Synthesis of 3,5- and 3,6-Linked Calix[*n*]naphthalenes

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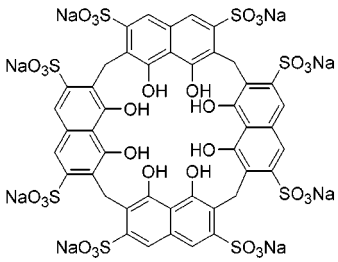
The preparation of calix[*n*]naphthalenes from derivatives of 2,7-dihydroxynaphthalene is described. 1,8-Dialkyl substitution is used to direct the regiochemistry of the acid-catalyzed condensation reactions. Acyclic peri substituents lead to a 3,5-linked calix[3]naphthalene, whereas cyclic peri substituents give predominantly a calix[5]naphthalene with the corresponding 3,6-linkage. The 3,6-linked calix[4]naphthalene is prepared in pure form by a dimerization strategy.

Introduction

Calix[*n*]arenes have become a central structural subunit for receptor design owing to their ease of synthesis, convenience of functionalization, and controllable conformations.[1] In particular, cavitands derived from resorcinol[2] possess rigid bowl-like cavities that are particularly well suited for many applications in molecular recognition. Larger cavities can be created with higher order calixarenes (typically hexameric or octameric), but conformational issues in these systems can become important.[3] Recently, large "deeper cavitands"[4] have been prepared by substitution of the calix[4]resorcinarenes. The cavities of these hosts are greatly expanded, leading to broader utility in molecular recognition.



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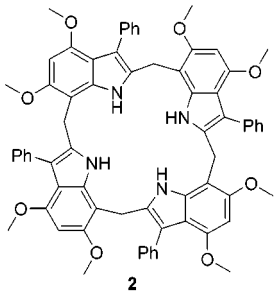
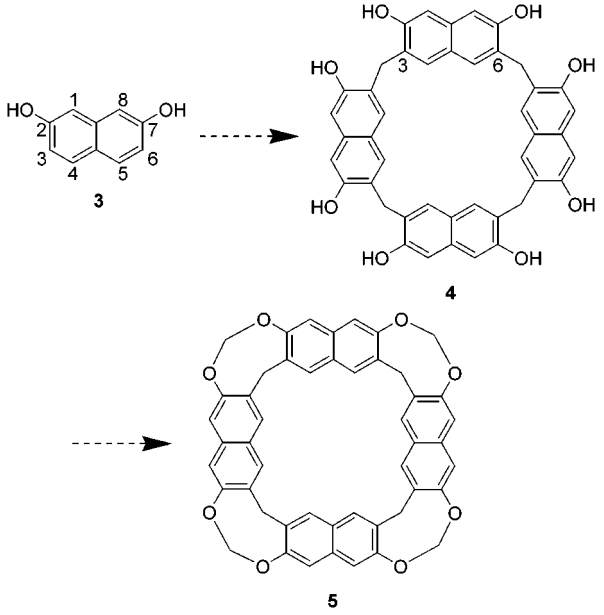


2

We have been interested in creating expanded calixarenes via the use of a larger base arene unit, which might be amenable to the preparation of larger rigid cavitands. These types of structures would in principle also have broad utility in molecular recognition and further enhance the tools for construction of molecular hosts. Several structures in the class of expanded calixarenes are known, including Poh's chromotropic acid derived calixarene (**1**),[5] Black's indole derived calixarene (**2**),[6] and others.[7] While these structures have an expanded calixarene base, and in some cases have shown some interesting recognition properties, they lack the rigidity of a cavitand. We originally envisioned a simple entry into this area by way of calixarenes such as compound **4** derived from the readily available 2,7-dihydroxynaphthalene (**3**) (Scheme 1). The 3,6-linkage of the naphthalene core would produce an expanded calixarene that would lend itself to the preparation of cavitands such as compound **5**. In addition to possessing a large rigid cavity, this structure could be further functionalized, enabling the construction of receptors.

