Efficient Synthesis of the Carcinogenic *anti*-Diol Epoxide Metabolite of 5-Methylchrysene

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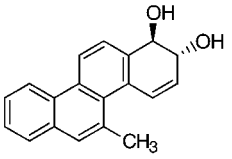
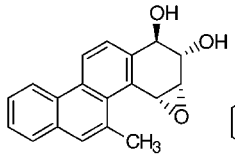
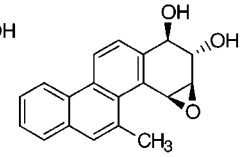
5-Methylchrysene is a relatively potent carcinogen that is present in cigarette smoke[1] and is a widespread contaminant of the human environment.[2] In contrast, chrysene and other monomethylchrysene isomers are inactive or exhibit only minimal biological activity. This difference may be a consequence of the presence of the methyl group of 5-methylchrysene in a bay region, which results in its distortion from planarity.[3,4] 5-Methylchrysene is metabolically activated by microsomal enzymes via formation of the *trans*-1,2-dihydro diol (**1**), which is further transformed to the *anti*- and *syn*-diol epoxides[5] (*anti*- and *syn*-**2**).[2,6−9] The latter bind covalently to DNA,



1



anti-**2**



syn-**2**

resulting in mutations that lead ultimately to tumorigenesis. The (+)-*anti*-diol epoxide enantiomer is considerably more mutagenic than the (−)-enantiomer in bacterial assays;[10] it is also more tumorigenic in mouse skin and in the lung of the newborn mouse.[7,8]

Although syntheses of **1** and **2** were reported, the synthetic methods entail a large number of steps and afford low overall yields.[11,12] Since these compounds continue to be urgently required for biological and other studies directed toward determination of their mechanism of action at the molecular-genetic level, there is need for a more convenient synthetic approach. We now report a new, more efficient synthetic route to the *trans*-1,2-dihydro diol (**1**), as well as an improved synthesis of its carcinogenic diol epoxide metabolite *anti*-**2**. The method is potentially applicable to the synthesis of analogous oxidized metabolites of other carcinogenic polycyclic aromatic hydrocarbons.

Results and Discussion

The synthetic route to the *trans*-1,2-dihydro diol **1** is based on 3-methyl-1-naphthaldehyde (**3b**), which was obtained from oxidation of 1,3-dimethylnaphthalene (**3a**) with ceric ammonium nitrate in 50% acetic acid by a modification of the published method (Scheme 1).[13] Wittig reaction of **3b** with the phosphonium salt prepared from 2,3-dimethoxybenzyl bromide, triphenylphosphine, and aqueous NaOH in CH_2Cl_2 at room temperature under argon furnished 1-[1-(3-methylnaphthyl)]-2-(2,3-dimethoxyphenyl)ethylene as a mixture of *Z* and *E* isomers (**4a** and **4b**) in a ratio of 35:65. The *E* isomer (**4b**) crystallized from the oily mixture on standing in the cold for 2 weeks. Recrystallization from MeOH gave pure **4b** as a white solid, mp 89 °C. The larger coupling constant exhibited by the olefinic protons of **4b** (J_{AB} = 16.0 Hz) relative to those of **4a** (J_{AB} = 7.4 Hz) were consistent with its assignment as the *E* isomer.

Photocyclodehydrogenation of the mixture of olefins was conducted in benzene solution in the presence of iodine and 1,2-epoxybutane. The latter served to scavenge the HI formed, thereby preventing its participation in secondary reactions.[14] Flash chromatography of the crude product gave a white solid, mp 160−161 °C, identified on the basis of its 300 MHz ^{1}H NMR spectrum, microanalysis, and mass spectrum as 1,2-dimethoxy-5-methylchrysene (**5a**). Demethylation of **5a** by treatment with BBr_3 provided 1,2-dihydroxy-5-methylchrysene (**5b**). In view of the known sensitivity of polycyclic aromatic hydroquinones to auto-oxidation, **5b** was isolated as its diacetate (**5c**).

