Synthesis of the Dihydrodiol and Diol Epoxide Metabolites of Chrysene and 5-Methylchrysene

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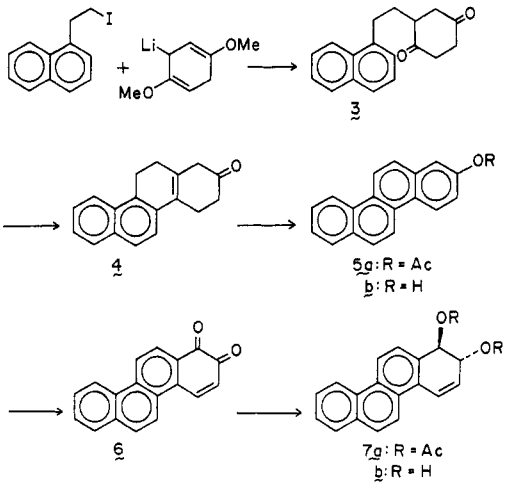
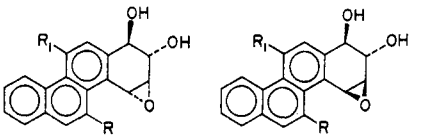
Carcinogenic polycyclic aromatic hydrocarbons are known to undergo enzymatic activation to diol epoxide metabolites bearing an epoxide ring in a bay molecular region. Introduction of a methyl group into a nonbenzo bay region position generally enhances carcinogenic activity. We now report efficient syntheses of the diastereomeric anti and syn bay region diol epoxide derivatives of both chrysene and 5-methylchrysene (5-MC) in both bay regions. The *anti*- and *syn*-1,2-diol-3,4-epoxide derivatives of 5-MC (**1b** and **2b**) are the first examples of synthetic diol epoxides with a methyl group in the same bay region as the epoxide ring. NMR analysis indicates that these diol epoxide derivatives and the related dihydrodiols, with the exception of **2b** and the *syn*-7,8-diol-9,10-epoxide of 5-methylchrysene (**2c**), exist preferentially in the diequational conformation in solution; **2b** and **2c** show a slight predominance of the diaxial conformer. All the synthetic diol epoxides were sufficiently stable to conduct biological experiments on tumorigenicity and DNA binding on mouse skin; the results confirm that **1b** is the major active carcinogenic form of 5-methylchrysene which binds covalently to DNA in vivo.

Methyl substitution in the bay region of a polycyclic aromatic hydrocarbon (PAH) often dramatically enhances carcinogenic activity.[1] For example, 5-methylchrysene is a relatively potent carcinogen and mutagen, whereas chrysene and the other isomeric monomethylchrysenes exhibit minimal mutagenic and carcinogenic activities.[2,3] Other examples of this effect include 7,12-dimethylbenz[*a*]anthracene,[4] 11-methylbenzo[*a*]pyrene,[5,6] 5,11-dimethylchrysene,[7] 7,14-dimethyldibenz[*a*,*h*]anthracene,[1] 7,14-dimethyldibenz[*a*,*j*]anthracene,[1] 3,6-dimethylcholanthrene,[1] and 15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-17-one.[8] The molecular basis of the bay region methyl effect is unknown. X-ray studies of 5-methylchrysene and 7,12-dimethylbenz[*a*]anthracene demonstrate significant distortion of the polycyclic ring systems from planarity[9-11] which may be expected to lead to decreased aromaticity of the angular benzo ring. It has been suggested that the greater olefinic character of the aromatic bonds in this molecular region may result in enhanced ease of enzymatic activation to the ultimate carcinogenic bay region diol epoxide metabolites and to increased reactivity of the latter with DNA.[1]

Comprehensive investigations of the molecular mechanism of the bay region methyl effect are dependent upon the development of methods for the synthesis of the biologically active bay region dihydrodiol and diol epoxide metabolites. We have focused our efforts on 5-methylchrysene which is uniquely suited for these studies by the possession of two dissimilar bay regions, only one of which contains a methyl group. We now report efficient syntheses of the diastereomeric anti and syn bay region diol epoxide derivatives of both chrysene (**1a**, **2a**) and 5-methylchrysene (**1b,c** and **2b,c**) in both bay regions. Two syntheses of the chrysene anti diol epoxide **1a** have previously been described.[12,13] The novel synthetic approach to **1a** which is now reported is more efficient than previous methods, requiring fewer steps and affording a higher overall yield.

Scheme I





Results

Synthesis of the *trans*-1,2-dihydrodiol of chrysene (**7b**) was accomplished via the reaction sequence in Scheme I. Alkylation of the lithium salt of 1,4-dimethoxycyclohexa-

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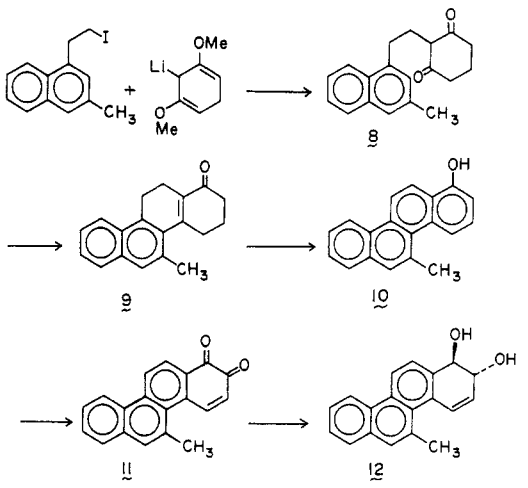
1,4-diene (generated in situ from reaction of the diene with *tert*-butyllithium in hexamethylphosphoric triamide) furnished the diketone **3** which underwent cyclization in polyphosphoric acid to yield 2-oxo-1,2,3,4,11,12-hexahydrochrysene (**4**). The NMR spectrum of **4** was entirely consistent with this structure and did not contain a vinylic proton peak characteristic of the isomeric 2-oxo-1,2,3,11,12,12a-hexahydrochrysene. Treatment of **4** with isopropenyl acetate, acetic anhydride, and *p*-toluenesulfonic acid gave the corresponding enol acetate derivative which was dehydrogenated directly with DDQ to yield 2-chrysenol acetate (**5a**). This method of synthesizing polycyclic phenols from ketones[14,15] is generally superior, in our experience, to conventional dehydrogenation with Pd/C or sulfur which often afford deoxygenated products. Methanolysis of **5a** gave 2-chrysenol (**5b**), and oxidation of this phenol with Fremy's salt [$(KSO_3)_2NO$] took place smoothly to yield chrysene-1,2-dione (**6**). Reduction of this quinone with $NaBH_4$ was conducted with oxygen bubbling through the reaction mixture to reoxidize any 1,2-dihydroxychrysene byproduct back to the quinone.[16-18] *trans*-1,2-Dihydroxy-1,2-dihydrochrysene (**7b**) was obtained via this route in good overall yield.

