THE JOURNAL OF Organic Chemistry

VOLUME 51, NUMBER 24

NOVEMBER 28, 1986

The 5-, 6-, and 10-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracenes. Comparative Acid-Catalyzed Isomerization to Exo Methylene Tautomers: A 6-Fluoro Peri Effect[1]

Donald T. Witiak,* Norman A. Abood, Shyamaprosad Goswami, and George E. Milo

Division of Medicinal Chemistry and Pharmacognosy, College of Pharmacy and Comprehensive Cancer Center, The Ohio State University, Columbus, Ohio 43210

Received May 28, 1986

Syntheses for 5-, 6-, and 10-fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracenes (**3–5**) from an aminotetralin–HCl **6**, fluorotetralin **14**, and tetrahydronaphthaldehyde **29**, respectively, are described. Comparative acid-catalyzed isomerization studies in refluxing benzene revealed that the 6-F analogue **4** equilibrates with 12- and 7-methylene tautomers **20** and **21** within 1 h. When the 12-methylene tautomer **20** was treated with *p*-toluenesulfonic acid in refluxing benzene the thermodynamic product ratio (**4**/**20**/**21** = 1.0:0.6:2.8) was obtained after 72 h. These data are markedly different than results observed for acid-catalyzed isomerization of 1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (TH-DMBA, **1**), 5F-TH-DMBA (**3**) or 10F-TH-DMBA (**5**) which after 72 h only afforded aryl to 7-methylene isomer ratios of 14:1, 8:1 and 8:1, respectively. The additional peri interaction between the 7-CH_3 and 6-F functions of **4** serves as explanation for the facile acid-catalyzed isomerization of **4** to the sterically least crowded, thermodynamically more stable 7-methylene tautomer **21**.

1,2,3,4-Tetrahydro-7,12-dimethylbenz[*a*]anthracene (**1**), unlike the well-studied parent polycyclic aromatic hydrocarbon (PAH) 7,12-dimethylbenz[*a*]anthracene (**2**), is mutagenic in three strains of *S. typhimurium* without (or with) metabolic activation,[2] is an effective initiator of human neonatal foreskin fibroblast cell transformation in culture,[3,4] and does not have an aromatic A-ring likely necessary for metabolic conversion to alkylating bay region diol epoxides.[5] The A-ring reduced PAH **1** also exhibited tumor initiating activity in female SENCAR[6] and Swiss[7] mice and induced mutations to 6-thioguanine-resistance in Chinese hamster V79 cells with secondary hamster embryo cells serving as metabolic activators.[6] Analogue **1** intercalates[8–10] 10.8 times better than the 5,6-dihydro derivative of **2**.[9] In human fibroblasts, **1**, but not **2**, was found associated with the nucleus (1.4×10^7 molecules/nuclear residue)[11] and formed two adducts with the cellular DNA as detected by ^{32}P postlabeling techniques.[12,13]

Monofluoro derivatives of **2** and its 12-desmethyl analogue have provided insight into metabolic processes leading to carcinogenesis.[6,14–17] Thus, the aryl–fluorine

(1) A preliminary account of this work was presented to the Division of Medicinal Chemistry at: Abood, N. A.; Witiak, D. T.; Goswami, S. P.; Bhat, H. B.; Kumari, H. L.; Milo, G. E. 192nd National Meeting of the American Chemical Society, Anaheim, CA, 1986.

(2) Inbasekaran, M. N.; Witiak, D. T.; Barone, K.; Loper, J. C. *J. Med. Chem.* **1980**, *23*, 278–281.

(3) Tejwani, R.; Witiak, D. T.; Inbasekaran, M. N.; Cazer, F. D.; Milo, G. E. *Cancer Lett.* **1981**, *13*, 119–127.

(4) Milo, G. E.; Mason, T. O.; Witiak, D. T.; Inbasekaran, M. N.; Cazer, F. D.; Gower, W. R. In *Polynuclear Aromatic Hydrocarbons*; Cooke, M., Dennis, A. J., Fisher, G., Eds.; Battelle: Columbus, OH, 1982; pp 537–549.

(5) Harvey, R. G. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 35–62.

(6) DiGiovanni, J.; Diamond, L.; Singer, J. M.; Daniel, F. B.; Witiak, D. T.; Slaga, T. J. *Carcinogenesis* **1982**, *3*, 651–655.

(7) Linjinsky, W.; Manning, W. B.; Andrews, A. W. *Carcinogenesis* **1983**, *4*, 1221–1224.

(8) LeBreton, P. R. *Book of Abstracts* 188th ACS National Meeting, Philadelphia, PA, Aug 26–31, 1984; American Chemical Society: Washington, DC, 1984; Abstract 124.

(9) Zegar, I. S.; Prakash, A. S.; Harvey, R. G.; LeBreton, P. R. *J. Am. Chem. Soc.* **1986**, *107*, 7990–7995.

(10) LeBreton, P. R. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; Washington, DC, 1985; pp 209–238.

(11) Kumari, H. L.; Abood, N. A.; Goswami, S. P.; Bhat, H. B.; Milo, G. E.; Witiak, D. T. ASBC Meeting, Washington, DC, June 8–13, 1986.

(12) Gupta, R. C.; Reddy, M. V.; Randerath, K. *Carcinogenesis* **1982**, *3*, 1081–1092.

(13) Gupta, R. C. *Cancer Res.* **1985**, *45*, 5656–5662.

(14) Newman, M. S. In *Carcinogenesis*; Freudenthal, R. I., Jones, P. W., Eds.; Raven: New York, **1976**; Vol. 1, pp 203–207.

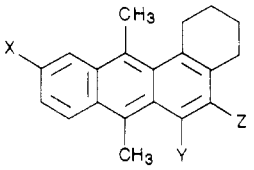
(15) Daniel, F. B.; Cazer, F. D.; D'Ambrosio, S. M.; Hart, R. W.; Kim, W. H.; Witiak, D. T. *Cancer Lett.* **1979**, *6*, 263–272.

(16) Sheikh, Y. M.; Hart, R. W.; Witiak, D. T. *Bioorg. Chem.* **1981**, *10*, 429–442.

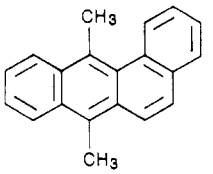
(17) Sheikh, Y. M.; Joyce, N. J.; Daniel, F. B.; Oravec, C. T.; Cazer, F. D.; Raber, J.; Braskar, D.; Witiak, D. T.; Hart, R. W.; D'Ambrosio, S. M. In *Polynuclear Aromatic Hydrocarbons*; Cooke, M., Dennis, A. J., Eds.; Battelle: Columbus, OH, 1981; pp 625–639.

0022-3263/86/1951-4499$01.50/0

bond which is of greater bond energy than the aryl–hydrogen bond (116 kcal/mole for fluorobenzene vs. 103 kcal/mole for benzene)[18] may block or reduce carcinogenicity if it is inserted onto a position critical to metabolism and/or bonding to the cellular target. Because **1** has a partially reduced A-ring, bay region diol epoxide metabolites are not likely ultimate carcinogenic candidates.[5] Rather, physical bonding to DNA,[9] radical cations,[19,20] or metabolism in the B-[21] and/or D-rings,[22,23] etc. could be of fundamental importance to initiation of the carcinogenic event. For purposes of exploring such possibilities in the 1,2,3,4-tetrahydro system **1** we desired samples of various monofluoro regioisomers. In this article we described the synthesis of 5-, 6-, and 10-fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracenes (**3**, **4**, and **5**, respectively) and



1, X = Y = Z = H
3, X = Y = H, Z = F
4, X = Z = H, Y = F
5, X = F, Y = Z = H



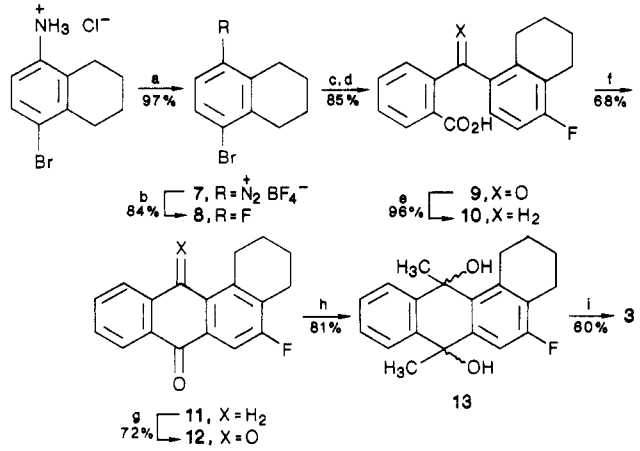
2

certain unpredicted chemical behaviors of the 6-fluoro analogue **4** wherein acid-catalyzed isomerization of **4** affords 7- and 12-methylene tautomers. The relative effectiveness of all fluoro regioisomers to transform human neonatal fibroblasts in culture as a function of their individual metabolism possibly leading to DNA adducts as assessed by ^{32}P postlabeling methodologies[12,13] is currently being explored.

Results and Discussion

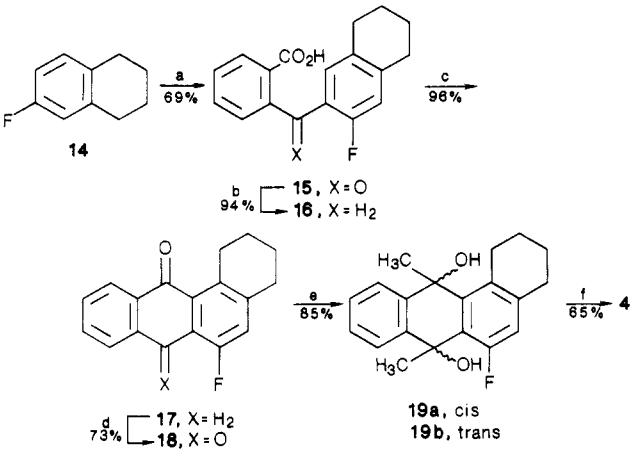
Synthesis of 5-F analogue **3** from the aminotetralin salt **6**[24] is summarized in Scheme I. Thermolysis of diazonium tetrafluoroborate **7** afforded bromofluorotetralin **8** (82% from **6**). The Grignard[25] of **8** underwent reaction with phthalic anhydride, affording keto acid **9** (85%). Zn/KOH reduction produced acid **10** (96%), cyclization (concentrated H_2SO_4) yielded anthrone **11** (68%), and dichromate oxidation afforded quinone **12** (72%). Treatment of **12** with excess MeMgBr yielded diastereomeric diols **13** (81%). Whereas $SnCl_2$/HCl reductive dehydration[26] of **13** afforded **3** in 26% yield and HI/MeOH–$SnCl_2$/HCl treatment[27] of **13** produced **3** in 27% yield, deoxygenation of diol **13** with $TiCl_3$/$LiAlH_4$[28] afforded **3** in 60% yield.

