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Supplementary Material Available: Spectral and analytical data for the new compounds (1 page). Ordering information is given on any current masthead page.

Synthesis of the Phenolic Derivatives of Highly Tumorigenic *trans*-7,8-Dihydroxy-7,8-dihydrobenzo[*a*]pyrene

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Two isomeric phenolic derivatives of *trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene (**42**), 3,7,8-trihydroxy-*trans*-7,8-dihydrobenzo[*a*]pyrene (**40**), and 1,7,8-trihydroxy-*trans*-7,8-dihydrobenzo[*a*]pyrene (**41**), have been prepared in order to probe their relevance in the carcinogenesis of benzo[*a*]pyrene. Two methods have been developed for the synthesis of the key intermediates 3-acetoxy-9,10-dihydrobenzo[*a*]pyrene (**25**) and 1-acetoxy-9,10-dihydrobenzo[*a*]pyrene (**26**). In one method, known 1-methoxypyrene-6-carboxaldehyde (**5**) and 1-methoxypyrene-8-carboxaldehyde (**6**) were homologated, and the resulting 4-(methoxypyrene)butanoic acids **14** and **18** were cyclized with polyphosphoric acid (PPA) at 105 °C to produce 3-methoxy- and 1-methoxy-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**19** and **21**, respectively). The PPA cyclization at low temperature (90 °C) produced primarily the undesired seven-membered ring ketones **23** and **24**, respectively. Demethylation of methoxy ketones **19** and **21** followed by successive reduction, dehydration, and acetylation afforded the key intermediates **25** and **26**. The second method involves bromination of the trimethylsilyl cyanide derivative **27** of 7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one followed by removal of the protecting group. 1-Bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**28**) was obtained as a major and 3-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**29**) as a minor products of this synthesis. These bromo ketones **28** and **29** were, subsequently, used to synthesize the key intermediates **25** and **26**, respectively. Prevost reaction of the acetoxyalkenes **25** and **26** followed by selective dehydrogenation of the resulting tetrahydro triesters **36** and **37** with DDQ and base-catalyzed hydrolysis produced **40** and **41**, respectively.

The burgeoning interest in studying the mechanism of carcinogenesis of polynuclear aromatic hydrocarbons (PAHs) stems from their ubiquitous occurrence in the environment and their carcinogenic properties.[3,4] It is now well recognized that PAHs are metabolized to highly reactive intermediates that are responsible for the cytotoxic, mutagenic, and carcinogenic effects of PAHs. Diol epoxide derivatives, especially bay-region diol epoxides, have been implicated as ultimate carcinogens of a number of PAHs.[5,6] However, the involvement of reactive intermediates other than diol epoxides in the carcinogenesis of PAHs has not been ruled out.[4] Therefore, it is indispensable that other reactive metabolites of PAHs, which are tentatively identified, be completely characterized and studied for their possible involvement in the metabolic activation of PAHs.

Recent studies[7] with PAHs have shown that these hydrocarbons can be metabolized to a new class of reactive intermediates which are tentatively characterized as the phenolic derivatives of diol epoxides. As reported for diol epoxides,[5,6] these derivatives are also capable of binding covalently to nuclear macromolecules and show mutagenic and cell transforming activities.[8-10] Since the covalent binding of phenolic diol epoxides of PAHs to nuclear macromolecules may also play a significant role in determining the susceptibilities of normal cells to be transformed to cancer cells, these phenolic diol epoxides and their precursors, phenolic dihydrodiols, are needed to study their biological relevance in PAH-induced carcinogenesis.

In the present study, we synthesized 1-hydroxy-*trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene and 3-hydroxy-*trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene, which are the suspected metabolites of the environmental carcinogen benzo[*a*]pyrene (BP, **1**)[11] and precursors to the highly reactive phenolic bay-region diol epoxides **2** and **3**. These phenolic diol epoxides have recently been tentatively characterized as the metabolites of *anti-trans*-7,8-dihydroxy-9,10-epoxy-7,8,9,10-tetrahydro-BP (**4**).[12,13] The

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(2) Adjunct Associate Research Professor in the Deparment of Chemistry, SUNY College, Buffalo, NY.

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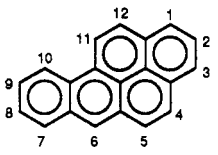

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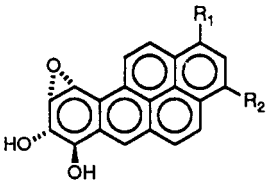