Scheme 1



3 **4** **5**

Over the last several years, Georghiou has pioneered and substantially developed the chemistry of calixarenes derived from naphthalene subunits. The term calix[4]-

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‡ University of Kansas.

(1) (a) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, England, 1998. (b) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933−8968.
(2) (a) Cram, D. J. *Science* **1983**, *219*, 1177−1183. (b) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, England, 1994; Chapter 5.
(3) Perrin, M.; Oehler, D. In *Calixarenes: A Versatile Class of Macrocyclic Compounds*; Vicens, J., Böhmer, V., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1991; pp 65−85.
(4) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, 1991−2005.
(5) Poh, B.-L.; Lim, C. S.; Khoo, K. S. *Tetrahedron Lett.* **1989**, *30*, 1005−1008.
(6) Black, D. S.; Craig, D. C.; Kumar, N. *Tetrahedron Lett.* **1995**, *36*, 8075−8078.
(7) Schwartz, E. B.; Knobler, C. B.; Cram, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 10775−10784.

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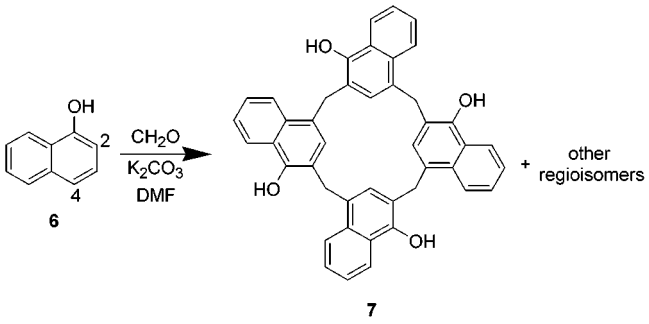
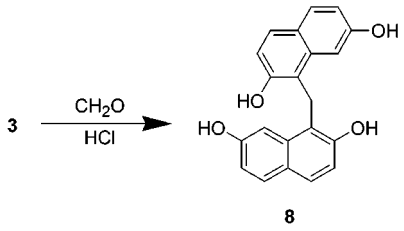
Scheme 2



Scheme 3



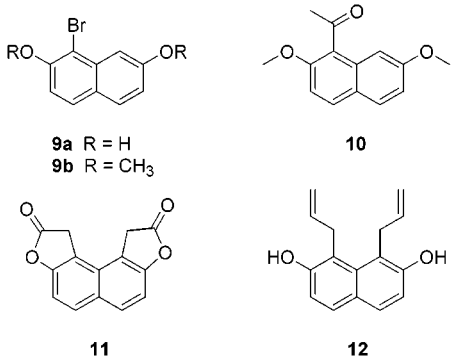
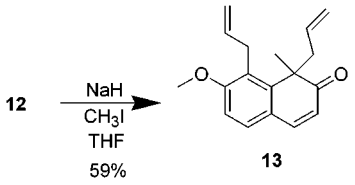


Figure 1. Representative naphthalene derivatives explored.

Scheme 4



naphthalene was coined to describe these structures, typically prepared from 1- or 2-naphthol or their derivatives.[8] For example, condensation of 1-naphthol with formaldehyde produces a mixture of regioisomeric calix[4]naphthalenes such as **7** (Scheme 2). Moreover, each isomer can be individually prepared by a convergent method.[9] Because the naphthalene units are linked at the C2 and C4 positions, this class of calixarenes has the same connectivity as a typical calixarene, yet with a deepened pocket owing to the naphthalene core. The deep binding pocket and the pendant functionality conspire to produce a versatile host that has been used to recognize a range of guests from metal ions[10] to [60]-fullerene.[11]

Despite the ample precedent for preparation of the 2,4-linked calix[4]naphthalenes, the analogous 3,6-linked isomer cannot be approached in a similar manner. It has been shown that 2,7-dihydroxynaphthalene (**3**) reacts with electrophiles, including formaldehyde, exclusively at the C1 position (Scheme 3),[12] thwarting a simple condensation strategy toward **4**. Thus, a properly functionalized derivative of **3** would be required in order to obtain the desired substitution pattern. Herein is described our synthetic approach to this general class of calixarenes.