Scheme I[a]



[a] (a) 6 N HCl, $NaNO_2$, HBF_4, 0 °C, 15 min; (b) 170 °C; (c) Mg, ethylene dibromide, THF/benzene (2:1), reflux, 45 min; (d) phthalic anhydride, benzene, reflux, 5 h; (e) Zn, 10% aqueous KOH, reflux, 26 h; (f) concentrated H_2SO_4, room temperature 1 h; (g) $K_2Cr_2O_7$, HOAc, reflux, 10 min; (h) CH_3MgBr, benzene/Et_2O (2:1), reflux, 7 h; (i) $TiCl_3$, $LiAlH_4$, THF, reflux, 3 h.

Scheme II[a]

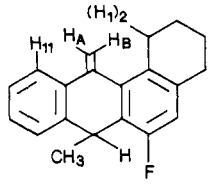


[a] (a) phthalic anhydride, $AlCl_3$, *o*-dichlorobenzene, 95 °C, 5 h; (b) Zn, 10% aqueous KOH, reflux, 21 h; (c) concentrated H_2SO_4, room temperature, 1 h; (d) $K_2Cr_2O_7$, HOAc, reflux, 20 min; (e) CH_3MgBr, benzene/Et_2O, reflux, 3 h; (f) $TiCl_3$, $LiAlH_4$, THF, reflux, 3 h.

6-Fluoro analogue **4** was synthesized from known fluorotetralin **14**[29,30] prepared according to literature methods.[29–32] Friedel–Crafts acylation[33,34] afforded keto acid derivative **15** (69%) whose structure was confirmed by ^{19}F and ^1H NMR spectroscopy (Scheme II). A characteristic doublet (J_{H5-F} = 11.5 Hz) for ortho coupling in the ^1H spectrum and doublet of doublets (J_{H5-F} = 11.3 Hz and J_{H8-F} = 7.6 Hz) for ortho and meta coupling of the fluorine resonance signal substantiated the structural assignment. Formation of **15** was accompanied by a mixture of less than 10% other regioisomers as determined by ^1H and ^{19}F

(18) Gordon, A. J.; Ford, R. A. *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*; Wiley: New York, 1972; p 113.
(19) Cavalieri, E.; Rogan, E. In *Polycyclic Hydrocarbons and Carcinogenesis*; Harvey, R. G., Ed.; ACS Symposium Series 283; American Chemical Society: Washington, DC, 1985; pp 289–305.
(20) Sullivan, P. D.; Ocasio, I. J.; Chen, X.; Bannoura, F. *J. Am. Chem. Soc.* **1986**, *108*, 157–260.
(21) Jerina, D. M.; Daly, J. W. *Science (Washington, D.C.)* **1974**, *185*, 573–582.
(22) Cooper, C. S.; Ribeiro, O.; Hewer, A.; Walsch, C.; Pal, K.; Grover, P. L.; Sims, P. *Carcinogenesis* **1980**, *1*, 233–243.
(23) MacNicoll, A. D.; Cooper, C. S.; Ribeiro, O.; Pal, K.; Hewer, A.; Grover, P. H.; Sims, P. *Cancer Lett.* **1981**, *11*, 243–249.
(24) Fenton, S. W.; Dewald, A. E.; Arnold, R. T. *J. Am. Chem. Soc.* **1955**, *77*, 979–984.
(25) Newman, M. S.; Tuncay, A. *J. Org. Chem.* **1980**, *45*, 348–349.
(26) Newman, M. S.; Kanakrajan, K. *J. Org. Chem.* **1980**, *45*, 2301–2304.
(27) Sandin, R. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1940**, *62*, 3098–3105.
(28) Walborsky, H. M.; Wust, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807–5808.
(29) Sy, M.; Thiault, G. A. *Bull. Soc. Chim. Fr.* **1965**, *5*, 1308–1315.
(30) Adcock, W.; Betless, P. D.; Rizvi, S. W. A. *Aust. J. Chem.* **1970**, *23*, 1921–1937.
(31) Newman, M. S.; Chatterji, R.; Seshadri, S. *J. Org. Chem.* **1961**, *26*, 2667–2669.
(32) Buckle, D. R.; Cantello, B. C. C.; Smith, H.; Smith, R. J.; Spicer, B. A. *J. Med. Chem.* **1977**, *20*, 1059–1064.
(33) Newman, M. S.; Zahm, H. V. *J. Am. Chem. Soc.* **1943**, *65*, 1097–1101.
(34) Eisenbraun, E. J.; Melton, R. G.; Webb, T. E. *Org. Prep. Proced. Int.* **1971**, *3*, 197–200.

Table I. NOE Enhancements for Four Protons of 6-Fluoro-1,2,3,4,7,12-hexahydro-7-methyl-12-methylenebenz[*a*]anthracene (20) Measured on a Degassed $CDCl_3$ Solution (0.22 M)

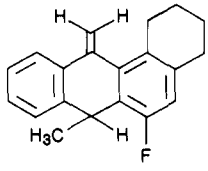


irradiated proton	ppm,[a] mult	obsd proton	ppm,[a] mult	% area increase
H-11	7.5, m	H-A	5.82, s	7
H-11	7.5, m	H-B	5.48, d	-1
H-A	5.82, s	H-11	7.5, m	14
H-A	5.82, s	H-B	5.48, d	30
H-A	5.82, s	H-1	2.8, m	-1
H-B	5.48, d	H-11	7.5, m	-4
H-B	5.48, d	H-A	5.82, s	32
H-B	5.48, d	H-1	2.8, m	10

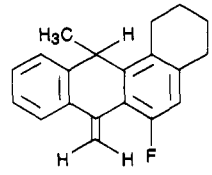
[a] Me_4Si as internal standard.

NMR. These 1-substituted tetralin isomers were easily separated from **15** by a single recrystallization from benzene. Reduction (Zn/KOH) afforded acid **16** (94%), ring closure (concentrated H_2SO_4) produced anthrone **17** (96%) and oxidation ($K_2Cr_2O_7$/HOAc) yielded quinone **18** (73%). Reaction with MeMgBr afforded a diastereomeric diol mixture (**19a**/**19b**; 3.4:1.0; 85%) isolated by selective crystallization of cis **19a** and chromatography on silica gel with CH_2Cl_2 of the mother liquor. Elution characteristics and product ratios were similar to those reported in the aromatic A-ring series.[35]

Conversion of selectively crystallized **19** (>95% cis) to target **4** was best carried out (65% yield) by using low-valent titanium.[28] With a modification of the $SnCl_2$/HCl reductive dehydration procedure[26] **4** was obtained in a maximum 23% yield. This modification employed excess $SnCl_2$ rather than excess HCl,[26] thereby limiting isomeric exo methylene tautomers **20** and **21** allowing for the isolation of **4**. Under these conditions only trace amounts



20

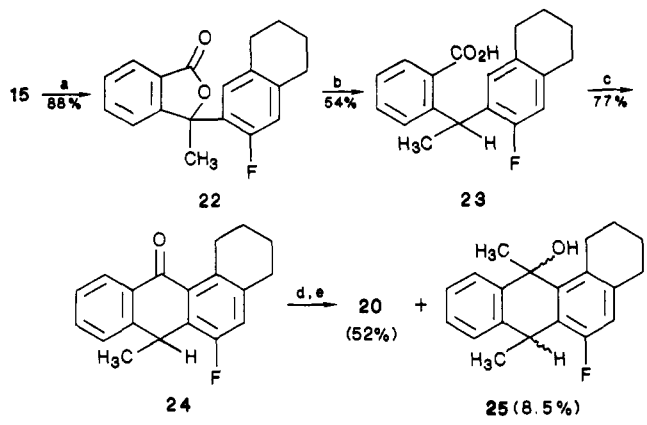


21

of **20** and **21** were produced, whereas with excess HCl, contamination of **4** with **20** and **21** precluded its purification. Utilization of tandem HI/MeOH–$SnCl_2$/HCl conditions[27] or previously published $SnCl_2$/HCl reductive dehydration procedures[26] transformed **19** into **4** in only 5–10% yields. Careful chromatography (silica gel, hexane) of contaminated **4** allowed for the separation of **21**, whereas **20** cochromatographed with **4**.

Exo methylene tautomer **20** was independently synthesized from keto acid **15** (Scheme III) and its structure confirmed by ^1H and ^{19}F NMR analysis. Reaction of **15** with MeMgBr afforded phthalide **22** (88%). Zn/KOH reduction produced acid **23** (54%) and ring closure (concentrated H_2SO_4) yielded anthrone **24** (77%). Without purification of intermediates, **15** was convertible to **24** in 61% overall yield. Refluxing **24** with MeMgBr for 3 h followed by careful acidification (4 N HCl) and additional

Scheme III[a]



[a] (a) CH_3MgBr, benzene/Et_2O, reflux, 2.5 h; (b) Zn, aqueous KOH, reflux, 20 h; (c) concentrated H_2SO_4, room temperature, 1 h; (d) CH_3MgBr, Et_2O, reflux, 3 h; (e) aqueous HCl (4 N), benzene/Et_2O, reflux, 4 h.

refluxing for 4 h produced **20** (52%) and alcohol intermediate **25** (8.5%) isolated by column chromatography [silica gel, CH_2Cl_2/hexane (1:1) for **20**; CH_2Cl_2 for **25**]. *Under these conditions there was no appreciable isomerization of 20 to 4.*

The structure of **20** was confirmed by 270-MHz proton NOE difference experiments (Table I). The alternating positive and negative NOE effect for the respective two and three spin systems[36] involving H-11, H-A, H-B, and H-1 confirmed the assignment of the exo methylene function to position 12 and established assignments for the two nonequivalent vinyl proton resonance signals. The most compelling evidence for the structural assignment was derived from the NOE effect obtained upon irradiation of H-B wherein the area of the resonance signal for H-1 and H-A is increased by 10% and 32%, respectively, and for H-11 decreased by 4%. Thus, the exo methylene function must be neighboring the benzyl methylene protons on C-1. Additionally, the methyl proton resonance signal for **20** was observed as the expected doublet (δ 1.34, J = 7 Hz) and the neighboring tertiary proton as a quartet (δ 4.38, J = 7 Hz). Compound **21** must also be an exo methylene tautomer owing to vinyl proton resonance signals at δ 5.8–5.9 (multiplet), and methyl proton resonance signal as an expected doublet at δ 1.28 (J = 7 Hz), and a tertiary proton resonance signal at δ 4.20 (quartet, J = 7 Hz). Since NOE experiments establish the structure for tautomer **20**, **21** must be the 7-methylene regioisomer.

The synthesis of 10-F analogue **5** from aldehyde **29** is found in Scheme IV. We prepared **29** via chloromethylation of tetralin, conversion to the acetate, hydrolysis, and oxidation according to the method of Wightman et al.[37] However, owing to formation of both 1- and 2-carboxaldehydes and their difficult separation the method is not suitable for the preparation of sufficient quantities for use as starting material. Preferably, **29** was prepared free of its regioisomer from aminotetralin (**26**) via the bromo compound **27**.[24] The corresponding Grignard **28** underwent reaction with Meyers' reagent [*N*-methyl-*N*-2-pyridinylformamide],[38] affording **29** in 58% overall yield from **26**.