2: R_1 = OH; R_2 = H
3: R_1 = H; R_2 = OH
4: R_1 = R_2 = H

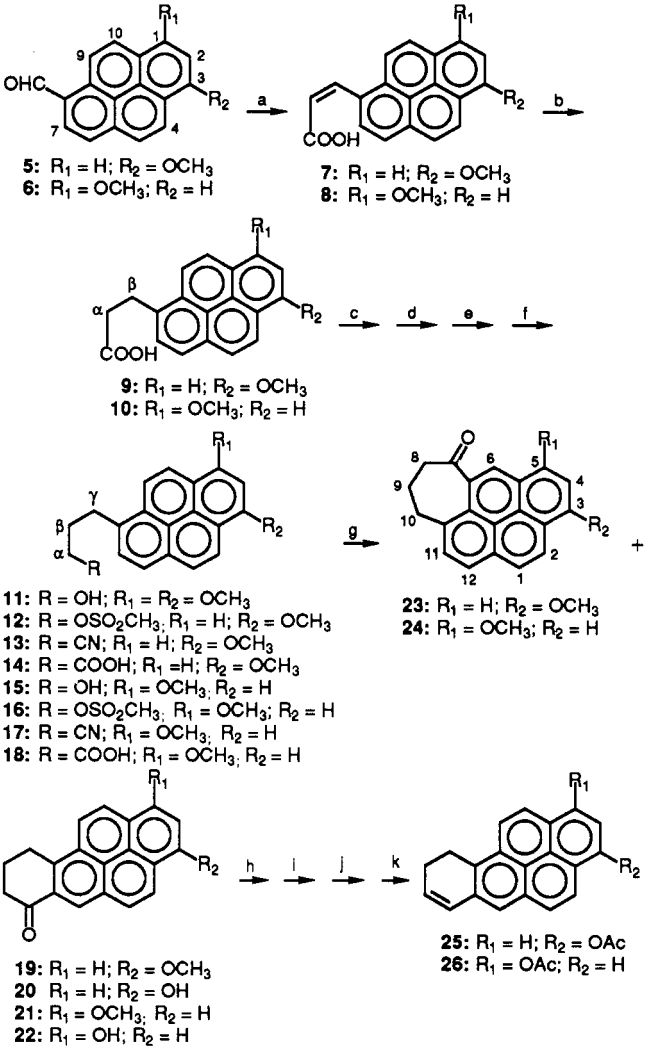
presence of hydroxyl function at the 1- or 3-position is expected to further stabilize the carbonium ion at the C-10 position of **2** and **3**, therefore making these molecules theoretically more reactive than **4**.

Results and Discussion

The procedures successfully used in the past in the synthesis of *trans*-7,8-dihydro-7,8-dihydroxy-BP (**42**) requires 9,10-dihydro-BP as a starting point.[14] Therefore, 3-acetoxy-9,10-dihydro-BP (**25**) and 1-acetoxy-9,10-dihydro-BP (**26**) were selected as starting intermediates for the synthesis of **40** and **41**, respectively. A detail synthesis of these acetoxyalkenes has not been reported previously.[15] We have used two different procedures for the synthesis of these alkenes. In one procedure, 1-methoxy 6-carboxaldehyde (**5**)[16] and 1-methoxy 8-carboxaldehyde (**6**)[16] were converted to the corresponding acetoxyalkenes **25** and **26** as shown in Scheme I The reaction of the corresponding aldehydes **5** and **6** with malonic acid in refluxing pyridine and a trace of piperidine went smoothly to produce 3-(1-methoxypyren-6-yl)-2-propenoic acid (**7**) and 3-(1-methoxypyren-8-yl)-2-propenoic acid (**8**) in quantitative yield. These α,β-unsaturated acids **7** and **8** were catalytically hydrogenated to **9** and **10**, respectively. Homologation of the propanoic acid derivatives **9** and **10** in four convenient steps (see Scheme I) produced the corresponding butanoic acid derivatives **14** and **18** in overall 75–80% yields.

We expected that cycloacylation reaction of **14** and **18** with polyphosphoric acid (PPA) at elevated temperature would provide the corresponding methoxy ketones **19** and **21**, by analogy to the results with the similar cyclization of other 4-arylbutanoic acids to cyclic ketones.[17,18] However, the results were erratic, especially with **14**, and produce variable yields. For example, cycloacylation of **14** with 50 times by weight of PPA at 85–90 °C produced mostly undesired seven-membered ketone 3-methoxy-7-oxo-7,8,9,10-tetrahydrocyclohepta[*cd*]pyrene (**23**). However, when the temperature was raised to 100–105 °C and stirring was continued to 2.5 h, the desired 3-methoxy-7-oxo-7,8,9,10-tetrahydro-BP (**19**) was isolated only in 20% yield. It appeared that with longer reaction time and higher temperature, the seven-membered ketone **23** rearranged to six-membered ketone **19**, but the reaction was always accompanied by the formation of the variable amounts of ethyl acetate insoluble polymeric products. The use of about a 100-fold excess of PPA, however, improved the yield of the desired six-membered ketone **19** to 40–53%. On the other hand, the cycloacylation of **18** with PPA at 100–105 °C for 1 h produced the desired ketone **21** in 70–75% yield. When the temperature was low (85–90 °C) and/or the reaction time was 30 min, the desired product was accompanied by the seven-membered ketone **24**.

Scheme I[a]



5: R_1 = H; R_2 = OCH_3
6: R_1 = OCH_3; R_2 = H
7: R_1 = H; R_2 = OCH_3
8: R_1 = OCH_3; R_2 = H
9: R_1 = H; R_2 = OCH_3
10: R_1 = OCH_3; R_2 = H
11: R = OH; R_1 = R_2 = OCH_3
12: R = OSO_2CH_3; R_1 = H; R_2 = OCH_3
13: R = CN; R_1 = H; R_2 = OCH_3
14: R = COOH; R_1 = H; R_2 = OCH_3
15: R = OH; R_1 = OCH_3; R_2 = H
16: R = OSO_2CH_3; R_1 = OCH_3; R_2 = H
17: R = CN; R_1 = OCH_3; R_2 = H
18: R = COOH; R_1 = OCH_3; R_2 = H
23: R_1 = H; R_2 = OCH_3
24: R_1 = OCH_3; R_2 = H
19: R_1 = H; R_2 = OCH_3
20 R_1 = H; R_2 = OH
21: R_1 = OCH_3; R_2 = H
22: R_1 = OH; R_2 = H
25: R_1 = H; R_2 = OAc
26: R_1 = OAc; R_2 = H

[a] Reagents: (a) Malonic acid/pyridine/morpholine; (b) H_2/Pd–C; (c) $LiAlH_4$/THF; (d) $MeSO_2Cl$–Et_3N/CH_2Cl_2; (e) KCN–aliquat 336/C_6H_6/H_2O; (f) KOH/$(CH_2OH)_2$; (g) PPA; (h) HBr/AcOH; (i) $NaBH_4$/EtOH; (j) *p*-TsOH/C_6H_6; (k) Ac_2O/pyridine.

