chstetler of Givaudan Corporation, Clifton, NJ, for a generous sample of cyclopentadecanone.

Registry No. **1a**, 3045-74-7; **1b**, 3045-76-9; **1c**, 24899-36-3; **1d**, 95784-87-5; **1e**, 95784-88-6; **1f**, 1027-10-7; **2a**, 95784-89-7; **2b**, 87336-89-8; **2c**, 95784-90-0; **2d**, 95784-91-1; **2e**, 95784-92-2; **2f**, 95784-93-3; **3e**, 95784-94-4; **4a**, 95784-95-5; **4b**, 95840-54-3; **4c**, 95784-97-7; **4d**, 95784-99-9; **4e**, 95785-01-6; **4f**, 95797-89-0; **5a**, 95784-96-6; **5b**, 95840-55-4; **5c**, 95784-98-8; **5d**, 95785-00-5; **5e**, 95785-02-7; **5f**, 95785-03-8; cyclodecanone, 1502-06-3; cyclododecanone, 830-13-7; cyclotridecanone, 832-10-0; cyclotetradecanone, 3603-99-4; cyclopentadecanone, 502-72-7.

Synthesis and Deamination of 7,12-Dihydrobenz[*a*]anthracen-7,12-imines. A New Benz[*a*]anthracene Synthesis

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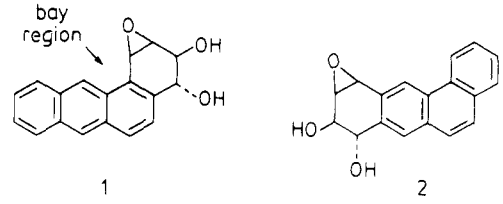
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Received August 3, 1984

The Diels–Alder reaction between isoindoles (**7**) and 1-naphthalyne, as generated from 1-bromo-2-fluoronaphthalene (**11a**), 1-bromo-2-iodonaphthalene (**11b**), or 1-bromo-2-naphthyl *p*-toluenesulfonate (**11c**), affords the corresponding 7,12-dihydrobenz[*a*]anthracen-7,12-imine (**17**). Oxidative deamination of **17** with *m*-chloroperbenzoic acid gives the polyhalogenated benz[*a*]anthracenes (**3**, **19a–d**) in fair to good overall yields. A similar sequence with **7** and 5,6,7,8-tetrafluoro-1-naphthalyne, as generated from 1,2,3,4-tetrafluoro-5-chloronaphthalene (**14a**), 1,2,3,4-tetrafluoro-5-bromonaphthalene (**14b**), or 6-bromo-1,2,3,4-tetrafluoro-5-naphthyl *p*-toluenesulfonate (**16**), gives, after deamination of the intermediate benzanthracenimine **18**, benz[*a*]anthracenes **5** and **19e** in low overall yield.

During their pioneering study of 4-(dimethylamino)-azobenzene carcinogenesis, Miller and Miller[1] first proposed and utilized fluorine substitution as a probe to determine metabolic sites of carcinogenesis vis-à-vis detoxification in this and related carcinogens. The rationale was that fluorine would block metabolism at that site without affecting the ability of the molecule as a whole to be metabolized. Miller and Miller,[2] in collaboration with Newman,[3] extended this concept to the study of carcinogenic benz[*a*]anthracenes. Subsequent years have seen this "fluorine probe" tool used in many studies of several carcinogenic polynuclear aromatic hydrocarbons (PAH): methyl-substituted benz[*a*]anthracenes,[2,4] 5-methylchrysene,[5] benzo[*a*]pyrene,[6] benzo[*c*]phenanthrene,[7] dibenz[*a*,*h*]anthracene,[8] dibenzo[*a*,*i*]pyrene,[9] and 3-methylcholanthrene.[10] Depending on the position of fluorine substitution, the carcinogenicity of the PAH[11] may be suppressed, elevated, or unaffected.

These studies have invariably[12] focused on monofluorine substitution to answer questions about metabolism at a single carbon atom or arene double bond. Because current theories of PAH carcinogenesis[11,13,14] involve diol epoxides (e.g., "bay-region" **1**[13] diol epoxide and "non-bay-region"



1 2

diol epoxide **2**[14]) in which four sites have been metabolized,

(1) (a) Miller, J. A.; Sapp, R. W.; Miller, E. C. *Cancer Res.* **1949**, *9*, 652. (b) Miller, J. A.; Miller, E. C.; Finger, G. C. *Ibid.* **1953**, *13*, 93. (c) *Ibid.* **1957**, *17*, 387.

(2) (a) Miller, E. C.; Miller, J. A. *Cancer Res.* **1960**, *20*, 133. (b) Miller, J. A.; Miller, E. C. *Ibid.* **1963**, *23*, 229.

(3) (a) Newman, M. S.; MacDowell, D.; Swaminathan, S. *J. Org. Chem.* **1959**, *24*, 509. (b) Newman, M. S. In "Carcinogenesis: Polynuclear Aromatic Hydrocarbons"; Freudenthal, R. I., Jones, P. W., Eds.; Raven Press: New York, 1976; Vol. 1, pp 203–207.

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(5) (a) Hecht, S. S.; Loy, M.; Mazzarese, R.; Hoffmann, D. *J. Med. Chem.* **1978**, *21*, 38. (b) Hecht, S. S.; Hirota, N.; Loy, M.; Hoffmann, D. *Cancer Res.* **1978**, *38*, 1694. (c) Hecht, S. S.; LaVoie, E.; Mazzarese, R.; Hirota, N.; Ohmori, T.; Hoffmann, D. *J. Natl. Cancer Inst.* **1979**, *63*, 855. (d) Amin, S.; Juchatz, A.; Furuya, K.; Hecht, S. S. *Carcinogenesis* **1981**, 2, 1027.

(6) (a) Blum, J.; Bergmann, E. D. *J. Org. Chem.* **1967**, *32*, 344. (b) Paulsen, H.; Lüttke, W. *Chem. Ber.* **1979**, *112*, 2907. (c) Buhler, D. R.; Unlu, F.; Thakker, D. R.; Slaga, T. J.; Newman, M. S.; Levin, W.; Conney, A. H.; Jerina, D. M. *Cancer Res.* **1982**, *42*, 4779. (d) Buening, M. K.; Levin, W.; Wood, A. W.; Chang, R. L.; Agranat, I.; Rabinovitz, M.; Buhler, D. R.; Mah, H. D.; Hernandez, O.; Simpson, R. B.; Jerina, D. M.; Conney, A. H.; Miller, E. C.; Miller, J. A. *J. Natl. Cancer Inst.* **1983**, *7*, 309.