Reaction of **29** with lithio reagent **30**, followed by hydrolysis afforded phthalide **31** in 53% yield. Catalytic

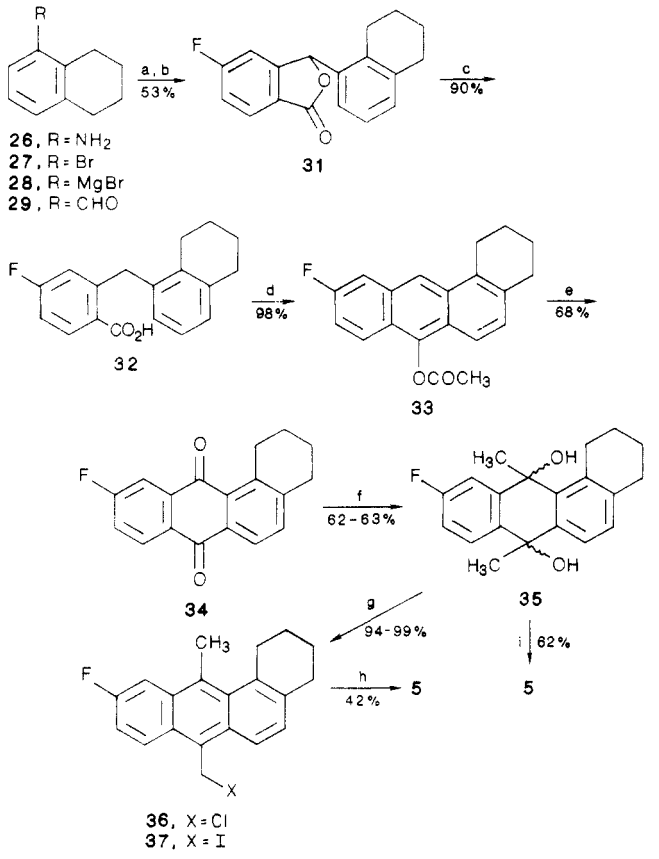
(35) Newman, M. S.; Fikes, L. E.; Hashem, M. M.; Kannan, R.; Sankaran, V. *J. Med. Chem.* **1978**, *21*, 1076–1078.

(36) Bell, R. A.; Saunders, J. K. *Can. J. Chem.* **1968**, *46*, 3421–3423.

(37) Wightman, R. H.; Laycock, D. E.; Avdovich, H. W. *J. Org. Chem.* **1978**, *43*, 2167–2170.

(38) Commins, D.; Meyers, A. I. *Synthesis* **1978**, 403–404.

Scheme IV[a]



[a] (a) 2-(4-Fluoro-2-lithiophenyl)-4,4-dimethyl-2-oxazoline (**30**), THF, 40 °C, 21 h; (b) aqueous HCl, 3.5 h, reflux; (c) H_2, 43 psi, room temperature, 6 h, Pd/C, HOAc; (d) $ZnCl_2$, Ac_2O, HOAc, 1 h, reflux; (e) $K_2Cr_2O_7$, HOAc, 0.5 h, reflux; (f) CH_3MgBr (4 h) or CH_3Li (3.5 h), reflux; (g) gaseous HCl, EtOAc, room temperature 1.5 h, or 40% aqueous HI, MeOH, 0 °C, 20 min; (h) $NaBH_4$, Me_2SO, 80 °C, 1 h; (i) $TiCl_3$, $LiAlH_4$, THF, reflux, 3 h.

hydrogenation provided acid **32** (90%) exhibiting a dibenzylic CH_2 proton resonance signal at δ 4.38. Zn/HCO_2H[39] or Zn/KOH reductions[25] of **31** afforded **32** in poor yields: 50% and 36%, respectively. Lewis acid catalyzed cyclization and acetylation[27] afforded **33** (98%), having a molecular ion m/e 308 and base peak owing to ketene loss at m/e 266. Careful oxidation (0.5 h) of **33** with $K_2Cr_2O_7$ produced anthraquinone **34** (68%) which upon reaction with CH_3MgBr or CH_3Li afforded diastereomeric diols[35] **35** (cis/trans 4:1 and 3.8:1, respectively) in 62% and 63% yields, respectively. The cis diol may be separated from the trans isomer by crystallization from benzene/petroleum ether or by chromatography on silica gel (60 mesh) with CH_2Cl_2. Diol **35**, having tertiary hydroxyl groups at benzylic carbon atoms, did not afford an M^+ peak in its 70-eV mass spectrum owing to facile loss of H_2O. Also, successive loss of two methyl groups yielding $M^+ - CH_3$ and $M^+ - 2(CH_3)$ ions is consistent with the assigned structure for **35**.

Dehydration and aromatization using gaseous HCl[40] or 48% aqueous HI[2,40] afforded 7-halomethyl intermediates **36** and **37** in nearly quantitative yields. As expected the ^1H NMR CH_2 resonance signal for the chloromethyl group is further downfield (δ 5.51) than the resonance signal for the iodomethyl function (δ 5.39). As is the case for 7-halomethyl derivative of **2**, **36** is more stable than **37**, which decomposes under ordinary light but is stable in the freezer. The iodomethyl intermediate is preferred since conversion to the target 10-fluorotetrahydro-PAH **5** using $NaBH_4/Me_2SO$[41] proceeds cleanly and in better yield. Again, both halomethyl compounds lacked M^+ ions in the 70-eV mass spectrum and exhibited ions at m/e 277 owing to halogen loss generating stabilizing carbonium ions which lose H giving conjugated olefinic ions at m/e 276. Other significant ions arising from m/e 276 likely result from loss of CH_3 and retro-Diels–Alder loss of C_2H_4 from ring A.

Comparative reduction methods affording **5** from **36** and **37** reveal for **36**, $SnCl_2/HCl$[26,40,42] (20%), $LiAlH_4$/THF (12%), $NaBH_4$/MeOH (15%), and $NaBH_4/Me_2SO$[41] (33%), and for **37**, $SnCl_2/HCl$[26] (28%), $LiAlH_4$/THF[43] (25%), $NaBH_4$/MeOH (23%) and $NaBH_4/Me_2SO$[41] (42%). Preferably, **35** was converted to **5** in 62% yield by using $TiCl_3/LiAlH_4$.[28]

The comparative isomerization of tetrahydrobenz[*a*]anthracene **4** and its 12-methylene tautomer **20** is found in Table II. In refluxing benzene containing TsOH, **4** equilibrated with methylene tautomers **20** and **21** within 1 h. In the absence of acid catalysis, no isomerization was observed after 3 h. When **20** was treated with TsOH in refluxing benzene, the thermodynamic isomeric product ratio was not obtained after 1 or 5 h. After 72 h, the product ratio was similar to the ratio observed when **4** was subjected to acid-catalyzed isomerization for 1 h. These data are markedly different than results observed for acid-catalyzed isomerization of TH-DMBA (**1**), 5F-TH-DMBA (**3**), or 10F-TH-DMBA (**5**) which after 72 h only afforded fully aromatic to 7-methylene isomer ratios of 14:1, 8:1, and 8:1, respectively. Thus, $\Delta G \pm SD(\mathbf{4} \rightleftarrows \mathbf{21}) = -0.8 \pm 0.1$ kcal/mol, $\Delta G(\mathbf{20} \rightleftarrows \mathbf{21}) = -1.5 \pm 0.5$ kcal/mol, and $\Delta G(\mathbf{4} \rightleftarrows \mathbf{20}) = 0.8 \pm 0.5$ kcal/mol. For **1**, **3**, or **5**, respective 7-methylene isomer ΔG = 1.9, 1.5, and 1.5 kcal/mol, respectively.

The rate of conversion of the fully aromatic PAH **4** to the 7-exo methylene isomer **21** is considerably faster than

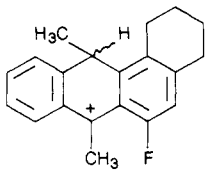
Table II. Comparative Isomerization of 6-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (4) and Its 12-Methylene Tautomer (20) in Refluxing Benzene in the Presence or Absence of Acid Catalysis

		product ratio[b]		
treated[a]	conditions	4	20	21[c]
4	reflux,[d,e] 1 h	1.0[f]	0.3 ± 0.1	3.1 ± 0.1
4	reflux,[d,e] 5 h	1.0	0.4 ± 0.2	3.1 ± 0.1
4	reflux,[g,h] 3 h	1.0	0.0	0.0
20	reflux,[d,e] 1 h	1.0	27 ± 1.0	2.0 ± 0.9
20	reflux,[d,e] 5 h	1.0	4.6 ± 0.8	3.2 ± 0.4
20	reflux,[d,e] 72 h	1.0	0.6 ± 0.1	2.8 ± 0.4
20	reflux,[g,h] 5 h	0.0	1.0	0.0

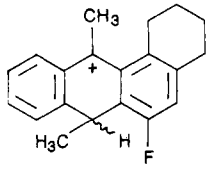
[a] 10 mg of PAH. [b] Determined by integration of ^1H NMR spectra in $CDCl_3$ of the vinyl proton resonance signals for **20** and **21** and H-8, H-11 multiplet for **4**. [c] The 7-methylene tautomer of **4**. [d] *p*-Toluenesulfonic acid (2.5 mg) in 5 mL of benzene. [e] The reaction mixture was passed through a disposable Pasteur pipet containing a 7-cm column of basic alumina (Woelm) and eluted with 6–8 mL of benzene. The eluate was concentrated under reduced pressure and traces of benzene were removed by repeated evaporation from CCl_4 under reduced pressure. The residue was dissolved in $CDCl_3$ for NMR studies. [f] Product ratios are reported relative to **4**. [g] Benzene (5 mL); no acid added. [h] Same workup as in *e*, but no column chromatography was necessary.

(39) Newman, M. S.; Blum, S. *J. Org. Chem.* **1964**, *29*, 1414–1416.
(40) Newman, M. S.; Sankaran, V. *Tetrahedron Lett.* **1977**, *24*, 2067–2068.
(41) Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maranoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259–2267.
(42) Wood, J. L.; Fieser, L. F. *J. Am. Chem. Soc.* **1940**, *62*, 2674–2681.
(43) Sheikh, Y. M.; Cazer, F. D.; Hart, R. W.; Witiak, D. T. *J. Org. Chem.* **1979**, *44*, 3715–3717.

isomerization of the 12-exo methylene isomer **20** to **21**. Thus, conversion of **20** to **4** is the slow step. Possibly, this reflects resonance stabilization by the 6-F group of the intermediate cation **38** derived from protonation of **4**.



