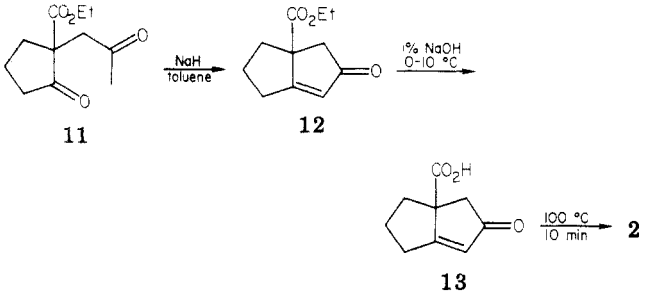
sodium hydride in toluene gave keto ester **12**.[7] After



bulb-to-bulb distillation, crude **12** was hydrolyzed under exceptionally mild conditions, 1% aqueous NaOH at 0–10 °C for 1.5 h. Extraction of the nonhydrolyzable impurities with chloroform and acidification gave the crude keto acid **13**, which was readily decarboxylated in a few minutes on a steam bath. The product **2** was >95% pure by NMR and GC but could be further purified if necessary by preparative GC.

Enone **2** is a mobile liquid with an exceptionally sweet aroma. Its structure was clear from its spectral properties. In particular the IR and UV spectra showed a conjugated cyclopentenone, the proton NMR spectrum showed one vinyl proton (δ 5.86), and the ^{13}C NMR spectrum and mass spectra were also consistent with the structure. In particular the IR and UV spectra showed a conjugated cyclopentenone, the proton NMR spectrum showed one vinyl proton (δ 5.86), and the ^{13}C NMR spectrum and mass spectra were also consistent with the structure. Finally chemical transformations of **2**, to be described in conjunction with the synthesis of **1**, confirm the structure.

The synthesis of **2** described here makes the substance available in amounts sufficient for further chemical manipulation.

Experimental Section

2-Acetonyl-2-(ethoxycarbonyl)cyclopentanone (11). (a) 2-(Ethoxycarbonyl)-2-propargylcyclopentanone (14). To a refluxing solution of potassium (26.2 g, 0.67 mol) in *tert*-butyl alcohol (850 mL) was added, under nitrogen and over 15 min, neat 2-(ethoxycarbonyl)cyclopentanone (95 g, 0.61 mol). After 15 min of further reflux, propargyl bromide (90.6 g, 0.61 mol) was added over 45 min (exothermic reaction). The *tert*-butyl alcohol (~600 mL) was removed by distillation and the cooled remaining mixture was poured onto ice (500 g). The organic layer was washed with water (3 × 200 mL), concentrated under reduced pressure, taken up in chloroform (750 mL), dried ($MgSO_4$), and distilled to give 95.6 g (81%) of pure **14**, bp 107 °C (4 torr), as a colorless liquid: IR (neat) 3280 (m), 2980 (m), 1750 (vs), 1725 (vs), 1470 (w), 1450 (w), 1425 (w), 1405 (w), 1330 (m), 1015 (m), 930 (w), 860 (w), 810 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.247 (t, 3 H, J = 7.3 Hz), 2.046 (t, 1 H, J = 2.7 Hz), 2.06–2.60 (m, 6 H), 2.680 and 2.687 (dd, 2 H, J = 2.7 and 17 Hz), 4.158 (q, 2 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 14.04, 19.79, 23.13, 32.57, 38.20, 58.75, 61.64, 70.99, 79.97, 170.23, 213.11; mass spetrum, m/e (relative intensity) 194 (5), 166 (38), 149 (26), 138 (53), 121 (79), 120 (28), 111 (54), 110 (31), 109 (37), 93 (92), 92 (44), 91 (96), 79 (74), 78 (30), 77 (95), 67 (40), 65 (84), 64 (23), 53 (32), 51 (22), 43 (27), 41 (37), 39 (100). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; h, 7.27. Found: C, 68.09; H, 7.34.