(7) (a) Bergmann, E. D.; Blum, J. *J. Org. Chem.* **1962**, *27*, 527. (b) Ittah, Y.; Jerina, D. M. *J. Fluorine Chem.* **1980**, *16*, 137.

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(9) (a) Boger, E.; O'Malley, R. F.; Sardella, D. F. *J. Fluorine Chem.* **1976**, *8*, 513. (b) Hecht, S. S.; LaVoie, E. J.; Bedenko, V.; Pingaro, L.; Katayama, S.; Hoffmann, D.; Sardella, D. J.; Boger, E.; Lehr, R. E. *Cancer Res.* **1981**, *41*, 4341.

(10) Newman, M. S.; Khanna, V. K. *J. Org. Chem.* **1980**, *45*, 4507.

(11) Reviews: (a) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218. (b) Dipple, A. *Cancer Res. Suppl.* **1983**, *43*, 2422s.

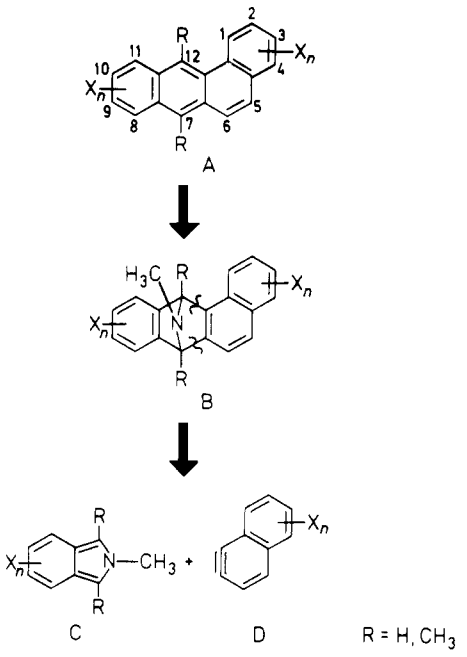
(12) The dibenzo[*a*,*i*]pyrene study[9] included a difluoro derivative in which a fluorine is in each of the two terminal rings, and the 7,14-difluoro derivative of dibenz[*a*,*h*]anthracene[8b] has been synthesized but apparently not yet screened for carcinogenicity.

(13) (a) Sims, P.; Grover, P. L.; Swaisland, A.; Pal, K.; Hewer, A. *Nature (London)* **1974**, *252*, 326. (b) Jerina, D. M.; Daly, J. W. In "Drug Metabolism—From Microbe to Man"; Parke, D. V., Smith, R. L., Eds.; Taylor and Francis: London, 1976; pp 13–32. (c) Nordqvist, M.; Thakker, D. R.; Yagi, H.; Lehr, R. E.; Wood, A. W.; Levin, W.; Conney, A. H.; Jerina, D. M. In "Molecular Basis of Environmental Toxicity"; Bhatnagar, R. S., Ed.; Ann Arbor Science Publishers: Ann Arbor, MI, 1980; pp 329–357. (d) Sims, P.; Grover, P. L. In "Polycyclic Hydrocarbons and Cancer"; Gelboin, H. V., Ts'o, P. O. P., Eds.; Academic Press: New York, 1981; pp 117–181.

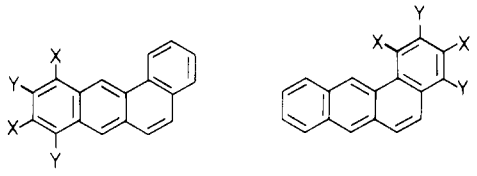
(14) (a) Cooper, C. S.; Ribeiro, O.; Hewer, A.; Walsh, C.; Pal, K.; Grover, P. L.; Sims, P. *Carcinogenesis* **1980**, *1*, 233. (b) MacNicoll, A. D.; Cooper, C. S.; Ribeiro, O.; Pal, K.; Hewer, A.; Grover, P. L.; Sims, P. *Cancer Lett.* **1981**, *11*, 243.

0022-3263/85/1950-1611$01.50/0

Scheme I



it seemed important to synthesize and have screened for carcinogenicity selected polyfluorinated PAH in which one (or both) of the terminal rings was completely "blocked" toward metabolism. Furthermore, it might be proposed that a meta arrangement of two fluorines would suffice to block metabolism in the substituted ring and be less susceptible to nucleophilic displacement than a tetrafluoro-substituted ring. Thus, one would predict that if the bay-region diol epoxide theory[13] is correct, then benzanthracenes **3** and **4** will be carcinogenic but **5** and **6** will

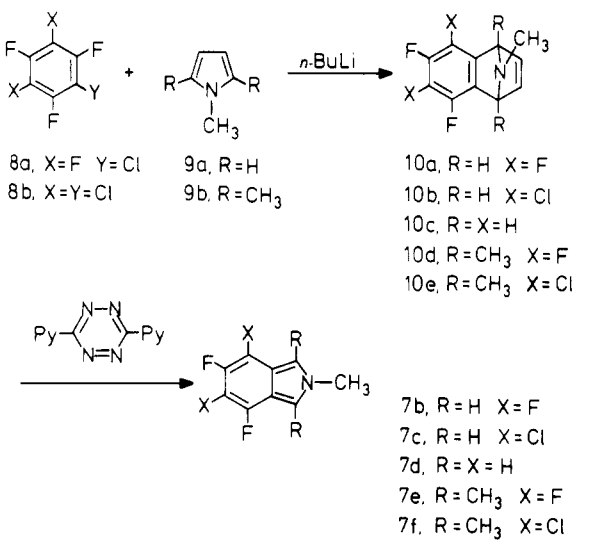


not be carcinogenic. However, if non-bay-region diol epoxides are important[14] then the reverse will be observed.

Moreover, the study of difluoro- and tetrafluoro-substituted PAH may resolve ambiguities that have been noted[4h] with monofluoro PAH, and the likelihood of (electrophilic) metabolic defluorination[6e] seems lessened in the projected polyfluorinated PAH targets. The only previous report of multiple fluorine substitution as a carcinogenesis probe, of which we are aware, involved a 2,4,6-trifluoroazobenzene derivative.[1b] This important study demonstrated that polyfluorinated arene rings can be used successfully as metabolic probes.

Therefore, the goal of this research effort was to develop a methodology for the efficient synthesis of polyfluorinated benz[*a*]anthracenes and the related 7,12-dimethylbenz[*a*]anthracene derivatives. Our synthetic approach to these PAH (A) (Scheme I) utilizes a Diels–Alder reaction between an isoindole (C) and an in situ generated 1-naphthalyne (D), followed by oxidative deamination of the resulting 7,12-dihydrobenz[*a*]anthracen-7,12-imine (B).