A comparison of the nuclear magnetic resonance spectrum (NMR) of seven-membered ketones **23** and **24** and six-membered ring ketones **19** and **21** with that of 7,8,9,10-tetrahydro-BP-7-one allowed their assignments as six-membered ring and seven-membered ring ketones. Thus, the chemical shift of H_6, H_8, H_9, and H_{10} of six-membered ketones **19** and **21** were virtually identical with those of the corresponding protons of known 7,8,9,10-tetrahydro-BP-7-one. However, the chemical shift of the H-10 triplet of the six-membered ketones **19** and **21** was 0.35 ppm downfield compared to that of the H_{10} triplet of the corresponding seven-membered ketones **23** and **24** (see Scheme I for structures and numbering schemes). The downfield shifts of the signal for H_{10} of the six-membered ketones compared to that of the seven-membered ketones was due to the edge deshielding by the proximate aromatic ring, since H_{10} of the six-membered ketones forms part of a "bay-region" in the hydrocarbon.[19] Furthermore, because of the presence of the methoxy substituent at the peri position (C-5), **24** showed an H_6 singlet that was 0.58

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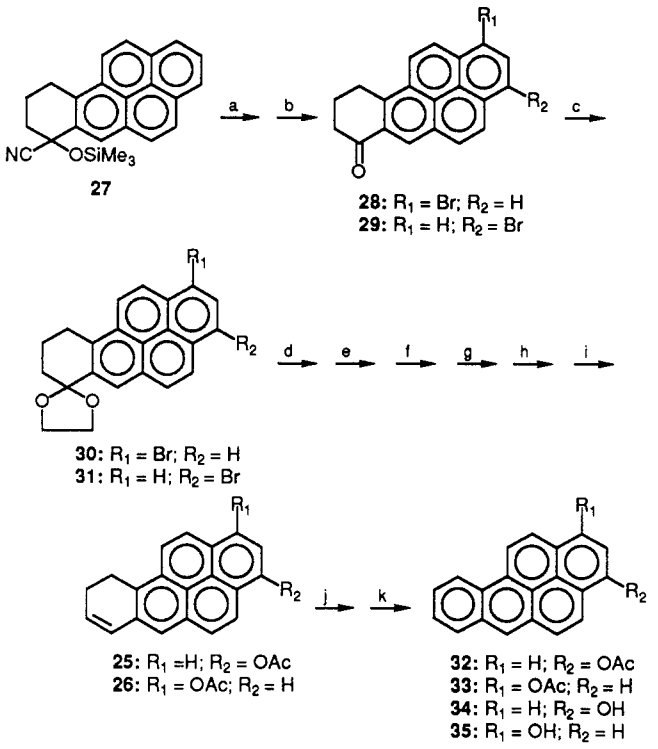
Scheme II[a]



[a] Reagents: (a) $Br_2/CH_2Cl_2/CCl_4$; (b) $AgF/THF/H_2O$; (c) $(CH_2OH)_2$-*p*-$TsOH/C_6H_6$; (d) Mg-$(CH_2Br)_2$/THF; (e) B_2H_6; (f) $H_2O_2/NaOH$; (g) $NaBH_4$/EtOH; (h) *p*-$TsOH/C_6H_6$; (i) Ac_2O/pyridine; (j) DDQ/dioxane; (k) K_2CO_3/THF/MeOH.

ppm downfield compared to that of isomeric **23**.

The kinetically controlled formation of the seven-membered ring ketones from the corresponding acids is understandable from the previous studies.[20,21] Most likely, the electron-donating property of methoxyl group at position 1 of the acids **14** and **18** activates the positions 5 and 9 for electrophilic substitution reactions, and, consequently, seven-membered ketones are produced. Since seven-membered ring ketones are isomerizable under the more forcing condition to six-membered ketones, it is likely that seven-membered ring ketones **23** and **24** are kinetic products of cyclization, whereas the six-membered ring ketones **19** and **21** are the thermodynamically stable products of cyclization.

The successive demethylation (HBr/AcOH), reduction ($NaBH_4$/EtOH), dehydration (H^+/benzene), and acetylation (Ac_2O/pyridine) of the six-membered ring ketones **19** and **21** finally produced the corresponding acetoxyalkenes **25** and **26** in 44–52% overall yields.

Concurrently, we have also developed a second procedure for the synthesis of acetoxyalkenes **25** and **26** (see Scheme II). In this alternate procedure, 7,8,9,10-tetrahydro-BP-7-one, as trimethylsilyl cyanide derivative **27**, was brominated and then deprotected to the free ketone by using the procedure of Pataki and Harvey[22] to produce a mixture of compounds which showed two major spots on silica gel plate with benzene as developing solvent (R_fs ~0.6 and 0.2). The ^1H NMR spectrum of the relatively nonpolar product(s), separated by column chromatography over dry column grade silica gel with benzene as eluant, indicated that it was the side chain brominated product(s) of 7,8,9,10-tetrahydro-BP-7-one. However, the relatively polar compound(s) which was eluted later from the column with benzene, contained only pyrene ring brominated derivative(s) of 7,8,9,10-tetrahydro-BP-7-one. Fractional recrystallization of this later product yielded pure 1-bromo-7,8,9,10-tetrahydro-BP-7-one (**28**). The product isolated from the mother liquor was found to be a mixture of two compounds on silica gel TLC (15% EtOAc–hexane). Therefore, further chromatography of the product isolated from the mother liquor over dry column-grade silica gel, using 12% ethyl acetate–cyclohexane as developing solvent, produced additional **28** and another product identified as 3-bromo-7,8,9,10-tetrahydro-BP-7-one (**29**). Because of the very small differences between the R_fs and the low solubility of the bromo ketones **28** and **29**, the minor compound **29** was difficult to separate from the mixture. However, by repeated chromatography of the mixture of **28** and **29**, we were able to obtain pure **29**. The overall yields of **28** and **29** from **27** were approximately 37 and 7%, respectively. The remaining mixture (~9%) eluted from the column contained **29** as a major compound.