Results and Discussion

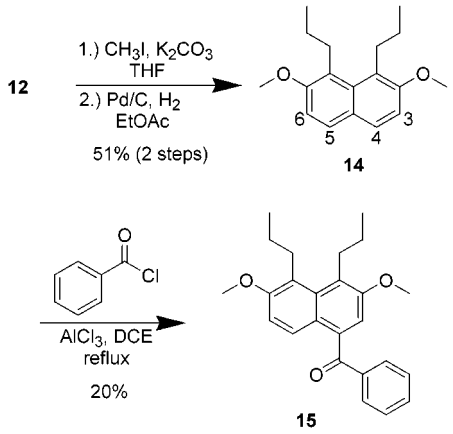
The simplest approach to obtaining the 3,6 reactivity pattern would be to block the C1 and C8 positions on the naphthalene ring. Such derivatives would then be amenable to the condensation reactions typically employed for calixarene formation. A variety of substituted 2,7-dihydroxynaphthalene derivatives are known and were examined, yet most were found to be unsatisfactory. Representative examples of these compounds are depicted in Figure 1.

Base-catalyzed reactions of monosubstituted derivatives such as 1-bromo-2,7-dihydroxynaphthalene (**9a**)[13] with formaldehyde were ineffective, leading only to uncharacterizable mixtures. Lewis acid-catalyzed reactions with methyl ethers such as **9b**[14] and **10**[15] suffered from dehalogenation and deacylation, respectively, and were similarly inappropriate. Thus, 1,8-dialkyl derivatives such as **11** and **12** were explored. While bis-lactones such as **11**[16] were too electronically deactivated for standard condensation reactions, the 1,8-bis-allyl compound **12**[17] initially appeared to be attractive. Base-catalyzed reaction of compound **12** with paraformaldehyde in refluxing xylene resulted in the formation of a highly insoluble material from which no structural elucidation was possible. Similar insolubility issues were reported in the analogous formation of phenol derived calixarenes.[18] Additionally, steric crowding of the peri substituents of compound **12** appears to impart unusual reactivity to the system. For instance, in one attempt to prepare the bis-methyl ether of **12**, the major isolated product was the mono-O-mono-C-alkylated **13** (Scheme 4). C-alkylations of this type are rare in ethereal solvents[19] and appear to be driven, in this case, by the relief of strain between the peri allyl groups.

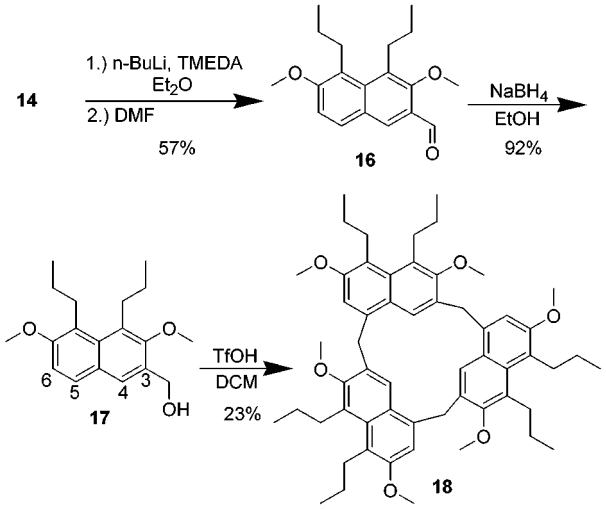
To circumvent these issues of insolubility and reactivity, compound **12** was methylated under mild conditions and hydrogenated to produce compound **14** (Scheme 5).[20]