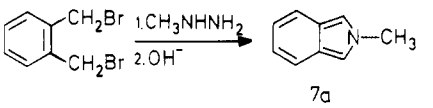
Scheme II



We[15] and Hart[16] have previously used this strategy to synthesize a variety of PAH. Moreover, Anderson[17] has used the cycloaddition reaction between isoindoles and benzynes to prepare 9,10-dihydroanthracen-9,10-imines.

Results and Discussion

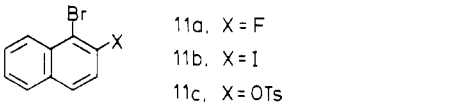
Synthesis of Isoindoles (C). With the exception of 2-methylisoindole (**7a**), which was prepared in 72% yield



from α,α'-dibromo-*o*-xylene by the method of Zeeh and König,[18] the halogenated isoindoles **7b–e** were prepared in 75–89% yield by using the excellent procedure of Priestley and Warrener[19] via naphthalenimines **10** (Scheme II), which were prepared as previously described.[15a–c,20]

These halogenated isoindoles were only moderately stable in air but could be purified by sublimation of short-path distillation prior to use. Of the new isoindoles synthesized in this study (**7c–f**) only **7d** gave a satisfactory combustion analysis.

Synthesis of 1-Naphthalyne (D) Precursors. To generate the unsubstituted 1-naphthalyne, we prepared three potential precursors: 1-bromo-2-fluoronaphthalene (**11a**), 1-bromo-2-iodonaphthalene (**11b**), and 1-bromo-2-



naphthyl *p*-toluenesulfonate (**11c**), each of whose synthesis

(15) (a) Gribble, G. W.; Allen, R. W.; Anderson, P. S.; Christy, M. E.; Colton, C. D. *Tetrahedron Lett.* **1976**, 3673. (b) Gribble, G. W.; Allen, R. W.; LeHoullier, C. S.; Eaton, J. T.; Easton, N. R., Jr.; Slayton, R. I.; Sibi, M. P. *J. Org. Chem.* **1981**, *46*, 1025. (c) Gribble, G. W.; Sibi, M. P.; Kumar, S.; Kelly, W. J. *Synthesis* **1983**, 502. (d) LeHoullier, C. S.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 1682. (e) LeHoullier, C. S.; Gribble, G. W. *Ibid.* **1983**, *48*, 2364.

(16) (a) Hart, H.; Ruge, B. *Tetrahedron Lett.* **1977**, 3143. (b) Sy, A.; Hart, H. *J. Org. Chem.* **1979**, *44*, 7. (c) Hart, H.; Teuerstein, A. *Synthesis* **1979**, 693. (d) Hart, H.; Shamouilian, S. *J. Org. Chem.* **1981**, *46*, 4874.

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(18) Zeeh, B.; König, K. H. *Synthesis* **1972**, 45.

(19) Priestley, G. M.; Warrener, R. N. *Tetrahedron Lett.* **1972**, 4295.

(20) Callander, D. D.; Coe, P. L.; Tatlow, J. C.; Uff, A. J. *Tetrahedron* **1969**, *25*, 25.

Scheme III

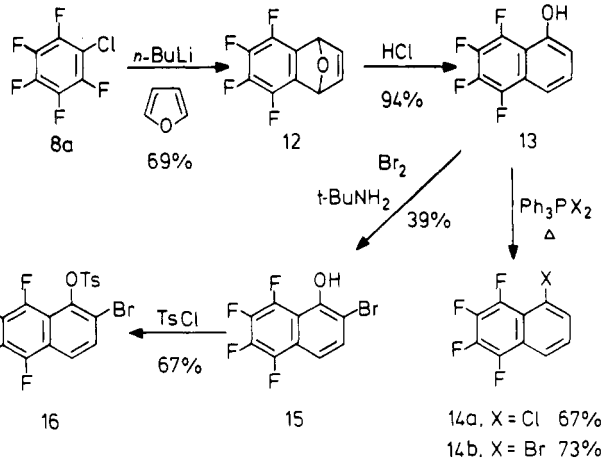


Table I. Synthesis of 7,12-Dihydrobenz[a]anthracen-7,11-imines (17)

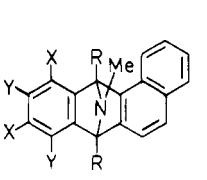
method[a]	isoindole	product	yield,[b] %
11a/A	7b	17a	51
11c/C	7b	17a	61
11c/C	7e	17b	91
11b/B	7e	17b	76
11a/A	7e	17b	40
11c/C	7a	17c	26
11b/B	7c	17d	57
11a/A	7c	17d	49
11a/A	7f	17e	39
11c/C	7f	17e	30

[a] See text and Experimental Section. [b] Yield refers to isolated and generally chromatographed material.

has been previously described[21-23] (cf. Experimental Section).

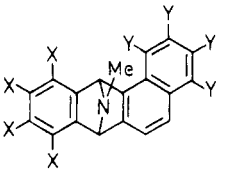
Likewise, several potential precursors to 5,6,7,8-tetrafluoro-1-naphthalyne were prepared, as summarized in Scheme III, starting with the easily prepared furan–tetrafluorobenzyne adduct **12**.[24] The derived naphthol **13**[24] was converted either to the chloro (**14a**) or bromo (**14b**) derivative with triphenylphosphine dihalide[25] or to bromo tosylate **16** by regioselective bromination[26] and tosylation. Bromide **14b** has also been prepared by the reaction of tetrafluorobenzyne and 2-bromothiophene,[27] but this method was less satisfactory in our hands.

Synthesis of 7,12-Dihydrobenz[a]anthracen-7,12-imines (B). The preparation of the 8,9,10,11-tetrahalogenated benzanthracenimines **17** is summarized in Table I. Generation of 1-naphthalyne according to the literature procedures[21b,22,23] and cycloaddition with various isoindoles could be achieved by using **11a** (Mg, method A), **11b** (Mg, method B), or **11c** (*n*-BuLi, method C) to give the desired **17**. Only difluoroisoindole **7d** failed to undergo the Diels–Alder reaction (method A), presumably because of exchange metalation between the acidic proton between the two fluorines of **7d** and the organometallic reagent. The benzanthracenimines **17** were somewhat labile and difficult to purify and therefore usually were immediately



17

a, R=H X=Y=F
b, R=CH_3 X=Y=F
c, R=H X=Y=H
d, R=H {X=F Y=Cl / X=Cl Y=F}
e, R=CH_3 {X=F Y=Cl / X=Cl Y=F}



18

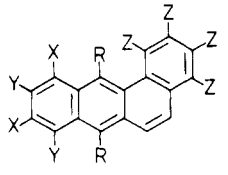
a, X=Y=F
b, X=H Y=F

converted to the respective benz[a]anthracenes (**19**) (vide infra).