38



39

Protonation of **20** would yield cation **39**, which cannot be resonance stabilized by fluorine. Additionally, an unfavorable steric interaction between the 7-CH_3 group and the 6-F substituent becomes more severe as the compound passes from a puckered **20** to a planar **4**. Although both 5- and 10-F groups (**3** and **5**) would have an inverse effect on stabilization of the respective cations, for these compounds no such CH_3–F peri interaction is present and little isomerization to exo methylene tautomers is possible since the fully aromatic system is thermodynamically most stable.

TH-DMBA PAH **1**, **3**, and **5** each have one peri interaction, but 6-F derivative **4** has an additional CH_3–F peri interaction serving to drive acid-catalyzed isomerization to the thermodynamically more stable 7-exo methylene compound **21**, which is sterically the least crowded of the two (**20** and **21**) exo methylene regioisomers formed. These data are in agreement with isomerization studies using polymethylated anthracenes.[44,45] At least two peri C-H_3–CH_3 interactions were required for isomerization to thermodynamically more stable less sterically crowded exo methylene tautomers. Carcinogenicity investigation with these PAH are of particular interest in light of a recent report describing the mutagenicity and carcinogenicity of various methylated anthracenes.[46]

Experimental Section

General. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Mass spectra were recorded with a Kratos MS-30 operating at 70 eV. Infrared spectra were recorded on a Beckman Model IR-4210 or 4230 spectrophotometer. ^1H NMR spectra were determined on a Brucker HX-90E or an IBM NR-80 spectrometer. NOE experiments were carried out on an IBM NR/270 FT-NMR spectrometer. Me_4Si was used as an internal standard, and chemical shifts are reported on the δ scale with peak multiplicities: d, doublet; dd, double of doublets; m, multiplet; s, singlet; t, triplet. Purification of compounds was carried out by column chromatography over silica gel 60 mesh (E. Merck) and 100–200 mesh (Fisher Scientific Co.) and also by preparative thin-layer chromatography (TLC) over precoated silica gel GF plates (E. Merck). THF, after distilling over CaH_2, was heated at reflux over Na and benzophenone and distilled under N_2 prior to use. Petroleum ether (boiling range 35–60 °C) was used for chromatography or crystallization. Synthesis and purification of the target PAH was always carried out under yellow light. Proof of purity was by HPLC (Varian 5000) using a Zorbax ODS 6.2 mm × 25 cm column with a UV monitor (254 nm) and gradient elution 60% MeOH to 100% MeOH over 30 min. *By this procedure any 7- or 12-oxidation products can be detected and were found to be absent in all samples submitted for biological investigations which are carried out under yellow light.* Elemental analyses were performed by Galbraith Laboritories, Inc., Knoxville, TN.

1-Bromo-4-fluoro-5,6,7,8-tetrahydronaphthalene (8). An aqueous solution of $NaNO_2$ (4.30 g/10 mL, 61 mmol) was added dropwise to an ice cooled, stirred mixture of **6**[24] (16.0 g, 61 mmol), H_2O (40 mL), and concentrated HCl (20 mL). The yellow solution was filtered and 48% HBF_4 (30 mL) was added to the ice-cooled filtrate. After the mixture was stirred for 15 min the diazonium tetrafluoroborate **7** [19.20 g (97%; mp 123–124 °C dec)] was filtered, washed with H_2O, MeOH/Et_2O (1:1), and Et_2O successively, and dried in a vacuum desiccator (room temperature, 1 torr) overnight: IR (KBr) 2280 (—$N^+\equiv N$) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.7–1.9 (m, 4 H, H-6, H-7), 2.7–2.9 (m, 2 H, H-5), 3.0–3.2 (m, 2 H, H-8), 8.12 (d, 1 H, J = 8.9 Hz, H-3), 8.44 (d, 1 H, J = 8.6 Hz, H-2).

In a round-bottom flask fitted with a reflux condenser, **7** (18.9 g, 58 mmol) was thermolyzed in a 170 °C oil bath for 20 min. The dark oil was taken up in hexane and filtered and the solvent removed under reduced pressure. Distillation afforded **8** (11.22 g, 82% based on **2**) as a colorless liquid: bp 88–89 °C (1.2 torr); ^1H NMR (Me_2SO-d_6) δ 1.6–1.9 (m, 4 H, H-6, H-7), 2.5–2.8 (m, 4 H, H-5, H-8), 6.95 (dd, 1 H, $J_{H-F} \simeq J_{ortho} \simeq$ 9 Hz, H-3), 7.42 (dd, 1 H, J_{ortho} = 8.9 Hz, J_{H-F} = 5.4 Hz, H-2). Anal. Calcd for $C_{10}H_{10}BrF$: C, 52.43; H, 4.40; F, 8.29. Found: C, 52.52; H, 4.44; F, 8.31.

2-[(4-Fluoro-5,6,7,8-tetrahydro-1-naphthalenyl)-carbonyl]benzoic Acid (9). A solution of **8** (10.00 g, 44 mmol) and ethylene dibromide (0.36 mL) in 105 mL of dry THF/benzene (2:1) was added dropwise over 1 h to a stirred mixture of sublimed Mg (2.91 g, 121 mmol) in THF (25 mL) under N_2 and refluxed for 45 min. The Grignard was injected into a warmed solution of phthalic anhydride (6.98 g, 47 mmol) in benzene (180 mL) and refluxed under N_2 for 5 h. The yellow reaction mixture was cooled in an ice bath and carefully quenched with 10% HCl solution (60 mL). The organic layer was separated and the aqueous layer extracted (Et_2O). The organic fractions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. Recrystallization (benzene) of the light yellow product gave **9** (11.10 g, 85%): mp 208–210 °C; IR (KBr) 2400–3200 (CO_2H) 1670 (C=O), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, H-6′, H-7′), 2.6–2.9 (m, 2 H, H-8′), 3.0–3.3 (m, 2 H, H-5′), 6.71 (dd, 1 H, J_{H-F} = J_{ortho} = 8.6 Hz, H-3′), 6.99 (dd, J_{ortho} = 8.6 Hz, J_{H-F} = 6.0 Hz, H-2′), 7.3–7.8 (m, 3 H, H-3, H-4, H-5), 7.9–8.1 (m, 1 H, H-6). Anal. Calcd for $C_{18}H_{15}FO_3$: C, 72.46; H, 5.07; F, 6.36. Found: C, 72.84; H, 5.03; F, 6.22.

2-[(4-Fluoro-5,6,7,8-tetrahydro-1-naphthalenyl)methyl]-benzoic Acid (10). A mixture of **9** (5.70 g, 19 mmol), Zn dust (42.0 g, activated by washing with dilute aqueous HCl), $CuSO_4$ (82 mg), and pyridine (5 mL) in 10% KOH solution (70 mL) was refluxed for 26 h. The reaction mixture was filtered while hot, and the filter cake was washed with H_2O. The filtrate was poured onto ice/concentrated HCl solution, and the white precipitate was filtered and dried affording **10** (5.24 g, 96%); mp 183–184 °C. The analytical sample melted at 183–184.5 °C (benzene/petroleum ether): IR (KBr) 2400–3200 (CO_2H), 1690 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, H-6′, H-7′), 2.5–2.9 (m, 4 H, H-5′, H-8′), 4.34 (s, 1 H, Ar-CH_2-Ar), 6.6–6.8 (m, 2 H, H-2′, H-3′), 6.9–7.1 (m, 1 H, H-3), 7.2–7.6 (m, 2 H, H-4, H-5), 8.0–8.2 (m, 1 H, H-6). Anal. Calcd for $C_{18}H_{17}FO_2$: C, 76.02; H, 6.03; F, 6.69. Found: C, 75.88; H, 6.09; F, 6.32.

5-Fluoro-2,3,4,12-tetrahydrobenz[*a*]anthracen-7(1*H*)-one (11). A mixture of **10** (5.20 g, 18 mmol) in concentrated H_2SO_4 (100 mL) was stirred at room temperature for 1 h. The red solution was poured onto ice and extracted (CH_2Cl_2). The organic fractions were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was triturated with MeOH, filtered, and dried, affording 3.75 g of crude **11**; mp 178–183 °C. Recrystallization (benzene/EtOH) afforded pure **11** (3.30 g, 68%): mp 184–189 °C; IR (KBr) 1650 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H, H-2, H-3), 2.6–2.9 (m, 4 H, H-1, H-4), 3.98 (s, 2 H, H-12), 7.3–7.7 (m, 3 H, H-9, H-10, H-11), 7.80 (d, 1 H, J_{H-F} = 10.2 Hz, H-6), 8.2–8.4 (m, 1 H, H-8). Anal. Calcd for $C_{18}H_{15}FO$: C, 81.17; H, 5.68; F, 7.14. Found: C, 81.23; H, 5.72; F, 7.04.

5-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione (12). To a refluxing mixture of $K_2Cr_2O_7$ (3.42 g, 12 mmol) in HOAc (60 mL) was added **11** (2.96 g, 11 mmol) in a single portion. After 10 min of refluxing, the hot solution was poured onto ice, filtered,

(44) Bowden, B. F.; Cameron, D. W. *J. Chem. Soc., Chem. Commun.* **1977**, 78, 79.
(45) Hart, H.; Ruge, B. *Tetrahedron Lett.* **1977**, *36*, 3143–3146.
(46) LaVoie, E. J.; Coleman, D. T.; Rice, J. E.; Geddie, N. G.; Hoffman, D. *Carcinogenesis* **1985**, *6*, 1483–1488.

and dried. Column chromatography (silica gel, CH_2Cl_2) afforded **12** (2.25 g, 72%) after recrystallization from benzene/EtOH: mp 166–167 °C; IR (KBr) 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H, H-2, H-3), 2.7–3.0 (m, 2 H, H-4), 3.3–3.5 (m, 2 H, H-1), 7.6–7.9 (m, 3 H, H-6, H-9, H-10), 8.1–8.3 (m, 2 H, H-8, H-11). Anal. Calcd for $C_{18}H_{13}FO_2$: C, 77.12; H, 4.68; F, 6.78. Found: C, 77.30; H, 4.74; F, 6.76.

***cis*/*trans*-5-Fluoro-1,2,3,4,7,12-hexahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (13).** An ether solution of 2.8 M MeMgBr (Aldrich, 15 mL, 42 mmol) was injected into a stirred solution of **12** (1.00 g, 3.6 mmol) in dry benzene (30 mL) under N_2 at room temperature. The yellow solution was refluxed for 7 h, cooled to room temperature, and slowly poured onto ice. The mixture was extracted (EtOAc), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was recrystallized from benzene/petroleum ether, affording **13** (0.93 g, 81%) as a diastereomeric mixture of diols: IR (KBr) 3150–3600 (OH) cm^{-1}. Anal. Calcd for $C_{20}H_{21}FO_2$: C, 76.88; H, 6.78; F, 6.08. Found: C, 77.04; H, 6.95; F, 6.02.