The treatment of the ethylene ketals **30** and **31** obtained from the bromo ketones **28** and **29**, respectively, with magnesium and diborane in the presence of the traces of ethylene dibromide resulted in a borane complex (Scheme II), which after being treated with alkaline hydrogen peroxide produced the corresponding hydroxy ketones **22** and **20** (see Scheme I for structures), respectively. The reaction which consisted of the formation of borane complex required absolute anhydrous condition and a slow addition of the ethylene dibromide solution during the reaction period. Otherwise, either reaction did not occur or a significant amount of 7,8,9,10-tetrahydro-BP-7-one was isolated from the mixture as a byproduct. The individual hydroxy ketones **22** and **20** were converted to the corresponding acetoxyalkenes **26** and **25** as shown in Scheme I. The overall yields of acetoxyalkenes based on ethylene ketals were 44–63%. The acetoxyalkene **25** obtained from bromo ketone **29** and from methoxy ketone **19**, respectively, has identical ^1H NMR, melting point, and TLC profiles. Furthermore **25** and **26** were dehydrogenated (DDQ/dioxane) and deacetylated (K_2CO_3), successively, to the corresponding phenols **34** and **35**, which exhibited UV spectra identical with those of authentic[23] 3-hydroxy-BP and 1-hydroxy-BP, respectively.

Both Scheme I and Scheme II provide a procedure for the synthesis of 3-acetoxy-9,10-dihydro-BP (**25**) and 1-acetoxy-9,10-dihydro-BP (**26**). However, extremely low regioselectivity in the bromination reaction that produces **29** in low yield (see Scheme II) renders Scheme I relatively more attractive for the synthesis of **25**.

Synthesis of 3-Hydroxy-*trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene (40) and 1-Hydroxy-*trans*-7,8-dihydro-7,8-dihydroxybenzo[*a*]pyrene (41). The acetoxyalkenes **25** and **26** were treated with silver benzoate and iodine (Prevost reagent) to produce *trans*-tetrahydrodibenzoates **36** and **37**, respectively, in 65–73% yield (Scheme III). The reaction was rapid and generally over in 1 h. The major identifiable byproduct of the reaction were *trans*-dihydrodibenzoates **38** and **39**, respectively. These products were formed only when the larger proportions of iodine in the Prevost reagent were used. The tetrahydrodibenzoates **36** and **37** were treated with an excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing dioxane resulted in dihydrodibenzoates **38** and **39**, respectively. Yields of the dihydrodibenzoates **38** and

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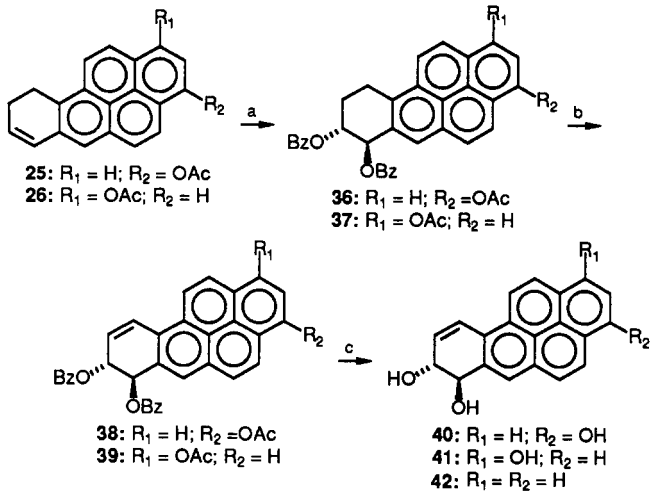
(23) Authentic 1-hydroxy-1 and 3-hydroxy-BP were obtained from reference repository at the National Cancer Institute, Bethesda, MD.

Scheme III[a]



[a] Reagents: (a) $BzOAg-I_2/C_6H_6$; (b) DDQ/dioxane; (c) NaOH/THF/MeOh.

39 were 63–74%. Conversion of dihydrodibenzoates **38** and **39** to phenolic dihydrodiols **40** and **41**, respectively, was effected in THF–MeOH using sodium hydroxide. Since the phenolic dihydrodiols were extremely sensitive to aereal oxidation under alkaline condition, all the solvents and reagents used in these reactions were flushed with oxygen-free argon. Under these conditions, the yield of the phenolic dihydrodiols was 80%.

The structures of phenolic dihydrodiols **40** and **41** and their corresponding synthetic intermediates were firmly established by their spectral properties, most revealing of which was the ^1H NMR spectrum (see the Experimental Section). The chemical shifts and the coupling constants of nonaromatic protons of **40** and **41** were virtually identical with those of the nonphenolic dihydrodiol, *trans*-7,8-dihydro-7,8-dihydroxy-BP (**42**).[24] Furthermore, we observed that the ^1H NMR data of **40** and its synthetic intermediates were nearly identical with that of **41** and its synthetic intermediates with respect to H_2, H_7, H_8, H_9, and H_{10} protons. However, the overall pattern of the chemical shifts of the remaining aromatic protons of the pyrene nucleus of 1-substituted BP derivatives was distinct from that of the corresponding 3-substituted BP derivatives.

Preliminary studies have indicated that the phenolic dihydrodiols **40** and **41** were virtually nonmutagenic compared to dihydrodiol **42** toward mutant strains TA98 and TA100 of *Salmonella typhimurium* in the presence of an activation system (S9). A detail of this study will be reported elsewhere.