The synthesis of the 1,2,3,4-tetrahalogenated benzanthracenimines **18** from the Diels–Alder reaction between isoindoles and 5,6,7,8-tetrafluoro-1-naphthalyne was much less satisfactory. Numerous attempts to generate this aryne from **14a**, **14b**, and **16** with alkyllithium reagents, phenyllithium, lithium diisopropylamide (LDA), and lithium 2,2,6,6-tetramethylpiperidide (LTMP), in the presence of isoindoles, led to decomposition or complex product mixtures. Occasionally, we did isolate the desired benzanthracenimine **18** but in these instances it was more convenient to convert the crude material to the corresponding benz[a]anthracene. The transient intermediate 5,6,7,8-tetrafluoro-1-naphthalyne appeared to be unusually susceptible to nucleophilic addition reactions and polymerization. For example, a byproduct in the reaction of **16** with phenyllithium appeared to be 5 (or 6) -phenyl-1,2,3,4-tetrafluoronaphthalene (mp 78–80 °C) and amine-addition compounds appeared to be present in the reactions of **14a,b** with LDA and LTMP.

We also converted naphthol **13** into its methyl ether (mp 105.5–106.5 °C) and tosylate (mp 143–144 °C) derivatives but attempts to metalate C-6 (position adjacent to the oxygen functionality) and to generate the tetrafluoronaphthalyne from these derivatives of **13** were unsuccessful. Thus, an efficient generation and trapping of tetrafluoronaphthalyne with isoindoles remains to be achieved.

Synthesis of Benz[a]anthracenes. Using our standard deamination procedure[15] with *m*-chloroperbenzoic acid (*m*-CPBA), we converted benzanthracenimines **17** and **18** into the corresponding benzanthracenes **3**, **5**, and **19** in yields ranging from 63% to 90% (see Experimental Section).



19

a, R=CH_3 X=Y=F Z=H
b, R=H {X=F Y=Cl Z=H / X=Cl Y=F}
c, R=CH_3 {X=F Y=Cl Z=H / X=Cl Y=F}
d, R=X=Y=Z=H
e, R=H X=Y=Z=F

No attempt has yet been made to separate dichloro difluoro isomers **19b** and **19c**, in order to establish the regiochemistry of the cycloaddition, although for the former we can discern two isomers by gas chromatography/mass spectrometry. Future work in this area will involve the separation of the dichloro difluoro isomers and their conversion into difluorobenzanthracenes (e.g., **4** and **6**) in order to test our proposed *meta*-difluoro probe concept. Preliminary results[28] indicate that this di-

(21) (a) Gribble, G. W.; LeHoullier, C. S.; Allen, R. W.; Gilbertson, J. J. *Org. Prep. Proced. Int.* **1981**, *13*, 349. (b) Wittig, G.; Benz, E. *Chem. Ber.* **1959**, *92*, 1999.
(22) Ward, E. R.; Pearson, B. D. *J. Chem. Soc.* **1959**, 1676.
(23) Tochtermann, W.; Stubenrauch, G.; Reiff, K.; Schumacher, U. *Chem. Ber.* **1974**, *107*, 3340.
(24) Coe, P. L.; Stephens, R.; Tatlow, J. C. *J. Chem. Soc.* **1962**, 3227.
(25) Schaefer, J. P.; Higgins, J. *J. Org. Chem.* **1967**, *32*, 1607.
(26) Pearson, D. E.; Wysong, R. D.; Breder, C. V. *J. Org. Chem.* **1967**, *32*, 2358.
(27) Coe, P. L.; Pearl, G. M.; Tatlow, J. C. *J. Chem. Soc. C* **1971**, 604.

dechlorination reaction will succeed.

In summary, the isoindole 1-naphthalyne cycloaddition/deamination methodology succeeds well for the synthesis of 8,9,10,11-tetrahalogenated benz[a]anthracenes but much less satisfactorily for the synthesis of 1,2,3,4-tetrahalogenated benz[a]anthracenes, apparently because of the aberrant reactivity of 5,6,7,8-tetrafluoro-1-naphthalyne.

Experimental Section

Melting points were determined with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Infrared spectra were recorded on a Perkin-Elmer 599 instrument. ^1H NMR spectra were obtained with a Hitachi Perkin-Elmer R-24 spectrometer, and ^{13}C NMR spectra were measured on a JEOL FX60Q Fourier transform NMR spectrometer. Tetramethylsilane was the internal reference. Low-resolution mass spectra were determined at 70 eV on a Finnigan 4023 GC/MS system. Woelm alumina was used for column chromatography, and thin-layer chromatography was performed on precoated (0.2 mm) silica gel 60 F_{254} plastic sheets (E. Merck). Phenyllithium and the alkyllithium reagents were standardized by titration against 2,5-dimethoxybenzyl alcohol.[30] Tetrahydrofuran was distilled from sodium/benzophenone. All reactions were performed in oven-dried (130 °C) glassware under nitrogen.

2-Methylisoindole (7a). This procedure is based on that reported by Zeeh and König[18] and as modified by Ponticello and Anderson.[17b] A mechanically stirred solution of α,α'-dibromo-*o*-xylene (15.0 g, 0.0568 mol) in dry Et_2O (150 mL) under N_2 at 20 °C was treated dropwise over 0.5 h with methylhydrazine (10.45 g, 0.227 mol). The solution was stirred for 12 h during which time a white solid formed. The Et_2O was decanted from the white solid, and the solid was treated with 20% aqueous NaOH (200 mL) and then refluxed under N_2 for 3 h. The resulting cloudy solution was extracted with $CHCl_3$ (3 × 150 mL), and the $CHCl_3$ extract was washed rapidly with H_2O (2 × 100 mL), dried (K_2CO_3), and evaporated in vacuo to afford 5.3 g (72%) of **7a** as a light yellow solid: mp 80–82 °C (lit.[18] mp 82–85 °C); ^1H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 6.9 (m, 2 H), 7.0 (s, 2 H), 7.5 (m, 2 H). This material was suitable for use in the aryne reactions, but it can be purified by sublimation[18] or distillation.

