Peri Fluoro Steric Effects: Syntheses and Comparative Acid-Catalyzed Isomerization of the 8-, 9-, and 11-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracenes to Exo Methylene Tautomers[1]

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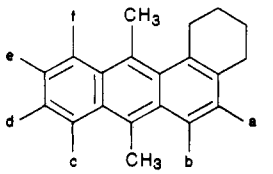
Facile and regiospecific syntheses for 8-, 9-, and 11-fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracenes (**4**, **5**, and **7**) from 5,6,7,8-tetrahydro-1-naphthaldehyde and the respective 2-(2-fluoro-6-iodophenyl)oxazoline **14**, 2-(2-bromo-5-fluorophenyl)oxazoline **15**, and 2-(3-fluorophenyl)oxazoline **16** are described. Comparative acid-catalyzed isomerization of these polycyclic aromatic hydrocarbons (PAH) to exo methylene tautomers in refluxing benzene is compared to our previously published studies employing the parent hydrocarbon **1** and the 5-, 6-, and 10-fluoro analogues (**2**, **3**, and **6**). The peri steric effect of 11-fluoro compound **7** was the most dramatic, providing 7-exo methylene isomer **45** in nearly quantitative yield. Substitution of fluorine at peri positions 6 and 8 afforded product ratios at equilibrium, whereas the 7-exo methylene tautomers (**41** and **42**) also were thermodynamically favored over the parent anthracene PAH or the respective 12-exo methylene isomers (**48** and **49**). Like the unsubstituted PAH **1**, where fluorine does not occupy a peri position such as in the 9- and 10-fluoro species **5** and **6**, no appreciable quantities of exo methylene tautomers were detected. Comparative $\Delta G°$ values for isomerization of 6-, 8-, and 11-fluoro isomers revealed that sandwiching the C_{12}-CH_3 group between the 11-fluoro and C_1-CH_2 functions in **7** and removing any possible 7-CH_2-F interaction [found in 6- and 8-F exo methylene tautomers (**41** and **42**)] in exo methylene product **45** led to a relative relief in steric interaction of approximately 1 kcal/mol.

Previously, we reported[2] comparative acid-catalyzed isomerization studies of 1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (TH-DMBA, **1**), 5F-TH-DMBA (**2**), 6F-TH-DMBA (**3**), and 10F-TH-DMBA (**6**). For **3**, a 6F peri steric effect was observed wherein equilibration with 7- and 12-methylene tautomers was established within 1 h and the 7-methylene tautomer was observed to be thermodynamically more stable than either **3** or its 12-methylene isomer. We desired samples of the remaining aryl-F regioisomers (**4**, **5**, **7**) to further explore peri steric effects and investigate structure–toxicity relationships (STR) as a function of metabolism, DNA binding, and carcinogenesis in cultured human neonatal fibroblast (HNF) cells.[1] In this article, we describe efficient and regiospecific syntheses of these compounds as well as comparative acid-catalyzed isomerization studies.



1, a = b = c = d = e = f = H
2, a = F, b = c = d = e = f = H
3, b = F, a = c = d = e = f = H
4, c = F, a = b = d = e = f = H
5, d = F, a = b = c = e = f = H
6, e = F, a = b = c = d = f = H
7, f = F, a = b = c = d = e = H

Results and Discussion

Synthetic Aspects. The three D-ring fluorinated (8-, 9-, and 11F-TH-DMBA) targets (**4**, **5**, and **7**) were synthesized from 5,6,7,8-tetrahydro-1-naphthaldehyde[2] and fluoro-substituted benzoyl chlorides (**8**, **9**, and **10**, respectively). Benzoyl chloride **10** is commercially available,[3] **8** was prepared from 2-fluoro-6-iodobenzoic acid,[4] and **9** was prepared by oxidation of 2-bromo-5-fluorotoluene[5] and treatment with $SOCl_2$. Oxazolines[6,7] (**14**, **15**, and **16**) were obtained via intermediate amides (**11**, **12**, and **13**) in 69–70% overall yields, respectively (Scheme I).

Grignards **17** and **18** underwent reaction with 5,6,7,8-tetrahydro-1-naphthylaldehyde to produce **20** (71%) and **21** (69%) after hydrolysis with $EtOH/H_2SO_4$ and lactonization.[8] The corresponding chloro-Grignard of **17** failed to provide any lactone. Regiospecific lithiation[9] at position 2 of **16** yielded **19**, which underwent reaction with 5,6,7,8-tetrahydro-1-naphthaldehyde to produce lactone **22** (67%) upon hydrolysis (HCl/H_2O). This regiospecific lithiation is significant since the approach allows for the elaboration of pure 11F-TH-DMBA (**7**), whereas, for example, alternative syntheses[10,11] of 11F-DMBA require separation of intermediates that could serve as 8F-DMBA precursors. Reduction[12] of lactones **20**–**22** afforded acids **23**–**25** (90–92%). Production of **23** free of **24** was confirmed by comparative NMR analysis of **23** and **24** (prepared from **15**). Additional evidence for these regioisomeric assignments was obtained by comparative TLC and NMR analysis of acetates **26**–**28** prepared by $ZnCl_2$/

(1) A preliminary account of this work was presented to the Division of Organic Chemistry. Goswami, S.; Witiak, D. T.; Kumari, H. L.; Milo, G. E. 30th National Organic Symposium, University of British Columbia, Vancouver, B.C., Canada, June 21–25, 1987. Biological properties and STR for the 5-, 6-, 10-, and 11F-TH-DMBA analogues have been reported: Witiak, D. T.; Kumari, H. L.; Goswami, S.; Abood, N. A.; Milo, G. E. Eleventh International Symposium on Polynuclear Aromatic Hydrocarbons, National Burea of Standards, Gaithersberg, MD, Sept 23–25, 1987.

(2) Witiak, D. T.; Abood, N. A.; Goswami, S.; Milo, G. E. *J. Org. Chem.* **1986**, *51*, 4499–4507.

(3) Aldrich Chemical Co., Milwaukee, WI.

(4) Lancaster Synthesis, Ltd., Windham, NH.

(5) Fairfield Chemical Co., Inc., Blythewood, SC.

(6) Meyers, A. I.; Gabel, R.; Mihelich, E. D. *J. Org. Chem.* **1978**, *43*, 1372–1379.

(7) Meyers, A. I.; Temple, D. C.; Haidukewyeh, D.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2787–2793.

(8) Sheikh, Y. M.; Ekwaribe, N.; Dhawan, B.; Witiak, D. T. *J. Org. Chem.* **1982**, *47*, 4341–4344.

(9) (a) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *52*, 713–719. (b) Regioselective lithiation of 3-fluorophenyloxazoline **16** was independently observed in our laboratories and previously reported. Abood, N. A.; Witiak, D. T.; Goswami, S.; Milo, G. E. Presented to the 1986 International Conference on Biomedical and Agricultural High Technology as a poster, November 12–14, 1986, Columbus, OH; Abst p 107.

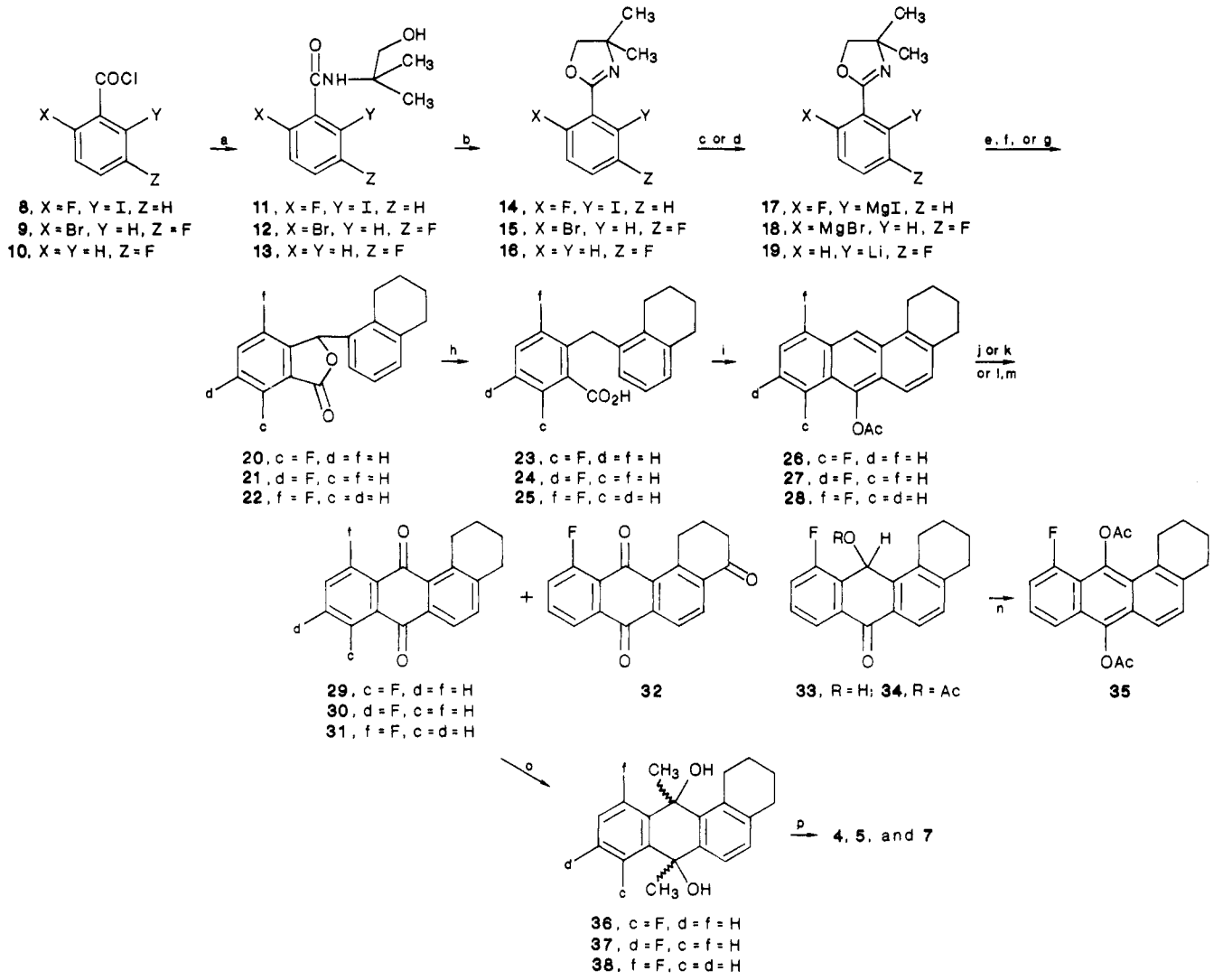
(10) Newman, M. S.; Blum, S. *J. Org. Chem.* **1964**, *29*, 1416–1418.