(8) Georghiou, P. E.; Li, Z. *Tetrahedron Lett.*, **1993**, *34*, 2887−2890.
(9) Georghiou, P. E.; Ashram, M.; Li, Z.; Chaulk, S. G. *J. Org. Chem.* **1995**, *60*, 7284−7289.
(10) Ashram, M.; Mizyed, S.; Georghiou, P. E. *J. Org. Chem.* **2001**, *66*, 1473−1479.
(11) (a) Mizyed, S.; Tremaine, P. R.; Georghiou, P. E. *J. Chem. Soc., Perkin Trans. 2* **2001**, 3−6. (b) Georghiou, P. E.; Mizyed, S.; Chowdhury, S. *Tetrahedron Lett.* **1999**, *40*, 611−614.
(12) Kallmayer, H.-J.; Schröder-Mann, S. *Sci. Pharm.* **1998**, *66*, 1−8.
(13) Bell, F.; Gibson, J. A.; Wilson, R. D. *J. Chem. Soc.* **1956**, 2335−2340.
(14) Wilson, R. D. *Tetrahedron* **1960**, *11*, 256−265.
(15) Gorelik, A. M.; Reznichenko, A. V.; Andronova, N. A.; Luk'yanets E. A. *J. Org. Chem. USSR* **1983**, *19*, 183−189.
(16) Fan, X.; Yanai, T.; Okazaki, H.; Yamaye, M.; Mizobe, H.; Kosugi, Y.; Kito, T. *J. Org. Chem.* **1995**, *60*, 5407−5413;
(17) Prajer-Janczewska, L.; Wróblewski, J. *Pol. J. Chem.* **1980**, *54*, 1431−1437.
(18) Gutsche, C. D.; Dhawan, B.; No, K. H.; Muthukrishnan, R. *J. Am. Chem. Soc.* **1981**, *103*, 3782−3792.
(19) (a) Topgi, R. S. *J. Org. Chem.* **1989**, *54*, 6125−6127. (b) Kornblum, N.; Berrigan, P. J.; le Noble, W. J. *J. Am. Chem. Soc.* **1963**, *85*, 1141−1147. (c) Kornblum, N.; Seltzer, R.; Haberfield, P. *J. Am. Chem. Soc.* **1963**, *85*, 1148−1154.
(20) Shorthill, B. J.; Glass, T. E. *Org. Lett.* **2001**, *3*, 577−579.

Scheme 5



Scheme 6



Interestingly, it was immediately clear that this molecule did not possess reactivity typical of aryl ethers. Simple Friedel−Crafts acylation reactions required forcing conditions to provide products in which reaction occurred at the electronically deactivated C4 position. For example, extended reaction of compound **14** with benzoyl chloride at elevated temperature gave compound **15** as the exclusive product in poor yield (Scheme 5). None of the product of C3 acylation was observed.[21] Additionally, electrophilic formylation of **14** ($TiCl_4$, $MeOCHCl_2$) gave low conversion to a mixture of regioisomers (ca. 1:1) of carboxaldehyde products.

The desired regiochemistry was obtained via directed lithiation of **14** followed by quenching with DMF to give aldehyde **16** (Scheme 6).[20] In anticipation of a well-precedented[6,22] acid-catalyzed cyclization of benzyl alcohols to calixarenes, the aldehyde was reduced to carbinol **17**. Upon treatment of **17** with catalytic triflic acid, a mixture of a calix[3]naphthalene and a calix[4]naphthalene was formed, along with acyclic oligomers of **17** (as indicated by mass spectrometry). The major isolable product was the 3,5-linked calix[3]naphthalene **18**. Once again, reaction took place at the electronically deactivated C5 position rather than the C6 position (Scheme 6).[23] The preference for formation of the cyclic trimer was independent of reaction concentration and appeared to be controlled by the geometry of the naphthalene linkage.