(b) Hydration of 14. A mixture of **14** (86 g, 0.44 mol), methanol (600 mL), water (150 mL), mercuric oxide impregnated Dowex 50 H^+ resin[8] (2.0 g, 200–400 mesh), and concentrated sulfuric acid (4 drops) was stirred at room temperature for 60 h, then filtered, and concentrated under vacuum. The residue was taken up in chloroform (400 mL) and the aqueous layer was extracted with chloroform (100 mL). The combined organic layers were dried ($MgSO_4$) and distilled to give 93.0 g (99%) of **11** as a colorless liquid: IR (neat) 2945 (m), 2910 (m), 1750 (vs), 1720 (vs), 1450 (m), 1420 (m), 1405 (s), 1368 (s), 1325 (m), 1282 (m), 1255 (m), 1230 (s), 1168 (s), 1148 (s), 1110 (m), 1050 (w), 1030 (m), 970 (w), 940 (w), 920 (w), 858 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.237 (t, 3 H, J = 7.3 Hz), 2.099 (d, 1 H, J = 18.3 Hz), 2.147 (s, 3 H), 1.95–2.65 (m, 6 H), 3.184 (d, 1 H, J = 18.3 Hz), 4.141 (q, 2 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.97, 19.79, 29.86, 33.24, 37.55, 47.42, 57.44, 61.44, 170.45, 205.14, 214.26; mass spectrum, m/e (relative intensity) 212 (0.4), 167 (12), 166 (34), 141 (7), 139 (15), 138 (7), 124 (21), 123 (26), 113 (13), 111 (32), 110 (8), 97 (17), 95 (28), 71 (8), 68 (8), 67 (20), 55 (13), 43 (100). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.14; H, 7.70.

Bicyclo[3.3.0]oct-1(2)-en-3-one (2). To a refluxing mixture of sodium hydride (4.0 g, 0.167 mol) in anhydrous toluene (300 mL) was added under nitrogen over 2 h a solution of **11** (8.0 g, 0.039 mol) in toluene (200 mL), and the resulting mixture was refluxed for 18 h. The mixture was cooled to 10 °C and carefully acidified with 10% hydrochloric acid (90 mL). The aqueous layer was separated and washed with ether (3 × 50 mL), and the combined organic layers were washed with saturated brine (50 mL) and dried ($MgSO_4$). After the solvent was removed under reduced pressure, the residue was distilled bulb-to-bulb at 100 °C (0.1 torr) to give 4.44 g of crude keto ester **12**. This product was treated with 1% aqueous sodium hydroxide (100 mL) for 1.5 h at 0–10 °C. The resulting mixture was washed with chloroform (50 mL), acidified with 10% hydrochloric acid, and extracted with chloroform (3 × 50 mL). The extract was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give a clear oil. This oil (impure **13**) was heated on a steam bath for 10 min (gas evolution), diluted with chloroform, washed with 5% aqueous sodium hydroxide (25 mL), and dried ($MgSO_4$) and the solvent evaporated to give 1.75 g (38% from **11**) of a mobile, sweet-smelling liquid which by NMR and GC was >95% pure **2**. Further purification was possible by preparative GC (5% FFAP on Chromosorb W-AWDMCS, 0.25 in. × 6 ft column, 160 °C): IR (neat) 2968 (s), 2875 (m), 1705 (vs), 1625 (s), 1452 (m), 1375 (w), 1315 (m), 1258 (w), 1176 (m), 1158 (m), 1108 (w), 1082 (w), 1028 (w), 932 (w), 872 (m), 835 (w), 819 (w) cm^{-1}; UV (MeOH) λ_{max} 228 nm (ϵ 12 200), 293 (62); ^1H NMR ($CDCl_3$) δ 1.7–3.0 (m, 9 H), 5.86 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.55, 26.30, 31.16, 42.36, 46.74, 124.79, 191.41, 210.93; mass spectrum, m/e (relative intensity) 122 (100), 121 (31), 107 (22), 95 (5), 94 (72), 79 (52); high-resolution mass spectrum, calcd for $C_8H_{10}O$ 122.07260, found 122.07317.

Acknowledgment. We are indebted to the National Institutes of Health (GM 15997) and the National Science Foundation (CHE 80-17746) for financial support of this research.