Synthesis of the corresponding bay region diol epoxide derivative, *trans*-1,2-dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydrochrysene (**1a**), was achieved through treatment of **7b** with *m*-chloroperbenzoic acid as previously reported.[12] The high resolution 500-MHz NMR spectra of **1a** and its dihydrodiol precursor were consistent with their structural assignments (Table I). The relatively large coupling constants for the carbinol protons of **1a** ($J_{1,2}$ = 8.6 Hz) and **7b** ($J_{1,2}$ = 10.8 Hz) support their existence predominantly in the diequatorial conformation.[12,19] The theoretically calculated values of $J_{1,2}$ for the diequatorial and diaxial conformation of both **1a** and **7b** are 12.7 ± 0.2 and 2.0 ± 0.1 Hz, respectively.[19] Based on the assumption that the observed couplings are the weighted average of the ratio of conformers, the percentages of the diequatorial conformers of **1a** and **7b** in solution are 62% and 82%, respectively.

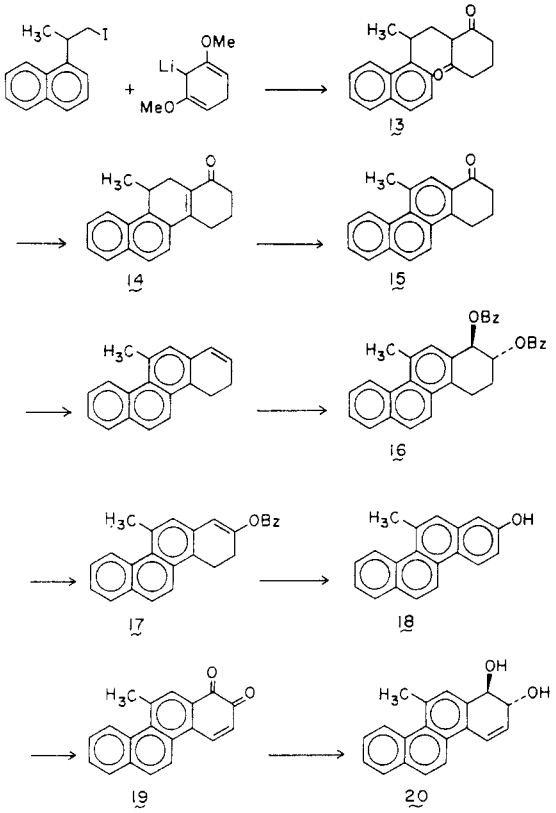
trans-1,2-Dihydroxy-*syn*-3,4-epoxy-1,2,3,4-tetrahydrochrysene (**2a**) was synthesized, also stereospecifically, via reaction of the 1,2-dihydrodiol **7b** with *N*-bromosuccinimide in moist dimethyl sulfoxide to generate the corresponding bromohydrin which underwent base-catalyzed cyclization to yield **2a**. The 500-MHz NMR spectrum of **2a** differed from that of **1a** and was fully consistent with the syn stereochemical assignment (Table I). The value of the coupling constant for the carbinol protons of **2a** ($J_{1,2}$ = 7.1 Hz) was smaller than those of **1a** and **7b**, indicative of an approximately equal mixture of the diequatorial and diaxial conformers in solution. The NMR data are in essential agreement with those of Whalen et al.[20] who reported $J_{1,2}$ = 6.8 Hz for **2a** from which may be deduced that the diaxial conformer is slightly favored (55%) over the diequatorial conformer (45%) in solution.

The 1,2-dihydrodiol of 5-methylchrysene and the corresponding anti diol epoxide (**1b**) were synthesized via a

Scheme II



Scheme III



route analogous to Scheme I but involving alkylation of 6-lithio-1,5-dimethoxycyclohexa-1,4-diene rather than 3-lithio-1,4-dimethoxycyclohexa-1,4-diene and proceeding via intermediacy of 1-hydroxy-5-methylchrysene (Scheme II). Details of this synthetic sequence were described in a preliminary publication.[21] Synthesis of the previously unknown syn diastereomer (**2b**) was accomplished in good overall yield from the 1,2-dihydrodiol of 5-methylchrysene via the bromohydrin intermediate by a procedure similar to that employed for **2a**.

The NMR spectra of the 1,2-dihydrodiol of 5-methylchrysene (**12**) and the related anti and syn diol epoxide derivatives (**1b** and **2b**) were similar to those of the corresponding derivatives of chrysene. The most notable differences were the larger values of the coupling constants of the carbinol protons of **12** and **2b**, indicative of a