5-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (3). Low-valent titanium[28] was prepared by slowly adding $LiAlH_4$ (24 mg, 0.64 mmol) to a stirred suspension of $TiCl_3$ (197 mg, 1.28 mmol) in dry THF (5 mL) under a stream of N_2 at 0 °C. The mixture was stirred at 0 °C for 10 min and refluxed for 1 h. To this black suspension was added **13** (100 mg, 0.32 mmol) at 0 °C under a stream of N_2. The mixture was refluxed for 3 h, cooled to 0 °C, quenched with 2 N HCl (2 mL), diluted with H_2O, and extracted (CH_2Cl_2). The organic fractions were combined, washed (H_2O), dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography (silica gel, hexane) of the yellow, fluorescent residue afforded 53 mg (60%) of **3** after recrystallization from CH_2Cl_2/MeOH: mp 116–116.5 °C; >99% pure by HPLC analysis; ^1H NMR ($CDCl_3$) δ 1.5–2.2 (m, 4 H, H-2, H-3), 2.8–3.0 (m, 2 H, H-4), 2.94 (s, 3 H, CH_3), 3.12 (s, 3 H, CH_3), 3.2–3.4 (m, 2 H, H-1), 7.3–7.6 (m, 2 H, H-9, H-10), 7.63 (d, 1 H, J_{H-F} = 12.7 Hz, H-6), 8.1–8.3 (m, 2 H, H-8, H-11). Anal. Calcd for $C_{20}H_{19}F$: C, 86.30; H, 6.88; F, 6.82. Found: C, 86.29; H, 6.87; F, 6.83.

2-[(3-Fluoro-5,6,7,8-tetrahydro-2-naphthalenyl)carbonyl]benzoic Acid (15) and Its Methyl Ester. To a stirred mixture of **14**[29,30] (5.25 g, 35 mmol) and phthalic anhydride (4.71 g, 32 mmol) in *o*-dichlorobenzene (50 mL) was added $AlCl_3$ (8.46 g, 64 mmol) in three portions over 15 min. The reaction mixture was stirred at 95 °C for 5 h. The deep red solution was poured onto ice/concentrated HCl and extracted (EtOAc). The organic fractions were combined, dried ($MgSO_4$), filtered, and evaporated under reduced pressure removing only the EtOAc. Petroleum ether (150 mL) was added to the *o*-dichlorobenzene fraction. Cooling yielded 8.20 g of pale yellow product, mp 174–182 °C. Recrystallization from benzene gave **15** (6.55 g, 69%) as pale yellow crystals (mp 179.5–184.5 °C) of sufficient purity for subsequent reactions. Fisher esterification provided an analytical sample of methyl ester: mp 107.5–109 °C (MeOH); IR (KBr) 1725 (CO_2Me), 1670 (ArCOAr), 1280 (C–O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, $2CH_2$), 2.6–2.9 (m, 4 H, 2 CH_2), 3.72 (s, 3 H, OCH_3), 6.74 (d, 1 H, J_{H-F} = 11.8 Hz, H-4′), 7.3–7.4 (m, 1 H, H-1), 7.4–7.7 (m, 3 H, H-3, H-4, H-5), 7.9–8.0 (m, 1 H, H-6). Anal. Calcd for $C_{19}H_{17}O_3F$: C, 73.05; H, 5.49; F, 6.09. Found: C, 73.05; H, 5.61; F, 6.06.

Alkaline hydrolysis of the methyl ester of **15** afforded analytically pure **15**: mp 184.5–186 °C (benzene/hexane); IR (KBr) 1670–1720 (C=O's), 2400–3300 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H, $2CH_2$), 2.6–2.9 (br s, 4 H, $2CH_2$), 6.72 (d, 1 H, J_{H-F} = 11.5 Hz, H-4′), 6.6–7.2 (br s, 1 H, CO_2H, exchangeable), 7.3–7.4 (m, 1 H, H-1′), 7.4–7.7 (m, 3 H, H-3, H-4, H-5), 8.0–8.1 (m, 1 H, H-6). Anal. Calcd for $C_{18}H_{15}O_3F$: C, 72.46; H, 5.07; F, 6.37. Found: C, 72.69; H, 5.15; F, 6.06.

2-[(3-Fluoro-5,6,7,8-tetrahydro-2-naphthalenyl)methyl]benzoic Acid (16). A solution of **15** (3.91 g, 13 mmol), $CuSO_4$ (60 mg), Zn dust (30 g; activated by washing with dilute HCl), and pyridine (4 mL) in 10% KOH solution was refluxed for 21 h. The hot mixture was filtered and the filter cake washed with H_2O. The filtrate was poured onto ice/concentrated HCl, and the white precipitate was filtered, washed with H_2O, and dried, affording **16** (3.51 g, 94%); mp 151–152 °C. The analytical sample melted at 157–158 °C (benzene/hexane): IR (KBr) 1690 (CO_2H), 2400–3200 (CO_2H) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H, $2CH_2$), 2.5–2.8 (m, 4 H, $2CH_2$), 4.41 (s, 3 H, $ArCH_2Ar$) 4.5–6.0 (br s, 1 H, CO_2H), 6.73 (d, 2 H, $J_{F-H-1'} \simeq J_{F-H-4'} \simeq$ 9.8 Hz, H-1′, H-4′), 7.1–7.6 (m, 3 H, H-3, H-4, H-5), 8.01 (dd, 1 H, J_{ortho} = 8.0 Hz, J_{meta} = 1.5 Hz, H-6). Anal. Calcd for $C_{18}H_{17}O_2F$: C, 76.02; H, 6.03; F, 6.69. Found: C, 75.79; H, 6.07; F, 6.47.

6-Fluoro-2,3,4,7-tetrahydrobenz[*a*]anthracen-12(1*H*)-one (17). A mixture of **16** (4.00 g, 14 mmol) in concentrated H_2SO_4 (100 mL) was stirred at room temperature for 1 h. The red solution was poured onto ice, and the yellow precipitate was filtered, washed with H_2O, and dried, affording **17** (3.61 g, 96%); mp 138.5–141.5 °C. The analytical sample melted at 144–144.5 °C (benzene/hexane): IR (KBr) 1655 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H, $2CH_2$), 2.7–3.0 (m, 2 H, H-4), 3.2–3.5 (m, 2 H, H-1), 4.22 (s, 2 H, H-7), 7.03 (d, 1 H, J_{H-F} = 9.9 Hz, H-5), 7.3–7.7 (m, 3 H, H-8, H-9, H-10), 8.1–8.3 (m, 1 H, H-11). Anal. Calcd for $C_{18}H_{15}OF$: C, 81.17; H, 5.68; F, 7.14. Found: C, 80.92; H, 5.69; F, 7.01.

6-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione (18). A mixture of **17** (3.60 g, 13 mmol) and $K_2Cr_2O_7$ (5.95 g, 20 mmol) in glacial HOAc (60 mL) was refluxed for 20 min. The reaction mixture was poured onto ice. The yellow precipitate was filtered, washed thoroughly with H_2O, dried, and chromatographed on a silica gel column with CH_2Cl_2 as eluent to give **18** (2.62 g, 73%) as yellow needles from benzene/EtOH: mp 190–191 °C; IR (KBr) 1670 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–2.0 (m, 4 H, $2CH_2$), 2.8–3.0 (m, 2 H, H-4), 3.2–3.4 (m, 2 H, H-1), 7.18 (d, 1 H, J_{H-F} = 12.1 Hz, H-5), 7.6–7.8 (m, 2 H, H-9, H-10), 8.1–8.3 (m, 2 H, H-8, H-11). Anal. Calcd for $C_{18}H_{13}O_2F$: C, 77.12; H, 4.68; F, 6.78. Found: C, 77.08; H, 4.70; F, 6.62.

***cis*-6-Fluoro-1,2,3,4,7,12-hexahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (19a) and *trans*-6-Fluoro-1,2,3,4,7,12-hexahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (19b).** A solution of 2.8 M MeMgBr in Et_2O (Aldrich) was added to a stirred solution of **18** (1.00 g, 3.6 mmol) in dry benzene (30 mL) at room temperature under N_2 and refluxed for 3 h. The ice-cooled solution was quenched by the dropwise addition of H_2O (20 mL). The benzene layer was decanted, and the aqueous layer was extracted (EtOAc). The organic fractions were combined, washed (saturated NaCl solution), and dried ($MgSO_4$). The solvent was evaporated, and the residue was crystallized from benzene/petroleum ether to give 0.63 g of white crystalline cis-diol **19a**. The analytical sample melted at 190.5–191.5 °C (benzene/petroleum ether). Column chromatography of the residue from the concentrated mother liquor (silica gel, CH_2Cl_2) gave 0.21 g of trans-diol **19b** after recrystallization from benzene/petroleum ether; mp 158–160 °C. An additional 0.09 g of *cis*-diol **19a** was eluted, providing a combined yield of 0.93 g (84%) of diols **19a** and **19b** (3.4:1.0).

cis-**19a**: IR (KBr) 3150–3600 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (d, 3 H, J = 0.7 Hz, 12-CH_3), 1.70 (d, 3 H, J = 0.95 Hz, 7-CH_3), 1.4–2.0 (m, 4 H, H-2, H-3), 2.49 (d, 1 H, J = 0.95 Hz, 12-OH), 2.7–2.9 (m, 2 H, H-4), 3.1–3.3 (m, 2 H, H-1), 3.46 (d, 1 H, J_{H-F} = 14.3 Hz, 7-OH, exchangeable), 6.80 (d, 1 H, J_{H-F} = 13.7 Hz, H-5), 7.2–7.4 (m, 2 H, H-9, H-10), 7.6–7.7 (m, 2 H, H-8, H-11). Anal. Calcd for $C_{20}H_{21}O_2F$: C, 76.88; H, 6.78; F, 6.08. Found: C, 76.68; H, 6.90; F, 5.91.

trans-**19b**: ^1H NMR ($CDCl_3$) δ 1.78 (s, 3 H, 12-CH_3), 1.87 (d, 3 H, J_{H-F} = 1.6 Hz, 7-CH_3), 1.7–2.1 (m, 4 H, H-2, H-3), 2.22 (s, 1 H, 12-OH, exchangeable), 2.7–2.9 (m, 2 H, H-4), 3.12 (d, 1 H, J_{H-F} = 9.9 Hz, 7-OH, exchangeable), 3.2–3.4 (m, 2 H, H-1), 6.87 (d, 1 H, J_{H-F} = 13.3 Hz, H-5), 7.3–7.5 (m, 2 H, H-9, H-10), 7.7–7.8 (m, 2 H, H-8, H-11).

6-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (4). The synthesis of **4** from **19a** (100 mg, 0.32 mmol) was carried out according to procedure for the preparation of **3**. The reaction mixture was refluxed for 3 h, cooled to 0 °C, diluted with H_2O (20 mL), and worked up accordingly. Column chromatography (silica gel, hexane) afforded 58 mg (65%) of **4** after recrystallization from benzene/MeOH: mp 69.5–70 °C; >99% pure by HPLC analysis; ^1H NMR ($CDCl_3$) δ 1.5–2.1 (m, 4 H, H-2, H-3), 2.8–3.0 (m, 2 H, H-4), 3.13 (s, 3 H, 12-CH_3), 3.23 (d, 3 H, J_{H-F} = 5.4 Hz, 7-CH_3), 3.0–3.3 (m, 2 H, H-1), 6.73 (d, 1 H, J_{H-F} = 15.3 Hz, H-5), 7.4–7.6 (m, 2 H, H-9, H-10), 8.2–8.6 (m, 2 H, H-8, H-11). Anal. Calcd for $C_{20}H_{19}F$: C, 86.30; H, 6.88; F, 6.82. Found: C, 86.10; H, 6.89; F, 6.82.

