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1,4-Difluoro-2,5-dimethoxybenzene as a Precursor for Iterative Double Benzyne−Furan Diels−Alder Reactions

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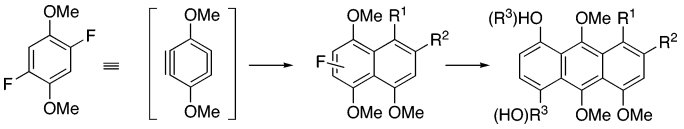

The use of 1,4-difluoro-2,5-dimethoxybenzene as a novel precursor for iterative two-directional benzyne−furan Diels−Alder reactions, using a range of 2- and 3-substituted furans, is reported. Substituted oxabenzonorbornadienes were synthesized following the initial Diels−Alder reaction, which upon ring opening under acidic conditions gave substituted naphthol derivatives. Highly substituted anthracenols were generated in the second benzyne−furan Diels−Alder reaction following acid-catalyzed isomerization of the cycloadducts.

Introduction

As part of our ongoing interest in diverse biologically active benz[*a*]anthracene antibiotics,[1] we sought to explore the use of derivatives of the double benzyne cyclohexa-1,2,3-trien-5-yne (**1**)[2,3] for the elaboration of polyfunctional anthraquinone derivatives from simple arene precursors (Figure 1). Hart has previously reported the double benzyne cycloaddition reactions of the diamine **2**[4] by lead tetraacetate oxidation in the presence of furans. In addition, he has prepared double furan, pyrrole, and cyclopentadiene cycloadducts from the tetrabromides **4** using lithium−bromine exchange and elimination of lithium bromide to generate intermediates equivalent to the double benzyne **3**.[5−8] With careful control of the butyllithium stoichiometry and with some substrates, Hart was able to prepare unsymmetrical double cycloadducts such as the pentacycle **5**. However, in many cases the greater solubility of the initial monocycloadduct, such as **6** at low temperature, relative to the starting tetrabromide **4**, was a problem for the efficient preparation of unsymmetrical double cycloadducts. Although the formation of **6** ($R^1 = R^2 = OMe$) was found to proceed in only modest yields (65%), the corresponding butyl and hexyl ethers **6** ($R^1 = R^2 = OBu$ or OC_6H_{13}) could be produced in better yields.[9−12] Recently, Lee and co-

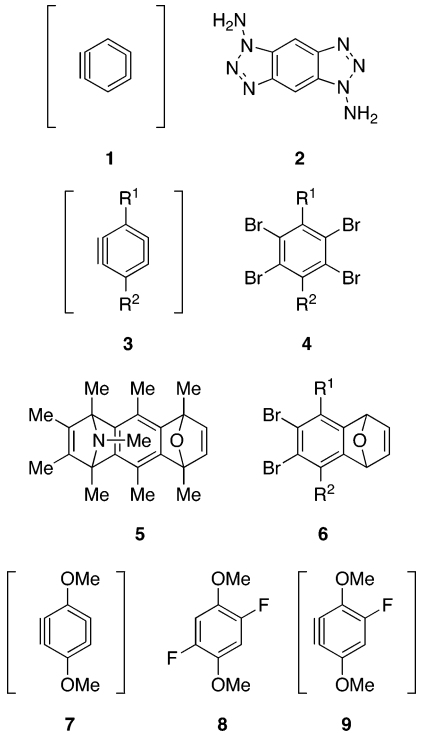

FIGURE 1. Two-directional benzyne−furan Diels−Alder reactions: compounds, intermediates, and products.