Reduction of either the hydroquinone **5b** or its diacetate **5c** with $NaBH_4$ in ethanol with O_2 bubbling through the solution provided the *trans*-1,2-dihydro diol of 5-me-

(1) Hecht, S. S.; Bondinell, W. E.; Hoffmann, D. *J. Natl. Cancer Inst.* **1974**, *53*, 1121.
(2) (a) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University Press: Cambridge, England, 1991. (b) Harvey, R. G. *Polycyclic Aromatic Hydrocarbons*; Wiley-VCH Publishers: New York, 1997.
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(5) The anti isomer is the isomer in which the epoxide function is on the face opposite the benzylic hydroxyl group, and the syn isomer has these groups on the same face.
(6) Melikian, A. A.; Amin, S.; Hecht, S. S.; Hoffmann, D.; Pataki, J.; Harvey, R. G. *Cancer Res.* **1982**, *44*, 2524.
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(12) The synthesis of **1** previously reported requires as the starting compound 2-[1-(3-methylnaphthyl)]ethyl iodide obtained by a six-step synthesis from 2-methylnaphthalene in 9% overall yield.[11] Conversion of 2-[1-(3-methylnaphthyl)]ethyl iodide to **1** entails five additional steps that furnish **1** in 10% yield. Thus, the overall yield of **1** from available precursors is less than 1% via an 11-step sequence.
(13) Sydnes, L. K.; Hansen, S. H.; Burkow, I. C.; Saethre, L. J. *Tetrahedron* **1985**, *53* 5205.
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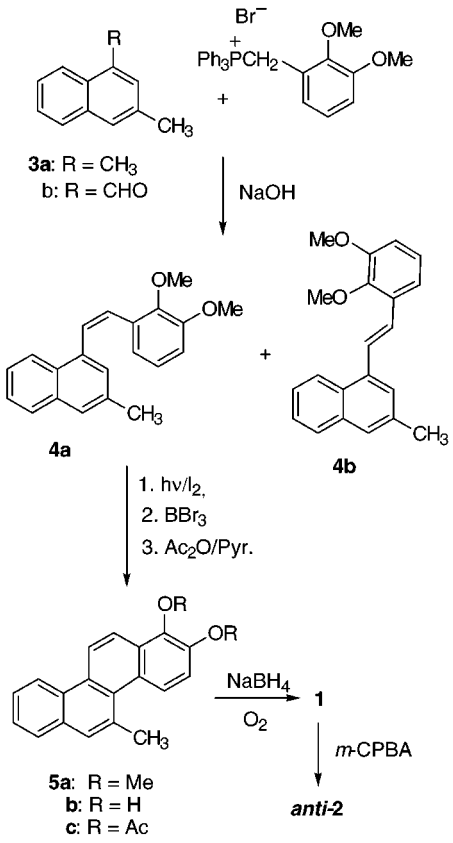
Scheme 1



thylchrysene (**1**).[11a,15] The yield of **1** was independent of whether the hydroquinone or its diacetate was employed. Trans stereoselectivity is consistent with previous findings for reductions of this type.[15] The 300 MHz ^{1}H NMR spectrum and other physical properties of **1** were in good agreement with those of an authentic sample, although its melting point was somewhat higher (200−201 °C) than reported earlier (188-189.5 °C).[11] Transformation of **1** to the corresponding *anti*-diol epoxide *anti*-**2** was carried out by treatment with *m*-chloroperbenzoic acid in anhydrous THF using an improved procedure that furnished pure *anti*-**2** in higher yield than previously reported.

This new synthetic route is considerably shorter than prior syntheses, requiring only four steps for the synthesis of **1** vs 10 steps by the most efficient of the older methods.[11] The overall yields of **1** and *anti*-**2** from 3-methyl-1-naphthaldehyde are 70% and 59%, respectively, which compare quite favorably with those reported for older synthetic methods (0.9% and 0.7%, respectively). 3-Methyl-1-naphthaldehyde was obtained pure in 41% yield from oxidation of 1,3-dimethylnaphthalene with ceric ammonium nitrate in HOAc, although a crude yield of 79% was claimed in the literature.[13] This aldehyde is reported to be obtained in 87% yield from photocatalytic oxidation of 1,3-dimethylnaphthalene in the presence of methyl viologen and $FeCl_2$.[16] In principle, the new synthetic approach to the oxidized metabolites of 5-methylchrysene reported herein may be appropriately modified for the synthesis of analogous dihydro diol and diol epoxide metabolites of other carcinogenic polycyclic hydrocarbons.