Registry No. **2**, 72200-41-0; **11**, 61771-77-5; **12**, 65898-66-0; **13**, 77320-45-7; **14**, 77320-46-8; 2-(ethoxycarbonyl)cyclopentanone, 611-10-9; propargyl bromide, 106-96-7.

(7) Use of other bases in this cyclization, such as potassium hydride or potassium *tert*-butoxide in refluxing toluene or THF, gave no yield improvement.

(8) Newman, M. S. *J. Am. Chem. Soc.* **1953**, *75*, 4740.

Anodic Fluorination of Benz[*a*]anthracene

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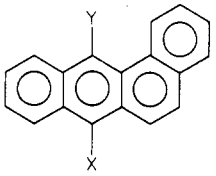
Whereas benz[*a*]anthracene (**1**) is a weak carcinogen, its 12-methyl (**2a**), 7-methyl (**3a**), and 7,12-dimethyl (**4a**) analogues become increasingly more carcinogenic.[1] All

Table I. Properties of Fluorobenz[a]anthracene Obtained upon Anodic Fluorination of Benz[a]anthracene (1)[a]

compd	M⁺, m/e	mp, °C (solvent)	^{19}F NMR, ppm	^{1}H NMR, ppm
12-fluorobenz[a]anthracene (2b)	246	141.1–141.6 (isooctane)	$^{19}F_{12}$, 43.20, s	H_7, 8.13, s
7-fluorobenz[a]anthracene (3b)	246	93.1–93.6 (isooctane)	$^{19}F_7$, 30.77, s	H_{12}, 8.92, s
7,12-difluorobenz[a]anthracene (4b)	264	135.2–136.2 (hexane)	38.67, 26.97 ($J_{7,12}$ = 23.5 Hz)	no aromatic singlets downfield

[a] ^{1}H and ^{19}F NMR chemical shifts (δ) were measured relative to internal Me_4Si and hexafluorobenzene, respectively. The ^{19}F spectra were proton noise decoupled. Satisfactory analytical data (±0.23% for C, H, and F) were obtained for 2b, 3b, and 4b with the exception that 2b was 0.47% low in carbon.

four of these compounds are thought to exert their carcinogenic activity via bay region 3,4-diol 1,2-epoxides,[2] but the basis for the increased carcinogenicity of the hydrocarbons upon methyl substitution is unknown. Tumor studies of the corresponding fluoro analogues **2b–4b** would be of considerable interest since fluorine is both small and electron withdrawing compared to methyl.



1, X = Y = H
2a, X = H; Y = CH_3
b, X = H; Y = F
3a, X = CH_3; Y = H
b, X = F; Y = H
4a, X = Y = CH_3
b, X = Y = F

Although 7-fluorobenz[a]anthracene (**3b**) had previously been synthesized by several routes, including photocyclization,[3] xenon difluoride intercalate fluorination,[4] and pyrolysis of the diazonium tetrafluoroborate,[5] compounds **2b** and **4b** had not been described.[6] The present report describes the use of electrolytic fluorination in the presence of fluoride-donating anions ($H_2F_3^-$ of $H_3F_4^-$) as a means of obtaining the desired fluoro derivatives of **1**. The tendency for positive charge localization at positions 7 and 12 of **1** was anticipated to provide the desired selectivity for capture of fluoride ion by the radical cations formed. Some controversy exists regarding the mechanism by which the anodic fluorination of aromatic hydrocarbons occurs.[7–10]

Controlled potential electrolysis of **1** at 1.10 Vs. Ag/Ag^+ (0.01 M) in acetonitrile containing $(CH_3)_4NF{\cdot}2HF$[11] was conducted by a previously described method.[12] After standard workup, the crude reaction product was chromatographed on Florisil to remove benz[a]anthracene 7,12-dione and other more polar reaction products. The dione is presumed to arise via hydrolysis of 7,12-difluoro **4b** on workup and chromatography (cf. ref 12). The mass spectrum of the crude fluorination product shows a molecular ion at m/e 302 corresponding to 7,12-difluoro **4b**. Analysis of the benz[a]anthracene fraction from the column by analytical HPLC (Figure 1) indicated the presence of three other UV-absorbing components in addition to **1**. Mass spectrometry identified these as two monofluoro and one difluoro derivative of **1**. Preparative recycle HPLC on a Whatan Magnum-9 Partisil column eluted with 1% CH_2Cl_2 in cyclohexane or with hexane provided each of these compounds in a pure state. Their properties are summarized in Table I.

