg, 83%) as a yellow solid, mp  $220\text{--}222^\circ\text{C}$  (lit.<sup>25a</sup>  $190\text{--}192^\circ\text{C}$ , lit.<sup>25b</sup>  $202\text{--}204^\circ\text{C}$ ):  $^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  8.98 (d, 1,  $J = 7.8$  Hz), 8.94 (d, 1,  $J = 8.0$  Hz), 8.52 (d, 1,  $J = 8.0$  Hz), 8.42 (s, 1), 8.25 (d, 1,  $J = 7.6$  Hz), 8.14 (d, 1,  $J = 8.8$  Hz), 8.09 (d, 1,  $J = 8.9$  Hz), 8.03 (dd, 1,  $J = 7.8\text{Hz}$ ), 7.77 (dd, 1,  $J = 7.2$  Hz), 7.70 (dd, 1,  $J = 7.1$  Hz), 7.26 (dd, 1,  $J = 10, 2.0$  Hz), 6.29 (dd, 1,  $J = 10, 2.2$  Hz), 5.44 (d, 1, exchangeable with  $\text{D}_2\text{O}$ ,  $J = 6.0$  Hz), 5.85?? (d, 1, exchangeable with  $\text{D}_2\text{O}$ ,  $J = 5.0$  Hz), 4.70–4.73 (br s, 1), 4.58–4.61 (br s, 1); MS,  $m/e$ , 336 ( $\text{M}^+$ , 12); 318 ( $\text{M}^+ - \text{H}_2\text{O}$ , 100); HRMS Calcd for  $\text{C}_{24}\text{H}_{16}\text{O}_2$ : 336.1150. Found: 336.1153; UV(EtOH)  $\lambda_{\text{max}}$  (e) 213 (5.97

$\times 10^4$ ), 252 ( $3.01 \times 10^4$ ), 267 ( $2.99 \times 10^4$ ), 292 ( $2.88 \times 10^4$ ), 304 ( $3.00 \times 10^4$ ), 345 ( $2.59 \times 10^4$ ), 361 ( $2.73 \times 10^4$ ) nm.

***trans*-11,12-dihydroxy-*anti*-13,14-epoxy-11,12,13,14-tetrahydrodibenzo[*def,p*]chrysene (4).**

To a solution of 3 (50 mg, 0.15 mmol) in 7.0 mL of freshly distilled THF was added dropwise a solution of *m*-CPBA (250 mg, 1.45 mmol) in 7.0 mL of THF at 0 °C. The mixture was stirred for 4h and then poured into 250 mL of cold EtOAc. The organic layer was washed with cold aqueous solution of NaOH, water, and then dried over Na<sub>2</sub>SO<sub>4</sub>. Evaporation of the solvent without heating gave 4 (45 mg, 86%) as a white solid, mp 173–175 °C (lit.<sup>25b</sup> 177–179 °C): <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>)  $\delta$  9.05 (d, 1, *J* = 7.9 Hz), 8.99 (d, 1, *J* = 8.0 Hz), 8.67 (d, 1, *J* = 8.1 Hz), 8.47 (s, 1), 8.30 (d, 1, *J* = 7.5 Hz), 8.18 (d, 1, *J* = 8.9 Hz), 8.15 (d, 1, *J* = 9.0 Hz), 8.07 (dd, 1, *J* = 7.8 Hz), 7.82 (dd, 1, *J* = 7.8 Hz), 7.76 (dd, 1, *J* = 7.9 Hz), 5.97 (d, 1, *J* = 6.2 Hz, exchangeable with D<sub>2</sub>O), 5.73 (d, 1, *J* = 5.0 Hz, exchangeable with D<sub>2</sub>O), 4.87 (t, 1, *J* = 7.0, 8.1 Hz), 4.77 (d, 1, *J* = 4.3 Hz), 3.82 (m, 1), 3.77 (d, 1, *J* = 4.2 Hz).

**Dibenzo[*def,p*]chrysene-11,12-dione (14).** A solution of 3 (17.5 mg, 0.052 mmol) and DDQ (47.5 mg, 0.21 mmol) in wet THF (9 mL, 1%) was stirred for 2 days. Water was added, and the precipitate was collected, washed with water and ether, and dried to yield 14 (15.2 mg, 87%) as a black solid, mp 270–272 °C (lit.<sup>25a</sup> 234–236 °C, lit.<sup>25b</sup> 278–280 °C): <sup>1</sup>H NMR  $\delta$  8.90 (d, 1, *J* = 7.5 Hz), 8.88 (s, 1), 8.82 (d, 1, *J* = 7.5 Hz), 8.49 (d, 1, *J* = 10.5 Hz), 8.30 (dd, 1, *J* = 8.0, 1.0 Hz), 8.22 (d, 1, *J* = 7.5 Hz), 8.14 (d, 1, *J* = 8.5 Hz), 8.11 (d, 1, *J* = 8.0 Hz), 8.10 (d, 1, *J* = 8.5 Hz), 7.85 (dd, 1, *J* = 8.0, 7.0 Hz), 7.73 (dd, 1, *J* = 8.0, 7.0 Hz), 6.57 (d, 1, *J* = 10.5 Hz); MS, *m/e*, 334 (M<sup>+</sup>, 70); 304 (M<sup>+</sup>, 100).

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