(15) The use of O_2 for oxidation of catechols to quinones in reductions of this type is well established: Reference 1a, Chapter 13, pp 306−329 and references therein. Platt, K.; Oesch, F. *Synthesis* **1982**, 459. Lee, H.; Harvey, R. G. *J. Org. Chem.* **1986**, *51*, 3502. Harvey, R. G. *Synthesis* **1986**, 605. Dai, W.; Abu-Shqara, E.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 4905.

(16) Santamaria, J.; Jroundi, R. *Tetrahedron Lett.* **1991**, *32* 4291.

Experimental Section

Materials and Methods. *m*-Chloroperbenzoic acid (Aldrich) was purified by washing with pH 7.4 phosphate buffer and drying under reduced pressure. (2,3-Dimethoxybenzyl)triphenylphosphonium bromide was prepared by heating an equimolar solution of 2,3-dimethoxybenzyl bromide and PPh_3 in a minimum volume of benzene at reflux for 5 h. THF was freshly distilled from $LiAlH_4$. The ^{1}H NMR spectra were recorded on a QE-400 MHz spectrometer in $CDCl_3$ with tetramethylsilane as internal standard unless otherwise stated. ***Caution****: The dihydro diol and diol epoxide derivatives of 5-methylchrysene are implicated as active carcinogenic metabolites and should be handled with caution in accord with "NIH Guidlines for the Laboratory Use of Chemical Carcinogens.".*

3-Methyl-1-naphthaldehyde (3b). To a stirred solution of 1,3-dimethylnaphthalene (1.0 g, 6.4 mmol) in 50% AcOH (250 mL) at 80 °C was added dropwise a solution of ceric ammonium nitrate (14.0 g, 25.5 mmol) in 50 mL of 50% AcOH. After being stirred for 1 h at 80 °C, the mixture was cooled and extracted with ether. The organic layer was washed with water and dried over $MgSO_4$. After evaporation of the solvent, the residue was chromatographed on a silica gel column eluted with hexane to afford **3b** (440 mg, 41%) as a pale yellow oil: ^{1}H NMR δ 2.55 (s, 3), 7.50−7.65 (m, 2), 7.45−7.75 (m, 3), 9.15 (d, 1, J = 8.3 Hz), 10.3 (s, 1, CHO).[13]

(*Z*)- and (*E*)-1-[1-(3-Methylnaphthyl)]-2-(2,3-dimethoxyphenyl)ethylene (4a and 4b). To a solution of **3b** (0.7 g, 4.1 mmol) and (2,3-dimethoxybenzyl)triphenylphosphonium bromide (2.44 g, 4.9 mmol) in CH_2Cl_2 (35 mL) was added 3.5 mL of 50% NaOH. The mixture was stirred at room temperature under argon overnight, and then 100 mL of water was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The extracts were combined and washed with water, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica gel (hexane/EtOAc 99:1) to afford a mixture of the *Z*- and *E*-isomers **4a** and **4b** (1.19 g, 95%) as a colorless oil: ^{1}H NMR δ 2.35 (s, 1.05, *Z*), 2.55 (s, 1.95, *E*), 3.84 (s, 1.05, *Z*), 3.88 (s, 1.95, *E*), 3.90 (s, 1.95, *E*), 3.92 (s, 1.05, *Z*), 6.43 (dd, 0.35, J = 7.4, 1.3 Hz, *Z*), 6.57 (t, 0.35, J = 8.0 Hz, *Z*), 6.68 (dd, 0.35, J = 7.4, 1.3 Hz, *Z*), 6.88 (dd, 0.65, J = 8.2, 1.3 Hz, *E*), 7.04−7.18 (m, 1.35, *E* + *Z*), 7.35 (dd, 0.65, J = 8.2, 1.3 Hz, *E*), 7.40−7.52 (m, 3.35, *E* + *Z*), 7.59 (br s, 0.65, *E*), 7.64 (d, 1, J = 1.5 Hz, *E*), 7.74−7.80 (m, 1, *E*), 7.90 (d, 0.65, J = 16.0 Hz, *E*), 8.02 (br d, 0.35, J = 8.0 Hz, *Z*), 8.14−8.18 (m, 0.65, *E*). This mixture was used directly for photocyclization. After this mixture was allowed to stand in the refrigerator for 2 weeks, part of the oil solidified. The white solid was collected by filtration and recrystallized from MeOH to give the *E*-isomer as white needles: mp 89 °C; ^{1}H NMR δ 2.55 (s, 3, Me), 3.88 (s, 3, MeO), 3.90 (s, 3, MeO), 6.88 (dd, 1, J = 8.2, 1.3 Hz), 7.12 (t, 1, J = 8.0 Hz), 7.35 (dd, 1, J = 8.2, 1.3 Hz), 7.42−7.50 (m, 3), 7.59 (d, 1, J = 3.0 Hz), 7.64 (d, 1, J = 1.5 Hz), 7.76−7.80 (m, 1), 7.90 (d, 1, J = 16.0 Hz), 8.14−8.18 (m, 1); MS (EI) *m*/*z* 304 $[M]^+$, 289, 273. Anal. Calcd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.96; H, 6.62.