6-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (4). Seven drops of concentrated HCl (0.18 g, 2 mmol) was added to a stirred suspension of $SnCl_2 \cdot 2H_2O$ (3.00 g, 13 mmol) in Et_2O (20 mL). The supernatant (~15 mL) was decanted after 10 min of stirring. Under yellow light, **19a** (0.6 mmol) was added to the supernatant in two portions, stirred at room temperature for 1 h, quenched with H_2O (10 mL), and stirred for 10 min. The yellow reaction mixture was diluted with H_2O and extracted (benzene). The organic fractions were combined, washed (saturated NaCl solution), dried ($MgSO_4$), and evaporated under reduced pressure. Chromatography of the residue (silica gel, hexane) gave **4** (0.41 g, 23%) as yellow needles after recrystallization (benzene/MeOH); mp 65–66 °C.

3-(3-Fluoro-5,6,7,8-tetrahydro-2-naphthalenyl)-3-methyl-1(3*H*)-isobenzofuranone (22). A solution of 2.8 M MeMgBr (Aldrich, 7.6 mL, 21 mmol) was slowly added to a rapidly stirring solution of **15** (2.00 g, 7 mmol) in dry Et_2O (64 mL) and dry benzene (16 mL) at room temperature under N_2. The dark mixture was refluxed for 2.5 h, cooled in an ice bath, quenched with dilute HCl solution, and warmed for 1 h. The mixture was extracted (Et_2O), and the organic layers were combined, washed (5% $NaHCO_3$ solution), dried ($MgSO_4$), and concentrated under reduced pressure. The residue crystallized from benzene–petroleum ether, affording **22** (1.75 g, 88%): mp 89–90 °C; IR (KBr) 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.6–1.8 (m, 4 H, $2CH_2$), 2.05 (d, 3 H, J_{H-F} = 1.6 Hz, CH_3), 2.6–2.8 (m, 4 H, $2CH_2$), 6.77 (d, 2 H, J_{H-F} = 12.7 Hz, H-4′), 7.19 (d, 1 H, J_{H-F} = 8.2 Hz, H-1′), 7.3–7.7 (m, 3 H, H-4, H-5, H-6), 7.8–8.0 (m, 1 H, H-7). Anal. Calcd for $C_{19}H_{17}O_2F$: C, 76.99; H, 5.79; F, 6.41. Found: C, 76.99; H, 5.90; F, 6.13.

2-[1-(3-Fluoro-5,6,7,8-tetrahydro-2-naphthalenyl)ethyl]benzoic Acid (23). A mixture of **22** (1.00 g, 3.4 mmol), $CuSO_4$ (12 mg), Zn dust (6.0 g, activated by treatment with dilute acid), and pyridine (8 drops) in 10% KOH (10 mL) was refluxed for 20 h. The hot mixture was filtered and the filter cake washed with H_2O. The filtrate was poured onto ice/concentrated HCl, and the white precipitate was filtered, washed with H_2O, and dried, affording **23** (0.54 g, 54%) as off-white crystals after recrystallization from benzene–petroleum ether: mp 132–134 °C; Ir (KBr) 3200–2500 (OH), 1680 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.61 (d, 3 H, J = 7.3 Hz, CH_3), 1.7–1.9 (m, 4 H, $2CH_2$), 2.6–2.8 (m, 4 H, $2CH_2$), 5.42 (q, 1 H, J = 7.1 Hz, $CHCH_3$), 6.65 (d, 1 H, J_{H-F} = 11.1 Hz, H-4′), 6.90 (d, 1 H, J_{H-F} = 7.9 Hz, H-1′), 7.1–7.6 (m, 3 H, H-3, H-4, H-5), 8.0–8.2 (m, 1 H, H-6).

6-Fluoro-2,3,4,7-tetrahydro-7-methylbenz[*a*]anthracen-12(1*H*)-one (24). A mixture of **23** (0.53 g, 1.8 mmol) in concentrated H_2SO_4 (7 mL) was stirred at room temperature for 1 h. The deep red solution was poured onto ice and extracted (EtOAc). The organic fractions were combined, washed (saturated $NaHCO_3$), dried ($MgSO_4$), and evaporated under reduced pressure. Column chromatography of the residue on silica gel with CH_2Cl_2 as eluent afforded **24** (0.38 g, 77%) as off-white crystals after recrystallization from petroleum ether: mp 104–105 °C; IR (KBr) 1665 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.49 (d, 3 H, J = 7.3 Hz, 7-CH_3), 1.6–2.1 (m, 4 H, H-2, H-3), 2.7–2.9 (m, 2 H, H-4), 3.0–3.7 (m, 2 H, H-1), 4.46 (q, 1 H, J = 7.0 Hz, H-7), 7.02 (d, 1 H, J_{H-F} = 10.5 Hz, H-5), 7.3–7.7 (m, 3 H, H-8, H-9, H-10), 8.0–8.2 (m, 1 H, H-11). Anal. Calcd for $C_{19}H_{17}OF$: C, 81.39; H, 6.12; F, 6.78. Found: C, 81.02; H, 6.25; F, 6.53.

6-Fluoro-1,2,3,4,7,12-hexahydro-7,12-dimethylbenz[*a*]anthracen-12-ol (25) and 6-Fluoro-1,2,3,4,7,12-hexahydro-7-methyl-12-methylenebenz[*a*]anthracene (20). A solution of 2.8 M MeMgBr (10 mL, Aldrich) was added to a solution of **24** (1.10 g, 3.9 mmol) in anhydrous Et_2O (30 mL). The purple solution was refluxed for 3 h and quenched by the dropwise addition of 4 N HCl (30 mL). Benzene (30 mL) was added, and the mixture was refluxed for 4 h. The organic layer was separated, and the aqueous layer was extracted (Et_2O). The organic fractions were combined, dried ($MgSO_4$), and evaporated under reduced pressure. The oily residue was chromatographed on a silica gel column with hexane–CH_2Cl_2 (1:1) as eluent to give **20** (0.56 g, 52%) as white crystals from EtOH; mp 107.5–108.5 °C. Compound **25** was eluted from the column by using CH_2Cl_2 as eluent, affording 0.10 g of white crystals upon trituration with petroleum ether; mp 150.5–152 °C.

25: IR (KBr) 3540 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (d, 3 H, J = 7.3 Hz, 7-CH_3), 1.79 (s, 3 H, 12-CH_3), 1.6–2.0 (m, 4 H, H-2, H-3), 2.05 (s, 1 H, 12-OH, exchangeable), 2.7–2.9 (m, 2 H, H-4), 3.1–3.3 (m, 2 H, H-1), 4.38 (q, 1 H, J = 7.3 Hz, H-7), 6.77 (d, 1 H, J = 10.2 Hz, H-5), 7.2–7.4 (m, 3 H, H-8, H-9, H-10), 7.7–7.9 (m, 1 H, H-11). Anal. Calcd for $C_{20}H_{21}OF$: C, 81.05; H, 7.14; F, 6.41. Found: C, 81.46; H, 7.27; F, 6.19.

20: ^1H NMR ($CDCl_3$) δ 1.34 (d, 3 H, J = 7.0 Hz, 7-CH_3), 1.5–2.2 (m, 4 H, H-2, H-3), 2.2–2.4 (m, 2 H, H-4), 2.4–2.8 (m, 2 H, H-1), 4.38 (q, 1 H, J = 7.0 Hz, H-7), 5.49 (d, 1 H, J = 0.9 Hz, bay region vinyl H), 5.82 (s, 1 H, vinyl H), 6.75 (d, 1 H, J_{H-F} = 9.8 Hz, H-5), 7.2–7.4 (m, 3 H, H-8, H-9, H-10), 7.4–7.6 (m, 1 H, H-11). MS, m/e calcd 278.1471, found 278.1481. Anal. Calcd for $C_{20}H_{19}F$: C, 86.30; H, 6.88; F, 6.82. Found: C, 86.16; H, 6.89; F, 6.52.

5,6,7,8-Tetrahydro-1-naphthaldehyde (29). A solution of 11.12 g (50 mmol) 1-bromo-5,6,7,8-tetrahydronaphthalene[24] (**27**) [prepared from 1-amino-5,6,7,8-tetrahydronaphthalene (**26**) (technical grade, Aldrich) and distilled] and 0.8 mL of ethylene dibromide in 50 mL of dry THF was added dropwise during 40 min under N_2 to a stirred mixture of 3.28 g (137 mmol) of Mg (Gold Label, Aldrich) in 20 mL of dry THF. The mixture was refluxed for 5 h. The cooled solution of Grignard reagent was slowly transferred under N_2 to a solution of 6.86 g (80 mmol) of *N*-methyl-*N*-2-pyridinylformamide (Meyers' reagent)[38] in 20 mL of dry THF at 0 °C. The mixture was stirred at 0 °C for 1 h and at room temperature for 1.5 h (TLC). The mixture was acidified with cold 10% aqueous HCl and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated under reduced pressure, affording 8.5 g of colorless oil; bp 105–107 °C (2.5 torr) [lit.[37] bp 85 °C (0.3 torr)]. The oil was further purified by chromatography over silica gel (100–200 mesh) with petroleum ether (200 mL) followed by 500 mL of petroleum ether–benzene (3:1) afforded 400 mg of starting 1-bromo-5,6,7,8-tetrahydronaphthalene. Petroleum ether–benzene (1:1) eluate afforded 7.7 g (83%) of **29**. An uncharacterized sticky semicrystalline solid (likely an air oxidation product of **29**) was subsequently isolated by using benzene and chloroform as eluants. **29**: ^1H NMR ($CDCl_3$) δ 10.24 (s, 1 H, CHO), 7.5–7.8 (m, 1 H, H-2), 7.2–7.4 (m, 2 H, H-3, H-4), 3.1–3.3 (m, 2 H, H-8), 2.6–2.9 (m, 2 H, H-5), 1.7–2.0 (m, 4 H, H-6, H-7).