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(2) Sato, T.; Arulmozhiraja, S.; Niino, H.; Sasaki, S.; Matsuura, T.; Yabe, A. *J. Am. Chem. Soc.* **2002**, *124*, 4512.
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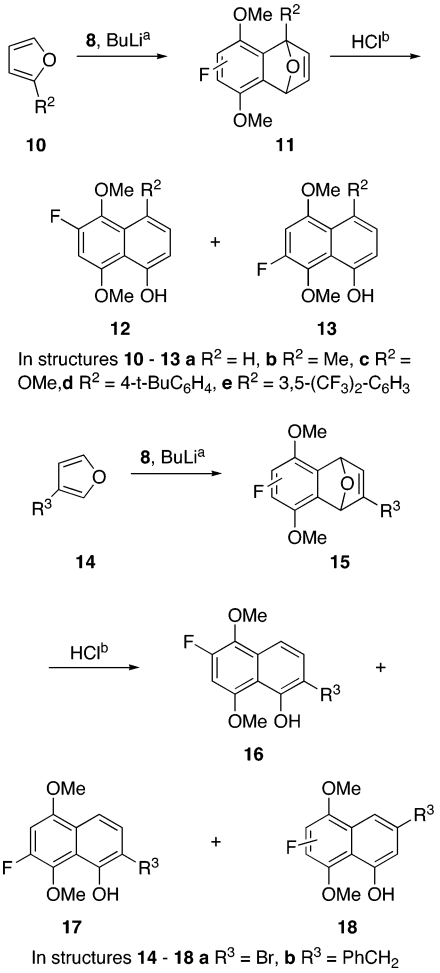
workers reported the use of benzobisoxadisiloles as synthetic equivalents for cyclohexa-1,2,3-trien-5-yne (**1**).[13] We considered that it should be possible to extend the Hart methodology with the use of double benzyne precursors of lower molecular weight than tetrabromides and we sought to examine 2,5-difluoro-1,4-dimethoxybenzene **8** as a precursor for the hypothetical intermediate **7** and its use in sequential double Diels–Alder reactions with two different furans. There is indirect precedent to support the expectation that difluoride **8** should be a useful reagent. 3-Fluoroanisole has been reported to undergo C-2 lithiation at −78 °C and the carbanion trapped with a range of electrophiles or transformed into fluorinated biphenyl derivatives via elimination on warming to produce the benzyne intermediate.[14–17] On the basis of known related transformations,[18,19] it is reasonable to speculate that benzyne **9** may undergo cycloaddition reactions regioselectively with monosubstituted furan derivatives.

Results and Discussions

Sequential addition of *n*-butyllithium (1 equiv) and furan **10a** to difluoride **8** in THF at −78 °C and warming up to 0 °C gave the cycloadduct **11a** (80%) yield. This product was subsequently aromatized, by treatment with 6 M hydrochloric acid, to provide the naphthol **13a** as the only product (86%). The initial benzyne **9** cycloaddition reaction was extended to a range of 2- and 3-substituted furans **10b–e** and **14a**,**b** to provide the adducts **11b–e** and **15a**,**b** respectively (45–76%) (Scheme 1, Table 1). The adducts **11b–e** were rearranged under acidic conditions to produce mixtures of naphthols **12** and **13** (1:1 to 1:0). In the same way, the adducts **15a** and **15b** were aromatized to produce naphthols **16**, **17**, and **18** (1:1:0 and 1:2:1, respectively). Attempted cycloaddition with 3-phenylfuran **14c**[20] was unsuccessful and only gave intractable mixtures consistent with the findings by Batt with this dienophile.[21] In most cases the isomeric naphthol derivatives were easily separated by chromatography and fully characterized. However, the naphthols **16b**, **17b**, and **18b**, derived from 3-benzylfuran[21] (**14b**) (entry 7), were only partially separable and **16b** and **18b** were characterized as a mixture. Assignments of the structures of the naphthols **12**, **13**, and **16–18** were carried out by X-ray crystallography (**13a** and **17a**) or NoESY NMR spectroscopy (see the Supporting Information).

SCHEME 1. Conversion of Difluoride 8 into Cycloadducts by Lithiation and Intermediacy of Benzyne 9[a]



[a] Reagents and conditions: (a) **8**, BuLi, THF, −78 to 0 °C; (b) HCl, H_2O, MeOH, Δ.