(11) Newman, M. S.; Blum, S. *J. Org. Chem.* **1964**, *29*, 1414–1416.

(12) Newman, M. S.; Tuncay, A. *J. Org. Chem.* **1980**, *45*, 348–349.

0022-3263/88/1953-0345$01.50/0

Scheme I[a]



[a] (a) $NH_2C(CH_3)_2CH_2OH$, CH_2Cl_2, room temperature; (b) $SOCl_2$, room temperature, 3 h; (c) Mg, THF, reflux, 1–2 h; (d) *n*-BuLi, THF, −40 °C, 2.5 h; (e) 5,6,7,8-tetrahydro-1-naphthaldehyde, THF, reflux, 12–18 h; (f) $EtOH/H_2SO_4$ (6%), reflux, 12 h; (g) HCl solution (4 N), reflux, 6 h; (h) Zn/KOH, pyridine, reflux, 20 h; (i) Ac_2O/AcOH, fused $ZnCl_2$, reflux, 0.5–1 h; (j) $K_2Cr_2O_7$/AcOH, reflux, 15–20 min; (k) CrO_3/AcOH, 65 °C, 45 min; (l) CrO_3/AcOH, room temperature, 1 h; (m) Ac_2O, pyridine, room temperature, 12 h; (n) Ac_2O, pyridine, reflux, 5 h; (o) CH_3MgBr, benzene, reflux, 4.0–4.5 h; (p) $LiAlH_4$, $TiCl_3$, THF, reflux, 3 h.

$HOAc/Ac_2O$ treatment[13] of acids **23–25** (83–95%), respectively.

Oxidation ($K_2Cr_2O_7$/HOAc) of acetates **26** or **27** produced anthraquinones **29** (71%) and **30** (70%), respectively, but in the case of the 11F isomer **28**, the 4-ketoanthraquinone **32** (40%) (M^+ 294, $C_{18}H_{11}O_3F$, 100%) was obtained at the expense of the desired anthraquinone **31** (30%).[14] Preferably, dione **31** was prepared from acetate **28** in 65% yield by controlled CrO_3/HOAc oxidation at an optimum temperature (65 °C). Under these conditions trione **32** (12%) also was isolated. At lower temperatures (<50 °C or room temperature), the hydroxyanthrone **33** (66%), a likely intermediate to **31**, was obtained. At temperatures >65 °C yields of undesired trione **32** increased.

Jones oxidation[15] at room temperature of acetate **28** produced hydroxyanthrone **33** (75%) characterized by ^1H NMR spectroscopy.[16] Reaction of hydroxyanthrone **33** with Ac_2O/pyridine at room temperature produced monoacetate **34**. Upon refluxing in pyridine/Ac_2O, hydroxyanthrone **33** aromatized to produce diacetate **35** (93%), exhibiting two arylacetyl methyl proton resonance signals (δ 2.60 and 2.48). A molecular ion at *m/e* 366, which

(13) Sandin, R. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1940**, *62*, 3098–3105.

(14) Proton resonance signals for the three A-ring methylene functions of fluoro trione **32** compared favorably with resonance signals observed for the desfluoro trione [Tochtermann, W.; Malchow, A.; Timm, H. *Chem. Ber.* **1978**, 1233–1238] previously prepared in our laboratories. [Inbasekaran, M. N.; Witiak, D. T.; Barone, K.; Loper, J. C. *J. Med. Chem.* **1980**, *23*, 278–281]. Methylene proton resonance signals for **32** [$\delta_{C\text{-}1}$ 3.7–3.5; $\delta_{C\text{-}3}$ 2.9–2.7; $\delta_{C\text{-}2}$ 2.4–2.0] compared favorably with those of desfluoro **32** [$\delta_{C\text{-}1}$ 3.8–3.4; $\delta_{C\text{-}3}$ 3.0–2.5; $\delta_{C\text{-}2}$ 2.5–1.9]. Additionally, resonance signals for protons at C_6 and C_8, peri to the C_7 carbonyl function of dione **31**, are downfield (δ 8.15–7.95) and easily distinguished from other aromatic proton signals. Similarly, for trione **32**, the three signals attributable to protons at C_5, C_6, and C_8 peri to carbonyl groups at C_4 and C_7 were also observed downfield (δ 8.53–8.25) from other aryl proton frequencies.

(15) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39–45.

(16) The OH proton resonance signal (δ 2.35; $CDCl_3$; exchange with D_2O) at C_{12} was observed coupled to the C_{12} methine proton δ 6.15, d, J = 6.7 Hz; singlet in D_2O) as well as the 11-F function (J = 1.6 Hz). ^1H NMR 500-MHz NOE experiments located the OH function at position 12. Thus, irradiation of H-12 (δ 6.15) exhibited a positive NOE effect (2.41% and 9.27%, respectively) on proton resonance signals attributable to C-1-H_A (δ 3.25–3.34) and C-1-H_B (δ 2.96–3.06) and on the OH proton resonance signal at C-12 (δ 2.45; 5.29%). No aromatic peri proton resonance signals were affected.

Table I. ^{1}H NMR Chemical Shifts for Peri Proton Resonance Signals in Fluoro Analogues 2-7

compd no.	fluoro group positn	δ^a H_6	H_8	H_{11}
2	5	7.63	8.1–8.3	8.1–8.3
3	6		8.2–8.6	8.2–8.6
4	8	8.06		7.99
5	9	7.98	7.77	8.25
6	10	8.00	8.25	7.80
7	11	8.00	8.00	

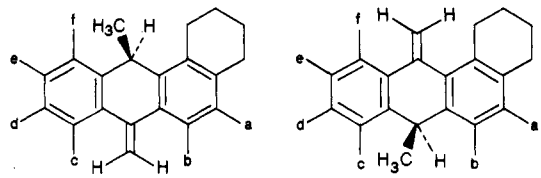
[a] In ppm.

successively loses two molecules of ketene (m/e 324 and 282) confirmed the structural assignment for the diacetate. Formation of **33** and its relative stability likely reflects C_1-CH_2 and 11F peri steric influences that are minimized when C_{12} is sp^3 rather than sp^2 hybridized. The driving force for aromatization (**33** → **35**) involves trapping of the enol form of the 7-keto function as the acetate.

Quinones **29–31** were converted to their respective diastereomeric dimethyl diols **36–38** in 75–80% yields by reaction[17] with methylmagnesium bromide in benzene. All three diols (**36, 37, 38**) did not yield molecular ions in their respective 70-eV mass spectra owing to facile loss of H_2O involving the tertiary hydroxy groups at bis(benzylic) carbons C_7 and C_{12}. The presence of two methyl groups in **36–38** was confirmed by their successive loss affording $M^+ - CH_3$ and $M^+ - 2(CH_3)$ ions. Diols **36–38** were converted in 70–79% yields to the respective fluoro targets **4, 5,** and **7** by deoxygenation and aromatization with low valent titanium.[18]

Peri proton resonance signals (Table I) are characteristically different for each of the six fluoro regioisomers (ref 2 and Experimental Section). Additional diagnostic ^{1}H NMR (270 MHz) resonance signals observed for 8F-TH-DMBA (**4**) involves coupling of the C_7-methyl protons with the 8F function providing a doublet at δ 3.16 (J = 5.03 Hz). The C_{12}-methyl proton signal of **4** is a singlet (δ 3.05). For 9F-TH-DMBA (**5**), the proton resonance signals for both methyl groups appeared as singlets (δ 2.95 and 3.15). For 11F-TH-DMBA (**7**), the C_{12}-methyl protons couple with the 11F function providing a doublet at δ 3.08 (J = 9.0 Hz) and the C_7-methyl proton signal is observed as a singlet (δ 3.0).