5-Fluoro-3-(5,6,7,8-tetrahydro-1-naphthalenyl)-1(3*H*)-isobenzofuranone (31). 4,4-Dimethyl-2-(4-fluorophenyl)oxazoline[47-49] (6.41 g, 33 mmol) distilled and dried under reduced pressure was dissolved in dry THF (42 mL). To the stirred and cooled (dry ice–chlorobenzene, −40 °C) solution was added dropwise during 30 min 24 mL of *n*-BuLi (39 mmol) in hexane (1.6 M). The mixture was stirred for 3 h, and 6.05 g (34.4 mmol) of **29** in 40 mL of dry THF was added. Stirring was continued at room temperature for 1.5 h and 40 °C for 21 h. Cold saturated NH_4Cl solution (40 mL) and a few drops of dilute aqueous HCl were added, and the mixture was extracted with Et_2O (2 × 60 mL) and 75 mL of Et_2O–benzene (1:1). The combined organic layer was washed with brine and dried ($MgSO_4$). Concentration under reduced pressure afforded a thick oil to which 160 mL of 4 N HCl solution was added. The mixture was refluxed for 4 h, cooled, and extracted with Et_2O and Et_2O–benzene (1:1). The combined extracts were washed with 10% $NaHCO_3$ solution (to remove 4-fluorobenzoic acid), H_2O, and brine and dried ($MgSO_4$). Concentration under reduced pressure afforded a viscous oil, which crystallized upon trituration with petroleum ether. The crystals were filtered and washed (MeOH) and recrystallized from $CHCl_3$–petroleum ether, affording 4.5 g (48%) of white needles; mp 118–119 °C. An additional 500 mg of **31** was isolated by column chromatography over silica gel (100–200 mesh) by elution with CH_2Cl_2, providing a total yield of 53%: IR (Nujol) 1750 (lactone C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.75–8.05 (m, 6 H, Ar), 6.65 (s, 1 H, H-3), 2.6–3.1 (m, 4 H, H-5′, H-8′), 1.6–2.1 (m, 4 H, H-6′, H-7′); MS, m/e (ionic component, relative intensity) 282 (M^+, $C_{18}H_{15}O_2F$, 9.7), 238 ($C_{17}H_{15}F$, $M^+ - CO_2$, 21.26), 237 ($C_{17}H_{14}F$, $M^+ - CO_2 - H$, 100). Anal. Calcd for $C_{18}H_{15}O_2F$: C,

(47) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372–1379.
(48) Newman, M. S.; Kannan, R. *J. Org. Chem.* **1979**, *44*, 3388–3390.
(49) Meyers, A. I.; Temple, D. C.; Haidukewyeh, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787–2793.

76.57; H, 5.37; F, 6.73. Found: C, 76.19; H, 5.47; F, 6.73.

4-Fluoro-2-[(5,6,7,8-tetrahydro-1-naphthalenyl)methyl]-benzoic Acid (32). To a solution of **31** (2.11 g, 7.5 mmol) in 40 mL of HOAc (dissolves on warming) was added 750 mg of 10% Pd/C (Matheson, Coleman and Bell) and hydrogenated in a Parr shaker at an initial pressure of 43 psi H_2 for 6 h. The mixture was filtered through Celite, and the Celite was washed with warm benzene and CH_2Cl_2. The combined filtrate was concentrated under reduced pressure, affording 1.92 g (90%) of white crystals (benzene–petroleum ether): mp 177–178 °C; ^1H NMR ($CDCl_3$) δ 6.6–8.2 (m, 6 H, Ar), 4.38 (s, 2 H, dibenzyl CH_2), 2.6–2.9 (m, 2 H, H-5′ or H-8′), 2.5–2.7 (m, 2 H, H-5′ or H-8′), 1.6–1.9 (m, 4 H, H-6′, H-7′); MS, *m/e* (ionic component, relative intensity) 284 ($C_{18}H_{17}O_2F$, M^+, 9.47). Anal. Calcd for $C_{18}H_{17}O_2F$: C, 76.03; H, 6.04; F, 6.68. Found: C, 75.95; H, 6.19; F, 6.51.

10-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracen-7-ol Acetate (33). Acid **32** (1.62 g, 5.26 mmol), Ac_2O (8.5 mL), AcOH (25 mL), and fused $ZnCl_2$ (450 mg) were heated at reflux for 1 h. The mixture was poured onto ice, and the crude solid was filtered, washed with H_2O, and air-dried, affording 1.7 g (98%) of white crystals (benzene–methanol): mp 134–135 °C; IR (Nujol) 1750 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.32 (s, 1 H, H-12), 7.1–8.0 (m, 5 H, Ar), 3.1–3.2 (m, 2 H, H-1), 2.8–3.0 (m, 2 H, H-4), 2.59 (s, 3 H, CH_3), 1.8–2.1 (m, 4 H, H-2, H-3); MS, *m/e* (ionic component, relative intensity) 308 ($C_{20}H_{17}O_2F$, M^+, 7.65), 266 ($C_{18}H_{15}OF$, M^+ – CH_2C=O, 100). Anal. Calcd for $C_{20}H_{17}O_2F$: C, 77.89; H, 5.57; F, 6.16. Found: C, 77.37; H, 5.66; F, 5.83.

10-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione (34). To the warm solution of **33** (1.62 g, 5.3 mmol) in 30 mL of HOAc was added 1.95 g of $K_2Cr_2O_7$. The mixture was heated at reflux for 30 min, cooled, and poured onto ice. Yellow crystals were separated by filtration, washed with 5% $NaHCO_3$ solution and H_2O, and dried (TLC, one major and two minor polar oxidation spots). The solid was chromatographed on silica gel (60 mesh) by using CH_2Cl_2 as eluant, affording 1.0 g (68%) of pure **34** (benzene–MeOH): mp 163–164 °C; IR (Nujol) 1655 (conjugated C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1–8.3 (m, 2 H, Ar), 7.80 (dd, 1 H, $J_{H\text{-}11,H\text{-}9}$ = 2.6 Hz, $J_{H\text{-}11,F}$ = 9 Hz, H-11), 7.3–7.5 (m, 2 H, Ar), 3.3–3.4 (m, 2 H, H-1), 2.8–3.0 (m, 2 H, H-4), 1.8–1.9 (m, 4 H, H-2, H-3); MS, *m/e* (ionic component, relative intensity) 280 ($C_{18}H_{13}O_2F$, M^+, 89.60). Anal. Calcd for $C_{18}H_{13}O_2F$: C, 77.12; H, 4.68; F, 6.78. Found: C, 77.34; H, 4.76; F, 6.50.

***cis*- and *trans*-10-Fluoro-1,2,3,4,7,12-hexahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (35).** To a mixture of **34** (956 mg, 3.4 mmol) in 28 mL of benzene was added dropwise 12.8 mL of MeMgBr (2.8 M, Et_2O, Aldrich) with stirring. The mixture was heated at reflux for 4 h, cooled, and poured onto ice–H_2O with stirring. The aqueous mixture was extracted with EtOAc, and the organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated under reduced pressure. The cis and trans products are best observed on TLC by spraying the silica gel plate with 2% H_2SO_4 (EtOH) following developing in $CHCl_3$–MeOH (95:5). The major cis isomer is more polar. The residue was crystallized from CH_2Cl_2–petroleum ether, affording 450 mg of nearly pure cis-diol (one spot on TLC). The mother liquor afforded 210 mg of a cis/trans (major trans, TLC) mixture of diols upon further recrystallization, and the filtrate was colored yellow due to presence of unreacted quinone. Total diol yield obtained was 62%. Chromatography of the 210 mg cis/trans mixture yielded another 80 mg of cis-diol, mp 187–188 °C (CH_2Cl_2–petroleum ether), and 110 mg of trans-diol, mp 140–141 °C: IR (Nujol) [cis] 3350 (br, OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ [cis] 7.0–7.8 (m, 5 H, Ar), 3.2–3.3 (m, 2 H, H-1), 2.8–2.9 (m, 2 H, H-4), 2.12 (s, 2 H, OH, D_2O exchangeable), 1.6–1.9 (m, 4 H, H-2, H-3), 1.67 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3); MS, *m/e* (ionic component, relative intensity) 312 [M^+ not found in MS 30 (70 eV)], 297 (M^+ – CH_3, 72.66), 294 (M^+ – H_2O, 30.92), 282 (297 – CH_3, 55.68), 279 (297 – H_2O, 100.00), 276 (294 – H_2O, 32.76), 264 (279 – CH_3, 27.31), 261 (279 – H_2O, 36.56), 248 (276 – C_2H_4, 9.04), 246 (264 – H_2O *or* 261 – CH_3, 13.52), 233 (261 – C_2H_4, 11.65), 220 (248 – C_2H_4, 14.53). Anal. Calcd for $C_{20}H_{21}O_2F$: C, 76.89; H, 6.79; F, 6.08. Found: C, 76.76; H, 6.74; F, 6.13.

Reaction of 34 with MeLi. To a solution of **34** (50 mg, 0.16 mmol) in 8.0 mL of dry THF was slowly added 0.5 mL of MeLi (1.6 M, Et_2O, Aldrich) under N_2. The mixture was stirred and heated under reflux for 3.5 h. After the mixture was cooled 10% NH_4Cl solution was added to it, which was subsequently extracted with Et_2O–benzene (1:1). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure, affording 35 mg (63%) of the crude cis/trans diol mixture.

7-(Chloromethyl)-10-fluoro-1,2,3,4-tetrahydro-12-methylbenz[*a*]anthracene (36). Through a solution of 103 mg (0.33 mmol) of *cis*-**35** in 25 mL of dry EtOAc held at room temperature was passed gaseous HCl for 1.5 h. The solution was kept in the refrigerator overnight and concentrated under reduced pressure, affording 102 mg (99%) of yellow solid: mp 143–146 °C; ^1H NMR ($CDCl_3$) δ 7.2–8.4 (m, 5 H, Ar), 5.51 (s, 2 H, CH_2Cl), 3.2–3.3 (m, 2 H, H-1), 3.07 (s, 3 H, CH_3), 3.0–2.8 (m, 2 H, H-4), 1.6–2.1 (m, 4 H, H-2, H-3); MS, *m/e* 277 (M^+ – Cl, 39.99), 276 (M^+ – HCl *or* 277 – H, 57.01), 264 (M^+ – CH_2Cl + H, 100), 261 (276 – CH_3, 35.69), 249 (277 – C_2H_4, 25.75), 248 (276 – C_2H_4, 30.18), 247 (261 – CH_2, 41.62), 233 (261 – C_2H_4, 42.51), 220 (248 – C_2H_4, 21.35).

10-Fluoro-1,2,3,4-tetrahydro-7-(iodomethyl)-12-methylbenz[*a*]anthracene (37). To an ice-cooled stirred solution of diol **35** (280 mg, 0.9 mmol) in 15 mL of MeOH (**35** dissolves in MeOH on warming) was added dropwise a solution of 8 mL of HI (48%) in 6 mL of MeOH at 0 °C. The mixture was stirred for 20 min in the dark. A yellow precipitate was formed, which was quickly filtered, washed with MeOH, and dried. ^1H NMR of this yellow solid (340 mg, 94%), mp 112–116 °C dec, indicated starting diol was absent. Although **37** is unstable in ordinary light, it is stable under yellow light for short periods and in the freezer: ^1H NMR ($CDCl_3$) δ 8.29–7.29 (m, 5 H, Ar), 5.39 (s, 2 H, CH_2I), 3.30–3.10 (m, 2 H, H-1), 3.10–2.90 (m, 2 H, H-4), 2.96 (s, 3 H, CH_3), 2.16–1.53 (m, 4 H, H-2, H-3); MS, *m/e* 277 (M^+ – I, 26.85), 276 (M^+ – HI, 72.76), 264 (M^+ – CH_2I + H, 65.18), 261 (276 – CH_3, 100), 249 (277 – C_2H_4, 15.18), 248 (276 – C_2H_4, 13.62), 246 (261 – CH_3, 33.46), 233 (261 – C_2H_4, 21.60), 220 (248 – C_2H_4, 25.29).