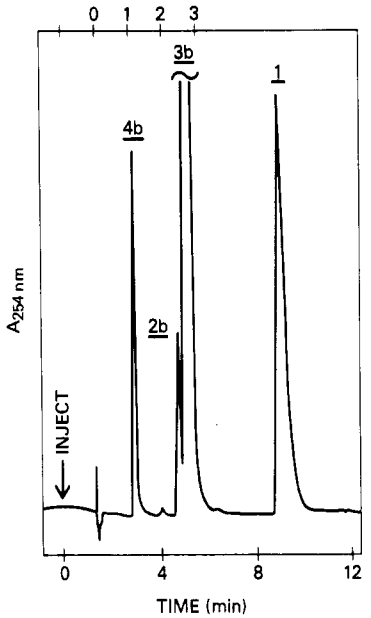


Figure 1. Analytical HPLC separation of fluorobenz[a]anthracenes obtained after prior chromatography on a Florisil column. A μPorasil column (Waters Associates) eluted with hexane at 3 mL/min was used to achieve the separation. Numbers at the top of the drawing indicate void volumes (k') for the column.

The structural assignments in Table I are based primarily on their NMR spectra and the fact that pure **3b** has been obtained by unequivocal synthesis.[5] The ^{1}H NMR spectrum of **1** has two characteristic downfield aromatic singlets for H_7 at δ 8.35 and for H_{12} at δ 9.15. In the spectra of **2a** and **2b**, the singlets for H_{12} are missing and H_7 appears as singlets at δ 8.19 and 8.13, respectively. In the spectra of **3a** and **3b**, the singlets for H_7 are missing and H_{12} appears as singlets at δ 9.08 and 8.92, respectively. Assignment of **4b** as 7,12-difluorobenz[a]anthracene rests on the facts that the characteristic singlets for H_7 and H_{12} in the ^{1}H NMR spectra of **1** are both missing and that a pair of doublets are present in the ^{19}F NMR spectrum. The large value of $^{5}J_{7,12}$ = 23.5 Hz may be related to the fact that the two fluorines occupy the meso anthracenic

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positions of **4b**. Even larger values of J_{para} for coupled fluorines have been reported.[13] Both NMR spectra and analytical HPLC established that the samples of **2a**, **3b**, and **4b** were free of cross-contamination.

Since the electrolysis was run at a controlled potential near the $E_{1/2}^{ox}$ of **1**,[14] it is unlikely that dications were formed. The pathway for the formation of **4b** more likely consists of the formation of radical cations from **2b** and/or **3b** and subsequent trapping by $H_2F_3^-$ near the controlled potential used. The marked preference for the formation **3b** relative to **2b** may be partially due to steric hindrance to the attack of the fluoride complex at C-12, since simple Huckel calculations indicate only a slight preference for the radical cation at C-7 relative to C-12.

Notably, **4b** is unstable to room light in CH_2Cl_2 but not in cyclohexane. Benz[*a*]anthracene 7,12-dione, **1**, **2b**, and **3b** were not detected among the products. Tumor studies, currently in progress, have been designed to evaluate the activity of **1** when fluoride and/or methyl are substituted at positions 7 and/or 12. Both 7-fluoro-12-methyl- and 7-methyl-12-fluorobenz[*a*]anthracene[15] are included in these studies.

Experimental Section

Methods. Melting points were determined on a Thomas-Hoover apparatus in capillary tubes and are corrected. NMR spectra were measured with a JEOL FX-100 spectrometer in $CDCl_3$ solvent. Mass spectra were obtained with a Finnigan 1015 mass spectrometer operated in the CI mode ($NO-N_2$). Analytical and preparative HPLC were done on a Waters Associates Model M6000 pump, and compounds were detected in the column effluent by absorbance (254 nm) and refractive index change. Synthesis of **3a** was as described [mp 138.0–138.5 °C (lit.[16] mp 139.6–140.0 °C)].