Experimental Section

^1H NMR spectra were recorded on a JEOL-270FX spectrometer in the Department of Biochemistry, the State University of New York, Buffalo, NY. Unless noted otherwise, $CDCl_3$ was used as the solvent with tetramethylsilane as an internal standard. Ultraviolet and fluorescence spectra were recorded on Perkin-Elmer Model Lambda-4B and LS-5B spectrophotometer, respectively. Mass spectra were obtained on a KRATOS MS80RFA spectrometer in the Department of Biophysics, State University of New York, Buffalo, NY. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were uncorrected. The purity of all the title compounds was judged to be >95% by TLC and ^1H NMR spectral studies. However, a small sample of each title compound was recrystallized before taking melting points, high-resolution mass spectra, and/or elemental analyses. All other intermediates except mesylates **12** and **16** isolated after usual workup was purified in small amount by preparative TLC before recording their ^1H NMR spectra.

1-Methoxypyrene-6-carboxaldehyde (5) and 1-Methoxypyrene-8-carboxaldehyde (6). These compounds were prepared in 15–18% yield according to the literature procedure.[16]

3-(1-Methoxypyren-6-yl)-2-propenoic Acid (7). A mixture of 1-methoxypyrene-6-carboxaldehyde (**5**) (4.4 g, 17 mmol), malonic acid (4.0 g, 38 mmol) in dry pyridine (20 mL), and dry piperidine (1 mL) was heated gradually to 80–85 °C. After the reaction mixture was stirred for 30 min at 80–85 °C, it was refluxed for 4 h, cooled to room temperature, and then poured onto 200 g of ice containing 50 mL of concentrated HCl. The brick-colored solid that separated out was filtered, washed thoroughly with water, and dried (4.4 g, 97%). A small sample of the solid was recrystallized from acetic acid to yield yellowish orange crystals: mp 283–285 °C dec; ^1H NMR ($CDCl_3$ + acetone-d_6) δ 4.20 (3 H, OCH_3, s), 6.70 (1 H, H_α, d), 7.66 (1 H, H_2, d), 7.48–8.86 (8 H, m) ($J_{\alpha,\beta}$ = 15 Hz, $J_{2,3}$ = 10 Hz); high-resolution mass spectrum mass obsd 302.0970, calcd 302.0943.

3-(1-Methoxypyren-6-yl)propanoic Acid (9). A solution of 2.35 g (7.75 mmol) of acid **7** in 350 mL of peroxide free THF was treated with 0.4 g of 10% Pd/C. The mixture was hydrogenated at 35 psi for 5 h. The catalyst was filtered, and the filtrate was distilled under reduced pressure to yield 2.30 g (98%) of yellow crystalline solid: mp 192–195 °C; ^1H NMR (DMSO-d_6) δ 2.80 (2 H, H_α, t), 3.62 (2 H, H_β, t), 4.18 (3 H, OCH_3, s), 7.58 (1 H, H_2, d), 7.85–8.45 (8 H, m) ($J_{\alpha,\beta}$ = 7 Hz, $J_{2,3}$ = 8.5 Hz); high-resolution mass spectrum mass obsd 304.1077, calcd 304.1099.

4-(1-Methoxypyren-6-yl)butanoic Acid (14). To an ice-cooled stirred solution of **9** (4.0 g, 13.2 mmol) in 100 mL of freshly distilled dry THF was added portionwise 1.0 g (26.3 mmol) of lithium aluminum hydride, under argon. After complete addition, the mixture was allowed to reflux for 30 min. The reaction mixture was cooled and poured onto 250 g of ice containing 10 mL of concentrated HCl, and the product was extracted with ethyl acetate (2 × 150 mL). The ethyl acetate solution was washed with water (1 × 100 mL), 10% NaOH (1 × 100 mL), and water (1 × 100 mL), successively. The organic phase was dried (Na_2SO_4) and distilled under reduced pressure to yield 3.80 g (99.7%) of 3-(1-methoxypyren-6-yl)propanol (**11**) as an oil.

To a stirred solution of **11** (3.8 g, 13.1 mmol) in 100 mL of dry CH_2Cl_2 (K_2CO_3) and triethylamine (8.5 mL, 61.1 mmol) at 0–5 °C was added dropwise a solution of methanesulfonyl chloride (4 mL, 51.7 mmol) during 30 min. After an additional 15 min of stirring at 0–5 °C, the reaction mixture was washed with ice-cold water (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL), and water (2 × 50 mL), successively. The organic phase was dried (Na_2SO_4) and distilled under reduced pressure to give 4.6 g (98.6%) of mesylate **12** as a dark oil.

A biphasic mixture of above mesylate **12** (4.6 g, 12.9 mmol), 1.0 g of tricaprylylmethylammonium chloride (aliquat 336), 100 mL of 15% aqueous KCN, and 100 mL of benzene was refluxed with vigorous stirring for 15 h. The reaction mixture was cooled, and the benzene layer was washed with water (4 × 100 mL), dried (Na_2SO_4), and distilled under reduced pressure to produce desired nitrile **13** as a reddish oil. This oil was refluxed with 15 g of KOH in 70 mL of ethylene glycol and 20 mL of water for 8 h. The mixture was cooled, diluted with 100 mL of water, extracted with 1:1 benzene–ether (2 × 75 mL), and then acidified. The grayish-colored solid thus precipitated out was filtered, washed with water, and dried to give 3.2 g (78%) of **14** as a gray crystalline solid: mp 170–172 °C; ^1H NMR ($CDCl_3$ + DMSO-d_6) δ 2.16 (2 H, H_β, m), 2.44 (2 H, H_α, t), 3.35 (2 H, H_γ, t), 4.17 (3 H, OCH_3, s), 7.50–8.44 (8 H, m) ($J_{\alpha,\beta}$ = 7.0 Hz, $J_{\beta,\gamma}$ = 6.0 Hz); high-resolution mass spectrum mass obsd 318.1260, calcd 318.1255.