1,2,3-Trimethyl-4,5,6,7-tetrafluoroisoindole (7e). The procedure of Priestley and Warrener[19] was used to prepare the halogenated isoindoles. To a magnetically stirred solution of 1,4,9-trimethyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (**10d**)[15c] (4.15 g, 0.0162 mol) in $CHCl_3$ (50 mL) was added in one portion 3,6-bis(2-pyridyl)-1,2,4,5-tetrazine (3.80 g, 0.0162 mol). The resulting magenta solution was refluxed for 24 h during which time vigorous gas evolution was observed. The solution was evaporated in vacuo, and the crude product was sublimed at 110 °C (0.5 torr) to give 2.78 g (75%) of **7e** as a yellow solid: mp 119–121 °C; ^1H NMR ($CDCl_3$) δ 2.5 (s, 6 H), 3.6 (s, 3 H).

2-Methyl-4,5,6,7-tetrafluoroisoindole (7b). The crude product obtained from **10a**[15b] after a reflux period of 4 h was sublimed at 110 °C (0.5 torr) to give **7b** as a light yellow solid in 89% yield: mp 172–174 °C (lit.[19] mp 178 °C); ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 7.2 (s, 2 H).

2-Methyl-4,6-dichloro-5,7-difluoroisoindole (7c). The crude product obtained from **10b**[15b] after a reflux period of 3 h was sublimed at 110 °C (0.5 torr) to give **7c** as a light yellow solid in 76% yield: mp 122–129 °C; ^1H NMR ($CDCl_3$) δ 4.0 (s, 3 H), 7.2 (s, 2 H).

1,2,3-Trimethyl-4,6-dichloro-5,7-difluoroisoindole (7f). The crude product obtained from **10e**[15c] after a reflux period of 24 h was sublimed at 110 °C (0.5 torr) to give **7f** as a yellow solid in 87% yield: mp 122–127 °C; ^1H NMR ($CDCl_3$) δ 2.5 (s, 3 H), 2.7 (s, 3 H), 3.6 (s, 3 H).

2-Methyl-4,6-difluoroisoindole (7d). The crude product obtained from **10c**[15c] after a reflux period of 3 h was sublimed at 110 °C (0.5 torr) to give **7d** as colorless flakes in 88% yield: mp 37–39 °C; ^1H NMR ($CDCl_3$) δ 3.8 (s, 3 H), 6.1–7.0 (m, 4 H).

Anal. Calcd for $C_9H_7NF_2$: C, 64.67; H, 4.22; N, 8.38. Found: C, 64.60; H, 4.22; N, 8.36.

1-Bromo-2-fluoronaphthalene (11a). This was prepared from 2-acetylnaphthalene in 42% yield as previously described.[21]

1-Bromo-2-iodonaphthalene (11b). To a mechanically stirred solution of 1-bromo-2-naphthylamine hydrochloride[21] (60.0 g, 0.231 mol) in concentrated HCl (150 mL) at 0 °C was added in small portions $NaNO_2$ (18.0 g, 0.264 mol). This solution was stirred for 30 min at 0 °C and then treated dropwise with a solution of I_2 (29.5 g, 0.116 mol) and KI (77.0 g, 0.464 mol) in H_2O (500 mL). The dark mixture was stirred at 0 °C for 1 h, and the resulting solids were collected by filtration and dissolved in Et_2O (500 mL). The dark red Et_2O solution was washed with saturated aqueous $Na_2S_2O_3$ (3 × 100 mL) and H_2O (2 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo to give a red solid. Chromatography over activity III basic alumina with hexane elution afforded 51.3 g (67%) of **11b** as a colorless solid: mp 92–93 °C (lit.[22] mp 94 °C).

1-Bromo-2-naphthyl *p*-Toluenesulfonate (11c). This was prepared in 91% yield from 1-bromo-2-naphthol with the procedure of Tochtermann:[23] mp 123–124 °C (lit.[23] mp 123–124 °C).

5,6,7,8-Tetrafluoro-1-naphthol (13). To a magnetically stirred solution of chloropentafluorobenzene (**8a**) (20.25 g, 0.100 mol) in dry Et_2O (200 mL) under N_2 at −78 °C was added dropwise *n*-butyllithium (1.5 M in hexane; 64.5 mL, 0.100 mol). The solution was stirred for 1 h at −78 °C and then treated dropwise with a solution of furan (15 g, 0.22 mol) in dry Et_2O (200 mL). The mixture was stirred for 1 h at −78 °C and then allowed to warm slowly to room temperature overnight. The reaction mixture was washed with H_2O (3 × 100 mL) and brine (1 × 100 mL), dried (Na_2SO_4), and evaporated in vacuo to afford 15.0 g (69%) of crude 5,6,7,8-tetrafluoro-1,4-epoxy-1,4-dihydronaphthalene (**12**), suitable for conversion to **13**. The material could be sublimed at 80–90 °C (2 torr).

A solution of the above endooxide **12** (15.0 g, 0.069 mol) in EtOH (250 mL) and concentrated HCl (150 mL) was refluxed for 24 h. The solution was concentrated in vacuo, poured into H_2O (500 mL), and extracted with Et_2O (3 × 50 mL). The Et_2O extract was dried (Na_2SO_4) and evaporated in vacuo. The resulting crude product was chromatographed over silica gel with hexane/Et_2O (4:1) to give 14.1 g (94%) of **13**: mp 126–127 °C (lit.[24] mp 124–125 °C).

1,2,3,4-Tetrafluoro-5-chloronaphthalene (14a). Into a slurry of triphenylphosphine (13 g, 0.050 mol) in acetonitrile (50 mL) at 0 °C was bubbled Cl_2 until a slight excess of Cl_2 was present (yellow green color). Small amounts of triphenylphosphine were then added until the solution became colorless. At this point **13** (10.0 g, 0.463 mol) was added, the ice bath was removed, and the acetonitrile was removed by simple vacuum distillation (water aspirator). The remaining mixture was heated at ca. 300 °C for 2 h and then allowed to cool. The resulting solid was extracted with pentane and the pentane solution was passed through activity III neutral Al_2O_3 to afford 7.3 g (67%) of **14a**: mp 83–85 °C; ^1H NMR ($CDCl_3$) δ 7.5 (m, 2 H), 7.95 (m, 1 H); mass spectrum, *m/e* 234, 232, 216, 198 (100%), 180, 163, 143.