Acid-Catalyzed Isomerization Studies.[19] Treatment of 11F-TH-DMBA (**7**) with p-TsOH in benzene afforded tautomer **45** in 85% yield as a light yellow crystalline solid (CH_2Cl_2/MeOH) following purification on alumina (Woelm) and silica gel (100–200 mesh; petroleum ether). In trifluoroacetic acid, compound **7** isomerized nearly quantitatively to 7-exo methylene isomer **45** within a few minutes at room temperature. ^{1}H NMR (500 and 270 MHz) spectra exhibited resonance signals for C_6 and C_8-H at δ 7.43–7.47 with methylene proton resonance signals at δ 5.5–5.6. For 11F-TH-DMBA (**7**), C_6- and C_8-H resonance signals are observed at δ 8.0. Thus, isomer ratios of the reaction mixture can be determined by integration of the respective C_6 and C_8 peri proton resonance signals. For tautomer **45**, the C_{12} methine proton signal appears as a quartet (δ 4.55, J = 7.0 Hz) and the C_{12} methyl signal as a doublet (δ 1.20) whereas, in the C-ring aryl PAH (**7**), the C_{12} methyl group signal appears in the downfield region multiplet (δ 3.08). Regioisomeric structure **45**, in part, was elucidated by 500-MHz proton NOE difference experiments.[20,21] Assignment of the aromatic protons in the 11F 7-exo methylene isomer **45** was confirmed by analysis of two-dimensional (**2D**) NMR experiments[22–24] [COSY and J-resolved spectroscopy (2D-J)] at 500 MHz in conjunction with NOE difference experiments.[25] Peri proton resonance signals (Table I) for all fluoro analogues were always observed downfield to the other aromatic proton resonance signals. Similarly, peri proton resonance signals for the 11F 7-exo methylene isomer **45** were observed to be downfield (δ 7.43–7.47) relative to the other aromatic proton signals of **45**, but upfield to the peri proton signals of the parent anthracene **7**.



39, a = b = c = d = e = f = H, **46**
40, a = F, b = c = d = e = f = H, **47**
41, b = F, a = c = d = e = f = H, **48**
42, c = F, a = b = d = e = f = H, **49**
43, d = F, a = b = c = e = f = H, **50**
44, e = F, a = b = c = d = f = H, **51**
45, f = F, a = b = c = d = e = H, **52**

Results of comparative acid-catalyzed (p-TsOH) isomerization in benzene of the parent anthracenes (**1–7**) to their respective 7- and 12-exo methylene tautomers (**39–45** and **46–52**) are found in Table II. When fluorine occupies peri positions 6 or 8 both exo methylene tautomers are in equilibrium with the parent anthracenes and the 7-exo methylene isomer is thermodynamically most stable. C_1-CH_2 steric interaction with the C_{12}-CH_3 in the parent anthracene is relieved when C_{12} becomes sp^3 hybridized. Additionally, tautomerization to 7-exo methylene isomers provides a puckered C-ring and relieves steric interaction with the peri fluoro functions at positions 6 and 8. When fluorine occupies positions 5, 9, or 10, there are no peri

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

(18) Walborsky, H. M.; Wust, H. H. *J. Am. Chem. Soc.* **1982**, *104*, 5807–5808.

(19) Isomerization studies were carried out under conditions identical with those described in the footnote to Table II of ref 2. Thus, 10 mg of PAH in 5 mL of benzene containing 2.5 mg of p-toluenesulfonic acid was heated at reflux for 72 h. For 11F-TH-DMBA (**7**), the same equilibration ratio was obtained after 1 h. Isolation and NMR spectral analysis conditions were identical with those reported in the footnote to Table II of ref 2.

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

(21) A strong positive NOE effect (+26%) was observed only for the overlapping resonance signals (δ 7.47) attributable to peri protons at C_6 and C_8 upon irradiation of the 7-exo methylene function. When the C_{12}-methine proton was irradiated, a positive NOE effect was observed for the C_1-methylene (+11%) and C_{12}-methyl (+7%) proton resonance signals. Thus, structure **45** is the 7- and not the 12-exo methylene isomer.

(22) Bax, A.; Lerner, L. *Science (Washington, D.C.)* **1986**, *232*, 960–967.

(23) Bax, A.; Ferretti, J. A.; Nashed, N.; Jerina, D. M. *J. Org. Chem.* **1985**, *50*, 3029–3034.

(24) Jackman, L. M.; Sternhell, S. In *Applications of Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; International Series of Monographs in Organic Chemistry; Barton, D. H. R., Doering, W., General Editors; Pergamon Press: Oxford, New York, Toronto, Sydney, Braunschweig, 1969; pp 348–349.

(25) 2D-COSY of the aromatic region of **45** demonstrated correlation of shifts at δ 7.47 with δ 7.03, establishing the H-5 and H-6 system. Similarly, the signal at δ 7.24 correlated with both δ 7.43 (H-8) and δ 7.00 (H-10), establishing H-9 at δ 7.24. From NOE difference experiments, the identification of the peri proton resonance signals (δ 7.43 and 7.47) (H-6 and H-8) was confirmed by observing the strong NOE effect upon irradiation of the 7-exo methylene function. Moreover, J-resolved 2D-NMR corroborated the above assignments and revealed D-ring-H,F couplings. The H,F-ortho-doublet for H-10 ($J_{H\text{-}10,F}$ = 9.5 Hz)[24] was centered at δ 7.00. Likewise, H,F-meta-coupling for H-9 ($J_{H\text{-}9,F}$ = 5.4 Hz)[24] was observed at δ 7.25, and H,F-para-coupling for H-8 ($J_{H\text{-}8,F}$ = 2.1 Hz)[24] was found at δ 7.43. The J-resolved 2D-NMR spectrum also revealed the proton–proton coupling constants ($J_{H\text{-}5,H\text{-}6}$ = 8.0 Hz; $J_{H\text{-}8,H\text{-}9}$ = 7.8 Hz; $J_{H\text{-}9,H\text{-}10}$ = 7.8 Hz).

Table II. Thermodynamic Product Ratios and Standard Free Energy Changes ($\Delta G°$) for TH-DMBA (1) and Its Six Aryl Fluoro Analogues 2-7. Comparative Acid-Catalyzed Isomerization to 7- and 12-Exo Methylene Tautomers[a]

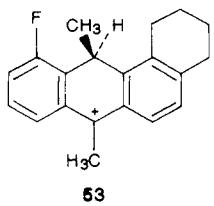
compd (no.)	product ratios[b] A[c]	B[d]	C[e]	$\Delta G°$ (A ⇄ B), kcal/mol	$\Delta G°$ (A ⇄ C), kcal/mol
TH-DMBA (1)[f]	13.0 ± 2.5	1.0	0		1.8 ± 0.2
5F (2)[f]	8.5 ± 0.5	1.0	0		1.5 ± 0.1
6F (3)[f]	1.0	2.8 ± 0.4	0.6 ± 0.1	0.8 ± 0.5	−0.8 ± 0.1
8F (4)	1.0	1.6 ± 0.2	0.3 ± 0.1	0.6 ± 0.1	−0.4 ± 0.2
9F (5)	8.0	1.0	0		1.5 ± 0.1
10F (6)[f]	10.5 ± 2.5	1.0	0		1.6 ± 0.2
11F (7)	1.0	10.5 ± 1.2	0	>3.3[g]	−1.3 ± 0.1

[a] Conditions and workup for the isomerization reactions were as previously described.[2,19] [b] Determined by integration of the unique aromatic and exo methylene proton resonance signals. [c] A = polycyclic aromatic hydrocarbons (PAH, 1–7). [d] B = 7-exo methylene tautomers (39–45) for the respective PAH. [e] C = 12-exo methylene tautomers (46–52) for the respective PAH. [f] Data derived from experiments conducted in ref 2. [g] Determination limited by the sensitivity of the ^{1}H NMR integration.

interactions with the methyl groups and there is little tautomerism to exo methylene isomers, a phenomenon also observed for TH-DMBA (1).[2]

The peri effect of fluorine was most dramatic when substitution was at position 11 since in the planar anthracene tautomer (7) the C_{12}-CH_3 function is now sandwiched between the 11F and C_1-CH_2 groups. C_7-CH_3 peri steric interactions with 6 or 8F functions can be minimized by rotation about the C_7–CH_3 bond, thereby placing two hydrogens of methyl on opposite sides of the Ar–F plane. Owing to the C_1-CH_2 interaction with the C_{12}-CH_3 group, rotation about the C_{12}–CH_3 bond to minimize the CH_3–F interaction is not effective. Additionally, it appears (Dreiding models) that relief of steric interaction at C-12 owing to sp^3 hybridization is accompanied by decreased steric interaction at C-7 in the exo methylene tautomer **45** when compared to the 6 and 8F analogues **41** and **42**, respectively, because the C-7 exo methylene group in **45** has no $7CH_2$–F interaction. The 11F group, having a van der Waals radius[26] of 1.35 Å, only slightly larger than the radius for H (1.2 Å), provides sufficient steric interaction with the C_{12}-CH_3 (2.0 Å) such that $\Delta G°$(**7** ⇄ **45**) − $\Delta G°$(**3** ⇄ **41**) = −0.9 ± 0.2 kcal/mol and $\Delta G°$(**7** ⇄ **45**) − $\Delta G°$(**4** ⇄ **42**) = −1.4 ± 0.2 kcal/mol and this difference in $\Delta G°$ values reflects a relief not only in steric interaction attributable to sandwiching but also to relative product stability.

The facile formation of nearly quantitative yields of the 7-exo methylene isomer **45** from 11F-TH-DMBA (**7**) as determined by ^{1}H NMR spectroscopy (80 MHz) in trifluoroacetic acid may be explained in terms of preferential formation of the sterically favored carbonium ion **53** as compared to **54**. Although carbonium ion **54** would be resonance stabilized with the lone electron pair on fluorine (as would also be the case when fluorine is substituted at position 9), this ion is disafavored owing to the pronounced steric interaction resulting from sandwiching the 12-methyl group between 11-F and C_1–CH_2 functions.[27]



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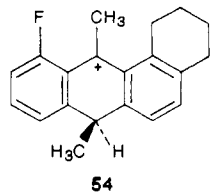

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(26) Gordon A. J.; Ford, R. A. In *The Chemists Companion. A Handbook of Practical Data, Techniques and References*; John Wiley and Sons: New York, 1972; pp 82–109.