3-Methoxy-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (19). A mixture of 4-(1-methoxypyren-6-yl)butanoic acid (**14**) (1.3 g, 4.08 mmol) and polyphosphoric acid 145 g) was stirred at room temperature for 30 min and at 100–105 °C for 2 h. The mixture was poured on ice (300–400 g). The solid that separated out was extracted with ethyl acetate (2 × 150 mL). The organic layer was washed with water (2 × 200 mL), 10% $NaHCO_3$ (2 × 200 mL), and water, successively. After being dried over Na_2SO_4, the ethyl acetate solution was concentrated to yield a semisolid, which was

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recrystallized from ethyl acetate to yield 660 mg (53%) of brownish yellow solid, mp 197–200 °C. The mother liquor contained a mixture of **19** and 3-methoxy-7-oxo-7,8,9,10-tetrahydrocyclohepta[*cd*]pyrene (**23**) as indicated by ^{1}H NMR spectroscopy. A small sample of **19** was further recrystallized from ethyl acetate to yield golden needles: mp 199–200 °C; ^{1}H NMR δ 2.38 (2 H, H_9, m), 2.86 (2 H, H_8, t), 3.57 (2 H, H_{10}, t), 4.16 (3 H, OCH_3, s), 7.58 (1 H, H_2, d), 7.95–8.20 (4 H, m), 8.37 (1 H, H_4, d), 8.77 (1 H, H_6, s) ($J_{1,2}$ = 8.2 Hz, $J_{4,5}$ = 9.2 Hz, $J_{8,9}$ = 6.5 Hz, $J_{9,10}$ = 5.6 Hz). Anal. Calcd for $C_{21}H_{16}O_2$: C, 84.0; H, 5.3. Found: C, 83.9; H, 5.5.

When the above reaction was carried out at 85–90 °C for 30 min, mostly **23** was isolated.

1-Bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (28) and 3-Bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (29). A solution of 6.16 g (38.5) mmol) of bromine in 350 mL of anhydrous CCl_4 was added dropwise during 3 h to a vigorously stirred solution of 7-cyano-7-((trimethylsilyl)oxy-7,8,9,10-tetrahydrobenzo[*a*]-pyrene[22] (**27**) (14.0 g, 37.9 mmol) at room temperature. After additional stirring for 1 h, the solution was washed with H_2O (2 × 200 mL), dried over anhydrous Na_2SO_4, and distilled under reduced pressure to yield a crude solid product. A solution of this product in 45 mL of THF and 45 mL of H_2O was stirred with 6.3 g of silver fluoride for 30 min. The reaction mixture was extracted with ethyl acetate (2 × 200 mL). The combined ethyl acetate layers were washed with water (2 × 100 mL), dried over anhydrous sodium sulfate and distilled under reduced pressure to yield 13.0 g of a crude solid. The column chromatography of the crude solid over dry column grade silica gel using benzene as eluant produced 7.1 g of the mixture of bromo ketones **28** and **29**. This mixture was recrystallized twice freom benzene to give 2.9 g (22%) of pure 1-bromo-1,2,3,4-tetrahydrobenzo[*a*]pyren-7-one (**28**).

The solid isolated from the mother liquor was further chromatographed repeatedly over dry column grade silica gel using 12% ethyl acetate–cyclohexane as eluant to produce 1.8 g (14%) of additional relatively nonpolar 1-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**28**), 0.85 g (6.5%) of 95% pure 3-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**29**), and 1.2 g (9.1%) of the mixture of **28** and **29**. A small sample of each bromo ketone was further recrystallized from benzene to yield pure **28** [mp 212–214 °C (lit.[21] mp 212–214 °C); ^{1}H NMR δ 2.42 (2 H, H_9, m), 2.90 (2 H, H_8, t), 3.64 (2 H, H_{10}, t), 7.87–8.50 (6 H, m), 8.85 (1 H, H_6, s) ($J_{8,9}$ = $J_{9,10}$ = 6 Hz)], and **29** [mp 214–215 °C; ^{1}H NMR δ 2.42 (2 H, H_9, m), 2.89 (2 H, H_8, t), 3.63 (2 H, H_{10}, t), 7.95–8.36 (6 H, m), 8.85 (1 H, H_6, s) ($J_{8,9}$ = 6.5 Hz, $J_{9,10}$ = 6.1 Hz); mass spectrum *m/e* (relative intensity) 348, 350 (M^+, 100:96), 292, 294 (30:28), 239 (29), 213 (55.4); high-resolution mass spectrum mass obsd 348.0125 and 350.0090, calcd 348.0149 and 350.0129].

3-Acetoxy-9,10-dihydrobenzo[*a*]pyrene (25). Method A. A solution of 3-methoxy-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**19**) (575 mg, 1.91 mmol) in glacial acetic acid (25 mL) and 48% aqueous HBr (4 mL) was refluxed for 2 h, under argon. The mixture was cooled and poured into water (100 mL). The red solid that separated out was filtered, washed with water, and dried to produce 3-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**20**), mp 293–295 °C dec.

The hydroxy ketone **20** was stirred for 30 min with sodium borohydride (400 mg, 11 mmol) in 25 mL of ethanol under argon. Most of the ethanol was distilled in vacuo, and the residue was diluted with water (25 mL). The mixture was adjusted to pH 7 by dilute HCl and then extracted with ethyl acetate (2 × 25 mL). The combined ethyl acetate solution was dried (Na_2SO_4) and concentrated under reduced pressure to produce 3,7-dihydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene.