TABLE 1. Preparation of Benzyne–Furan Cycloadducts from Difluoride 8

entry	furan	cycloadduct (%)	naphthols (%)	isomer ratio[a]
1	**10a**	**11a** (80)	**13a** (86)	0:1[b]
2	**10b**	**11b** (76)	**12b** + **13b** (79)	1:1[b]
3	**10c**	*c*	**12c** + **13c** (80)	1:1[d]
4	**10d**	*c*	**12d** + **13d** (90)	5:1[b]
5	**10e**	**11e** (64)	**12e** (68)	1:0[b]
6	**14a**	**15a** (45)	**16a** + **17a** (79)	1:1[b]
7	**14b**	**15b** (56)	**16b**, **17b** + **18b** (82)	1:2:1[e]

[a] Isomer ratio refers to **12**:**13** for entries 1–5, **16a**:**17a** for entry 6, and **16b**:**17b**:**18b** for entry 7. [b] Isomers separated and fully characterized. [c] Intermediate cycloadducts not isolated but converted directly into naphthols. [d] Isomers inseparable and characterized as a mixture. [e] Isomers partially separable, **17b** characterized as a single isomer and **16b**/**18b** characterized as a mixture.

To carry out the second benzyne–furan Diels–Alder reaction, protection of the free phenol was required. *O*-Methylation of phenol **13a**, lithiation, benzyne formation, and trapping with furan **10a** gave the cycloadduct **21a** (63%), which was aromatized under acidic conditions to produce the anthracenols **22a** and **23a** (82%, 4:1). The second benzyne–furan (**10a**) cycloaddition reaction was

(9) Choi, M. T. M.; Yang, Q.; Mak, T. C. W.; Ng, D. K. P. *J. Chem. Res., Synop.* **2002**, 644.
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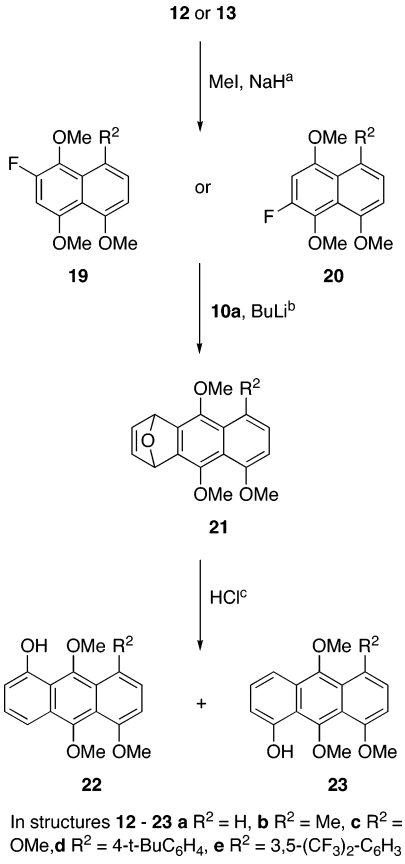
SCHEME 2. Second Benzyne–Furan Diels–Alder Reactions[a]



[a] Reagents and conditions: (a) MeI, NaH, DMF, 20 °C; (b) **10a**, BuLi, THF, −78 to 0 °C; (c) HCl, H_2O, THF Δ.

TABLE 2. Preparation of Cycloadducts and Anthracenols from Fluoronaphthalenes and Furan (10a)

entry	fluoronaphthalene (%)	cycloadduct (%, ratio)	anthracenols (%)	isomer ratio[a]
1	**20a** (100)	**21a** (63, −)	**22a** + **23a** (82)[b]	4:1
2	**19b**(89)	**21b** (88, −)	**22b** + **23b** (85)[b]	1:1
3	**20b** (81)	**21b** (86, −)		
4	**19c** (81)	**21c** (61, −)	**22c** (83)	
5	**19d** (81)[c]	**21d** (70, −)	**22d** + **23d** (71)[b]	2:1
6	**19e** (94)	**21e** (82, −)	**22e** + **23e** (83)[b]	3:1
7	**24** (85)	**25** (74, −)	**26a** + **26b** (78)[b]	2:1