(27) Similarly, when methyl is sandwiched between two methyl groups such as in 1,4,5,8,9-pentamethylanthracene, the carbonium ion generated in trifluoroacetic acid is detected exclusively at position 10. Hart, H.; Jiang, J. B.; Gupta, R. K. *Tetrahedron Lett.* **1975**, 4639–4642.

Whereas electronic effects of fluorine are relatively well understood, steric effects of fluorine are less well appreciated. Such steric effects are important to recognize since fluorine is of contemporary interest to our understanding of structure–activity relationships (SAR) of drugs.[9a,28] Furthermore, the biological importance of peri fluoro steric and/or electronic effects relative to STR is well-documented; oxidative metabolism,[29–33] carcinogenesis,[29–33] and conformational preference of dihydrodiol metabolites[31,34–36] all can be inhibited or affected by peri fluoro substituents in polycyclic aromatic hydrocarbons.

Experimental Section

General. Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra (Nujol) were recorded on a Beckman Model IR-4210 spectrophotometer. ^{1}H NMR spectra were determined on a Brucker HX-90E or an IBM NR-80 spectrometer. 2D-NMR (COSY and *J*-resolved) and NOE experiments at 500 MHz were carried out on a Bruker AM-500 spectrometer. Me_4Si was used as an internal standard and $CDCl_3$ as solvent; chemical shifts are reported on the δ scale. Mass spectra were recorded with a Kratos MS-30 spectrometer operating at 70 eV and chemical ionization mass spectra were recorded on a Finnigan-4021 instrument. Column chromatographic purification was carried out on silica

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gel 60 (E. Merck) and 100–200-mesh (Davison Chemical). THF was routinely dried by distilling over CaH_2 followed by refluxing over Na and benzophenone and was distilled under N_2 prior to use. Petroleum ether (bp range 35–60 °C) was used for chromatography or crystallization. The final step in the synthesis as well as the purification by chromatography and crystallization of the target PAH was always carried out under yellow light. The purity of all final targets (>99% pure) was checked by HPLC (Varian 5000) on a Zorban ODS 6.2 mm × 25 cm column with a UV monitor (254 nm) and gradient elution 60% MeOH to 100% MeOH over 30 min. No exo methylene tautomers or 7- or 12-oxide products were found to be present in any sample submitted for biological investigated (carried out under yellow light). Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

2-Fluoro-6-iodobenzoyl Chloride (8) and *N*-(2-Methyl-3-hydroxypropyl)-2-fluoro-6-iodobenzamide (11). A mixture of 2-fluoro-6-iodobenzoic acid (Lancaster Synthesis, Ltd.) (20 g; 75.2 mmol) and $SOCl_2$ (26.78 g; 225 mmol) was stirred at room temperature for 20 h. The excess $SOCl_2$ was removed in vacuo and the liquid acid chloride (8) (22.0 g; 77.3 mmol) was dissolved in CH_2Cl_2 (25 mL). This solution was added dropwise to a stirred solution of 2-amino-2-methyl-1-propanol (13.8 g; 154.7 mmol) in 30 mL of CH_2Cl_2 at 0 °C. Stirring was continued for 3.5 h. The white precipitate was filtered and washed with Et_2O. The filtrate was concentrated under reduced pressure and the combined solids were crystallized from Et_2O/CH_2Cl_2 containing a few drops of CH_3OH affording 22.8 g (90%) of 2-fluoro-6-iodobenzamide 11, mp 168–169 °C. IR 3140–3500 (NH and OH), 1630 (CONH) cm^{-1}.

2-Bromo-5-fluorobenzoyl Chloride (9) and *N*-(2-Methyl-3-hydroxypropyl)-2-bromo-5-fluorobenzamide (12). 2-Bromo-5-fluorobenzoic acid[37] was prepared by oxidation[37,38] of commercially available 2-bromo-5-fluorotoluene (Fairfield Chemical Co.). The oxidation[38] was carried out by gently refluxing 2-bromo-5-fluorotoluene with excess $KMnO_4$ in H_2O affording 2-bromo-5-fluorobenzoic acid (70%), mp 158–159 °C. Acid chloride 9 was prepared from this acid (10 g; 45.8 mmol) and $SOCl_2$ (7.3 g; 61.3 mmol) by stirring at room temperature for 12 h and at 45 °C for 3 h. Excess $SOCl_2$ was removed in vacuo and the residual liquid 2-bromo-5-fluorobenzoyl chloride (9) (10 g; 42.1 mmol) was converted to fluorobenzamide 12 (12.8 g; 97%) following the same procedure as described for 11, mp 177–178 °C IR 3130–3540 (-CONH and OH), 1630 (-CONH) cm^{-1}.

2-(2-Fluoro-6-iodophenyl)-4,4-dimethyl-2-oxazoline (14). Benzamide 11 (17.5 g; 51.9 mmol) was treated dropwise with $SOCl_2$ (20.6 g; 173 mmol) and stirred for 2.5 h. After removal of the excess $SOCl_2$ in vacuo, the solution was poured into dry Et_2O (100 mL) and stirred with a glass rod to initiate precipitation. The solid was filtered and the residue was neutralized with NaOH solution (20%) and extracted with Et_2O. The Et_2O extract was dried ($MgSO_4$) and concentrated in vacuo to afford an oil, which solidifed upon cooling. Recrystallization from CH_2Cl_2/petroleum ether afforded white flakes (11.6 g; 70%), mp 61–62 °C. An analytical sample was prepared by chromatography over silica gel (100–200 mesh) using benzene as eluant followed by crystallization (CH_2Cl_2/petroleum ether) affording white crystals: mp 64–65 °C; IR (Nujol) 1655 cm^{-1}; ^1H NMR δ 1.60 (6 H, s, $2CH_3$), 3.9 (2 H, s, OCH_2), 7.0–7.7 (3 H, Ar); MS, *m/e* (ionic component, relative intensity) 319.9981 and 318.9890 ($C_{11}H_{11}ONFI$, M^+, 21.81 and 18.62, respectively). Anal. Calcd for $C_{11}H_{11}ONFI$: C, 41.39; H, 3.45; N, 4.39; F, 5.96; I, 39.79. Found: C, 41.48; H, 3.48; N, 4.43; F, 5.92; I, 39.82.

2-(2-Bromo-5-fluorophenyl)-4,4-dimethyl-2-oxazoline (15). Benzamide 12 (16.5 g; 57.1 mmol) was treated dropwise with $SOCl_2$ (24 g; 20.1 mmol) and stirred for h at room temperature. The mixture was worked up similar to the procedure used for 14 to afford oxazoline 15 (11.1 g; 70%). Crystallization from CH_2Cl_2/petroleum ether produced white needles: mp 56–57 °C; IR 1650 cm^{-1}; ^1H NMR δ 1.4 (s, 6 H, $2CH_3$), 4.1 (s, 2 H, OCH_2), 6.9–7.7 (m, 3 H, Ar); MS, *m/e* 273.0058 and 271.0071 ($C_{11}H_{11}ONFBr$, M^+, 15.96 and 15.61 respectively). Anal. Calcd for $C_{11}H_{11}ONFBr$: C, 48.55; H, 4.05; N, 5.15; F, 6.99; Br, 29.39. Found: C, 48.43; H, 4.21; N, 5.13; F, 7.07; Br, 29.45.

N-(2-Methyl-3-hydroxypropyl)-3-fluorobenzamide (13) and 2-(3-Fluorophenyl)-4,4-dimethyl-2-oxazoline (16). 3-Fluorobenzoyl chloride (11.9 g; 75.1 mmol, Aldrich) in CH_2Cl_2 (35 mL) was treated with a solution of 2-amino-2-methyl-1-propanol (14.7 g; 165 mmol) in CH_2Cl_2 (35 mL) at 0 °C following a procedure similar to the one used for the preparation of 11 and 12 to afford white crystals of 13 (15.2 g, 96%): mp 149–151 °C (CH_2Cl_2/Et_2O); ^1H NMR δ 1.3 (6 H, s, $2CH_3$), 1.65 (s, 2 H, CH_2OH), 6.05 (br s, 1 H, NH), 7.15–7.55 (m, 4 H, Ar). Amide 13 was cyclized by treatment with $SOCl_2$ followed by the usual workup to afford 10.0 g (69%) of oxazoline 16: bp 83–84 °C (2.5 mm); ^1H NMR δ 1.35 (s, 6 H, $2CH_3$), 4.1 (2 H, s, OCH_2), 7.0–7.8 (m, 4 H, Ar); MS, *m/e* 193.0891 ($C_{11}H_{12}NOF$, M^+, 7.2). Anal. Calcd for $C_{11}H_{12}NOF$: C, 68.39; H, 6.22; N, 7.25; F, 9.84. Found: C, 68.27; H, 6.36; N, 7.10; F, 9.67.