The above dihydroxy derivative was refluxed in dry benzene (60 mL) containing *p*-toluenesulfonic acid (25 mg) for 1 h under Ar. The mixture was cooled, washed with water, dried (Na_2SO_4), and concentrated under reduced pressure to yield a residue. The residue was stirred with Ac_2O (10 mL) and pyridine (2 mL) for 3 h, and the reaction mixture was worked up as usual to produce crude 3-acetoxy-9,10-dihydrobenzo[*a*]pyrene (**25**). This crude product was further pufified by flash chromatography over silica gel using first hexane for removing relatively nonpolar impurities. Further elution of the column with 1:1 benzene/hexane produced 310 mg (51.8% based on **19**) of pure **25**: mp 166–168 °C dec; ^{1}H NMR δ 2.32–2.72 (2 H, H_9, m), 2.55 (3 H, CH_3CO, s), 3.50 (2 H, H_{10}, t), 6.28 (1 H, H_8, m), 6.85 (1 H, H_7, dt), 7.60–8.30 (7 H, m) ($J_{7,8}$ = 9.6 Hz, $J_{7,9}$ = 1.3 Hz, $J_{8,9}$ = 4.0 Hz, $J_{9,10}$ = 8.2 Hz); high-resolution mass spectrum mass obsd 312.1133, calcd 312.1150.

3-Hydroxybenzo[*a*]pyrene (34). A solution of 1-acetoxy-9,10-dihydrobenzo[*a*]pyrene (**25**) (15 mg) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 35 mg) in anhydrous peroxide free dioxane (2 mL) was refluxed under argon for 1 h. The solvent was removed in vacuo, and the residue dissolved in chloroform was passed through a small column of basic alumina. The residue obtained after evaporation of chloroform was recrystallized from acetone–petroleum ether to afford pure 3-acetoxybenzo[*a*]pyrene (**32**): mp 169–170 °C (lit.[25] mp 169–170 °C); ^{1}H NMR δ 2.57 (3 H, CH_3CO, s), 7.74–8.33 (8 H, m), 8.51 (1 H, H_6, s), 9.00–9.10 (2 H, H_{10} and H_{11}, m).

The solvolysis of **32** with anhydrous potassium carbonate in THF–MeOH at 0 °C for 30 min yielded **34**, which showed identical TLC profile and UV spectrum with the authentic 3-hydroxybenzo[*a*]pyrene.[23]

1-Acetoxy-9,10-dihydrobenzo[*a*]pyrene (26). Method B. A stirred mixture of 1.18 g (3 mmol) of 1-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyrene-7-one ethylene ketal (**30**) [obtained in 93% yield by refluxing 1-bromo-7,8,9,10-tetrahydrobenzo[*a*]pyren-7-one (**28**) (vide supra), ethylene glycol, and *p*-toluenesulfonic acid for 15 h, mp 208–209 °C dec; ^{1}H NMR δ 2.04–2.40 (4 H, $H_{8,9}$, m), 3.49 (2 H, H_{10}, t), 4.16–4.50 (4 H, OCH_2CH_2O, m), 7.96–8.50 (7 H, m) ($J_{9,10}$ = 6.3 Hz)], magnesium turnings (400 mg), and diborane (6 mL from a 2 M solution in THF) in dry THF in argon was treated under reflux with a solution of ethylene dibromide (10 drops in 20 mL of dry THF) during 90 min. Further workup of the reaction mixture, and subsequent treatment of the isolated product in each step, was performed as described in the synthesis of **25** (method B) to produce crude 1-acetoxy-9,10-dihydrobenzo[*a*]pyrene (**26**). Crude **26** was further purified by flash chromatography (see method A) to afford 415 mg (44%) of pure **26**: mp 194–195 °C; ^{1}H NMR δ 2.40–2.76 (2 H, H_9, m), 2.55 (3 H, CH_3CO, s), 3.49 (2 H, H_{10}, t), 6.27 (1 H, H_8, m), 6.85 (1 H, H_7, m), 7.64–8.36 (7 H, m) ($J_{7,8}$ = 9.5 Hz, $J_{7,9}$ = 1.6 Hz, $J_{8,9}$ = 4.5 Hz, $J_{9,10}$ = 8.3 Hz); high-resolution mass spectrum mass obsd 312.1106, calcd 312.1150.

1-Hydroxybenzo[*a*]pyrene (35). The reaction of 1-acetoxy-9,10-dihydrobenzo[*a*]pyrene (**26**) (10 mg) with DDQ (25 mg) of dioxane (2 mL) was performed as described in the preparation of **32** to produce 1-acetoxybenzo[*a*]pyrene (**33**): mp 202–203 °C; ^{1}H NMR δ 2.59 (3 H, CH_3CO, s), 7.70–8.35 (8 H, m), 8.53 (1 H, H_6, s), 9.0–9.11 (2 H, H_{10} and H_{11}, m).