[a] Isomer ratio refers to **22**:**23** for entries 1–6, **26a**:**26b** for entry 7. [b] Isomers inseparable and characterized as a mixture. [c] Mixture of isomers (**19d**:**20d** = 5:1) obtained from mixture of isomers (**12d**:**13d** = 5:1).

extended to a range of fluorides **19**, **20**, and **24** to provide the adducts **21** and **25** (61–88%) and the corresponding anthracenols **22**, **23**, and **26** (71–85%) on acid-catalyzed isomerization (Scheme 2, Table 2, Figure 2). In addition, the reaction and aromatization was extended to 2-methylfuran (**10b**) and 2-methoxyfuran (**10c**) to provide the cycloadducts **27** and anthracenols **28** (Scheme 2, Table 3, Figure 2). In most cases, the isomeric mixtures of anthracenol derivatives could not be separated by chromatography but were characterized as mixtures. Structures of the major isomers were characterized by NoESY NMR spectroscopy (see the Supporting Information).

It is germane to comment briefly on the regioselectivities of the transformations in Tables 1–3. The direction

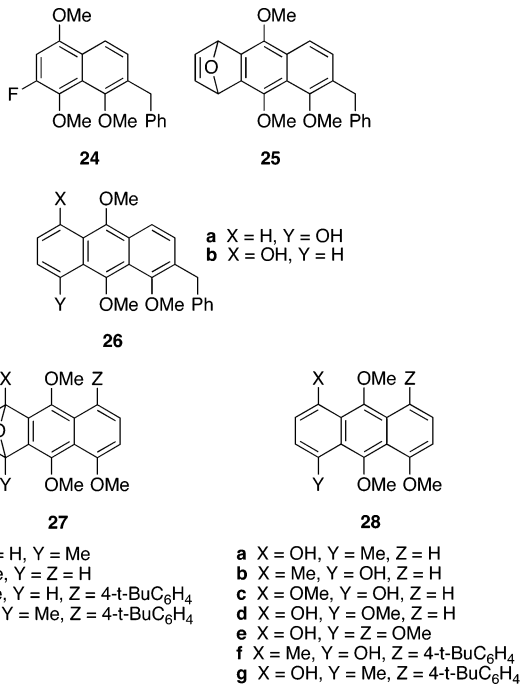


FIGURE 2. Naphthalene and anthracene derivatives prepared with two-directional benzyne–furan Diels–Alder reactions from difluoride **8**.

of the acid-catalyzed ring opening of the cycloadduct **11a** was controlled by preferential formation of the more stabilized carbenium ion **29** (Figure 3) on scission of the bridgehead C–O bond. The influence of relative carbenium ion stability on the direction of opening of benzyne–furan cycloadducts has previously been reported by Giles and Sargent.[22] In addition, it is important to note the benzylic carbenium ion stabilizing effects of an aryl fluorine substituent by resonance.[23] The cycloadducts **11c** and **11d** (Table 1, entries 3 and 4) were found to be especially prone to isomerization to a naphthol on account of the electron-donating R^2 substituents. The regioselectivities of the cycloadditions of 2-arylfurans **10d** and **10e** with the benzyne **9** favoring formation of the isomers **12** over isomers **13**, following acid-catalyzed isomerization, are consistent with the known inductive polarization of 4-fluorobenzyne.[24] Since the yield of the naphthol **12e** was only modest, it is possible that the apparent high selectivity was the result of partial decomposition during manipulation rather than regiospecific cycloaddition. The lack of regioselectivity in the cycloadditions of benzyne **9** with furans **10b**[19,25] and **10c**[26–29] was surprising given reports of their reactions with other benzynes. Finally, the preference for formation of the 2-benzylnaphthols **16b** and **17b** (Table 1, entry 7) presumably was the result of phenonium ion[30] **30** participation during the acid-catalyzed rearrangement. Furan **10a** (Table 2) and