Anodic Fluorination. The electrolyses were conducted in a 300-mL resin flask with platinum electrodes. The Ag/Ag^+ (0.01 M) reference electrode was made from polyethylene tubing with a porous Vycor plug and was placed as close to the anode as possible. Current was supplied by a modified Lingane-Jones potentiostat[17] constructed in the Boston College Electronics Shop. Acetonitrile was obtained from Burdick and Jackson and $(C_4H_9)_4NF\cdot 2HF$ from Ozark Mahoniny. The solvent was introduced through a column of alumina. Additions of the salt and benz[*a*]anthracene (Aldrich) were made in a drybox. Argon was passed through the cell during the electrolysis. The current at the start was approximately 500 mA, and the electrolysis was stopped when it had fallen to 10 mA. In a typical run, 1.10 g of **1** was dissolved in 200 mL of 0.5 M solution of the electrolyte and was electrolyzed at 1.1 Vs. Ag/Ag^+ (0.01 M) for 3.75 h. After evaporation of the solvent, the residue was washed with water to remove the salt.

Chromatographic Isolation. In a typical experiment, 1.2 g of crude fluorination product was applied to the top of a Florisil column (2 × 23 cm, 100–200 mesh, Fisher) packed in CH_2Cl_2. Elution with 120 mL of CH_2Cl_2 removed all of the unreacted **1** and the fluorinated derivatives of **1** from the column (730 mg). A gradient of acetone in hexane up to pure acetone eluted first an unidentified red band (34 mg) followed by a yellow band (315 mg). A combination of analytical techniques, including mixture melting point, identified this material as benz[*a*]anthracene-7,12-dione (Aldrich). The benz[*a*]anthracene fraction was further separated by HPLC on a Whatman Magnum-9 Partisil column eluted with 1% CH_2Cl_2 in cyclohexane (11 mL/min, 230 psi). Each injection consisted of 70 mg of the mixture in 10 mL of mobile phase to provide 140 mg of **1**, 42 mg of **4b**, and 472 mg of the mixture of **2b** and **3b**. The very small α value (~1.12) for the latter two compounds required subsequent chromatography for their separation. The same column was used, but the solvent was changed to hexane (10 mL/min). Samples of 85 mg of the mixture were injected onto the column in 5 mL of hexane. A combination of selective peak shavings during four recycles allowed a 90% recovery of the pure components: **2b** (39 mg) and **3b** (386 mg). Properties of the three fluoro compounds are given in Table I.

Acknowledgment. We are grateful to Dr. H. J. C. Yeh of the NIH for determining the NMR spectra and to Professor M. S. Newman of the Ohio State University for a sample of **2a** which was synthesized as previously described.[18] We also thank Dr. J. M. Sayer of the NIH for examining the photostability of **4b**.

Registry No. **1**, 56-55-3; **2b**, 77450-63-6; **3b**, 23683-26-3; **4b**, 77450-64-7.

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A Reaction Mechanism Change in the Lewis Acid Catalyzed Perezone-Pipitzol Transformation

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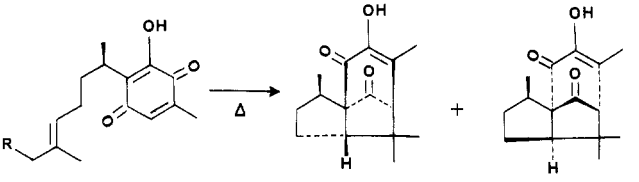
Although perezone (**1a**) has been known[1] since 1852, its transformation into pipitzols (**2** and **3**) was first performed almost a century ago[2] and recognized as an irreversible rearrangement[3] in 1913; it was not until 1965 that the structure of the starting sesquiterpenic benzoquinone[4] (**1a**) and those of the thermal rearrangement cedranolides[5] (**2** and **3**) were established. The chirality of perezone (**1a**) has been known[6] since 1954, while that of the pipitzols (**2** and **3**) was rigorously proven very recently.[7] The remarkable thermolysis **1** → **2** + **3** was postulated[4a,8] and



1 a: R = H; b: R = D **2** **3**

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