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Table I. 500-MHz ^{1}H NMR Spectral Data on the Bay Region Dihydrodiol and Diol Epoxide Derivatives of Chrysene and 5-Methylchrysene[a]

compound	H_1	H_2	H_3	H_4	H_5	H_6	H_7	H_8	H_9	H_{10}	H_{11}	H_{12}	CH_3
1,2-diol (**7b**)	4.74	4.35	6.16	7.31	8.17	7.84	7.96	7.62	7.67	8.79	8.74	7.89	
		$J_{1,2}$ = 10.8; $J_{2,3}$ = 1.5; $J_{3,4}$ = 10.2; $J_{5,6}$ = 9.1; $J_{7,8}$ = 7.8; $J_{9,10}$ = 8.3; $J_{11,12}$ = 8.5 Hz											
1a (*anti*)	4.51	3.85	3.76	4.98	8.41	7.92	8.00	7.65	7.69	8.81	8.86	7.97	
		$J_{1,2}$ = 8.6; $J_{3,4}$ = 4.4; $J_{5,6}$ = 9.2; $J_{7,8}$ = 7.6; $J_{9,10}$ = 8.0; $J_{11,12}$ = 8.7 Hz											
2a (*syn*)	4.69	3.80	3.73	4.69	8.26	7.93	7.98	7.64	7.68	8.79	8.84	7.77	
		$J_{1,2}$ = 7.1; $J_{2,3}$ = 1.4; $J_{3,4}$ = 2.7; $J_{5,6}$ = 9.1; $J_{7,8}$ = 7.7; $J_{9,10}$ = 8.2; $J_{11,12}$ = 8.6 Hz											
1,2-diol (**12**)	4.75	4.48	6.16	7.36		7.63	7.82	7.58	7.58	8.71	8.76	8.00	2.90
		$J_{1,2}$ = 11.5; $J_{3,4}$ = 10.4; $J_{11,12}$ = 8.5 Hz											
1b (*anti*)	4.53	3.81	3.69	4.87		7.74	7.87	7.61	7.61	8.74	8.86	7.95	2.95
		$J_{1,2}$ = 8.6; $J_{3,4}$ = 4.5; $J_{11,12}$ = 8.7 Hz											
2b (*syn*)	4.67	3.47	3.71	4.55		7.73	7.86	7.61	7.61	8.75	8.94	7.91	3.02
		$J_{1,2}$ = 9.6; $J_{3,4}$ = 4.4; $J_{7,8}$ = 6.9; $J_{9,10}$ = 8.1; $J_{11,12}$ = 8.6 Hz											
7,8-diol (**20**)	7.67	7.63	7.63	8.81		7.74	4.70	4.33	6.11	7.27	8.15	7.81	3.09
		$J_{1,2}$ = 7.2; $J_{3,4}$ = 8.1; $J_{7,8}$ = 10.8; $J_{8,9}$ = 1.8; $J_{9,10}$ = 10.3; $J_{11,12}$ = 9.0 Hz											
1c (*anti*)	8.02	7.65	7.65	8.82		7.80	4.49	3.83	3.73	4.94	8.40	7.88	3.09
		$J_{1,2}$ = 7.4; $J_{1,3}$ = 1.5; $J_{3,4}$ = 7.9; $J_{7,8}$ = 8.7; $J_{9,10}$ = 4.5; $J_{11,12}$ = 9.2 Hz											
2c (*syn*)	8.02	7.67	7.67	8.86		7.67	4.68	3.73	3.71	4.61	8.24	7.92	3.10
		$J_{1,2}$ = 7.6; $J_{3,4}$ = 8.2; $J_{7,8}$ = 7.2; $J_{9,10}$ = 4.1; $J_{11,12}$ = 9.1 Hz											

[a] The spectra were taken in Me_2SO-d_6; deuterium oxide was added prior to the measurement of the spectra in order to simplify the patterns by elimination of couplings to the hydroxyl protons. Chemical shifts are relative to tetramethylsilane.

somewhat larger proportion of the diequatorial conformers of **12** and **2b** (89% and 71%, respectively) relative to those of **7b** and **2a** in solution.

The dihydrodiol and diol epoxide derivatives of 5-methylchrysene in the alternative terminal benzo ring were synthesized by another modification of the same general synthetic approach (Scheme III). Alkylation of 6-lithio-1,5-dimethoxycyclohexa-1,4-diene with 1-iodo-2-(1-naphthyl)propane furnished the diketone **13** which cyclized in polyphosphoric acid to yield 7-oxo-5,6,7,8,9,10-hexahydro-5-methylchrysene (**14**). Attempts to dehydrogenate **14** to **15** with DDQ or *o*-chloranil were unsuccessful. However, this transformation was readily achieved with trityl trifluoroacetate generated in situ from trityl alcohol in refluxing trifluoroacetic acid.[22] Conversion of **15** to the desired β-phenol, i.e., 5-methyl-2-chrysenol, was carried out by the method developed earlier for the preparation of phenols of this type in the benz[*a*]anthracene series.[14] Reduction of the carbonyl group of **15** with $NaBH_4$ followed by acidic dehydration of the resulting alcohol gave 9,10-dihydro-5-methylchrysene. Prévost reaction of this hydrocarbon with silver benzoate and iodine furnished the corresponding *trans*-tetrahydrodiol dibenzoate **16**. Attempts to dehydrogenate **16** directly to the dibenzoate of the corresponding dihydrodiol **20** with the usual reagents, DDQ or NBS, were unsuccessful, apparently due to competing reactions on the methyl group. Accordingly, the alternative synthetic route via the phenolic intermediate 5-methylchrysen-8-ol (**18**) was investigated. Acid-catalyzed elimination of benzoic acid from **16** yielded 9,10-dihydro-5-methylchrysen-8-ol benzoate (**17**). Dehydrogenation of the latter with DDQ and acidic hydrolysis furnished **18**.

The 7,8-dihydrodiol of 5-methylchrysene (**20**) was synthesized from **18** via oxidation with Fremy's reagent to 5-methylchrysene-7,8-dione (**19**) followed by reduction with $NaBH_4$ in the presence of O_2. Conversion of **20** to the corresponding anti diol epoxide derivative (**1c**) was readily accomplished by the usual methods. Thus treatment of **20** with *m*-chloroperbenzoic acid afforded smoothly *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydro-5-methylchrysene (**1c**). Reaction of **20** with *N*-bromosuccinimide in moist dimethyl sulfoxide furnished the bromohydrin derivative which on treatment with potassium *tert*-butoxide underwent cyclization to yield *trans*-7,8-dihydroxy-*syn*-9,10-epoxy-7,8,9,10-tetrahydro-5-methylchrysene (**2c**). The anti and syn isomers were obtained as pure white solids.