7-Fluoro-3-(5,6,7,8-tetrahydro-1-naphthalenyl)-1(3*H*)-isobenzofuranone (20). Oxazoline 14 (4.87 g; 15.3 mmol) was dissolved in 30 mL of dry THF. Sublimed Mg (468 mg; 19.5 mmol) was added followed by 2–3 drops of CH_2BrCH_2Br. The mixture was gently heated under reflux (N_2) for 1 h (Mg dissolved). The solution containing Grignard 17 was treated dropwise with dry 5,6,7,8-tetrahydro-1-naphthaldehyde (2.45 g; 15.3 mmol) and heated under reflux for 12 h. The mixture was cooled and quenched with 75 mL of 20% aqueous NH_4OH solution and extracted repeately with Et_2O. The combined Et_2O extracts were washed with H_2O and dried ($MgSO_4$) and the solvent was removed in vacuo. The oily residue was hydrolyzed by refluxing the $EtOH/H_2SO_4$ (6%, 40 mL) for 12 h and the excess EtOH was removed in vacuo. The residue was diluted with H_2O and extracted with Et_2O. The combined Et_2O extracts were washed with cold H_2O followed by 5% aqueous $NaHCO_3$ solution and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was crystallized from CH_2Cl_2/petroleum ether affording 3.1 g (71%) of white crystals: mp 131–132 °C. The analytical sample was prepared by chromatography (silica gel/benzene) and recrystallization (CH_2Cl_2/petroleum ether) producing white crystals, mp 136–137 °C: IR 1755 cm^{-1} (unsaturated γ-lactone C=O); ^1H NMR (270 MHz) δ 1.75–1.95 (m, 4 H, H-6′ and H-7′), 2.8–2.90 (m, 2 H, H-5′), 2.90–3.00 (m, 2 H, H-8′), 6.65 [s, 1 H, H-3 (lactonic)], 6.70–7.70 (m, 6 H, Ar); MS, *m/e* 282 (M^+, $C_{18}H_{15}O_2F$, 33.19); 254 ($C_{17}H_{15}OF$, $M^+ - CO$, 10.52); 238 ($C_{17}H_{15}F$, $M^+ - CO_2$, 22.51); 237 ($C_{17}H_{14}F$, $M^+ - CO_2 - H^\bullet$, 100). Anal. Calcd for $C_{18}H_{15}O_2F$: C, 76.57; H, 5.37; F, 6.73. Found: C, 76.66; H, 5.31; F, 6.53.

6-Fluoro-3-(5,6,7,8-tetrahydro-1-naphthalenyl)-1(3*H*)-isobenzofuranone (21). Oxazoline 15 (4.6 g; 16.9 mmol) was converted to Grignard 18 by refluxing in dry THF with Mg (515 g; 21.6 mmol) for 2 h followed by treatment with 5,6,7,8-tetrahydro-1-naphthaldehyde (2.7 g; 16.9 mmol) in 30 mL of dry THF. The mixture was heated at reflux for 14 h and worked up according to the procedure used for the preparation of 20. In this case, the intermediate adduct, obtained as an oily residue, solidified on triturating with petroleum ether. Hydrolysis and lactonization with $EtOH/H_2SO_4$ (6%) produced lactone 21 as white needles (3.3 g; 69%: mp 132–133 °C (CH_2Cl_2/petroleum ether followed by washing with MeOH). The analytical sample was prepared by chromatography (silica gel/100–200 mesh using benzene and CH_2Cl_2 as eluant) followed by crystallization producing needles: mp 135–136 °C; IR 1760 cm^{-1} (unsaturated γ-lactone C=O); ^1H NMR δ 1.7–2.1 (m, 4 H, H-6′, H-7′), 2.7–3.1 (m, 4 H, H-5′, H-8′), 6.5–7.9 (m, 6 H, Ar), 6.75 (s, 1 H, H-3); MS was similar to that observed for 20; relative intensities differed. anal. Calcd for $C_{18}H_{15}O_2F$: C, 76.57; H, 5.37; F, 6.73. Found: C, 76.57; H, 5.61; F, 6.57.

4-Fluoro-3-(5,6,7,8-tetrahydro-1-naphthalenyl)-1(3*H*)-isobenzofuranone (22). Distilled and dried oxazoline 16 (5.92 g; 28.1 mmol) was dissolved in dry THF (36 mL) and cooled to −40 °C (dry ice/chlorobenzene bath). *n*-BuLi (22.4 mL; 1.6 M, hexane, 35.5 mmol) was added over 0.5 h and stirred for 2 h at −40 °C. A solution of dry 5,6,7,8-tetrahydro-1-naphthaldehyde (4.7 g; 29.4 mmol) in dry THF (36 mL) was added. The mixture was warmed to room temperature and stirred at 40 °C for 18 h. The mixture was quenched with saturated NH_4Cl solution (40

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mL) and extracted with Et_2O and Et_2O–benzene (1:1). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo to afford a thick oil that was hydrolyzed by refluxing with HCl solution (4 N, 150 mL) for 6 h. The mixture was cooled and extracted with Et_2O and Et_2O–benzene (1:1). The combined organic extract was washed with 10% $NaHCO_3$ solution (to remove 3-fluorobenzoic acid), dried ($MgSO_4$), and concentrated to give a viscous oil, which crystallized upon trituration with petroleum ether affording 5.8 g (67%) of white needles. The analytical sample was prepared by chromatography over silica gel using benzene and $CHCl_3$ as eluant followed by crystallization providing needles (CH_2Cl_2/petroleum ether): mp 168–169 °C; IR 1750 cm^{-1}; ^1H NMR (270 MHz) δ 1.8–1.9 (m, 4 H, H-6′, H-7′), 2.78–2.85 (m, 2 H, H-5′ or H-8′), 2.95–3.05 (m, 2 H, H-8′ or H-5′), 6.60–7.55 (m, 7 H, 6 Ar-H and H-3); MS was similar to that observed for **20**. Anal. Calcd for $C_{18}H_{15}O_2F$: C, 76.57; H, 5.37; F, 6.73. Found: C, 76.50; H, 5.47; F, 6.77.

6-Fluoro-2-[(5,6,7,8-tetrahydro-1-naphthalenyl)methyl]benzoic Acid (23). A mixture of **20** (2.7 g; 9.6 mmol), pyridine (4 mL), $CuSO_4$ (55 mg), Zn dust [27 g; stirred with dilute HCl for 15 min, filtered and washed (H_2O) and dried in vacuo], and 10% KOH solution (53 mL) was heated at reflux for 20 h. The hot mixture was filtered and washed (hot H_2O). The filtrate was cooled and slowly poured onto ice containing concentrated HCl solution (approximately 20 mL) with stirring. The precipitate was filtered, washed with H_2O, and dried to afford a white solid (2.5 g; 92%), mp 174–175 °C. An analytical sample was prepared by chromatography over silica gel using $CHCl_3$–benzene (1:1) as eluant followed by crystallization from $CHCl_3$ containing a few drops of benzene–petroleum ether yielded white needles of **23**: mp 176–177 °C; IR 3300–2400 (carboxyl OH), 1695 (carboxyl C=O) cm^{-1}; ^1H NMR δ 1.60–1.85 (m, 4 H, H-6′ and H-7′), 2.40–2.65 (m, 2 H, H-5′ or H-8′), 2.65–2.90 (m, 2 H, H-8′ or H-5′), 4.15 (s, 2 H, benzylic CH_2), 6.70–7.45 (m, 6 H, Ar); MS, *m/e* 284.1191 ($C_{18}H_{17}O_2F$, M^+, 5.56). Anal. Calcd for $C_{18}H_{17}O_2F$: C, 76.02; H, 6.04; F, 6.68. Found: C, 75.96; H, 6.13; F, 6.46.

5-Fluoro-2-[(5,6,7,8-tetrahydro-1-naphthalenyl)methyl]benzoic Acid (24). Lactone **21** (2.1 g; 7.5 mmol) was reduced with Zn/KOH by using a procedure similar to that employed to prepare **23** to afford white needles of **24** (1.92 g; 90%): mp 184–185 °C ($CHCl_3$/petroleum ether); IR 3200–2400 (COOH), 1690 (COOH) cm^{-1}; ^1H NMR δ 1.6–1.95 (m, 4 H, H-6′, H-7′), 2.45–2.90 (m, 4 H, H-5′ and H-8′), 4.35 [s, 2 H, bis(benzylic) CH_2], 6.30–7.95 (m, 6 H, Ar); MS, *m/e* 284.1227 ($C_{18}H_{17}O_2F$, M^+, 6.54). Anal. Calcd for $C_{18}H_{17}O_2F$: C, 76.02; H, 6.04; F, 6.68. Found: C, 76.15, H, 6.10; F, 6.13.

3-Fluoro-2-[(5,6,7,8-tetrahydro-1-naphthalenyl)methyl]benzoic Acid (25). Lactone **22** (3.6 g; 9.6 mmol) was reduced following a procedure similar to the one used to prepare **23** to afford white needles of **25** (3.3 g, 90%): mp 192–193 °C (CH_2Cl_2/petroleum ether); IR 3300–2400 (COOH), 1690 (COOH) cm^{-1}; ^1H NMR δ 1.65–2.0 (m, 4 H, H-6′ and H-7′), 2.65–2.90 (m, 4 H, H-5′ and H-8′), 4.35 [br d (couples with 3-F), 2 H, bis(benzylic) CH_2], 6.3–7.9 (m, 6 H, Ar); MS was similar to that for **24**. Anal. Calcd for $C_{18}H_{12}O_2F$: C, 76.02; H, 6.04; F, 6.68. Found: C, 76.04; H, 6.25; F, 6.61.

