Hz), 2.15 (dt, 2 H, J = 7.3, 7.1 Hz), 5.29 (dt, 1 H, J = 10.8, 7.3 Hz), 5.65 (dt, 1 H, J = 15.0, 7.2 Hz), 5.94 (dd, 1 H, J = 10.8, 10.9 Hz), 6.30 (dd, 1 H, J = 15.0, 10.9 Hz), (*E,E* isomer, **4b**) δ 0.98 (t, 6 H, J = 6.5 Hz), 1.20–1.48 (m, 16 H), 2.04 (dt, 4 H, J = 7.2, 6.7 Hz), 5.52–5.60 (m, 2 H), 6.00 (dd, 2 H, J = 14.3, 7.2 Hz); MS, m/z 222 (M^+), 138, 100, 96, 82, 68, 54 (100%). Anal. Calcd for $C_{16}H_{30}$: C, 86.4; H, 13.6. Found: C, 86.1; H, 13.8.

8,10-Octadecadiene (**3c** and **4c**): IR (neat) 3090, 3000, 2900, 1490, 1400, 1000, 960 cm^{-1}; NMR (*E,Z* isomer, **3c**) δ 0.90 (t, 6 H, J = 6.5 Hz), 1.25–1.45 (m, 20 H), 2.08 (dt, 2 H, J = 7.6, 7.2 Hz), 2.16 (dt, 2 H, J = 7.6, 7.2 Hz), 5.30 (dt, 1 H, J = 10.8, 7.6 Hz), 5.65 (dt, 1 H, J = 15.1, 7.6 Hz), 5.93 (dd, 1 H, J = 11.0, 10.8 Hz), 6.32 (dd, 1 H, J = 15.1, 11.0 Hz), (*E,E* isomer, **4c**) δ 0.87 (t, 6 H, J = 6.5 Hz), 1.20–1.44 (m, 20 H), 2.04 (dt, 4 H, J = 7.1, 6.1 Hz), 5.50–5.64 (m, 2 H), 5.99 (dd, 2 H, J = 14.3, 7.2 Hz); MS, m/z 250 (M^+, 100%), 124, 110, 96, 82. Anal. Calcd for $C_{18}H_{34}$: C, 86.3; H, 13.7. Found: C, 86.2; H, 13.8.

(*E*)-3-Ethyl-3,5-octadiene (**6a**): IR 3020, 2950, 2870, 1620, 1460, 1380, 970 cm^{-1}; NMR δ 0.95–1.10 (m, 9 H), 2.00–2.35 (m, 6 H), 5.55 (dt, 1 H, J = 15.0, 7.2 Hz), 5.76 (d, 1 H, J = 7.6 Hz), 6.30 (dd, 1 H, J = 15.0, 7.6 Hz); MS, m/z 138 (M^+), 109 (100%), 95, 81, 79, 67, 55. Anal. Calcd for $C_{10}H_{18}$: C, 86.9; H, 13.1. Found: C, 86.7; H, 13.0.

(*E*)-4-Propyl-4,6-decadiene (**6b**): IR 3020, 2950, 2850, 1620, 1460, 1380, 960 cm^{-1}; NMR δ 0.90–1.05 (m, 9 H), 1.31–1.52 (m, 6 H), 1.98–2.12 (m, 6 H), 5.57 (dt, 1 H, J = 15.0, 7.3 Hz), 5.79 (d, 1 H, J = 7.8 Hz), 6.25 (dd, 1 H, J = 15.0, 7.8 Hz); MS, m/z 180 (M^+), 141, 137, 123, 109, 95 (100%), 81, 67. Anal. Calcd for $C_{13}H_{24}$: C, 86.7; H, 13.3. Found: C, 86.4; H, 13.2.

Reductive Cleavage of the C–S Bond of Substituted 2-Sulfolenes. Substituted 2-sulfolene **9** (1 mmol) in toluene was added dropwise to a suspension of ultrasonically dispersed potassium (2.5 mmol) in toluene at room temperature. The irradiation was continued for 15 min, upon which time MeI (4 mmol) was added, and the reaction mixture was stirred for another 20 min. With the precipitate in the solution, saturated NH_4Cl was added, and the layers were separated. The aqueous layer was extracted with $CHCl_3$, and the combined organic layers were dried and concentrated under reduced pressure. The crude oil was purified with HPLC (LiChrosorb; hexane/ethyl acetate, 1:1) to give the pure product.

Methyl 3-pentenyl sulfone (**11a**): IR (neat) 3020, 3000, 2960, 2930, 2860, 1460, 1300, 1130, 1120, 960, 750 cm^{-1}; ^{1}H NMR δ 1.68 (d, 3 H, J = 6.8 Hz), 2.51–2.56 (m, 2 H), 2.89 (s, 3 H), 3.02–3.06 (m, 2 H), 5.42 (dq, 1 H, J = 15.0, 6.8 Hz), 5.60 (dt, 1 H, J = 15.0, 6.5 Hz); ^{13}C NMR δ 17.84, 25.72, 40.85, 54.67, 126.21, 128.64; MS, m/z 150 (M^+), 149, 81, 69, 68 (100%), 67, 53, 41. Anal. Calcd for $C_6H_{12}O_2S$: C, 48.6; H, 8.2. Found: C, 48.3, H, 8.2.