The 500-MHz NMR spectra (Table I) of the 7,8-dihydrodiol (**20**) and the related anti and syn diol epoxide derivatives (**1c** and **2c**) were fully consistent with their structural assignments. The chemical shifts and splitting patterns of the protons in the oxidized rings of each of these compounds matched closely those of the corresponding derivatives of chrysene. Apparently the 5-methyl group has minimal effect on the structure or conformation of the terminal oxidized ring.

Discussion

The syntheses of chrysene and 5-methylchrysene derivatives outlined above provide efficient synthetic approaches to these molecules entailing relatively few steps. The synthesis of the chrysene 1,2-dihydrodiol (**7b**) via Scheme I entails five steps and affords **7b** in 12% overall yield. This compares favorably with our previous synthetic approach[12] which furnished **7b** in 4% yield in six steps from chrysene and the alternative method of Karle et al.[13] which provided **7b** in 1% overall yield from naphthalene in 12 steps.[23] The synthesis of the 7,8-dihydrodiol of 5-methylchrysene (**20**) in Scheme III affords this compound in higher overall yield (13%) than the photochemical route recently described by Amin et al.[24] (1.4%) and is more readily adaptable to preparation on large scale. The methods in Schemes I–III are also applicable, in principle, to the synthesis of a wider range of substituted derivatives of chrysene as well as other peri-condensed PAH ring systems.

The synthesis of the chrysene 1,2-dihydrodiol (Scheme I) is the first example of the alkylation of a 1,4-dimethoxycyclohexadiene to generate an alkylated 1,4-diketone intermediate (**3**) for the preparation of β-phenol derivatives of PAH. Alkylation of a 1,3-dimethoxycyclohexadiene was utilized in our prior studies[21,25] to generate alkylated 1,3-diketone intermediates for the preparation of α-phenols. However, α-phenols are generally less practical than β-

(22) Fu, P. P.; Harvey, R. G. *Tetrahedron Lett.* **1974**, 3217.

(23) The procedure of Karle et al.[13] is based on 1-oxo-1,2,3,4-tetrahydrochrysene which was itself synthesized from naphthalene by the methods described by J. W. Cook and R. Schoental (*J. Chem. Soc.* **1945**, 228) and Haworth, R. D. (*J. Chem. Soc.* **1932**, 1125). Separation of isomeric products was necessary at several stages of this synthesis.

(24) Amin, S.; Hecht, S. S.; Hoffmann, D. *J. Org. Chem.* **1981**, *46*, 2394.

(25) Pataki, J.; Harvey, R. G. *J. Org. Chem.* **1982**, *47*, 20.

phenols as intermediates for the synthesis of dihydrodiols, since their oxidation with $(KSO_3)_2NO$ or $(PhSeO)_2O$ affords predominantly para- rather than orthoquinones.[26] An exception is the oxidation of 1-hydroxy-5-methylchrysene (**10**) to 5-methylchrysene-1,2-dione (**11**). In this case oxidation occurs preferentially at the ortho position of the α-phenol as a consequence of steric interference by the bay region methyl group with oxidation in the para region.

The synthetic route to 5-methylchrysen-8-ol (**18**) (Scheme III) provides a method for the conversion to β-phenols of the α-ketonic intermediates (e.g., **15**) obtained from the alkylation of 1,3-dimethoxycyclohexadiene and cyclization. This synthetic approach was devised prior to development of the more convenient direct method for the preparation of β-phenols in Scheme I. It is likely that **18** could be synthesized by appropriate modification of the method in Scheme I, although this has not been demonstrated experimentally.

Like other PAH diol epoxides,[17] all of the anti and syn diol epoxide derivatives synthesized herein underwent relatively facile hydrolysis[27] and decomposed on heating. However, these compounds could be stored indefinitely in a freezer as the pure, dry solids. The diol epoxides **1b** and **2b** which bear a methyl group in the bay region are the first examples of synthetic diol epoxide derivatives of this type.[17] Their relative stability was somewhat surprising in view of the instability of the analogous diol epoxide derivative of 7,12-dimethylbenz[*a*]anthracene (DMBA) which also contains a methyl group in the bay region.[28,29] Initial attempts to isolate the DMBA diol epoxide from epoxidation of the corresponding dihydrodiol were unsuccessful,[30] although a small amount of this intermediate was trapped by reaction with DNA in situ.[28] More recently efficient syntheses of both the anti and syn diol derivatives of DMBA have been achieved in our laboratory, and the exceptional chemical reactivity of these intermediates has been confirmed.[29] The greater stability of **1b** and **2b** relative to the DMBA analogues appears to be partially a function of lower steric strain. X-ray crystallographic studies indicate that DMBA is more severely distorted from planarity than 5-methylchrysene.[11] The latter partially relieves steric compression by in-plane expansion of the bay region angle.

The synthetic dihydrodiol and diol epoxide derivatives of chrysene and 5-methylchrysene were employed in biological studies of metabolism, mutagenicity, tumorigenicity, and covalent binding to DNA in mouse skin. While metabolism of 5-methylchrysene afforded the dihydrodiols in both terminal rings (**12** and **20**) approximately equally,[31] **1b**, the anti diol epoxide isomer in the methyl-substituted bay region, was the predominant DNA bound metabolite formed in vivo.[32] Moreover, **1b** exhibited the highest level of tumorigenicity and mutagenicity of the four possible bay region diol epoxide isomeric derivatives of 5-methylchrysene.[33,34] The principal site of attack of **1b** on DNA was the 2-amino group of deoxyguanosine,[32] identical with the major site of covalent binding of the analogous bay region diol epoxide metabolite of the potent carcinogenic hydrocarbon benz[*a*]pyrene.[35] Kinetic studies of the covalent binding of **1b** and **2c** to DNA in vitro recently conducted by Kim et al.[36] indicate that **1b** reacts to a greater extent with DNA to form covalent products. The higher tumorigenicity of **1b** correlates with its higher level of covalent binding to nucleic acids.