8-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracen-7-ol Acetate (26). A mixture of acid **23** (2.0 g; 7.2 mmol), Ac_2O (11 mL), AcOH (25 mL), and fused $ZnCl_2$ (350 mg) was heated at reflux for 45 min. The cooled mixture was poured onto ice and the solid filtered, washed with H_2O, and air-dried to afford white flakes of **26** (2.0 g; 90%): mp 126–127 °C (benzene/MeOH). An analytical sample was prepared by column chromatography on silica gel (100–200 mesh) using benzene as eluant followed by crystallization to produce white flakes: mp 129–130 °C; IR 1760 (phenyl acetate) cm^{-1}; ^1H NMR δ 1.8–2.1 (m, 4 H, H-2 and H-3), 2.55 (s, 3 H, O_2CCH_3), 2.8–8.3 (m, 2 H, H-4), 3.05–3.30 (m, 2 H, H-1), 6.9–7.9 (m, 5 H, Ar), 8.45 (br s, 1 H, H-12); MS, *m/e* 308.1213 ($C_{20}H_{17}O_2F$, M^+, 9.91), 266 ($C_{18}H_{15}OF$, $M^+ - CH_2{=}C{=}O$, 100). Anal. Calcd for $C_{20}H_{17}O_2F$: C, 77.89; H, 5.57; F, 6.16. Found: C, 77.39; H, 5.67; F, 6.22.

9-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracen-7-ol Acetate (27). Acid **24** (1.6 g; 5.7 mmol) was converted to the enol acetate **27** by using a procedure similar to the one used for the preparation of **26** to afford white needles (1.45 g; 83%): mp 134–135 °C (purified by chromatography over silica gel using benzene as eluant and crystallization from CH_2Cl_2/MeOH); IR 1755 (phenyl acetate C=O) cm^{-1}; ^1H NMR δ 1.70–2.10 (m, 4 H, H-2 and H-3), 2.6 (s, 3 H, O_2CCH_3), 2.75–3.05 (m, 2 H, H-4), 3.10–3.35 (m, 2 H, H-1), 6.65–8.70 (m, 6 H, Ar); MS, *m/e* 308.1210 ($C_{20}H_{17}O_2F$, M^+, 10.49), 282 ($C_{18}H_{15}O_2F$, $M^+ - C_2H_2$, 9.46), 266 ($C_{18}H_{15}OF$, $M^+ - CH_2{=}C{=}O$, 100). Anal. Calcd for $C_{20}H_{17}O_2F$: C, 77.89; H, 5.57; F, 6.16. Found: C, 78.16; H, 5.81; F, 5.67.

11-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracen-7-ol Acetate (28). Acid **25** (2.7 g; 9.4 mmol) was cyclized to the enol acetate **28** (2.76 g; 95%): mp 141–142 °C (benzene/MeOH) by using fused $ZnCl_2/Ac_2O$ following a procedure similar to that used for the preparation of **26**: IR 1755 cm^{-1}; ^1H NMR δ 1.80–2.20 (m, 4 H, H-2 and H-3), 2.60 (s, 3 H, O_2CCH_3), 2.70–3.00 (m, 2 H, H-4), 3.10–3.35 (m, 2 H, H-1), 6.95–7.80 (m, 5 H, Ar), 8.65 (s, 1 H, H-12); MS was similar to that observed for **26**. Anal. Calcd for $C_{20}H_{17}O_2F$: C, 77.80; H, 5.57; F, 6.16. Found: C, 77.97; H, 5.86; F, 6.17.

8-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione (29). Acetate **26** (2.5 g; 8.12 mmol) was added to a hot solution of $K_2Cr_2O_7$ (3.0 g; 10.1 mmol) in AcOH (45 mL) and heated at reflux for 15 min. The mixture was cooled, poured onto ice/H_2O, and stirred with a glass rod. The yellow precipitate was filtered, washed thoroughly with cold H_2O, and dried in vacuo. The crude quinone was chromatographed over silica gel (100–200 mesh) by using CH_2Cl_2 as eluant. Crystallization from CH_2Cl_2/MeOH afforded yellow needles of **29** (1.62 g; 71%): mp 202–203 °C; IR 1660 (conjugated C=O) cm^{-1}; ^1H NMR δ 1.85–2.05 (m, 4 H, H-2 and H-3), 2.90–3.10 (m, 2 H, H-4), 3.35–3.55 (m, 2 H, H-1), 7.35–7.95 (m, 3 H, Ar), 8.10–8.25 (m, 2 H, H-6 and H-11); MS, *m/e* 280.0854 ($C_{18}H_{13}O_2F$, M^+, 93.27). Anal. Calcd for $C_{18}H_{13}O_2F$: C, 77.12; H, 4.69; F, 6.78. Found: C, 76.96; H, 4.69; F, 6.68.

9-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione (30). Acetate **27** (1.2 g; 3.9 mmol) was oxidized by refluxing with $K_2Cr_2O_7$ (1.45 g; 4.9 mmol) in AcOH (22 mL) for 20 min and worked up as for **29**. The crude yellow quinone was purified by chromatography over silica gel (100–200 mesh) using CH_2Cl_2 as eluant followed by crystallization from CH_2Cl_2/MeOH affording yellow needles of **30** (775 mg; 70%): mp 163–164 °C; IR 1655 (quinone C=O) cm^{-1}; ^1H NMR δ 1.75–1.95 (m, 4 H, H-2 and H-3), 2.80–3.05 (m, 2 H, H-4), 3.25–3.55 (m, 2 H, H-1), 7.30–7.55 (m, 2 H, H-10 and H-5), 7.75–8.35 (3 H, H-8, H-6 and H-11); MS, *m/e* 280.0913 ($C_{18}H_{13}O_2F$, M^+, 91.90). Anal. Calcd for $C_{18}H_{13}O_2F$: C, 77.12; H, 4.69; F, 6.78. Found: C, 77.08; H, 4.87; F, 6.62.

11-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-dione (31) and 11-Fluoro-2,3-dihydrobenz[*a*]anthracene-4,7,12-(1*H*)-trione (32). To a stirred mixture of acetate **28** (1.8 g; 5.8 mmol) and 25 mL of AcOH was added dropwise a solution of CrO_3 (3.0 g; 30 mmol) in 16 mL of AcOH and 5 mL of H_2O. The mixture was stirred at 65 °C in an oil bath for 45 min and cooled. The mixture was poured onto ice/H_2O affording a yellow precipitate which was filtered, washed thoroughly with H_2O, and dried in vacuo. The yellow residue was chromatographed over silica gel (100–200 mesh). The initial CH_2Cl_2 eluates afforded pure yellow needles of dione **28** (1.1 g; 65%): mp 196–197 °C (CH_2Cl_2/MeOH); IR 1660 (quinone C=O) cm^{-1}; ^1H NMR δ 1.70–2.00 (m, 4 H, H-2 and H-3), 2.80–3.05 (m, 2 H, H-4), 3.20–3.45 (m, 2 H, H-1), 7.20–7.80 (m, 3 H, H-10, H-9 and H-5), 7.95–8.15 (m, 2 H, H-6 and H-8); MS, *m/e* 280.0887 ($C_{18}H_{13}O_2F$, M^+, 72.27). Anal. Calcd for $C_{18}H_{13}O_2F$: C, 77.12; H, 4.69; F, 6.78. Found: C, 77.09; H, 4.95; F, 6.89.

Trione **32** (204 mg; 12%) was isolated from the later CH_2Cl_2 eluates as well as 2% MeOH–$CHCl_3$ eluates to afford yellow flakes: mp 182–183 °C ($CHCl_3$/MeOH); IR 1670 (C=O) cm^{-1}; ^1H NMR δ 1.95–2.35 (m, 2 H, H-2), 2.65–2.88 (m, 2 H, H-3), 3.48–3.70 (m, 2 H, H-1), 7.35–7.85 (m, 2 H, H-9 and H-10), 8.25–8.53 (m, 3 H, H-5, H-6, and H-8); MS, *m/e* 294.0702 ($C_{18}H_{11}O_3F$, M^+, 100), 266 ($C_{17}H_{11}O_2F$, $M^+ - CO$, 34.95), 238 ($C_{16}H_{11}OF$, 266 – CO, 28.24), 210 ($C_{15}H_{11}F$, 238 – CO, 9.26). Anal. Calcd for $C_{18}H_{11}O_3F$: C, 73.46; H, 3.78; F, 6.46. Found: C, 73.23; H, 3.89; F, 6.04.

11-Fluoro-1,3,4,12-tetrahydro-12-hydroxybenz[*a*]anthracen-7(2*H*)-one (33). Acetate **28** (500 mg; 1.6 mmol) was dissolved in warm AcOH (5 mL) and cooled. To this solution was slowly added dropwise and with stirring (room temperature, 5 min) a solution of CrO_3 (330 mg; 3.3 mmol) in 5 mL of AcOH and 1 mL of H_2O. The mixture was stirred for 1 h at room temperature and poured onto ice/H_2O. The light yellow precipitate was fil-

tered, dried, and chromatographed [silica gel (60 mesh), CH_2Cl_2]. Initial CH_2Cl_2 eluates afforded yellow needles of dione **31** (55 mg; 12%). The later CH_2Cl_2 eluates and subsequent 5% MeOH–$CHCl_3$ eluates afforded hydroxyanthrone **33** (300 mg; 65.5%): mp 201–203 °C; IR 3400 (br, OH), 1635 (conjugated C=O) cm^{-1}; ^1H NMR (90 MHz) δ 1.75–2.00 (m, 4 H, H-2 and H-3), 2.35 (dd, 1 H, $J_{OH,H}$ = 6.7 Hz; $J_{OH,F}$ = 1.6 Hz, 12-OH, undergoes D_2O exchange), 2.8–3.0 (m, 2 H, H-4), 3.0–3.3 (m, 2 H, H-1), 6.15 (d, $J_{H,OH}$ = 6.7 Hz; singlet on D_2O exchange), 7.15–7.60 (m, 3 H, Ar, H-5, H-9, and H-10), 7.95–8.15 (m, 2 H, H-6 and H-8); ^1H NMR (500 MHz) δ 1.8–2.0 (m, 4 H, H-2 and H-3), 2.45 (m, 1 H, 12-OH), 2.85–3.05 (m, 2 H, H-4), 2.96–3.06 (m, 1 H, H_A-1 or H_B-1), 3.25–3.34 (m, 1 H, H_B-1 or H_A-1), 6.15 (d, $J_{H,OH}$ = 6.67 Hz, 1 H, H-12), 7.25 (d, $J_{H\text{-}5,H\text{-}6}$ = 8.07 Hz, 1 H, H-5), 7.35–7.40 (m, 1 H, H-10), 7.45–7.50 (m, 1 H, H-9), 7.96–8.05 (m, 2 H, H-6 and H-8); MS, *m/e* 282 ($C_{18}H_{15}O_2F$, M^+, 10.83), 264 ($C_{18}H_{13}OF$, $M^+ - H_2O$, 100). Anal. Calcd for $C_{18}H_{15}O_2F$: C, 76.57; H, 5.37; F, 6.73. Found: C, 76.72; H, 5.58; F, 6.70.