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TABLE 3. Preparation of Cycloadducts and Anthracenols from Fluoronaphthalenes and 2-Methylfuran (10b) or 2-Methoxyfuran (10c)[a]

entry	fluoronaphthalene (%)	cycloadducts (%, ratio)	anthracenols (%)	isomer ratio[b]
1	**20a**	**27a** and **27b** (92, 1:2)	**28a** + **28b** (61%)[c]	1:1
2	**19d**[c]	**27c** and **27d** (70, 1:1)	**28f** + **28g** (87)[c]	1:1
3	**20a**	*d*	**28c** + **28d** (83)[c]	5:3
4	**19c**	*d*	**28e** (84)	

[a] Furan **10b** in entries 1 and 2, furan **10c** in entries 3 and 4. [b] Isomer ratio refers to **28a**:**28b** for entry 1, **28f**:**28g** for entry 2, **28c**:**28d** for entry 3. [c] Isomers inseparable and characterized as a mixture. [d] Cycloadduct not isolated but directly aromatized. [e] Chromatographically separated **28c** and **28d** characterized as a single isomers.

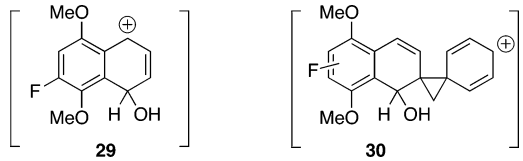

FIGURE 3. Proposed carbenium ion intermediates in the synthesis of naphthols from cycloadducts **11a** and **16b**.

2-substituted furans **10b** and **10c** (Table 3) could be utilized in the second Diels–Alder reaction (Scheme 2, Figure 2). In general the regioselectivites of the cycloaddition and rearomatization reactions were low except in the examples (Table 2, entry 4 and Table 3, entry 4) when only one anthracenol product was possible.

In conclusion, we have identified a new iterative double benzyne–furan Diels–Alder precursor **8** that may be used to generate a range of substituted naphthols and anthracenols in moderate to high yield. Further aspects of the chemistry of the double benzyne cyclohexa-1,2,3-trien-5-yne (**1**) will be reported in due course.