3-Hexenyl methyl sulfone (**11b**): IR (neat) 3010, 2960, 2875, 1460, 1300, 1140, 970 cm^{-1}; NMR δ 0.95 (t, 3 H, J = 6.5 Hz), 1.80–2.20 (m, 2 H), 2.32–2.70 (m, 2 H), 2.88 (s, 3 H), 2.82–3.18 (m, 2 H), 5.25–5.80 (m, 2 H); MS, m/z 162 (M^+), 147, 121, 94, 82 (100%), 69, 68, 55, 41. Anal. Calcd for $C_7H_{14}O_2S$: C, 51.8; H, 8.7. Found: C, 51.7; H, 8.8.

Methyl 1-methyl-3-pentenyl Sulfone (**11c**): IR (neat) 3060, 3020, 2880, 1650, 470, 1300, 1130, 1110, 1020, 970 cm^{-1}; NMR δ 1.21–1.32 (d, 3 H, J = 7.5 Hz), 1.68 (d, 3 H, J = 6.0 Hz), 2.00–2.38 (m, 2 H), 2.50–2.78 (m, 1 H), 2.86 (s, 3 H), 5.25–5.70 (m, 2 H); MS, m/z 162 (M^+), 108, 82 (100%), 68. Anal. Calcd for $C_7H_{14}O_2S$: C, 51.8; H, 8.7. Found: C, 51.9; H, 8.6.

1-Ethyl-3-hexenyl methyl sulfone (**11d**): IR (neat) 3000, 2960, 2860, 1470, 1300, 1140, 970 cm^{-1}; NMR δ 0.98 (t, 3 H, J = 7.0 Hz), 1.08 (t, 3 H, J = 7.0 Hz), 1.40–2.20 (m, 4 H), 2.25–2.62 (m, 2 H), 2.65–2.85 (m, 1 H), 2.81 (s, 3 H), 5.17–5.82 (m, 2 H); MS, m/z 190 (M^+), 131, 110 (100%), 95, 81. Anal. Calcd for $C_9H_{18}O_2S$: C, 56.8; H, 9.5. Found: C, 56.4, H, 9.4.

1-Butyl-3-octenyl methyl sulfone (**11e**): IR (neat) 3000, 2950, 2900, 1480, 1130, 970 cm^{-1}; NMR δ 0.89 (t, 6 H, J = 6.5 Hz), 1.15–1.50 (m, 10 H), 1.75–2.10 (m, 2 H), 2.30–2.80 (m, 3 H), 2.80 (s, 3 H), 5.35–5.55 (m, 2 H); MS, m/z 246 (M^+), 242, 166 (100%), 100, 96. Anal. Calcd for $C_{13}H_{26}O_2S$: C, 63.4; H, 10.6. Found: C, 63.4; H, 10.7.

1-Heptyl-3-undecenyl methyl sulfone (**11f**): IR (neat) 2970, 2950, 2860, 1470, 1300, 1100, 970 cm^{-1}; NMR δ 0.85 (t, 6 H, J = 6.0 Hz), 1.12–1.48 (m, 22 H), 1.70–2.10 (m, 2 H), 2.36–2.80 (m, 3 H), 2.80 (s, 3 H), 5.35–5.60 (m, 2 H); MS, m/z 330 (M^+), 306, 250 (100%), 222, 194, 165, 152, 138, 124, 110, 96, 82. Anal. Calcd for $C_{19}H_{38}O_2S$: C, 69.0; H, 11.6. Found: 68.9; H, 11.8.

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Synthesis of a Sterically Impeded Analogue of the Carcinogenic Anti Diol Epoxide Metabolite of Benzo[*a*]pyrene

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Synthesis is described of *trans*-7,8-dihydroxy-7,8-dihydro-1-isopropylbenzo[*a*]pyrene and the corresponding bay region diol epoxide derivative, *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydro-1-isopropylbenzo[*a*]pyrene. These compounds are analogues of the proximate and ultimate carcinogenic metabolites of benzo[*a*]pyrene that differ from the latter in their possession of an isopropyl group in the 1-position remote from the ring that undergoes metabolic activation. These compounds were utilized in separate metabolism and DNA binding studies to test the hypothesis that intercalation of active diol epoxide metabolites into DNA is an essential step in the mechanism of PAH carcinogenesis.