1,2-Dimethoxy-5-methylchrysene (5a). Argon was bubbled through a solution of **4** (1.2 g, 3.95 mmol) and iodine (1 g, 3.95 mmol) in benzene (1.2 L) for 15 min, and then 1,2-epoxybutane (10 mL) was added. The mixture was irradiated with a Hanovia 450 W medium-pressure mercury lamp through a Pyrex filter for 2 h. TLC showed the reaction to be complete. The solvent was concentrated under vacuum to 100 mL, and then the solution was washed with 10% $Na_2S_2O_3$ and water and dried over $MgSO_4$. The crude product was purified by flash chromatography on a Florisil column eluted with hexane/CH_2Cl_2 (7:3) to yield **5a** (1.1 g, 92%) as a white solid: mp 160−161 °C (hexane−CH_2Cl_2); ^{1}H NMR δ 3.19 (s, 3, Me), 4.07 (s, 6, MeO), 7.38 (d, 1, J = 7.5 Hz), 7.56−7.68 (m, 2), 7.82 (s, 1), 7.88 (dd, 1, J = 7.8, 1.5 Hz), 8.36 (dd, 1, J = 9.3, 0.7 Hz), 8.70−8.78 (m, 3);

MS (EI) *m*/*z* 302 $[M]^+$, 287. Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.30; H, 5.96.

1,2-Dihydroxy- and 1,2-Diacetoxy-5-methylchrysene (5b and 5c). To a solution of **5a** (1.1 g, 3.64 mmol) in dry CH_2Cl_2 (110 mL) at −10 °C was added 15 mL of BBr_3 solution (1 M in CH_2Cl_2). The resulting yellowish solution was stirred at −10 °C for 10 min and then at 23 °C for 2 h. Ice (40 g) was added, and CH_2Cl_2 was removed under reduced pressure. Filtration of the aqueous suspension furnished hydroquinone **5b** (920 mg, 92%) as a gray solid: mp 211−213 °C (MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.11 (s, 3), 7.27 (d, 1, J = 9.4 Hz), 7.50−7.70 (m, 2), 7.87 (s, 1), 7.91 (d, 1, J = 8.0 Hz), 8.20−8.40 (m, 2), 8.72 (d, 1, J = 9.4 Hz), 8.78 (d, 1, J = 8.0 Hz), 9.0 (br s, 1, exchangeable with D_2O), 9.61 (br s, 1, exchangeable with D_2O).