1,2,3,4-Tetrafluoro-5-bromonaphthalene (14b). To a mixture of triphenylphosphine (6.7 g, 0.0026 mol) in acetonitrile (5 mL) at 0 °C were added over 15 min Br_2 (4.1 g, 0.0026 mol) and then in one portion a solution of **13** (5.0 g, 0.00231 mol) in acetonitrile (10 mL). The mixture was heated at 60–70 °C for 1 h and then at 120 °C under vacuum (water aspirator) to remove the solvent. The remaining thick syrup was heated at 350 °C for 1 h and then allowed to cool to room temperature. The solid residue was extracted with pentane (4 × 25 mL). The pentane extract was washed with 20% aqueous KOH (2 × 25 mL), dried (Na_2SO_4), and then passed through neutral Al_2O_3 to furnish 4.69 g (73%) of **14b** as colorless needles: mp 83–85 °C (lit.[27] mp 84–85 °C); ^1H NMR ($CDCl_3$) δ 7.3 (m, 1 H), 7.9 (m, 2 H).

6-Bromo-1,2,3,4-tetrafluoro-5-naphthol (15). A mechanically stirred solution of *tert*-butylamine (11.6 mL, 0.100 mol) in toluene (800 mL) at −25 to −30 °C under N_2 was treated dropwise with

(28) We have found that the method of Satoh[29] ($PdCl_2$, $NaBH_4$, MeOH) converts 5,7-dichloro-6,8-difluoro-1,4-dimethylnaphthalene into 5,7-difluoro-1,4-dimethylnaphthalene in 82% yield, identical with an authentic sample.

(29) Satoh, T.; Mitsuo, N.; Nishiki, M.; Nanba, K.; Suzuki, S. *Chem. Lett.* **1981**, 1029.

(30) Winkle, M. R.; Lansinger, J. M.; Ronald, R. C. *J. Chem. Soc., Chem. Commun.* **1980**, 88.

Br_2 (2.4 mL, 0.050 mol) while the temperature was lowered to −78 °C. To this was added over 2.5 h a solution of **13** (21.6 g, 0.100 mol) in CH_2Cl_2 (1000 mL). The mixture was stirred at −78 °C for 3 h and then allowed to warm to room temperature overnight. The mixture was extracted with cold 10% aqueous NaOH (3 × 100 mL). The basic extract was acidified with concentrated HCl (ice cooling) and then extracted with Et_2O (3 × 100 mL). The Et_2O extract was dried (Na_2SO_4) and concentrated in vacuo. The resulting solid was flash chromatographed over silica gel (230–400 mesh) with hexane/$CHCl_3$ (95:5) to give 11.4 g (39%) of **15**: mp 61–62 °C; ^1H NMR ($CDCl_3$) δ 6.4 (d, 1 H), 7.4 (m, 1 H), 7.6 (m, 1 H); mass spectrum, *m/e* 296, 294, 187, 186 (100%), 167, 147, 136, 117.

Anal. Calcd for $C_{10}H_3F_4BrO$: C, 40.71; H, 1.02; Br, 27.08. Found: C, 40.76; H, 1.04; Br, 27.08.

6-Bromo-1,2,3,4-tetrafluoro-5-naphthyl *p*-Toluenesulfonate (16). A solution of **15** (3.00 g, 0.0101 mol) and *p*-toluenesulfonyl chloride (3.0 g, 0.015 mol) in dry pyridine (50 mL) was stirred at 20 °C under N_2 for 24 h. The mixture was poured into H_2O (400 mL) and extracted with Et_2O (5 × 50 mL). The Et_2O extract was dried (Na_2SO_4) and evaporated in vacuo to afford a solid. Crystallization from $CHCl_3$/MeOH gave 2.99 g (67%) of **16**: mp 161–162 °C; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3 H), 7.40 (m, 2 H), 7.73 (m, 4 H); mass spectrum, *m/e* 450, 448, 295, 293, 267, 265, 91 (100%).

Anal. Calcd for $C_{17}H_9F_4BrO_3S$: C, 45.45; H, 2.02. Found: C, 45.58; H, 2.15.

13-Methyl-8,9,10,11-tetrafluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine (17a) (Method C). To a magnetically stirred solution of **7b** (1.66 g, 8.17 mmol) and 1-bromo-2-naphthyl tosylate (**11c**) (3.00 g, 8.00 mmol) in dry THF (50 mL) under N_2 at −78 °C was added dropwise via syringe *n*-butyllithium (1.50 M in hexane; 6.0 mL, 9.0 mmol). The solution was allowed to warm slowly to room temperature overnight and then evaporated in vacuo to give a dark residue. The residue was dissolved in CH_2Cl_2, preabsorbed onto a small amount of activity III basic alumina, and then chromatographed over activity III basic alumina. Elution with hexane/Et_2O (1:1) afforded **17a** as a yellow solid which was slightly impure by TLC. The crude solid was dissolved in Et_2O (50 mL) and extracted with cold 6 N HCl (2 × 50 mL). The acidic extract was cooled in an ice bath, basified with NaOH (pellets), and extracted with CH_2Cl_2 (3 × 50 mL). The CH_2Cl_2 extract was washed (H_2O), dried (Na_2SO_4), and evaporated in vacuo to give 1.6 g (61%) of **17a** as a pale yellow solid. Recrystallization from hexane gave the analytical sample: mp 105–106 °C; ^1H NMR ($CDCl_3$) δ 2.35 (s, 3 H), 5.4 (m, 1 H), 5.8 (m, 1 H), 7.2–8.0 (m, 6 H); IR (neat) 3070, 2960, 2810, 1495, 1280, 1050, 760 cm^{-1}; mass spectrum, *m/e* 329.0822 (M^+, calcd 329.0828), 314, 300, 287, 42 (100%). The hydrochloride had mp 168–170 °C (acetone).

Anal. Calcd for $C_{19}H_{11}NF_4$: C, 69.30; H, 3.36; N, 4.25. Found: C, 69.26; H, 3.41; N, 4.23.

7,12,13-Trimethyl-8,9,10,11-tetrafluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine (17b) (Method C). The procedure was the same as that for **17a** using isoindole **7e** and **11c** except that the acid extract was avoided to preclude ring opening.[31] Chromatography of the crude reaction product over activity III basic alumina with hexane/Et_2O (1:1) elution afforded **17b** as a light yellow oil in 91% yield: ^1H NMR ($CDCl_3$) δ 2.0 (s, 3 H), 2.1 (s, 3 H), 2.4 (s, 3 H), 7.0–7.9 (m, 5 H), 8.2 (m, 1 H); mass spectrum, *m/e* 357.1138 (M^+, calcd 357.1141).