Carcinogenic polycyclic aromatic hydrocarbons (PAH), such as benzo[*a*]pyrene, require activation by the P-450 microsomal enzymes to exhibit their mutagenic and carcinogenic potential.[1-3] Benzo[*a*]pyrene (BP) (**1a**) has been most intensively investigated, and its principal biologically active metabolite has been identified as (+)-*trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (**3a**), commonly referred to as (+)-*anti*-BPDE.[4] Considerable evidence has implicated DNA as the critical target,[1,3] and covalent binding of *anti*-BPDE to DNA and RNA in mammalian cells has been shown to take place principally on guanosine to form a 2-aminodeoxyguanosine adduct.[5,6] Kinetic studies are consistent with a mechanism

(1) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218; *Am. Sci.* **1982**, *70*, 386.
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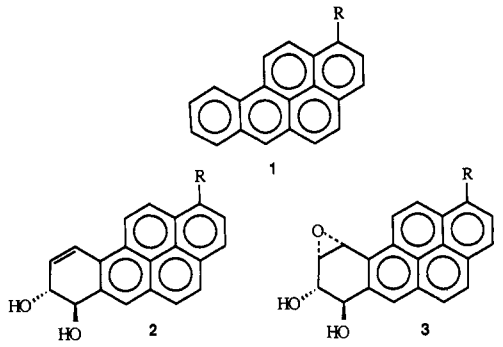
(3) Harvey, R. G. *Polycyclic Hydrocarbons and Carcinogenesis*; ACS Symp. Series No. 283; American Chemical Society: Washington DC, 1985.
(4) Weinstein, I. B.; Jeffrey, A. M.; Jennette, K. W.; Blobstein, S. H.; Harvey, R. G.; Harris, C.; Autrup, H.; Kasai, H.; Nakanishi, K. *Science (Washington D.C.)* **1976**, *193*, 592.

0022-3263/87/1952-2226$01.50/0



a: R = H; b: R = Me; c: R = Et; d: R = i-Pr; e: R = t-Bu.

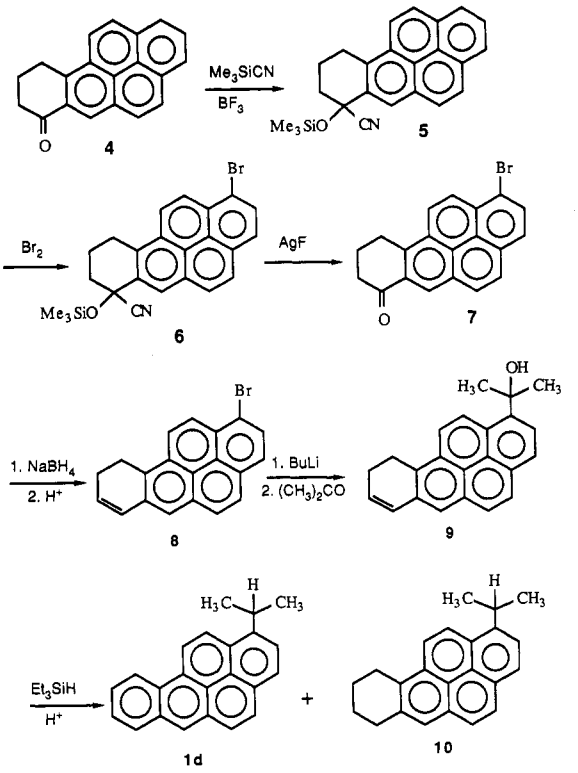
involving rapid initial formation of an *anti*-BPDE–DNA intercalation complex, followed by slow protonation to yield an intercalated triol carbocation intermediate that undergoes either hydration to tetrols (major path) or covalent binding to DNA (minor path) and rearrangement of this adduct to a more stable structure in which the PAH ring system is bound externally in the minor groove of the DNA helix.[7,8] However, it has not been possible to rule out an alternative mechanism in which adduct formation involves direct covalent interaction external to the DNA helix.

In order to probe the role of intercalation, the series of 1-alkylbenzo[a]pyrene derivatives (**1b–e**) (R = Me, Et, *i*-Pr, *t*-Bu) was synthesized and submitted for mutagenicity and tumorigenicity tests.[9] The findings demonstrated an inverse relation between alkyl group size and biological activity, consistent with intercalation of the active diol epoxide intermediates **3b–e** into DNA being an essential step in the mechanism of PAH carcinogenesis. The patterns of metabolism of **1b–e** by liver microsomes resembled that of BP and were independent of alkyl group size.[10] No significant decrease in the level of formation of the corresponding trans 7,8-dihydro diols **2b–e**, the potential metabolic precursors of **3b–e**, was observed, indicating that 1-alkyl substitution does not interfere with metabolic activation to the dihydro diol stage.[11] In order to confirm the tentative assignment of the dihydro diol metabolites and to obtain the corresponding diol epoxides for DNA binding studies, we undertook their synthesis. We now report the synthesis of the trans 7,8-dihydro diol of 1-isopropylbenzo[a]pyrene (**2d**) and its anti diol epoxide derivative **3d**.

Results and Discussion

The synthesis of **2d** is based upon the readily available 7,8,9,10-tetrahydrobenzo[a]pyren-7-one (**4**) (Scheme I).

Scheme I



Introduction of the isopropyl group into the 1-position of **4** was achieved via the 1-bromo intermediate **7**. Attempted synthesis of **7** by direct bromination of **4** afforded mainly 8-bromo-7,8,9,10-tetrahydrobenzo[a]pyren-7-one. Bromination in the 1-position of **4** was effected by conversion of the carbonyl group to its trimethylsilyl cyanide derivative **5** followed by treatment with bromine to yield the product **6**. The protecting group was removed by treatment of **6** with silver fluoride.