Experimental Section

Materials and Methods. 2-(1-Naphthyl)ethyl iodide was synthesized from 2-(1-naphthyl)ethanol by reaction with P_2I_4 by the method previously employed for the preparation of 2-(2-naphthyl)ethyl iodide.[25] The 1,4- and 1,5-dimethoxycyclohexa-1,4-dienes were synthesized from 1,4-dimethoxybenzene and 1,3-dimethoxybenzene, respectively, by a modification of the Birch reduction procedure[37] using lithium in place of sodium. 1,4-Dimethoxycyclohexa-1,4-diene was obtained in 75% yield as a crystalline solid, mp 53.5–55 °C, lit.[27] mp 54 °C; NMR δ 2.83 (s, 4, CH_2), 3.55 (s, 6, CH_3), 4.57 (s, 2, vinylic). 1,5-Dimethoxycyclohexa-1,4-diene: bp 102–104 °C (20 mmHg), lit.[27] bp 95 °C (18 mmHg); NMR δ 2.81 (s, 4, CH_2), 3.55 (s, 6, CH_3), 4.64 (s, 2, vinylic).

m-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.5 phosphate buffer and drying under reduced pressure. *N*-Bromosuccinimide (NBS) was crystallized from water prior to use. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene. Fremy's salt $[(KSO_3)_2NO]$ was freshly prepared according to the literature method.[38] Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$. Ether was dried over sodium.

The NMR spectra were obtained on a Varian EM360 spectrometer or the University of Chicago 500-MHz NMR spectrometer in $CDCl_3$, Me_2SO-d_6, or acetone-d_6 as appropriate, with tetramethylsilane as an internal standard. Integration was consistent with all structural assignments. Melting points are uncorrected. All new compounds gave satisfactory microanalysis for C, H within ±0.3% and/or mass spectra consistent with the assigned structures. The ultraviolet spectra were obtained on a Perkin-Elmer Lamda 5 spectrometer in ethanol unless otherwise indicated.

1-Iodo-2-(1-naphthyl)propane was synthesized from ethyl 1-naphthylacetate in three steps. To stirred suspension of NaH (25.20 g, 1.05 mol) in refluxing 1,2-dimethoxyethane (1 L) was added a solution of ethyl 1-naphthylacetate (214.1 g, 1 mol) and MeI (149.1 g, 1.05 mol) in the same solvent (500 mL) over 70 min under N_2. The mixture was then refluxed for 4 h, and additional portions of MeI (12 g each) were added after 2, 2.5, and 3 h. The mixture was cooled and filtered to remove NaI, and the solution was concentrated to a small volume. Water and benzene were added. The organic layer was washed with water and saturated brine and then dried and the solvent was removed under vacuum. Distillation of the residue gave ethyl 2-(1-naphthyl)propionate (167 g, 73%): bp 143–144 °C (1.8 mmHg); NMR δ 1.13 (t, 3, CH_3), 1.62 (d, 3, CH_3), 4.11 (q, 2, CH_2), 4.40 (q, 1, CH), 7.43–8.23 (m, 7, Ar).

A solution of ethyl 2-(1-naphthyl)propionate (90.9 g, 0.4 mol) in anhydrous ether (300 mL) was added dropwise to a suspension of $LiAlH_4$ (11.4 g, 50% excess) in ether (900 mL) over 100 min under N_2. The mixture was stirred for 3 h at room temperature, cooled in an ice bath, and decomposed by dropwise addition of an aqueous saturated Na_2SO_4 solution. The precipitate was filtered and washed with ether, and the solvent was evaporated.

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Distillation of the residue gave 2-(1-naphthyl)-1-propanol (68.0 g, 91%): bp 145–147 °C (1.7 mmHg); NMR δ 1.53 (d, 3, CH_3), 1.77 (s, 1, CH), 3.93 (d, 2, CH_2), 3.79–4.06 (m, 1, CH), 7.49–8.37 (m, 7, Ar).

The above alcohol (14.90 g, 80 mmol) was added to a stirred solution of P_2I_4 (12.0 g, 21 mmol) in dry CS_2 (400 mL) under an argon atmosphere at 0 °C. The resulting brown solution was stirred for 15 min in an ice bath and then for 168 h at ambient temperature. Solid K_2CO_3 (10 g) was added, and after 10 min a saturated solution of K_2CO_3 was added. The mixture was stirred for an additional 10 min and then diluted with CH_2Cl_2. Conventional workup gave 1-iodo-2-(1-naphthyl)propane (14.65 g, 62%): bp 152–154 °C (1.4 mmHg); NMR δ 1.52 (d, 3, CH_3), 3.40 (d, 2, CH_2), 3.68 (m, 1, CH), 7.23–8.02 (m, 7, Ar).

2-[2-(1-Naphthyl)ethyl]cyclohexane-1,4-dione (3). 1-4-Dimethoxycyclohexa-1,4-diene (4.21 g, 30 mmol) was added to a solution of *tert*-butyllithium (14.5 mL of a 2 M solution in pentane) in anhydrous THF (150 mL) at −78 °C under N_2. The solution was stirred for 1 h and then hexamethylphosphoramide (6.01 g, 33.6 mmol) was added. Stirring was continued for 10 min, and then 2-(1-naphthyl)ethyl iodide (7.32 g, 26 mmol) in dry THF (20 mL) was added. After 10 min, the reaction was quenched by the addition of brine (50 mL). Hexane was added, and the mixture was worked up conventionally to afford the enol ether intermediate (8.16 g). A solution of the latter in acetone (150 mL) was stirred with 1 N HCl (50 mL) for 1 h under N_2. Removal of the solvent under reduced pressure gave an oil which was taken up in CH_2Cl_2, washed with water, and again evaporated to yield crude **3** (7.55 g). Chromatography on Florisil gave on elution with benzene–ether (7:3) pure **3** (4.07 g, 59%) as an oil which was employed directly in the next step: NMR δ 2.60 (s, 4, CH_2), 2.41–3.23 (m, 7, CH_2 and CH), 7.42–8.03 (m, 7, Ar).

2-Oxo-1,2,3,4,11,12-hexahydrochrysene (4). The diketone **3** (4.0 g) was heated with polyphosphoric acid (60 g) at 50 °C for 1 h, stirring intermittently with a spatula. Ice water was added, and the mixture was extracted with CH_2Cl_2. The usual workup gave a solid residue which was triturated with ether to yield **4** (2.98 g, 79%): mp 121–124 °C; NMR δ 1.24–3.56 (m, 10, CH_2), 7.22–7.96 (m, 6, Ar).