10-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (5) from 37. To a mixture of **37** (330 mg, 0.82 mmol) and 10 mL of dry Me_2SO was added slowly and with stirring $NaBH_4$ (180 mg). The mixture was heated at 80 °C (oil bath) for 1 h and cooled, poured into H_2O, and extracted with petroleum ether (30 mL) and benzene (3 × 30 mL). The organic fractions were mixed, washed with saturated brine, dried ($MgSO_4$), and evaporated under reduced pressure to afford a yellow residue. The residue was chromatographed over silica gel (100–200 mesh). Petroleum ether eluates gave a total yield of 95 mg (42%) of pure yellow crystals of **5** (strongly UV fluorescent-blue): mp 123–124 °C [crystallized from a few drops of CH_2Cl_2 by addition of EtOH (freezer)]; ^1H NMR ($CDCl_3$) δ 8.34–7.06 (m, 5 H, Ar), 3.35–3.15 (m, 2 H, H-1), 3.04 (s, 3 H, CH_3), 3.02 (s, 3 H, CH_3), 3.1–2.85 (m, 2 H, H-4), 2.01–1.62 (m, 4 H, H-2, H-3); MS, *m/e* (ionic component, relative intensity) 278 ($C_{20}H_{19}F$, M^+, 100.00), 263 ($C_{19}H_{16}F$, M^+ – CH_3, 35.74), 248 ($C_{18}H_{13}F$, 263 – CH_3, 19.56), 220 (248 – C_2H_4, 11.20). Anal. Calcd for $C_{20}H_{19}F$: C, 86.28; H, 6.90; F, 6.83. Found: C, 86.09; H, 7.04; F, 6.57.

Alternate Synthesis of 5 from Diol 34. The synthesis of **5** from **34** (90 mg, 0.29 mmol) was carried out according to the procedure for the preparation of **3**. The reaction mixture was refluxed for 3 h, cooled to 0 °C, quenched with 2 N HCl (2 mL), diluted with water, and worked up accordingly. Column chromatography (silica gel, petroleum ether) afforded **5** (50 mg, 62%) after crystallization from CH_2Cl_2/MeOH: mp 123.5–124 °C; >99% pure by HPLC analysis.

Acknowledgment. Support of this work by the Environmental Protection Agency through Grant R81-1125-010 is gratefully acknowledged. Mass spectra obtained at The Ohio State University Chemical Instrumentation Center were produced by C. R. Weisenberger. FT-NMR spectra from the IBM NR 80 in the Ohio State University Comprehensive Cancer Center were produced by Charles W. Palmer, Jr. NOE experiments were carried out by Jack Fowble in the Division of Medicinal Chemistry. N.A.A. gratefully acknowledges support as a predoctoral fellow on National Cancer Institute Grant No. T32-CA-09498.

Registry No. **3**, 104761-43-5; **4**, 104761-44-6; **5**, 104761-45-7; **6**, 104761-46-8; **7**, 104761-48-0; **8**, 104761-49-1; **9**, 104761-50-4; **10**, 104761-51-5; **11**, 104761-52-6; **12**, 104761-53-7; *cis*-**13**, 104761-54-8; *trans*-**13**, 104761-42-4; **14**, 2840-40-6; **15**, 104761-55-9; **15** (methyl

ester), 104761-73-1; **16**, 104761-56-0; **17**, 104761-57-1; **18**, 104761-58-2; **19a**, 104761-59-3; **16b**, 104761-66-2; **20**, 104761-60-6; **22**, 104761-61-7; **23**, 104761-62-8; **24**, 104761-63-9; **25**, 104761-64-0; **26**, 2217-41-6; **27**, 6134-55-0; **29**, 41828-13-1; **31**, 104778-46-3; **32**, 104761-67-3; **33**, 104761-68-4; **34**, 104761-69-5; *cis*-**35**, 104761-70-8; *trans*-**35**, 104761-65-1; **36**, 104761-71-9; **37**, 104761-72-0; phthalic anhydride, 85-44-9; 4,4-dimethyl-2-(4-fluorophenyl)oxazoline, 71171-94-3.

Vinylic Organoboranes. 1. A Convenient Synthesis of Acetylenes via the Reaction of Lithium (1-Alkynyl)organoborates with Iodine[1]

Akira Suzuki,[2] Norio Miyaura, Shigeo Abiko, and Mitsuomi Itoh

Department of Chemical Process Engineering, Hokkaido University, Sapporo, Japan

M. Mark Midland, James A. Sinclair,[3] and Herbert C. Brown*

Richard B. Wetherill Laboratory, Purdue University, West Lafayette, Indiana 47907

Received February 6, 1986

Lithium (1-alkynyl)organoborates, readily prepared from organoboranes and lithium acetylides, undergo a facile reaction at low temperature with iodine to form internal acetylenes in high yield. Unlike conventional methods for the preparation of acetylenes via nucleophilic displacement, the reaction is applicable to both primary and secondary as well as aromatic and functionally substituted groups. The use of lithium acetylide–ethylenediamine for the formation of the organoborate extends the reaction to terminal acetylenes. This reaction occurs with complete retention of the configuration about the boron–carbon bond. The procedure, with its exceptionally broad applicability, provides a simple, general route to internal and terminal acetylenes.

Background

The discovery of the facile hydroboration of alkenes in 1957[4,5] made trialkylboranes readily available. Systematic investigation of these trialkylboranes soon demonstrated that they have a rich chemistry, ideal as intermediates in organic synthesis.[6] The later hydroboration of acetylenes,[7] dienes[8] and allenes[9] made available vinylic and other unsaturated organoboranes. These unsaturated organoboranes proved to have an even richer chemistry than the original trialkylboranes.[10]

The highlights of these studies were presented in the form of communications and in reviews,[9-13] but it proved impossible to keep up with the flood of developments by publishing the full papers. Consequently, much fascinating chemistry was not being made available to chemists utilizing this chemistry.

An effort is being made to remedy this deficiency. A series of papers under the title "Organoboranes for Synthesis" is being prepared for publication. These describe the detailed studies on the saturated organoboranes. A second series of papers dealing with the chemistry of the unsaturated organoboranes is being prepared for publication under the series title "Vinylic Organoboranes". Finally, a third series, "Pheromones via Organoboranes", will describe the development of general methods for the synthesis of classes of pheromones containing a specific structural feature.

Introduction

Acetylenes have been important intermediates in a variety of pheromone synthesis.[14] The conventional approach to the required acetylenes involves a nucleophilic displacement of a halide or sulfonate by the acetylide anion.[15] The reaction is limited to those primary derivatives which readily participate in S_N2 substitution processes. Furthermore, because of the reactivity of the acetylide anion, labile functional groups may not be present in the reactants.

Organoboranes have provided a number of mild, highly regio- and stereospecific methods for achieving carbon–carbon bond formations.[16] These reactions overcome the problems associated with conventional substitution processes. In recent years lithium (1-alkynyl)organoborates

(1) A preliminary account of this work has appeared: Suzuki, A.; Miyaura, N.: Abiko, S.; Itoh, M.; Brown, H. C.; Sinclair, J. A.; Midland, M. M. *J. Am. Chem. Soc.* **1973**, *95*, 3080. Midland, M. M.; Sinclair, J. A.; Brown, H. C. *J. Org. Chem.* **1974**, *39*, 731.

(2) Assistance provided by a cooperative research program under NSF Grant No. GP27742X is acknowledged.

(3) Graduate research assistant on Grant No. GM10937 from the National Institutes of Health.

(4) Brown, H. C.; Subba Rao, B. C. *J. Org. Chem.* **1952**, *22*, 1136.

(5) Brown, H. C. *Hydroboration*; Benjamin: New York, 1962. Second printing with Nobel Lecture, Benjamin/Cummings: Reading, MA, 1980.

(6) Brown, H. C.; Kramer, G. W.; Levy, A. B.; Midland, M. M. *Organic Syntheses via Boranes*; Wiley-Interscience: New York, 1975.

(7) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1961**, *83*, 3834. Brown, H. C.; Gupta, S. K. *Ibid.* **1972**, *94*, 4370. Brown, H. C.; Scouten, C. G.; Liotta, R. *Ibid.* **1979**, *101*, 96.

(8) Brown, H. C.; Zweifel, G.; Nagase, K. *J. Am. Chem. Soc.* **1962**, *84*, 190. Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Org. Chem.* **1978**, *43*, 1058.

(9) Brown, H. C.; Liotta, R.; Kramer, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 2966.

(10) Brown, H. C. "The Rich Chemistry of Vinylic Organoboranes" in *Organic Synthesis Today and Tomorrow*; Trost, B. M., Hutchinson, C. R., Eds.; Pergamon Press: New York, 1981; pp 121-137.

(11) Pelter, A.; Smith, K. "Organic Boron Compounds" in *Comprehensive Organic Chemistry*; Barton, D., Ollis, W. D., Eds.; Pergamon Press: New York, 1979; Vol. 3, Part 14.

(12) Brown, H. C.; Zaidlewicz, M.; Negishi, E. "Organoboron Compounds in Organic Synthesis" in *Comprehensive Organometallic Chemistry*, Wilkinson, G., Stone, F. G. A., Eds.; Pergamon Press: New York, 1982, Vol. VII, Chapters 45.1-45.11.

(13) Mikhailov, B. M.; Bubnov, Y. N. *Organoboron Compounds in Organic Synthesis*; Harwood Academic Publishers: New York, 1984.

(14) For reviews, see: Brand, J. M.; Young, J. C.; Silverstein, R. M. *Fortschr. Chem. Org. Naturst.* **1979**, *37*, 1. Rossi, R. *Synthesis* **1978**, 413. Shorey, H. H.; McKelvey, J. J., Jr. *Chemical Control of Insect Behavior*; Wiley: New York, 1977. Jacobson, M., Ed. *Insecticides of the Future*; Marcel Dekker: New York, 1975.

(15) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1971. Buehler, C. A.; Pearson, D. E. *Survey of Organic Synthesis*; Wiley-Interscience: New York, 1970.

(16) For reviews, see: (a) Onak, T. *Organoborane Chemistry*; Academic Press: New York, 1975. (b) Cragg, G. M. L. *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973. (c) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972. (d) References 5, 6, 11, 12, and 13.

0022-3263/86/1951-4507$01.50/0