The site of substitution of the bromo group was proven to be the 1-position by conversion of **7** to 1-isopropylbenzo[a]pyrene (**1d**). Reduction of the carbonyl group of **7** with $NaBH_4$ followed by acid-catalyzed dehydration gave 1-bromo-9,10-dihydrobenzo[a]pyrene (**8**), which on treatment with *n*-butyllithium and acetone furnished the alkylated product **9**. Reduction of the alcohol function of **9** with triethylsilane in trifluoroacetic acid was accompanied by disproportionation of the dihydroaromatic ring to yield an mixture of 1-isopropylbenzo[a]pyrene (**1d**) and 7,8,9,10-tetrahydro-1-isopropylbenzo[a]pyrene (**10**). The physical properties and NMR spectrum of **1d** were identical with those of an authentic sample independently synthesized from 1-acetylbenzo[a]pyrene.[9]

Conversion of **9** to the trans 7,8-dihydro diol of 1-isopropylbenzo[a]pyrene was accomplished via the synthetic sequence depicted in Scheme II. Prevost reaction of **9** with silver benzoate/I_2 furnished the corresponding trans-dibenzoate **11**. Acid-catalyzed dehydration of the latter gave *trans*-7,8-bis(benzoyloxy)-1-isopropenyl-7,8,9,10-tetrahydrobenzo[a]pyrene, which was hydrogenated over a Pt catalyst to yield *trans*-7,8-bis(benzoyloxy)-1-isopropyl-7,8,9,10-tetrahydrobenzo[a]pyrene (**12**). Attempts to introduce a double bond into the 9,10-position of **12** with DDQ or NBS by the usual methods[12–14] were

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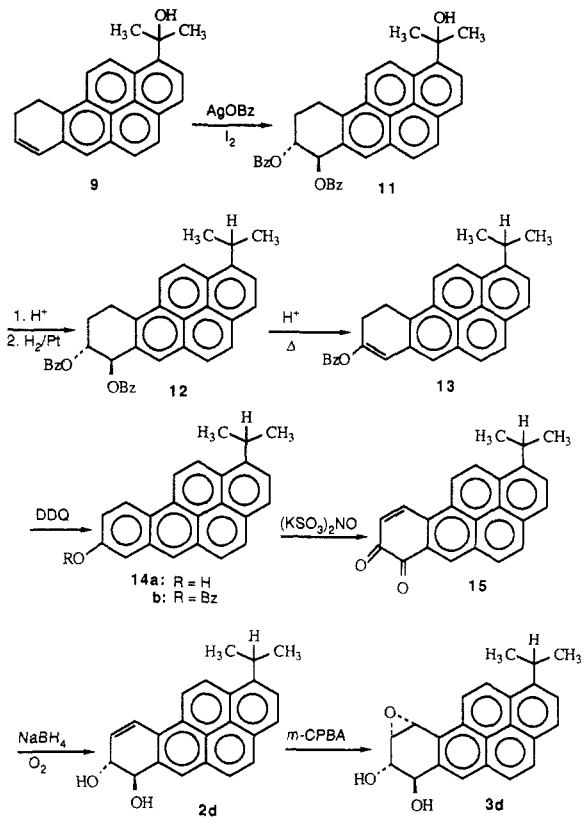
(10) The most notable differences were significantly decreased levels of phenolic metabolites in the substituted ring and formation of additional products arising from oxidation of the alkyl groups.

(11) In the absence of authentic standards, the structures of the dihydro diols and other oxidized metabolites of **1b–e** were assigned mainly on the basis of their HPLC relative retention times in comparison with the analogous known metabolites of BP and their UV spectra.

(12) This transformation is most efficiently achieved in the case of the unsubstituted parent BP compound by reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene: Harvey, R. G.; Fu, P. In *Polycyclic Hydrocarbons and Cancer*: Gelboin, H. V., Ts'o, P. O. P., Eds.; Academic Press: New York, 1978; pp 133–165.

Scheme II



unsuccessful, probably due to competitive attack by these reagents on the relatively more acidic benzylic position of the isopropyl group. Therefore, an alternative strategy for the synthesis of the 7,8-dihydro diol was adopted. This method entailed acid-catalyzed elimination of benzoic acid from **12** to form the enol benzoate derivative **13**, which was directly dehydrogenated with DDQ to yield the phenol benzoate **14b**. Acidic hydrolysis of **14b** furnished the free phenol which then was oxidized with Fremy's salt[13-15] in a two-phase benzene–water system in the presence of Adogen 464 to yield 1-isopropylbenzo[*a*]pyrene-7,8-dione (**15**) in good overall yield. Reduction of **15** with $NaBH_4$ in ethanol with oxygen gas bubbling through the reaction mixture took place stereospecifically to yield the trans dihydro diol **2d**. The utility of O_2 for the reoxidation of catechol byproducts back to quinones in reductions of this type has been previously demonstrated.[13-19]

The trans dihydro diol **2d** was transformed smoothly and stereospecifically to the desired anti diol epoxide derivative of 1-isopropylbenzo[*a*]pyrene (**3d**) on treatment with *m*-chloroperbenzoic acid at room temperature.