2-Chrysenol (5b). A solution of **4** (2.90 g, 11.7 mmol) and *p*-toluenesulfonic acid (250 mg) in isopropenyl acetate (125 mL) and acetic anhydride (25 mL) was heated at reflux for 18 h. The dark solution was poured into ice water and stirred for 30 min. The mixture was extracted with EtOAc, and the extract was washed twice with 5% $NaHCO_3$ solution and dried, and the solvent was evaporated. A small sample of the crude enol acetate recrystallized from EtOAc melted at 150–152 °C.

The crude enol acetate in dry benzene (100 mL) was heated at reflux with DDQ (5.45 g, 24 mmol) for 30 min under N_2. The mixture was cooled, the hydroquinone was filtered and washed with benzene, and the filtrate was concentrated and absorbed on a column of Florisil. Elution with benzene gave **5a** (2.31 g, 69%): mp 233–233.5 °C, lit.[39] mp 229–230 °C; NMR δ 2.37 (s, 3, CH_3), 7.27–8.86 (m, 11, Ar).

A solution of **5a** (2.30 g) and *p*-toluenesulfonic acid (600 mg) in methanol (200 mL) was heated at reflux for 7 h. Water (70 mL) was added slowly to the hot solution which was allowed to stand at ambient temperature overnight. The crystals of **5b** were filtered and washed with MeOH–H_2O (3:1) to yield pure **5b** (1.71 g, 87%): mp 265–267 °C, lit.[39] mp 273–275 °C (in an evacuated sealed tube).

Chrysene-1,2-dione (6). To a vigorously stirred solution of **5b** (1.10 g, 4.5 mmol) in benzene (600 mL) were added 5 drops of Adogen 464 and a solution of Fremy's salt (3 g) in 100 mL of M/6 KH_2PO_4 and 75 mL of H_2O. After 1 h, the precipitated quinone was filtered, washed with H_2O and MeOH, and dried to obtain **6** (861 mg, 74%): mp 260–261 °C; NMR (Me_2SO-d_6) δ 6.46 (d, 1, H_3), 7.60–8.81 (m, 9, H_{4-12}); UV λ_{max} (ε) 261 (32 000), 305 (21 800), 319 (24 800).

***trans*-1,2-Dihydroxy-1,2-dihydrochrysene (7b).** A suspension of **6** (750 mg) and $NaBH_4$ (1.5 g) in ethanol (250 mL) was stirred for 8 h while O_2 was bubbled into the solution. Stirring was continued for 45 h in the open flask. The mixture was partitioned between EtOAc and water and worked up conventionally to afford the crude dihydrodiol (815 mg). This was dissolved in pyridine (10 mL) and acetic anhydride (2 mL) and allowed to stand overnight. After the usual workup, the acetylated product was chromatographed on Florisil. The diacetate was eluted with benzene. Recrystallization from MeOH furnished pure **7a** (586 mg, 58%): mp 184–185.5 °C, lit.[13] mp 176–177 °C.

The diacetate **7a** (580 mg) was dissolved in THF (140 mL) and MeOH (60 mL) and NH_3 gas was bubbled into the solution for 1 h at 0 °C and 4 h at room temperature. Water (350 mL) was added and the solid which separated was filtered and dried. The product (461 mg) which still contained about 20% diacetate (by NMR) was recrystallized from EtOH to yield pure **7b** (275 mg): mp 263–265 °C, lit.[12] mp 266–267 °C; NMR Table I; UV λ_{max} (ε) 223 (74 160), 248 (37 080), 272 (40 670), 284 (29 900).

***trans*-1,2-Dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydrochrysene (1a).** A solution of **7b** (100 mg, 0.38 mmol) in anhydrous THF (30 mL) was stirred with *m*-chloroperbenzoic acid (656 mg, 3.8 mmol) for 1.5 h under N_2. The solution was diluted with ether (100 mL) and washed twice with ice-cold 2 N NaOH and once with ice water. The solvent was removed under reduced pressure avoiding heating. The solid residue (100 mg) was triturated with dry ether to yield **1a** (62 mg): 222–224 °C dec, lit.[12] mp 225–227 °C; NMR Table I; UV λ_{max} (ε) 216 (37 870), 259 (54 390), 301 (11 160).

3α-Bromo-1β,2α,4β-trihydroxy-1,2,3,4-tetrahydrochrysene. To a solution of **7b** (131 mg, 0.5 mmol) in Me_2SO (20 mL) and water (0.5 mL) was added NBS (200 mg, 1.30 mmol). The solution was stirred for 1 h at room temperature. The usual workup followed by trituration of the residue with cold ether afforded the bromohydrin product (120 mg, 67%) as a white solid: mp 154–155 °C; NMR (500 MHz, Me_2SO-d_6–D_2O) δ 4.12 (d, 1, H_2), 4.66 (m, 2, $H_{1,3}$), 5.57 (s, 1, H_4), 7.64 (t, 1, H_8), 7.69 (t, 1, H_9), 7.85 (d, 1, H_{12}), 7.90 (d, 1, H_6), 7.98 (d, 1, H_7), 8.11 (d, 1, H_5), 8.82 (m, 2, $H_{10,11}$); $J_{5,6}$ = 9.2; $J_{7,8}$ = 7.2; $J_{11,12}$ = 8.6 Hz.

***trans*-1,2-Dihydroxy-*syn*-3,4-epoxy-1,2,3,4-tetrahydrochrysene (2a).** To a solution of the bromohydrin (32 mg, 0.089 mmol) in dry THF (7 mL) was added potassium *tert*-butoxide (17 mg) in *tert*-butyl alcohol (1 mL). The mixture was stirred for 1 h at room temperature under N_2. Since the diol epoxide is readily hydrolyzed, the workup must be conducted as rapidly as possible at low temperature. The solution was chilled in an ice bath and cold ether was added. The ether extracts were washed with ice water and dried over $MgSO_4$, and the solvent was removed in an evaporator with a dry ice condenser. The solid residue was triturated with cold ether to yield **2a** (24 mg, 98%): mp 175–177 °C; NMR Table I; UV λ_{max} (ε) 215 (16 630), 260 (28 380), 280 (8320), 300 (5870).