Experimental Section

7-Fluoro-5,8-dimethoxy-1-naphthol (13a). *n*-BuLi (2.5 M in hexanes; 0.46 mL, 1.15 mmol) was added with stirring to difluoride **8** (200 mg, 1.15 mmol) in dry THF (4 mL) at −78 °C and the reaction mixture was maintained at this temperature for 15 min. After this time, furan (**10a**) (0.13 mL, 1.73 mmol) was added and the mixture allowed to warm to 0 °C over 2 h before being quenched with H_2O (5 mL), extracted with Et_2O (2 × 15 mL), dried (Na_2SO_4), rotary evaporated, and chromatographed (4:1 CH_2Cl_2:hexanes to 1:0 CH_2Cl_2:hexanes) to give the cycloadduct **11a** (205 mg, 80%) as a clear oil: R_f 0.28 (CH_2Cl_2); IR (KBr, thin film) ν_{max} 1631, 1611, 1496, 1436, 1249 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.09 (dd, 1H, J = 1.5, 5.5 Hz), 7.04 (dd, 1H, J = 1.5, 5.5 Hz), 6.38 (d, 1H, J_{H-F} = 13.0 Hz), 5.97 (s, 1H), 5.92 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.5 (d, J_{C-F} = 247.5 Hz), 147.8 (d, J_{C-F} = 9.0 Hz), 143.4, 142.2, 141.7, 136.7 (d, J_{C-F} = 14.0 Hz), 130.9, 99.3 (d, J_{C-F} = 24.0 Hz), 80.8 (d, J_{C-F} = 2.5 Hz), 80.1, 61.5, 56.3; MS (CI, NH_3) *m/z* 223 (M + H)$^+$; HRMS (CI) *m/z* calcd for $C_{12}H_{12}FO_3$ (M + H)$^{+\bullet}$ 223.0771, found (M + H)$^+$ 223.0761. Aqueous HCl (6 M, 10 mL) was added with stirring to the cycloadduct **11a** (1.92 g, 8.64 mmol) in MeOH (40 mL) and the mixture heated at reflux for 3 h. Upon cooling to 20 °C, crystals formed which were filtered off and washed with cold MeOH, and recrystallized from MeOH to give the naphthol **13a** (1.66 g, 86%) as pale yellow needles: R_f 0.25 (1:1 hexanes:CH_2Cl_2); mp 71–72 °C (MeOH); IR (KBr, thin film) ν_{max} 3313, 1626, 1519, 1445, 1378, 1246, 1169, 1046, 983, 811 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.39 (s, 1H), 7.69 (dd, 1H, J = 1.0, 8.5 Hz), 7.31 (t, 1H, J = 8.0 Hz), 6.96 (d, 1H, J = 7.5 Hz), 6.56 (d, 1H, J_{H-F} = 13.5 Hz), 4.11 (d, 3H, J_{H-F} = 1.5 Hz), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9 (d, J_{C-F} = 6.5 Hz), 152.6 (d, J_{C-F} = 10.5 Hz), 150.3 (d, J_{C-F} = 243.0 Hz), 134.7 (d, J_{C-F} = 12.0 Hz), 126.1, 124.6, 117.5 (d, J_{C-F} = 3.0 Hz), 113.3, 112.1, 96.0 (d, J_{C-F} = 26.5 Hz), 62.8 (d, J_{C-F} = 6.5 Hz), 55.9; MS (CI, NH_3) *m/z* 223 (M + H)$^+$; HRMS (CI) *m/z* calcd for $C_{12}H_{12}FO_3$ (M + H)$^+$ 223.0771, found (M + H)$^+$, 223.0769. Anal. Calcd for $C_{12}H_{11}FO_3$: C, 64.86; H, 4.99. Found: C, 64.94; H 4.82. Crystal data for **13a**: $C_{12}H_{11}FO_3$, M = 222.21, monoclinic, $P2_1/n$ (no. 14), a = 16.500(6) Å, b = 3.962(3) Å, c = 17.251(7) Å, β = 113.076(13)°, V = 1037.5(11) Å^3, Z = 4, D_c = 1.423 g cm^{-3}, μ(Cu Kα) = 0.962 mm^{-1}, T = 293 K, colorless needles; 1544 independent measured reflections, F^2 refinement, R_1 = 0.066, wR_2 = 0.190, 974 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 120°], 150 parameters; CCDC 261199.

2-Fluoro-1,4,8-trimethoxynaphthalene (20a). NaH (60% dispersion in mineral oil; 23 mg, 0.56 mmol, 1.24 equiv) followed by MeI (79 mg, 0.56 mmol, 1.24 equiv) were added to naphthol **13a** (100 mg, 0.45 mmol) in dry DMF (1 mL) and the mixture was stirred for 18 h at 20 °C. H_2O was added to quench the reaction and the mixture extracted with EtOAc (2 × 25 mL), dried (Na_2SO_4), rotary evaporated, and chromatographed (1:1 CH_2Cl_2:hexanes) to give ether **20a** (106 mg, 100%) as a white solid: R_f 0.30 (1:1 hexanes:CH_2Cl_2); mp 86–87 °C (hexanes:CH_2Cl_2); IR (KBr, thin film) ν_{max} 1600, 1458, 1420, 1365, 1273, 1124, 1078, 751 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, J = 0.5, 8.5 Hz), 7.32 (t, 1H, J = 8.0 Hz), 6.92 (d, 1H, J = 7.5 Hz), 6.69 (d, 1H, J = 12.0 Hz), 3.99 (s, 3H), 3.95 (s, 3H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2 (d, J_{C-F} = 7.0 Hz), 153.3 (d, J_{C-F} = 240.5 Hz), 152.0, 135.9 (d, J_{C-F} = 13.5 Hz), 125.0, 124.6, 121.4, 114.7, 107.6, 96.6 (d, J_{C-F} = 27.5 Hz), 62.7, 56.3, 55.9; MS (CI, NH_3) *m*/z 237 (M + H)$^+$, 254 (M + NH_4)$^+$; HRMS (CI) *m/z* calcd for $C_{13}H_{14}FO_3$ (M + H)$^+$ 237.0927, found (M + H)$^+$ 237.0923. Anal. Calcd for $C_{13}H_{13}FO_3$: C, 66.09; H, 5.55. Found: C, 66.14; H 5.45.