The usual hydrolysis of **33** with potassium carbonate in THF–MeOH at 0 °C for 30 min afforded **35**, which was found to possess indentical TLC profile and UV spectrum with those obtained from authentic 1-hydroxybenzo[*a*]pyrene.[23]

3-Acetoxy-*trans*-7,8-bis(benzoyloxy)-7,8,9,10-tetrahydrobenzo[*a*]pyrene (36). Iodine (278 mg, 1.10 mmol) was added to a suspension of silver benzoate (600 mg, 2.62 mmol) in dry benzene (50 mL), under argon. The mixture was stirred until iodine color disappeared, and then acetoxyalkene **25** (312 mg, 1.0 mmol) was added. After the reaction mixture was stirred for 20 min at room temperature, it was refluxed for 1 h, cooled to room temperature, and then filtered. The filtrate was concentrated under reduced pressure to yield a solid that was chromatographed over dry column grade silica gel (Merck). The elution of the column with chloroform produced 400 mg (73%) of pure **36**. Further elution of the column produced a trace amount of a product later characterized as 3-acetoxy-*trans*-7,8-bis(benzoyloxy)-7,8-dihydrobenzo[*a*]pyrene (**38**). The amount of **38** was increased as the larger proportion of iodine was used. A small sample of **36** was recrystallized from EtOAc–petroleum ether to give colorless crystals: mp 242–243 °C dec; ^{1}H NMR δ 2.24–2.84 (2 H, H_9, m), 2.55 (3 H, CH_3CO, s), 3.73 (2 H, H_{10}, m), 5.78 (1 H, H_8, m), 6.97 (1 H, H_7, d), 7.20–8.48 (17 H, m) ($J_{7,8}$ = 5.9 Hz); high-resolution mass spectrum mass obsd 554.1780, calcd 554.1730.

3-Acetoxy-*trans*-7,8-bis(benzoyloxy)-7,8-dihydrobenzo[*a*]pyrene (38). A mixture of 332 mg (0.6 mmol) of **36** and 408 mg (1.8 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 25 mL of freshly distilled dioxane (Na) was refluxed,

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under argon, for 4 h. The mixture was cooled, concentrated in vacuo, and passed through a small column of basic alumina. The compound was eluted with ethyl acetate and then recrystallized from ethyl acetate–petroleum ether to give 209 mg (63%) of pure **38** as a light yellow crystal: mp 182–183 °C; ^{1}H NMR δ 2.52 (3 H, CH_3CO, s), 6.22 (1 H, H_8, m), 6.47 (1 H, H_9, dd), 7.06 (1 H, H_7, d), 7.28–8.42 (18 H, m) ($J_{7,8}$ = 7.6) Hz, $J_{8,9}$ = 3.5 Hz, $J_{8,10}$ = 1.5 Hz, $J_{9,10}$ = 10 Hz); high-resolution mass spectrum mass obsd 552.1443, calcd 552.1572.

3-Hydroxy-*trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene (40). Triester **38** (83 mg, 0.15 mmol) was dissolved in deaerated THF (2 mL) and MeOH (2 mL), and 30 mg of powdered NaOH was added. The mixture was stirred at room temperature, under Ar, for 1 h. The reaction mixture was then adjusted to pH 6–7 with dilute HCl and extracted with ethyl acetate (50 mL). The ethyl acetate solution was washed with water (1 × 15 mL), dried (Na_2SO_4), and concentrated under reduced pressure to yield a yellowish brown solid. The solid was triturated with 25% ethyl acetate–hexane and filtered to give 40.7 mg (90%) of pure triol **40**: mp 360 °C dec; ^{1}H NMR (270 MHz, DMSO-d_6 + CD_3OD) δ 4.42 (1 H, H_8, d), 4.88 (1 H, H_7, d), 6.16 (1 H, H_9, dd), 7.44 (1 H, H_{10}, dd), 7.54 (1 H, H_2, d), 7.98–8.28 (5 H, m), 8.29 (1 H H_6, s) ($J_{1,2}$ = 8.2 Hz, $J_{7,8}$ = 10.6 Hz, $J_{8,9}$ = $J_{8,10}$ = 1.0 Hz, $J_{9,10}$ = 10.2 Hz); high-resolution mass spectrum mass obsd 302.0956, calcd 302.0944; UV (1% THF–EtOH) λ_{max} (ϵ) 389.7 (22 500), 370.6 (22 300), 350 (sh, 12 900), 298.9 (13 200), 286.2 (14 200); the fluorescence spectrum (0.25% THF–EtOH, excitation at 391 or 260 nm) exhibited an emission, with a maximum at 429 nm.

Supplementary Material Available: Synthetic methods and spectral data (^{1}H NMR, MS, and/or UV) for **8**, **10**, **18**, **21**, **25** (method B), **26** (method A), **37**, **39**, and **41** and ^{1}H NMR data for **11**, **12**, **13**, **20**, and **23** (6 pages). Ordering information is given on any current masthead page.

Conversion of Unsaturated Alcohols into Functionalized Tetrahydrofurans and Tetrahydropyrans via Nitrile Oxide Dipolar Cycloadditions[1]

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The intramolecular nitrile oxide cycloaddition (INOC) of a series of unsaturated oximino ethers has been investigated. The synthesis of the olefinic nitrile oxides involves treating an unsaturated alcohol with a α-bromoalkanal *O*-(trimethylsilyl)oxime in the presence of fluoride ion followed by subsequent sodium hypochlorite oxidation. The nitrile oxides were not isolated but spontaneously underwent intramolecular cycloaddition to give fused five- and six-membered ring ethers. The preferred stereoisomer in the formation of the five-membered ring ethers is trans, whereas in the six-membered ring ethers the cis isomer predominates. MM2 calculations help rationalize the observed stereoselectivity. The ratio of diastereomeric products from the INOC reaction appears to correlate with product stabilities. Simple heating of some of the oximino ethers led to intramolecular cycloaddition. The ring closure apparently proceeds subsequent to a tautomeric equilibration of the oxime with a transient nitrone which is trapped by the neighboring π-bond.

In recent years intramolecular nitrile oxide–olefin cycloadditions (INOC) have been of considerable synthetic and mechanistic interest, especially since the resulting isoxazoline ring can serve as a precursor to hydroxy ketones or to other functional groups.[3-9] Substituted and functionalized tetrahydrofurans and pyrans are of interest as analogues of carbohydrates.[10,11] This is particularly true if these compounds can be prepared in a stereoselective manner. On the basis of previous work by us and others on intramolecular dipolar cycloadditions,[12-22] we envisioned

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