The crude **5b** (820 mg, 3.0 mmol) was dissolved in Ac_2O (14 mL) and pyridine (20 mL), and the solution was stirred at room temperature for 16 h. The reaction mixture was poured into ice−water (500 mL), and the precipitate was collected by filtration and purified by flash chromatography on a column of silica gel eluted with hexane/CH_2Cl_2 (1:1) to yield the diacetate **5c** (960 mg, 89%) as white needles: mp 183−183.5 °C (MeOH−CH_2Cl_2); ^{1}H NMR δ 2.39 (s, 3), 2.52 (s, 3), 3.19 (s, 3), 7.49 (d, 1, J = 9.5 Hz), 7.58−7.68 (m, 2), 7.86 (s, 1), 7.90 (d, 1, J = 8.1 Hz), 8.01 (d, 1, J = 9.3 Hz), 8.69 (d, 1, J = 9.7 Hz), 8.79 (d, 1, J = 9.3 Hz), 8.88 (d, 1, J = 9.5 Hz); MS (CI) *m*/*z* 358 $[M]^+$, 316, 274. Anal. Calcd for $C_{23}H_{18}O_4$: C, 77.08; H, 5.06. Found: C, 77.24; H, 5.14.

***trans*-1,2-Dihydroxy-1,2-dihydro-5-methylchrysene (1)**. To a solution of **5c** (400 mg, 1.1 mmol) in EtOH (120 mL) was added $NaBH_4$ (810 mg, 22 mmol). The reaction mixture was stirred at room temperature for 24 h with O_2 slowly bubbling through the solution, and then the solvent was removed under vacuum without heating and 100 mL of cold water was added. The resulting suspension was extracted with EtOAc, and the organic layer was washed with water and dried over Na_2SO_4. The crude product was recrystallized from acetone−hexane to afford **1** (350 mg, 88%) as a white solid: mp 200−201 °C (acetone) (lit.[11b] mp 188−189.5 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.84 (s, 3), 4.30 (m, 1), 4.57 (dd, 1, J = 5.5, 11.5 Hz), 5.25 (d, 1, J = 4.9 Hz, exchangeable with D_2O), 5.64 (d, 1, J = 5.5 Hz, exchangeable with D_2O), 6.07 (dd, 1, J = 2.0, 10.4 Hz), 7.29 (d, 1, J = 10.4 Hz), 7.50−7.60 (m, 2,), 7.63 (s, 1), 7.81 (d, 1, J = 7.5 Hz), 7.88 (d, 1, J = 8.3 Hz), 8.70 (d, 1, J = 7.5 Hz), 8.77 (d, 1, J = 8.5 Hz); after addition of D_2O, the signals at 4.57 and 4.30 assigned to H_1 and H_2, respectively, changed to 4.55 (d, 1, J = 11.5 Hz) and 4.30 (dd, 1, J = 2.0, 11.5 Hz). Preparation of **1** from the crude hydroquinone **5b** by the same procedure gave **1** in 87% yield.

***trans*-1,2-Dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydro-5-methylchrysene (*anti*-2)**. *Because of the facility of thermal decomposition and acid-catalyzed hydrolysis of this and other diol epoxides it is important to avoid heating and acids and to minimize contact time with water during workup*. To a solution of **1** (110 mg, 0.4 mmol) in dry THF (20 mL) under argon was added *m*-chloroperbenzoic acid (688 mg, 4 mmol). The solution was stirred at room temperature for 1 h and then concentrated under vacuum without heating to 4 mL. Hexane (40 mL) was added, and the precipitate was collected by filtration and washed with 10 mL of hexane−THF (9:1) to provide *anti*-**2** (98 mg, 85%) as a white solid: mp 158−160 °C (lit.[11b] mp 158−161 °C); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.94 (s, 3, Me), 3.67 (br d, 1, J = 4.4 Hz), 3.78−3.83 (m, 1), 4.48−4.54 (m, 1), 4.86 (d, 1, J = 4.4 Hz), 5.57 (d, 1, J = 4.7 Hz, exchangeable with D_2O), 5.78 (d, 1, J = 5.9 Hz, exchangeable with D_2O), 7.58−7.64 (m, 2), 7.74 (s, 1), 7.87 (dd, 1, J = 2.0, 8.0 Hz), 7.94 (d, 1, J = 8.5 Hz), 8.74 (br d, 1, J = 8.0 Hz), 8.86 (d, 1, J = 8.5 Hz); after addition of D_2O, the signals assigned to H_1−H_4 changed to 4.50 (d, 1, J = 8.8 Hz), 3.79 (d, 1, J = 1.8, 8.8 Hz), 3.68 (dd, 1, J = 1.8, 4.4 Hz), 4.85 (d, 1, J = 4.4 Hz), respectively.

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