The high resolution NMR spectrum of the quinone **15**, the dihydro diol **2d**, and the diol epoxide **3d** were entirely consistent with these structural assignments. The NMR spectrum of **15** exhibited a pair of vinylic protons at δ 6.55 and δ 8.10, readily distinguishable by their characteristic coupling ($J_{9,10}$ = 10.4 Hz). These were assigned to H_9 and H_{10}, respectively. The shift of the H_{10} vinylic proton into the aromatic region is consistent with its interaction with

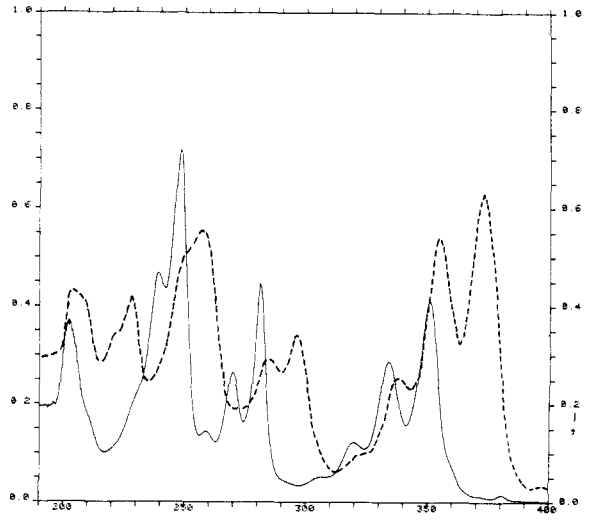


Figure 1. Ultraviolet spectra of *trans*-7,8-dihydroxy-7,8-dihydro-1-isopropylbenzo[*a*]pyrene (**2d**) (– – –) and *trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8-dihydro-1-isopropylbenzo[*a*]pyrene (**3d**) (—) in absolute ethanol.

H_{11} in the sterically crowded bay region. The H_6 proton appeared as a characteristic singlet at exceptionally low field (δ 8.77) due to the effect of the adjacent carbonyl function.

The most significant feature of the NMR spectrum of the dihydro diol **2d** was the relatively large value of the coupling constant of the carbinol protons ($J_{7,8}$ = 10.6 Hz), supporting existence of the dihydro diol predominantly in the diequatorial conformation.[20] This finding is consistent with previous observations for the dihydro diols of benzo[*a*]pyrene and other sterically unhindered dihydro diols.[20]

The UV spectra of **2d** and **3d**, which are required for biological studies, are presented in Figure 1.

Biological Investigations. These compounds have been utilized as authentic standards in biological studies to identify the products of metabolism and nucleic acid binding of 1-isopropylbenzo[*a*]pyrene. Comparison of HPLC retention time and UV absorption and fluorescence spectra of the synthetic **2d** with those of the metabolite of 1-isopropylbenzo[*a*]pyrene tentatively identified earlier as the 7,8-dihydro diol showed good agreement,[9] confirming its structural assignment. Metabolism of **2d** with rat liver microsomes gave as the principal product a mixture of isomeric tetrols that may be assumed to arise from hydrolysis of the diol epoxide metabolite **3d** (and/or its syn isomer), demonstrating that **2d** is capable of undergoing enzymatic activation to a bay-region diol epoxide. Therefore, the weak mutagenic and tumorigenic activity of 1-isopropylbenzo[*a*]pyrene[9] is unlikely to be due to its failure to undergo enzymatic activation to **3d**. The simplest interpretation of these observations is that the bulky isopropyl group of 1-isopropylbenzo[*a*]pyrene sterically retards intercalation of the active metabolite between the base pairs of the DNA helix. These findings strongly support the hypothesis that intercalation is an essential step in the mechanism of PAH carcinogenesis.

Further support for the critical role of intercalation is provided by DNA binding studies which indicate that **3d** binds covalently to DNA much less efficiently than the parent unalkylated compound *anti*-BPDE.[21]

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Experimental Section

Materials and Methods. 7,8,9,10-Tetrahydrobenzo[a]pyren-7-one (4) was synthesized by cyclization of 4-(1-pyrenyl)butanoic acid (Aldrich Chemical Co.) in liquid HF by the method described.[22] Fremy's salt [$(KSO_3)_2NO$] was freshly prepared according to the literature method.[23] 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was recrystallized from benzene. *m*-Chloroperbenzoic acid was purified by washing with pH 7.5 phosphate buffer and drying under reduced pressure. Tetrahydrofuran (THF) was freshly distilled from $LiAlH_4$. Ether was dried over sodium.

The NMR spectra were obtained on a Varian EM 360 spectrometer or the University of Chicago 500-MHz NMR spectrometer in $CDCl_3$ or Me_2SO-d_6 with tetramethylsilane as an internal standard. Integration was consistent with the molecular structural assignments. The ultraviolet spectra were obtained on the Perkin-Elmer Lamda 5 spectrometer in ethanol unless specified otherwise. All new compounds gave microanalyses for C, H within ±0.4% and/or mass spectra consistent with the assigned structures.