3α-Bromo-1β,2α,4β-trihydroxy-1,2,3,4-tetrahydro-5-methylchrysene. *trans*-1,2-Dihydroxy-1,2-dihydro-5-methylchrysene (**12**) was prepared as previously described.[21] Reaction of **12** (70 mg, 0.25 mmol) with NBS (72 mg) in Me_2SO (20 mL) and water (0.6 mL) by the procedure described above for the analogous reaction of **7b** afforded the bromohydrin product (50 mg, 54%) as a white solid: mp 123–124 °C; NMR (Me_2SO-d_6–D_2O) δ 3.0 (s, 3, CH_3), 4.3 (d of d, 1, H_2), 4.8 (m, 1, CH_3), 4.9 (d, 1, H_1, $J_{1,2}$ = 8.2 Hz, $J_{2,3}$ = 2.5 Hz), 6.2 (d, 1, H_4, $J_{3,4}$ = 4.0 Hz), 7.4–8.1 (m, 5, Ar), 8.7 (m, 1, H_{10}), 8.9 (d, 1, H_{11}).

***trans*-1,2-Dihydroxy-*syn*-3,4-epoxy-1,2,3,4-tetrahydro-5-methylchrysene (2b).** Reaction of the above bromohydrin (50 mg, 0.13 mmol) with potassium *tert*-butoxide (22.4 mg, 0.2 mmol) was conducted by the procedure employed for the preparation of **2a**. Trituration of the solid residue with cold ether afforded **2b** (32 mg, 82%) as a white solid: mp 155–157 °C dec; NMR Table I; UV λ_{max} (ε) 194 (11 200), 206 (11 580), 209 (12 280), 220 (17 220), 260 (36 290).

2-[2-(1-Naphthyl)propyl]cyclohexane-1,3-dione (13). 1,5-Dimethoxycyclohexa-1,4-diene (14.02 g, 0.10 mol) was added to a solution of *tert*-butyllithium (49 mL of a 2.3 M solution in pentane, 0.112 mol) in anhydrous THF (400 mL) cooled to −78 °C under N_2. The solution was stirred for 1 h, 20.4 mL of HMPA (21 g, 0.117 mol) was added, and stirring was continued for an additional 10 min. 1-Iodo-2-(1-naphthyl)propane (29.6 g, 0.10 mol) in THF (25 mL) was added and the cooling bath was removed. After 5 min the dark solution turned light green. The reaction was quenched after 10 min by the addition of 200 mL of saturated

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brine and worked up by the procedure employed for the preparation of **3** without chromatography. The crystalline product (23.28 g, 83%) melted at 173–178 °C. A sample of **13** recrystallized from EtOH melted at 178–180 °C.

7-Oxo-5,6,7,8,9,10-hexahydro-5-methylchrysene (14). The diketone **13** (6 g) was stirred with polyphosphoric acid (180 g) at 115 °C for 1 h. Ice water was added, and the mixture was allowed to stand overnight. The solid was filtered, washed with H_2O, and dried. The solids from four similar experiments were combined and dissolved in benzene (350 mL) and the solution was extracted with two 50-mL portions of 2 N NaOH. The combined alkaline solutions, after acidification with HCl, gave **13** (624 mg). The benzene solution was concentrated and adsorbed on a column of Florisil. Elution with benzene followed by crystallization from acetone–hexane gave **14** (13.93 g, 62%): mp 160.5–161.5 °C.

7-Oxo-7,8,9,10-tetrahydro-5-methylchrysene (15). A solution of **14** (10.49 g, 40 mmol) and triphenylcarbinol (12.50 g, 48 mmol) in CF_3CO_2H (200 mL) was heated at reflux for 48 h. The solution was cooled, triphenylmethane (5.22 g) was filtered, and the filtrate was evaporated to dryness. The residue was chromatographed on Florisil. The fractions eluted with benzene gave, after recrystallization from acetone–hexane, **15** (7.84 g, 75.3%): mp 140–141 °C; NMR δ 2.12 (m, 2, CH_2), 2.54 (t, 2, CH_2), 2.98 (s, 3, CH_3), 3.18 (t, 2, CH_2), 7.31–8.90 (m, 7, Ar).

9,10-Dihydro-5-methylchrysene. To a stirred solution of **15** (7.80 g) in THF (125 mL) and MeOH (25 mL) was added $NaBH_4$ (5 g) in small portions over 1.5 h. Stirring was continued for another 4.5 h and then most of the solvent was removed under reduced pressure. The residual solution was chilled and water was added. The crystalline precipitate was filtered, washed with water, and dried. The crude alcohol (7.88 g) was heated at reflux in 200 mL of benzene with tosic acid (200 mg) for 1 h. The usual workup gave a solid residue which was recrystallized from hexane to yield 9,10-dihydro-5-methylchrysene (6.69 g, 92%): mp 79–80 °C.

***trans*-7,8-Dihydroxy-5-methyl-7,8,9,10-tetrahydrochrysene, Dibenzoate Ester (16).** Dry silver benzoate (13.85 g, 60.5 mmol) and iodine (7.68 g, 30.3 mmol) in dry benzene (550 mL) were heated at reflux for 20 min. A solution of 9,10-dihydro-5-methylchrysene (6.60 g, 27 mmol) in 100 mL of dry benzene was added, and the mixture was heated at reflux with vigorous stirring for 4 h. After cooling, the solid was filtered, and the filtrate was concentrated to about 100 mL. On standing, the dibenzoate crystallized out (8.42 g): mp 190–194 °C; NMR δ 2.41–2.67 (m, 2, CH_2), 3.11 (s, 3, CH_3), 3.47 (t, 2, CH_2), 5.48–5.80 (m, 1, H_8), 6.73 (d, 1, H_7), 7.51 (s, 1, H_6), 7.58–8.98 (m, 7, Ar). Concentration and recrystallization of the mother liquors gave an additional crop of **16** (2.05 g): mp 186–190 °C. Total yield of **16** was 10.47 g (80%).