5,9,10-Trimethoxy-1-anthracenol (22a)[31] and 8,9,10-Trimethoxy-1-anthracenol (23a). Cycloadduct **21a** (82 mg, 63%), prepared from fluoride **20a** and furan **10a** as for **11a** and chromatography (1:1 Et_2O:hexanes), was obtained as a yellow oil: R_f 0.21 (1:1 Et_2O:hexanes); IR (KBr, thin film) ν_{max} 1648, 1604, 1521, 1448, 1366, 1325, 1264, 1075 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, 1H, J = 8.5 Hz), 7.39 (t, 1H, J = 8.0 Hz), 7.00 (ca. s, 2H), 6.93 (d, 1H, J = 7.5 Hz), 6.21 (s, 1H), 6.07 (s, 1H), 4.06 (s, 3H), 3.99 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.5, 144.7, 144.6, 141.3, 140.9, 134.7, 130.5, 127.6, 126.3, 119.7, 115.6, 107.8, 81.3, 79.6, 63.1, 60.6, 56.3; MS (CI, NH_3) *m*/z 285 (M + H)$^+$; HRMS (CI) *m/z* calcd for $C_{17}H_{17}O_4$ (M + H)$^+$, 285.1127, found (M + H)$^+$ 285.1116. Subsequent aromatization, using hydrochloric acid in THF and chromatography (3:2 CH_2Cl_2:hexanes), as for **12a**, gave an inseparable mixture (4:1) of the anthracenols **22a** and **23a** (67 mg, 82%) as a yellow oil: R_f 0.51 (7:3 CH_2Cl_2:hexanes); IR (KBr, thin film) ν_{max} 3374, 1414, 1377, 1253, 1121 cm^{-1}; ^{1}H

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NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 0.2 H), 9.80 (s, 0.8H), 7.91 (dd, 1H, J = 1.0, 9.0 Hz), 7.76 (dd, 1H, J = 1.0, 9.0 Hz), 7.37 (m, 2H), 6.91 (dd, 1H, J = 1.0, 7.5 Hz), 6.78 (d, 1H, J = 7.5 Hz), 4.09 (s, 2.4H), 4.08 (s, 0.6H), 4.07 (s, 2.4H), 4.06 (s, 0.6H), 4.01 (s, 0.6H), 4.00 (s, 2.4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 155.7, 154.5, 153.1, 149.8, 148.9, 148.6, 147.1, 127.8, 127.2, 127.0, 126.4, 125.9, 125.6, 118.5, 116.6, 115.2, 114.2, 113.9, 113.0, 109.7, 108.8, 108.6, 104.1, 103.8, 64.7, 63.9, 63.3, 62.6, 56.1; MS (CI, NH_3) m/z 285 $(M + H)^+$; HRMS (CI) m/z calcd for $C_{17}H_{17}O_4$ $(M + H)^+$ 285.1127, found $(M + H)^+$ 285.1131.

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Supporting Information Available: Additional experimental procedures and structural data for all new compounds; X-ray crystallographic structures for **13a** and **17a**; copies of ^1H NMR, ^{13}C NMR, and NoESY NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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