7-Cyano-7-(trimethylsiloxy)-7,8,9,10-tetrahydrobenzo[a]pyrene (5). *All operations were conducted in a well-ventilated hood.* In a flame-dried flask were placed 31.44 g (0.115 mol) of 4 and 64 mL of trimethylsilyl cyanide. Five drops of BF_3 etherate was added, and the solution was heated at 100 °C for 1 h under N_2. The solution was allowed to cool and then 400 mL of water was added, and the mixture was stirred for an additional 30 min. The solid precipitate was filtered, washed well with water, and dried to yield 5 (42.3 g, 98%): NMR δ 0.25 (s, 9, Me_3Si), 2.41 (m, 2, H_9), 2.82 (t, 2, H_8), 3.55 (t, 2, H_{10}), 8.01, 8.17 (apparent singlets, 7, aromatic), 8.47 (s, 1, H_6).

1-Bromo-7,8,9,10-tetrahydrobenzo[a]pyren-7-one (7). A solution of Br_2 in 250 mL of CCl_4 was added dropwise over 3.5 h to a stirred solution of 5 (10.00 g, 27 mmol) in 600 mL of CH_2Cl_2. After being stirred for an additional hour, the solution was washed twice with water. The organic layer was dried over $MgSO_4$, and the solvents were removed under reduced pressure. The crude 6 (11.77 g) was dissolved in THF (30 mL), water (30 mL) and AgF (4.5 g, 35 mmol) were added, and the mixture was stirred for 30 min. The silver salts were filtered, the filtrate was diluted with 300 mL of benzene, washed twice with water, and dried, and the solvent was removed. The residue (9.02 g) was chromatographed on 270 g of Florisil. Elution with benzene–ether (95:5) gave a solid product, which on recrystallization from benzene yielded 7 (4.13 g) in two crops, mp 212–214 °C and 209–213 °C, respectively.

1-Bromo-9,10-dihydrobenzo[a]pyrene (8). Sodium borohydride (3.38 g, 89 mmol) was added in small portions over 1 h to a solution of 7 (3.38 g, 9.7 mmol) in 500 mL of THF and 200 mL of methanol. Stirring was continued for 2 h more, then most of the solvent was removed, water was added, and the resulting solid was filtered and dried. This product (3.44 g) was taken up in benzene (250 mL) and heated at reflux with 250 mg of *p*-toluenesulfonic acid for 1 h. The solution was cooled, washed with $NaHCO_3$ solution, dried, concentrated under reduced pressure to a small volume, and filtered through a column of Florisil (30 g). Elution with benzene (300 mL) and evaporation of the solvent gave a crystalline solid (3.13 g) that was recrystallized from benzene-ether to yield pure 8 (2.71 g, 84% based on 7): mp 146–147 °C; NMR δ 2.51 (m, 2, H_9), 3.42, (t, 2, H_{10}), 6.18 (m, 1, H_8), 6.81 (d, 1, H_7), 7.30–8.09 (m, 6, Ar), 8.32 (s, 1, H_6).

1-(2-Hydroxy-2-propyl)-9,10-dihydrobenzo[a]pyrene (9). To a solution of *n*-butyllithium (19.6 mL of 2.5 M, 48.8 mmol) in 225 mL of dry THF at −78 °C under N_2 was added 8 (7.39 g, 22 mmol). The dark solution was stirred for 45 min, and then 3.92 mL (50 mmol) of dry acetone was added dropwise from a syringe. Stirring was continued for an additional 3 h at low temperature and 45 min at room temperature. Then water was added, and the mixture was extracted with CH_2Cl_2. The extract was dried and the solvent was evaporated under reduced pressure. Chromatography of the residue (7.38 g) on Florisil furnished on elution with benzene–ether (9:1) compound 9 (5.91 g, 85%), which failed to crystallize: NMR δ 1.88 (s, 6, CH_3), 2.43 (m, 2, H_9), 3.38 (t, 2, H_{10}), 6.17 (m, 1, H_8), 6.77 (d, 1, H_7), 7.34–9.09 (m, 7, Ar).

1-Isopropylbenzo[a]pyrene (1d) and 1-Isopropyl-7,8,9,10-tetrahydrobenzo[a]pyrene (10). To a solution of 9 (1.05 g, 3.36 mmol) in dry CH_2Cl_2 (25 mL) were added Et_3SiH (3.7 mmol) and F_3CCO_2H (2.85 mL, 37 mmol), and the resulting dark solution was stirred for 2 h and allowed to stand for 22 h. The solution was poured into 100 mL of saturated $NaHCO_3$ solution and dried, and the solvent was removed. The residue was chromatographed on Florisil. Elution with hexane gave initially following recrystallization from hexane 382 mg of 10: mp 136–137 °C; NMR δ 1.55 (d, 6, $(CH_3)_2CH$), 1.86–2.10 (m, 4, $H_{8,9}$), 3.29 (t, 4, $H_{7,10}$), 3.81–4.14 (m, 1, methine), 7.65–9.00 (m, 7, Ar). Later hexane eluates gave following recrystallization from hexane 114 mg of 1d: mp 134.5–135 °C (lit.[9] mp 135–136 °C, lit.[24] mp 128–130 °C), mmp with authentic 1d 135–136 °C: NMR δ 1.55 (d, 6, $(CH_3)_2CH$), 3.73–4.16 (m, 1, methine), 7.78–8.98 (m, 11, Ar); this spectrum was identical with that of authentic 1d.