5-Methylchrysen-8-ol (18). A solution of **16** (4.00 g) and *p*-toluenesulfonic acid (200 mg) in benzene (200 mL) was heated at reflux for 24 h. After cooling, the solution was washed twice with $NaHCO_3$ solution and dried, and the solvent was removed under reduced pressure. The crude 9,10-dihydro-5-methylchrysen-8-ol benzoate (2.97 g) was dissolved in dry benzene (120 mL) along with DDQ (2.10 g) and heated at reflux for 30 min under N_2. The solution was cooled and the hydroquinone was filtered. The filtrate was washed with 1 N NaOH and with water, dried, concentrated to a small volume, and adsorbed on a column of Florisil. Elution with benzene and recrystallization of the product from acetone yielded the phenol benzoate **17** (2.10 g, 71%): mp 159–160 °C.

A solution of **17** (1.3 g) in glacial acetic acid (100 mL) containing 20 mL of concentrated HCl was heated at reflux for 24 h. The usual workup followed by recrystallization from benzene gave **18** (784 mg, 85%): mp 196.5–197 °C, lit.[24] mp 165–167 °C; NMR (acetone-d_6) δ 3.18 (s, 3, CH_3), 7.27 (d, 1, H_9), 7.28 (s, 1, H_7), 7.58 (m, 1, H_2), 7.62 (m, 1, H_3), 7.74 (s, 1, H_6), 7.98 (d, 1, H_{12}), 8.01 (dd, 1, H_1), 8.68 (dd, 1, H_{10}), 8.70 (s, 1, OH), 8.73 (dd, 1, H_{11}), 8.95 (d, 1, H_4); $J_{1,2}$ = 7.5 Hz, $J_{9,10}$ = 8.7 Hz, $J_{11,12}$ = 9.0 Hz; UV λ_{max} (ϵ) 276 (99 800), 217 (26 400). The discrepancy between the reported melting point of **18** and that observed herein appears to be primarily due to the greater purity of the present sample. The structural assignment of **18** is supported by its mode of synthesis and by its high resolution proton NMR spectrum which is entirely consistent with this structure; spin-decoupling experiments were performed to confirm the chemical shift assignments, and deuterium oxide exchange was used to identify the OH peak.

5-Methylchrysene-7,8-dione (19). Oxidation of **18** with Fremy's salt (1.80 g) was carried out by the procedure described for the preparation of **6**. The product mixture was extracted with CH_2Cl_2. The extract was dried and evaporated under reduced pressure, and the residue was triturated with MeOH. Recrystallization of the product gave **19** (518 mg, 82%): mp 203–205 °C; NMR (Me_2SO-d_6) δ 3.09 (s, 3, CH_3), 6.45 (d, 1, H_9), 7.68–8.95 (m, 8, Ar + H_{10}); UV λ_{max} (ϵ) 261 (34 825), 305 (23 900), 325 (23 900).

***trans*-7,8-Dihydroxy-7,8-dihydro-5-methylchrysene (20).** A suspension of **19** (400 mg, 1.47 mmol) and $NaBH_4$ (1.20 g, 3.17 mmol) in ethanol (100 mL) was stirred while O_2 was bubbled into the solution for 28 h, when it became colorless. The solution was partitioned between CH_2Cl_2 and H_2O. Conventional workup gave the crystalline dihydrodiol **20** (364 mg, 91%): mp 188–191 °C; a sample recrystallized from EtOH–benzene had mp 191–191.5 °C; NMR Table I; UV λ_{max} (ϵ) 223 (48 300), 248 (32 200), 270 (38 640), 316 (13 340).

***trans*-7,8-Dihydroxy-*anti*-9,10-epoxy-5-methyl-7,8,9,10-tetrahydrochrysene (1c).** Oxidation of **20** (100 mg, 0.36 mmol) with *m*-chloroperbenzoic acid (625 mg, 3.62 mmol) by the procedure described for the preparation of **1a** (reaction time 2 h) gave **1c** (75 mg, 71%): mp 193–196 °C; NMR Table I; UV λ_{max} (ϵ) 214 (29 110) 259 (66 540), 294 (12 000), 305 (12 100).

9α-Bromo-7β,8α,10β-trihydroxy-7,8,9,10-tetrahydro-5-methylchrysene. Reaction of **20** (88 mg, 0.32 mmol) with NBS (100 mg, 0.65 mmol) in Me_2SO (15 mL) and H_2O (0.5 mL) by the procedure described for oxidation of **7b** afforded the bromohydrin derivative (72 mg, 61%) as a white solid: mp 154–155 °C; NMR (500 MHz, acetone-d_6–D_2O) δ 3.13 (s, 3, CH_3), 4.31 (d of d, 1, H_8), 4.78 (t, 1, H_9), 4.87 (d, 1, H_7), 5.74 (d, 1, H_{10}), 7.61–7.64 (m, 2, $H_{2,3}$), 7.81 (s, 1, H_6), 7.85 (d, 1, H_{12}), 7.97 (d of d, 1, H_1), 8.24 (d, 1, H_{11}), 8.90 (d, 1, H_4); $J_{1,2}$ = 7.4; $J_{1,3}$ = 1.5; $J_{3,4}$ = 8.3; $J_{7,8}$ = 8.2; $J_{8,9}$ = 2.8; $J_{9,10}$ = 3.0; $J_{11,12}$ = 9.1 Hz.

***trans*-7,8-Dihydroxy-*syn*-9,10-epoxy-5-methyl-7,8,9,10-tetrahydrochrysene (2c).** Reaction of the above bromohydrin (36 mg, 0.10 mmol) with potassium *tert*-butoxide (27 mg) was carried out by the procedure employed for the preparation of **2a** (30 min reaction time). Trituration of the crude solid product with cold ether provided **2c** (22 mg, 76%) as a white solid: mp 180–181 °C; NMR Table I; UV λ_{max} (ϵ) 213 (17 540), 256 (44 900), 304 (7360).

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