7,12,13-Trimethyl-8,10-dichloro-9,11-difluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine and 7,12,13-Trimethyl-9,11-dichloro-8,10-difluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine (17e) (Method C). The procedure was the same as that for **17b** using isoindole **7f** and **11c**. Chromatography of the crude reaction product over activity III basic alumina with hexane/Et_2O (5:1) elution gave **17e** as a light orange oil in 30% yield: ^1H NMR ($CDCl_3$) δ 2.1 (s, 3 H), 2.3 (s, 3 H), 2.4 (s, 3 H), 7.1–7.7 (m, 5 H), 8.2 (m, 1 H); mass spectrum, *m/e* 389.0542 (M^+, calcd 389.0550).

13-Methyl-8,10-dichloro-9,11-difluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine and 13-Methyl-9,11-dichloro-8,10-difluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine (17d) (Method B). To a magnetically stirred solution of **7c** (5.25 g, 22.2 mmol) and 1-bromo-2-iodonaphthalene (**11b**) (7.40 g, 22.2 mmol) in dry THF (75 mL) under N_2 at −78 °C were added oven-dried Mg turnings (0.55 g, 23 mmol). Formation of the Grignard reagent was initiated by adding a crystal of I_2 and ten drops of 1,2-dibromoethane. The mixture was refluxed for 24 h and then evaporated in vacuo. The resulting brown residue was chromatographed as described for **17a** to give 4.6 g (57%) of **17d** as a light orange oil: ^1H NMR ($CDCl_3$) δ 2.2 (s, 3 H), 5.2 (m, 1 H), 5.6 (m, 1 H), 7.1–7.7 (m, 6 H); mass spectrum, *m/e* 360.0297 (M^+, calcd 360.0284).

13-Methyl-8,9,10,11-tetrafluoro-7,12-dihydrobenz[*a*]anthracen-7,12-imine (17a) (Method A). A flask was charged with Mg (0.7 g, 0.03), a solution of **11a** (0.5 g) in THF (5 mL), a crystal of I_2, and several drops of 1,2-dibromoethane. To this mixture was added dropwise over 45 min a solution of **11a** (4.5 g; total = 5.0 g, 0.022 mol) and **7b** (6.0 g, 0.03 mol) in THF (50 mL) while heating to reflux. After addition was complete the mixture was refluxed for 48 h. The solvent was removed in vacuo, and the residue was chromatographed as described for **17a** under method C to give 3.7 g (51%) of **17a** as an amber syrup. The ^1H NMR spectrum of this material was identical with that for **17a** prepared earlier.

13-Methyl-7,12-dihydrobenz[*a*]anthracen-7,12-imine (17c) (Method C). This reaction was carried out in the same manner as for the preparation of **17a** (method C) employing the following materials: **7a** (1.5 g, 0.012 mol), **11c** (4.35 g, 0.012 mol), *n*-butyllithium (1.6 M in hexane; 7.2 mL, 0.012 mol), and THF (35 mL). The usual workup and chromatography gave 0.5 g (26%) of **17c** as a pale yellow solid: mp 93–95 °C; ^1H NMR ($CDCl_3$) δ 2.4 (s, 3 H), 5.2 (s, 1 H), 5.6 (s, 1 H), 6.9–8.1 (m, 10 H); mass spectrum, *m/e* 257.1246 (M^+, calcd 257.1205).

7,12-Dimethyl-8,9,10,11-tetrafluorobenz[*a*]anthracene (19a). To a magnetically stirred solution of **17b** (3.27 g, 9.16 mmol) in $CHCl_3$ (50 mL) under N_2 at 25 °C was added in one portion *m*-chloroperbenzoic acid (1.25 g, 9.20 mmol). The solution was stirred at 25 °C for 24 h. The reaction can be monitored by TLC. Chromatography of the resulting yellow solution over activity III basic alumina with hexane elution gave 2.30 g (77%) of **19a** as a yellow solid. Recrystallization from 95% EtOH afforded the analytical sample: mp 138–139 °C; ^1H NMR ($CDCl_3$) δ 3.1 (m, 6 H), 7.2–8.0 (m, 5 H), 8.3 (m, 1 H); IR (KBr) 1670, 1510, 1370, 1075, 1050, 1020, 960, 930, 810, 750 cm^{-1}; UV (95% EtOH) λ_{max} 378 nm (log ε 3.45), 362 (3.55), 357 (3.51), 345 (3.45), 338 (3.35), 308 (4.05), 287 (4.45), 265 (4.21), 232 (4.50).

Anal. Calcd for $C_{20}H_{12}F_4$: C, 73.16; H, 3.68. Found: C, 73.14; H, 3.70.

8,9,10,11-Tetrafluorobenz[*a*]anthracene (3). The procedure was the same as that for **19a**. Chromatography of the product that precipitated during the reaction and then recrystallization from 95% EtOH afforded **3** as light yellow needles: 65% yield; mp 257–258 °C; IR (KBr) 1680, 1595, 1500, 1350, 1030, 990, 950, 880, 810, 750 cm^{-1}; UV (95% EtOH) λ_{max} 387 nm (log ε 3.00), 366 (3.36), 357 (3.59), 349 (3.66), 341 (3.74), 332 (3.71), 325 (3.70), 301 (3.97), 278 (4.77), 258 (4.38), 240 (4.33), 224 (4.58).

Anal. Calcd for $C_{18}H_8F_4$: C, 72.00; H, 2.69; F, 25.31. Found: C, 71.80; H, 2.85; F, 25.39.

8,10-Dichloro-9,11-difluorobenz[*a*]anthracene and 9,11-Dichloro-8,10-difluorobenz[*a*]anthracene (19b). The procedure was the same as that for **19a**. The yield of crude product which precipitated during the reaction was 97%. Recrystallization from 95% EtOH afforded **19b** as an off-white solid: 68% yield; mp 209–210 °C; IR (KBr) 1635, 1610, 1595, 1500, 1430, 1310, 1250, 1060, 940, 915, 880, 810, 765, 740, 710, 685 cm^{-1}; UV (95% EtOH) λ_{max} 392 nm (log ε 3.11), 373 (3.59), 355 (3.78), 338 (3.78), 324 (3.68), 306 (4.02), 282 (4.82), 245 (4.34), 230 (4.51), 224 (4.50). GLC and HPLC analysis indicated that the isomers were present in about equal amounts but no attempt was made to separate them.

Anal. Calcd for $C_{18}H_8Cl_2F_2$: C, 64.88; H, 2.42; Cl, 21.28. Found: C, 64.93; H, 2.43; Cl, 21.28.