***trans*-7,8-Dihydroxy-1-(2-hydroxy-2-propyl)-7,8,9,10-tetrahydrobenzo[a]pyrene Dibenzoate (11).** Dry silver benzoate (7.74 g, 34 mmol) and I_2 (4.2 g, 16.6 mmol) were heated in 380 mL of dry benzene for 20 min. A solution of 9 (4.79 g, 15 mmol) in 100 mL of dry benzene was added and the mixture was heated at reflux for 4 h. After cooling, the reaction mixture was filtered, and the filtrate was concentrated to about 50 mL. The precipitate was filtered to yield 11 (5.14 g, 61%): mp 192–194 °C; NMR δ 1.94 (s, 6, CH_3), 2.31–2.51 (m, 2, H_9), 3.55 (t, 2, H_{10}), 5.42–5.72 (m, 1, H_8), 6.61 (d, 1, H_7), 7.40–9.12 (m, 17, Ar).

***trans*-7,8-Dihydroxy-1-isopropyl-7,8,9,10-tetrahydrobenzo[a]pyrene Dibenzoate (12).** A solution of 11 (4.5 g) and *p*-toluenesulfonic acid (300 mg) in benzene (300 mL) was heated at reflux for 30 min. After cooling, the solution was washed with 5% $NaHCO_3$ solution, dried, concentrated to a small volume, and adsorbed on a column of Florisil (40 g). Elution with benzene (400 mL) gave, after evaporation of the solvent, *trans*-7,8-dihydroxy-1-isopropyl-7,8,9,10-tetrahydrobenzo[a]pyrene dibenzoate (4.02 g), mp 195–197 °C. The latter was dissolved in 225 mL of ethyl acetate and hydrogenated over a 10% Pt/C catalyst (2 g) for 72 h. The catalyst was filtered and the filtrate evaporated to dryness to yield 2.80 g of product. The catalyst was extracted twice with boiling EtOAc (100 mL) to give another 0.98 g of product. Recrystallization of the combined product from EtOAc furnished pure 12 (3.42 g, 78%): mp 186.5–187.5 °C; NMR δ 1.54 (d, 6, CH_3), 2.50–2.73 (m, 2, H_9), 3.70 (t, 2, H_{10}), 4.00–4.23 (m, 1, methine), 5.62–5.92 (m, 1, H_8), 6.96 (d, 1, H_7), 7.42–8.47 (m, 17, Ar).

1-Isopropylbenzo[a]pyren-8-ol (14a). A solution of 12 (3.0 g) and *p*-toluenesulfonic acid (200 mg) in benzene (200 mL) was heated at reflux for 24 h. The cold solution was washed with 5% $NaHCO_3$ solution, dried, concentrated to a small volume, and adsorbed on a column of Florisil (30 g). Elution with benzene (300 mL) and evaporation to dryness gave 13 (2.2 g), which was dehydrogenated directly with DDQ (1.20 g, 5.3 mmol) in refluxing benzene (150 mL) for 30 min under N_2. Conventional workup provided 2.08 g of a solid residue, which was chromatographed on Florisil (65 g). Elution with hexane–benzene (1:1) provided 1.56 g of material that was crystallized from EtOAc to yield 14b (1.14 g, 50%): mp 198–198.5 °C; NMR δ 1.54 (d, 6, CH_3), 3.89–4.16 (m, 1, methine), 7.37–9.03 (m, 15, Ar).

A solution of 14b (1.5 g) was heated at reflux in 150 mL of glacial acetic acid and 18 mL of concentrated HCl for 40 min under N_2. The product was worked up conventionally and adsorbed on a short column of Florisil (20 g). Elution with CH_2Cl_2 (400 mL) yielded 14a (592 mg, 72%): mp 215–216 °C.

1-Isopropylbenzo[a]pyrene-7,8-dione (15). To a vigorously stirred solution of 14a (590 mg, 1.9 mmol) in 100 mL of benzene were added a solution of freshly prepared Fremy's salt (2.4 g), in 100 mL of $^1/_6$ M KH_2PO_4 and 72 mL of water and 5 drops of Adogen 464. The mixture was stirred for 1 h and then extracted 3 times with CH_2Cl_2. The combined extracts were dried and evaporated to dryness. The residue was triturated with benzene and the undissolved solid (516 mg) was recrystallized from benzene to yield 15 (442 mg, 72%): mp 251–252 °C; NMR (500 MHz) δ 1.55 (d, 6, CH_3, J = 8 Hz), 4.09 (m, 1, methine), 6.55 (d, 1, H_9, $J_{9,10}$ = 10.4 Hz), 8.10 (d, 1, $J_{9,10}$ = 10.3 Hz), 8.0–8.5 (m, 6, Ar), 8.77 (s, 1, H_6).