11-Fluoro-1,3,4,12-tetrahydro-12-hydroxybenz[*a*]anthracen-7(2*H*)-one Acetate (34). Hydroxyanthrone **33** (20 mg; 0.07 mmol) was dissolved in pyridine (1.5 mL) and Ac_2O (2.0 mL). The solution was stirred at room temperature overnight and poured onto ice/H_2O. HCl solution (2 N, 3 mL) was added to neutralize. The mixture was extracted with CH_2Cl_2 and the organic layer was washed with H_2O and dried ($MgSO_4$). The oily residue obtained after evaporation of solvent in vacuo was chromatographed over silica gel (100–200 mesh) by using benzene as eluant followed by crystallization from CH_2Cl_2/MeOH to afford acetate **34** (15 mg; 65%): mp 110–111 °C; IR 1730 (acetate) cm^{-1}; ^1H NMR δ 1.65–2.00 (m, 4 H, H-2 and H-3), 1.95 (s, 3 H, 12-O_2CCH_3), 2.70–3.10 (m, 4 H, H-1 and H-4), 7.20–7.65 (m, 4 H, H-5, H-9, H-10, and H-12), 7.95–8.10 (m, 2 H, H-6 and H-8); CIMS (CH_4 as reagent gas), *m/e* (ionic component, relative intensity) 325.08 (MH^+, 15.36), 283.1 ($MH^+ - CH_2{=}C{=}O$, 5.5), 265.1 ($MH^+ - CH_3CO_2H$ or 283.1 – H_2O, 100); EIMS, *m/e* 282.1081 ($C_{18}H_{15}O_2F$, $M^+ - CH_2{=}C{=}O$, 5.63), 264 ($C_{18}H_{13}OF$, $M^+ - CH_3CO_2H$ or 282 – H_2O, 100).

11-Fluoro-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-diol Diacetate (35). A mixture of hydroxyanthrone **33** (50 mg; 0.18 mmol), pyridine (3.0 mL), and Ac_2O (3.0 mL) was heated at reflux under N_2 for 5 h, poured onto ice/2 N aqueous HCl (4 mL), and extracted with CH_2Cl_2. The organic layer was washed thoroughly with H_2O and dried ($MgSO_4$) and the residue obtained, following removal of solvent in vacuo, was chromatographed [silica gel (100–200 mesh)/CH_2Cl_2] to afford white needles of diacetate **35** (60 mg; 92.5%): mp 194–195 °C (CH_2Cl_2/MeOH); IR 1755 (phenyl acetate C=O) cm^{-1}; ^1H NMR δ 2.10–2.60 (m, 4 H, H-2 and H-3), 2.48 (s, 3 H, 7-O_2CCH_3), 2.60 (s, 3 H, 12-O_2CCH_3), 2.80–3.90 (m, 4 H, H-1 and H-4), 6.90–7.75 (m, 5 H, Ar); MS, *m/e* 366 ($C_{22}H_{19}O_4F$, M^+, 6.73), 324 ($C_{20}H_{17}O_3F$, $M^+ - CH_2{=}C{=}O$, 15.76), 282 ($C_{18}H_{15}O_2F$, 324 – $CH_2{=}C{=}O$, 100). Anal. Calcd for $C_{22}H_{19}O_4F$: C, 72.13; H, 5.19; F, 5.19. Found: C, 72.31; H, 5.38; F, 5.10.

***cis*- and *trans*-8-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (36).** Quinone **29** (1.7 g; 6.0 mmol) was dissolved under N_2 in warm dry benzene (75 mL). CH_3MgBr (30 mL, 3 M solution in Et_2O, Aldrich) was added dropwise. The mixture was heated at reflux for 4 h, cooled, and poured onto ice/H_2O with stirring. The mixture was extracted repeatedly with EtOAc and the organic layer was washed with H_2O, dried ($MgSO_4$), and concentrated in vacuo. The major cis diol (more polar) can be separated in near pure form from the residue by crystallization (CH_2Cl_2/petroleum ether containing a few drops of benzene) and also from the mother liquor by chromatography [silica gel (100–200 mesh)/CH_2Cl_2]. The analytical sample of the major cis isomer melted at 173–174 °C. The total yield of **36** including pure cis and the diastereoisomeric mixture recovered from the mother liquor was 1.40 g (75%): IR (cis) 3140–3500 (br, OH) cm^{-1}; ^1H NMR (270 MHz) δ 1.63 (s, 3 H, 7-CH_3 or 12-CH_3), 1.70 (s, 3 H, 12-CH_3 or 7-CH_3), 1.80–2.00 (m, 4 H, H-2 and H-3), 2.55 [s, 1 H, OH (D_2O exchangeable)], 2.78–2.85 (m, 2 H, H-4), 3.16–3.26 (m, 2 H, H-1), 3.28 [s, 1 H, OH (D_2O exchangeable)], 6.95–7.05 (m, 1 H, H-9), 7.07 (d, $J_{H\text{-}5,H\text{-}6}$ = 8.2 Hz, 1 H, H-5), 7.35–7.25 (m, 1 H, H-10), 7.55 (d, $J_{H\text{-}6,H\text{-}5}$ = $J_{H\text{-}11,H\text{-}10}$ = 8.4 Hz, 2 H, H-6 and H-11); MS, *m/e* 297.1300 ($C_{19}H_{18}O_2F$, $M^+ - CH_3$, 100), 294 ($C_{20}H_{19}O$, $M^+ - H_2O$, 7.06), 282 ($C_{18}H_{15}O_2F$, 297 – CH_3, 55.06), 279 ($C_{19}H_{16}OF$, 297 – H_2O, 28.10), 276 ($C_{20}H_{17}F$, 294 – H_2O, 15.08), 264 ($C_{18}H_{13}OF$, 279 – CH_3, 22.85), 261 ($C_{19}H_{14}F$, 279 – H_2O, 17.37), 246 ($C_{18}H_{11}F$, 264 – H_2O or 261 – CH_3, 7.36). Anal. Calcd for $C_{20}H_{21}O_2F$: C, 76.89; H, 6.79; F, 6.08. Found: C, 76.31; H, 6.93; F, 5.99.

***cis*/*trans*-9-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (37).** To a mixture of quinone **30** (710 mg; 2.54 mmol) and dry benzene (40 mL) was added CH_3MgBr (14 mL, 3.0 M solution in Et_2O, Aldrich) dropwise under N_2. The mixture was heated at reflux for 4.5 h and worked up similar to that for the preparation of **36** to afford white crystals of diol **37** (633 mg; 80%): mp 170–171 °C (nearly pure *cis*-**37**, more polar; crystallized from CH_2Cl_2/benzene/petroleum ether); IR 3100–3500 (br, OH) cm^{-1}; ^1H NMR (270 MHz) δ 1.15 (s, 3 H, 7-CH_3 or 12-CH_3), 1.70 (s, 3 H, 12-CH_3 or 7-CH_3), 1.80–2.00 (m, 4 H, H-2 and H-3), 2.1 [s, 1 H, OH (exchangeable with D_2O)], 2.2 [s, 1 H, OH (exchangeable with D_2O)], 2.75–2.90 (m, 2 H, H-4), 3.20–3.30 (m, 2 H, H-1), 7.00–7.78 (5 H, Ar). MS was similar to that for **36**; only relative intensities differed. Anal. Calcd for $C_{20}H_{21}O_2F{\cdot}5H_2O$: C, 74.77; H, 6.85; F, 5.92. Found: C, 75.02; H, 6.84; F, 5.85.

***cis*/*trans*-11-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene-7,12-diol (38).** Dione **31** (615 mg; 2.2 mmol) was converted to diol **38** by heating at reflux with CH_3MgBr (12 mL, 3 M solution in Et_2O, Aldrich) in 32 mL of benzene following a procedure similar to that for the preparation of **36** to afford white needles of diol **38** (548 mg; 80%). The major and more polar cis isomer (425 mg), mp 200–201 °C, was separated and purified by crystallization from CH_2Cl_2/petroleum ether (containing few drops of MeOH for quick dissolving). The mother liquor afforded a mixture (123 mg) of *cis*- and *trans*-**38** (mostly trans): IR (cis) 3120–3500 (OH) cm^{-1}; ^1H NMR (cis) δ 1.50 (s, 3 H, 7-CH_3), 1.60–2.00 (m, 4 H, H-2 and H-3), 1.93 (d, $J_{CH_3\text{-}F}$ = 1.1 Hz, 3 H, 12-CH_3), 2.25 [s, 1 H, 7-OH (exchangeable with D_2O)], 2.65–2.95 (m, 2 H, H-4), 3.0 [s, 1 H, 12-OH (exchangeable with D_2O)], 3.10–3.55 (m, 2 H, H-1), 6.90–8.10 (m, 5 H, Ar); MS was similar to those observed for **36** and **37**; only relative intensities differed. Anal. Calcd for $C_{20}H_{21}O_2F{\cdot}2H_2O$: C, 76.01; H, 6.84; F, 6.01. Found: C, 76.04; H, 6.83; F, 5.94.