7,12-Dimethyl-8,10-dichloro-9,11-difluorobenz[*a*]anthracene and 7,12-Dimethyl-9,11-dichloro-8,10-difluorobenz[*a*]anthracene (19c). The procedure was the same as that for **19a**. The crude reaction mixture was chromatographed over activity III basic alumina, with hexane elution, and then re-

(31) Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2698.

crystallized from 95% EtOH to afford **19c** as a bright yellow solid: 63% yield; mp 138–140 °C; IR (KBr) 1605, 1420, 1385, 1350, 875, 810, 760, 685 cm^{-1}; UV (95% EtOH) λ_{max} 397 nm (log ϵ 3.19), 376 (3.38), 355 (3.28), 350 (3.16), 338 (2.96), 315 (3.99), 296 (4.46), 292 (4.45), 238 (4.55).

Anal. Calcd for $C_{20}H_{12}Cl_2F_2$: C, 66.50; H, 3.35; Cl, 19.63. Found: C, 66.46; H, 3.38; Cl, 19.62.

Benz[*a*]anthracene (19d). The usual procedure using **17c** and *m*-CPBA gave after chromatography **19d** as colorless flakes: 90% yield; mp 165 °C; identical with an authentic sample (IR, UV, TLC, ^1H NMR, mmp = 165 °C).

1,2,3,4,8,9,10,11-Octafluorobenz[*a*]anthracene (19e). To a magnetically stirred solution of **16** (0.700 g, 1.56 mmol) and **7b** (0.292 g, 1.56 mmol) in dry THF (50 mL) under N_2 at −78 °C was added dropwise via syringe phenyllithium (1.46 M in cyclohexane; 1.068 mL, 1.56 mmol). The solution was stirred for 1 h at −78 °C and then allowed to warm to room temperature over 3 h. The mixture was concentrated in vacuo and the residue dissolved in Et_2O (250 mL). The Et_2O solution was washed with H_2O (5 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to afford crude 13-methyl-1,2,3,4,8,9,10,11-octafluoro-7,12-dihydrobenz[*a*]-anthracen-7,12-imine (**18a**) as a brown paste. This material exhibited appropriate ^1H NMR and mass spectra. A solution of crude **18a** and *m*-chloroperbenzoic acid (1 g, 5 mmol) in $CHCl_3$ (50 mL) was stirred under N_2 at 20 °C for 24 h. The solution was concentrated in vacuo and the residue was chromatographed over activity III basic alumina with hexane elution to afford 0.22 g (38% from **7b**) of **19e** as a yellow solid: mp 173–174 °C; UV (95% EtOH) λ_{max} 387 nm (log ϵ 3.20), 368 (3.38), 356 (3.69), 3.48 (3.73), 340 (3.85), 332 (3.80), 325 (3.81), 298 (4.27), 274 (4.76), 270 (4.76), 220 (4.48); mass spectrum, *m/e* 372 (M^+, 100), 352, 341, 321, 303, 186.

Anal. Calcd for $C_{18}H_4F_8$: C, 58.08; H, 1.08. Found: C, 58.16; H, 1.58.

1,2,3,4-Tetrafluorobenz[*a*]anthracene (5). The same procedure as described above for the preparation of **19e** but employing **7a**, **14b**, and LTMP followed by oxidation with *m*-CPBA gave **5** (ca. 25% overall yield) as yellow needles from benzene: mp 220–225 °C.

Anal. Calcd for $C_{18}H_8F_4$: C, 72.00; H, 2.69. Found: C, 72.10; H, 2.72.

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Registry No. **3**, 62209-62-5; **5**, 95785-05-0; **7a**, 33804-84-1; **7b**, 38053-09-7; **7c**, 95785-06-1; **7d**, 95785-07-2; **7e**, 95785-08-3; **7f**, 95785-09-4; **8a**, 344-07-0; **10a**, 5875-75-2; **10b**, 76137-28-5; **10c**, 86909-51-5; **10d**, 54989-05-8; **10e**, 86909-55-9; **11a**, 342-55-2; **11b**, 90948-03-1; **11c**, 42768-98-9; **12**, 715-44-6; **13**, 715-32-2; **14a**, 95785-10-7; **14b**, 31322-32-4; **15**, 95785-11-8; **16**, 95785-12-9; **17a**, 62209-95-4; **17a**·HCl, 95785-13-0; **17b**, 95785-14-1; **17c**, 95785-15-2; **17d** (isomer 1), 95785-16-3; **17d** (isomer 2), 95785-17-4; **17e** (isomer 1), 95785-18-5; **17e** (isomer 2), 95785-19-6; **18a**, 95785-20-9; **19a**, 95785-21-0; **19b** (isomer 1), 95785-22-1; **19b** (isomer 2), 95785-23-2; **19c** (isomer 1), 95785-24-3; **19c** (isomer 2), 95785-25-4; **19d**, 56-55-3; **19e**, 95785-26-5; 1-bromo-2-naphthylamine hydrochloride, 80413-60-1; α,α'-dibromo-*o*-xylene, 91-13-4; methylhydrazine, 60-34-4; 1-bromo-2-naphthol, 573-97-7; furan, 110-00-9.

Synthesis and Cyclization of Polymer-Supported 12-Hydroxydodecanoic Thiol Esters

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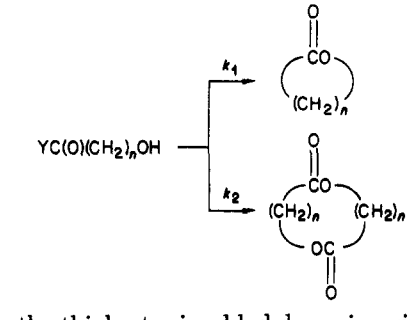
12-Hydroxydodecanoic thiol esters were synthesized on 2% cross-linked polystyrene supports to test the ability of the support to improve yields of intramolecular cyclization to lactone. With mercuric trifluoroacetate in dichloromethane, 0.03 M polymer-supported 12-hydroxydodecanoic thiol ester cyclized to 13% 12-dodecanolide and 19% of the corresponding diolide. Under otherwise similar conditions, 0.01 M model thiol ester gave <2% each of monolide and diolide. In acetonitrile, 0.01 M model thiol ester gave 26% and 35% yields of monolide and diolide.

Many methods of synthesis of macrocyclic lactones have been developed recently because of the importance of macrolide antibiotics.[1-3] The most generally useful methods, such as thermal transesterifications of 2-pyridinethiol esters[4,5] and cyclizations of less activated thiol esters promoted by thiophilic metal salts,[2,6] effect closure of an ω-hydroxy carboxylic acid under neutral conditions. The cyclizations must be performed by a high dilution method to minimize formation of dimeric and higher oligomeric byproducts which arise from intermolecular rather than intramolecular transesterification (eq 1).



(1)

Typically the thiol ester is added dropwise with a syringe

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