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***trans*-7,8-Dihydroxy-7,8-dihydro-1-isopropylbenzo[*a*]pyrene (2d).** Oxygen gas was bubbled into a stirred solution of **15** (400 mg, 1.23 mmol) and $NaBH_4$ (1.5 g, 40 mmol) in 200 mL of ethanol for 8 h. The solution was partitioned between CH_2Cl_2 and water, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated to a small volume until the dihydro diol **2d** began to crystallize. Filtration gave **2d** (352 mg, 87%): mp 211-212 °C dec, NMR (500 MHz) δ 1.48 (d, 6, CH_3), 4.07 (m, 1, methine), 4.48 (d, 1, H_7), 4.91 (m, 1, H_8, $J_{7,8}$ = 10.6 Hz), 6.22 (m, 1, H_9, $J_{9,10}$ = 10.1 Hz), 7.50 (d, 1, H_{10}, $J_{9,10}$ = 10.2 Hz), 7.9-8.5 (m, 7, Ar); UV λ_{max} (ethanol) 373 nm (ϵ 48 260), 354 (40 800), 337 (20 500), 295 (27 900), 283 (24 960), 255 (45 800).

***trans*-7,8-Dihydroxy-*anti*-9,10-epoxy-1-isopropyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene (3d).** A solution of **2d** (100 mg, 0.3 mmol) in anhydrous THF (20 mL) was stirred with *m*-chloroperbenzoic acid (540 mg, 3 mmol) for 2 h under N_2. The solution was diluted with ether and washed twice with ice-cold 2 N NaOH and once with ice water. The solvent was removed under reduced pressure at 40 °C bath temperature. The solid residue (101 mg) was triturated with dry ether to yield **3d** (61 mg): mp 175-177 °C; NMR (500 MHz) (Me_2SO-d_6) δ 1.49 (d, 6, CH_3), 4.09 (m, 1, methine), 4.13 (m, 1, H_8), 4.26 (m, 1, H_9), 4.91 (m, 1, H_7), 5.03 (dd, 1, H_{10}), 7.99-8.58 (m, 7, Ar); UV λ_{max} (ethanol) 350 nm (ϵ 34 700), 334 (24 200), 281 (37 500), 269 (22 350), 248 (60 250), 239 (39 400), 202 (31 260).

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Registry No. **1d**, 4648-83-3; **2d**, 107616-95-5; **3d**, 107616-96-6; **4**, 3331-46-2; **5**, 107616-82-0; **6**, 107616-83-1; **7**, 107616-84-2; **8**, 107616-85-3; **9**, 107616-86-4; **10**, 107616-87-5; **11**, 107616-88-6; **12**, 107616-90-0; **13**, 107616-91-1; **14a**, 107616-93-3; **14b**, 107616-92-2; **15**, 107616-94-4; *trans*-7,8-dihydroxy-1-isopropenyl-7,8,9,10-tetrahydrobenzo[*a*]pyrene dibenzoate, 107616-89-7.

Ruthenium-Catalyzed Selective Addition of Carboxylic Acids to Alkynes. A Novel Synthesis of Enol Esters

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Carboxylic acids react with alkynes in the presence of a catalytic amount of bis(η^5-cyclooctadienyl)ruthenium/trialkylphosphine/maleic anhydride in toluene at 60-80 °C to give enol esters having a terminal methylene group in good to excellent yields with high regioselectivity. The deuterium distributions in the products of the reaction of acetic acid-*d* with 1-hexyne and ethyl propargyl carbonate were examined. Kinetic measurements revealed that the rate has first-order dependence on carboxylic acid, alkyne, and the initial concentration of the ruthenium catalyst.

Introduction

Enol esters are well-known intermediates for carbon-carbon bond formation in organic synthesis.[1] Three major methods are available for the synthesis of enol carboxylates: (1) the treatment of aldehydes or ketones under either acid or basic conditions with appropriate acid anhydride or chloride;[2] (2) the acetoxylation of olefins promoted by palladium acetate;[3,4] (3) the addition reaction of carboxylic acids to alkynes,[5] in which mercury salts are very useful catalysts. However, since the mercury salts are very toxic, development of safer catalysts has been required. On the other hand, characteristic organic syntheses catalyzed by ruthenium complexes have been developed in recent years.[6] Rotem and Shvo reported the first example of the addition of carboxylic acids to acetylenes catalyzed by $Ru_3(CO)_{12}$.[6b] In the course of our study on characteristic ruthenium-catalyzed organic syntheses,[7] a novel selective addition of carboxylic acids to alkynes catalyzed by bis(η^5-cyclooctadienyl)ruthenium (A)/PR_3/maleic anhydride (eq 1) was found and reported briefly.[7a,b] In this report, the scope of this reaction is described in detail. On the basis of kinetic studies and reactions with

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