8-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (4). Low valent titanium[18] was prepared by slow addition of $LiAlH_4$ (250 mg, 6.7 mmol) to a stirred suspension of $TiCl_3$ (2.0 g; 13.0 mmol) in dry THF (60 mL) under a stream of N_2 at 0 °C. The mixture was stirred at 0 °C for 15 min and heated at reflux for 1 h. To this black suspension was added diol **36** (1.0 g; 3.2 mmol) under N_2 and yellow light at 0 °C. The mixture was heated at reflux for 3 h, cooled, quenched with ice/H_2O, and extracted with CH_2Cl_2. The combined organic extract was washed thoroughly with H_2O, dried (Na_2SO_4), and concentrated in vacuo affording a yellow fluorescent viscous residue. Column chromatography [silica gel (100–200 mesh), petroleum ether] afforded 700 mg (79%) of yellow shining flakes, mp 112–113 °C, following recrystallization from CH_2Cl_2/MeOH (anhydrous): ^1H NMR (270 MHz) δ 1.60–1.70 (m, 2 H, H-3 or H-2), 1.85–1.97 (m, 2 H, H-2 or H-3), 2.92–3.00 (m, 2 H, H-4), 3.05 (s, 3 H, 12-CH_3), 3.16 (d, $J_{CH_3,F}$ = 5.03 Hz, 3 H, 7-CH_3), 3.20–3.25 (m, 2 H, H-1), 7.00–7.10 (m, 1 H, H-9), 7.15 (d, $J_{H\text{-}5,H\text{-}6}$ = 9.15 Hz, 1 H, H-5), 7.99 (d, $J_{H\text{-}11,H\text{-}10}$ = 8.87 Hz, 1 H, H-11), 8.06 (d, $J_{H\text{-}6,H\text{-}5}$ = 9.13 Hz, 1 H, H-6); MS, *m/e* 278.1477 ($C_{20}H_{19}F$, M^+, 100), 263 ($C_{19}H_{16}F$, $M^+ - CH_3$, 22.00), 248 ($C_{18}H_{13}F$, 263 – CH_3, 15.66). Anal. Calcd for $C_{20}H_{19}F$: C, 86.28; H, 6.90; F, 6.83. Found: C, 85.98; H, 6.94; F, 6.72.

9-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (5). The synthesis of **5** from **37** (215 mg; 0.69 mmol) was carried out according to the procedure for the preparation of **4**. The reaction mixture was refluxed for 3 h, cooled, quenched with ice/H_2O, and worked up accordingly. Column chromatography [silica gel (100–200 mesh), petroleum ether] afforded **5** (135 mg; 70.5%), mp 138–139 °C, after recrystallization from CH_2Cl_2/MeOH (anhydrous): ^1H NMR (270 MHz) δ 1.65–1.75 (m, 2 H, H-3 or H-2), 1.88–2.00 (m, 2 H, H-2 or H-3), 2.90–3.05 (m, 2 H, H-4), 2.95 (s, 3 H, 7- or 12-CH_3), 3.15 (s, 3 H, 12- or 7-CH_3), 3.23–3.30 (m, 2 H, H-1), 7.16 (d, $J_{H\text{-}5,H\text{-}6}$ = 9.08 Hz, 1 H, H-5), 7.25–7.30 (m, 1 H, H-10), 7.77 (dd, $J_{H\text{-}8,H\text{-}10}$ = 2.6 Hz, $J_{H\text{-}8,F\text{-}9}$ = 11.9 Hz, H-3), 7.98 (d, $J_{H\text{-}6,H\text{-}5}$ = 9.06 Hz, H-6), 8.25 (dd, $J_{H\text{-}11,H\text{-}10}$ = 6.0 Hz, $J_{H\text{-}11,F\text{-}9}$ = 9.60 Hz, H-11); MS was similar to that

observed for 4, relative intensities differed. Anal. Cald for $C_{20}H_{19}F$: C, 86.28; H, 6.90; F, 6.83. Found: C, 85.96; H, 6.89; F, 6.68.

11-Fluoro-1,2,3,4-tetrahydro-7,12-dimethylbenz[*a*]anthracene (7). PAH 7 was synthesized from diol 38 (270 mg; 1.0 mmol) according to the procedure used for the synthesis of 4 employing low valent titanium prepared by reduction of $TiCl_3$ with $LiAlH_4$. The usual workup and chromatographic purification (silica gel/petroleum ether) followed by crystallization (CH_2Cl_2/MeOH) afforded 7 (180 mg; 75%) as yellow flakes: mp 82.5–83.5 °C; ^1H NMR (270 MHz) δ 1.65–1.75 (m, 2 H, H-3 or H-2), 1.90–2.00 (m, 2 H, H-2 or H-3), 2.95 (t, J = 6 Hz, 2 H, H-4), 3.0 (s, 3 H, 7-CH_3), 3.08 (d, $J_{CH_3,F\text{-}9}$ = 9 Hz, 3 H, 12-CH_3), 3.25 (t, J = 5.8 Hz, 2 H, H-1), 7.05–7.13 (m, 1 H, H-10), 7.17 (d, $J_{H\text{-}5,H\text{-}6}$ = 9.09 Hz, 1 H, H-5), 7.28–7.37 (m, 1 H, H-9), 8.00 (d, $J_{H\text{-}6,H\text{-}5}$ = $J_{H\text{-}8,H\text{-}9}$ = 9.0 Hz, 2 H, H-6 and H-8); MS was similar to those observed for 4 or 5. Anal. Calcd for $C_{20}H_{19}F$: C, 86.28; H, 6.90; F, 6.83. Found: C, 86.51; H, 7.10; F, 6.72.

11-Fluoro-1,2,3,4,7,12-hexahydro-12-methyl-7-methylenebenz[*a*]anthracene (45). Fifteen milligrams of *p*-TsOH was added to a solution of 11F-TH-DMBA (7) (60 mg, 0.22 mmol) in 25 mL of dry benzene ($CaCl_2$/distilled). The mixture was heated under gentle reflux in an oil bath at 80 °C for 1 h. The mixture was cooled and chromatographed on basic alumina (Woelm) using benzene as eluant. The eluate was concentrated in vacuo and the oily residue was rechromatographed over silica gel (100–200 mesh) by using petroleum ether as eluant. The eluate, upon concentration in vacuo followed by crystallization from CH_2Cl_2/anhydrous MeOH, afforded 51 mg (85%) of light yellow crystals: mp 72–73 °C; ^1H NMR (500 MHz) δ 1.20 (d, $J_{CH,H}$ = 6.95 Hz, 3 H, 12-CH_3), 1.65–1.9 (m, 4 H, H-2 and H-3), 2.65–2.95 (m, 4 H, H-1 and H-4), 4.55 (q, $J_{H,CH}$ = 7.0 Hz, 1 H, H-12), 5.5–5.6 (m, 2 H, H-7), 6.95–7.04 (m, 2 H, H-5 and H-10), 7.18–7.25 (m, 1 H, H-9), 7.43–7.47 (m, 2 H, H-8 and H-6); MS, m/e 278.1482 ($C_{20}H_{19}F$, M^+, 19.13), 263 ($C_{19}H_{16}F$, $M^+ - CH_3$, 100). Anal. Calcd for $C_{20}H_{19}F$: C, 86.28; H, 6.90; F, 6.83. Found: C, 86.29; H, 6.89; F, 6.55.

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Dicyclopenta[*ef*,*kl*]heptalene (Azupyrene) Chemistry. Electrophilic Substitution on 1- and 4-Substituted Azupyrenes. Substituent Spectral Effects for Mono- and Disubstitution Derivatives

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The orientation of electrophilic substitution on monosubstituted azupyrenes has been investigated by the trifluoroacetylation of 1-methylazupyrene, the acetylation of 1-acetylazupyrene, 1-(trifluoroacetyl)azupyrene, and methyl azupyrene-1-carboxylate, the bis(diaminomethylation) of azupyrene, and the nitration of 4-nitroazupyrene. The results only partially correlate with predictions based on simple (e.g., resonance structure) considerations of the intermediate arenium ions. ^1H NMR and ultraviolet/visible spectral shifts are correlated for a number of 1-, 4-, 1,2-, 1,4-, 1,6-, 1,7-, and 2,5-substituted derivatives.

Electrophilic Disubstitution. Previous studies[2,3] showed that electrophilic monosubstitution of azupyrene occurs at the 1- and 4-positions with the former favored (from 3:2 to 13:1) in protonation, acetylation, trifluoroacetylation, halogenation, thiocyanation, and aminomethylation, but the latter dominant (35:1) for nitration. MNDO calculations of E_a values for trifluoroacetylation and nitration correlated with the results for these reactions.[2] It was then desired to determine the position(s) of substitution on 1- and 4-substituted compounds.

The monosubstitution studies together with earlier observations on the behavior of a large number of 1-substituted azulenes[4] with electrophiles pointed to the open positions on the five-ring compounds and the 4- or 9-positions on the seven-ring compounds for the introduction of the second substituent on a 1-substituted azupyrene. Consideration of resonance stabilization or destabilization of the intermediate arenium ion by the group on the 1-position showed positions 2, 6, and 9 favored with an

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