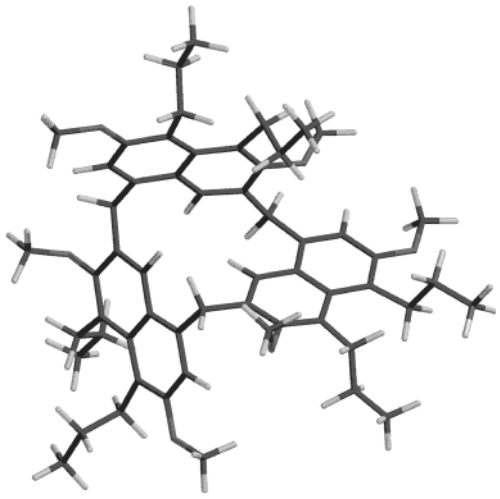
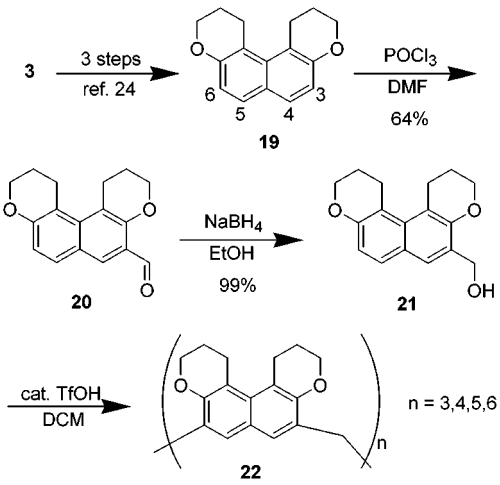


Figure 2. Energy-minimized conformation of trimer **18**.

Scheme 7



The lowest energy conformation of **18** (Macromodel 6.5) is shown in Figure 2. The structure is rather rigid and adopts an interesting twisted propeller-like conformation as a result of the 3,5-linkage. The substituents around each naphthalene core are in alternating inside−outside (geared) positions in order to minimize steric interactions. While lacking a defined cavity, the rigid structure of trimer **18** represents a novel and potentially useful scaffold.

To obtain the desired 3,6 linkage, alternate substitution patterns of the naphthalene ring were explored, including cyclic ethers such as **19**[24] (Scheme 7). Compound **19** has the same 1,8 dialkyl groups as **17**, yet the substituents are constrained into rings. In contrast to the reactivity of compounds **14** and **17**, electrophiles added smoothly to the C3 position of **19** with no trace of the alternate regioisomers. Thus, formylation of **19** under Vilsmeier conditions[25] gave aldehyde **20** in good yield (Scheme 7). Reduction of the formyl group with $NaBH_4$

(21) The regiochemistry of compound **15** was confirmed by a combination of HMQC and NOESY NMR experiments.

(22) Falana, O. M.; Emile, A.-F.; Keehn, P. M.; Stevenson, R. *Tetrahedron Lett.* **1994**, *35*, 65−68.

(23) As determined by 2D-NMR experiments, see ref 20.

(24) Venugopalan, B.; Balasubramanian, K. K. *Heterocycles* **1985**, *23*, 81−92.

(25) Vilsmeier, A.; Haack, A. *Ber. Dtsch. Chem. Ges.* **1927**, *60*, 119−122.

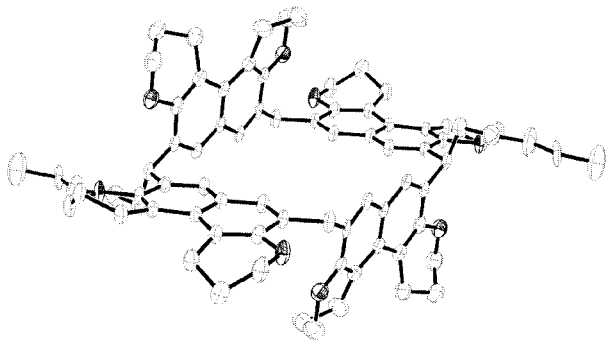
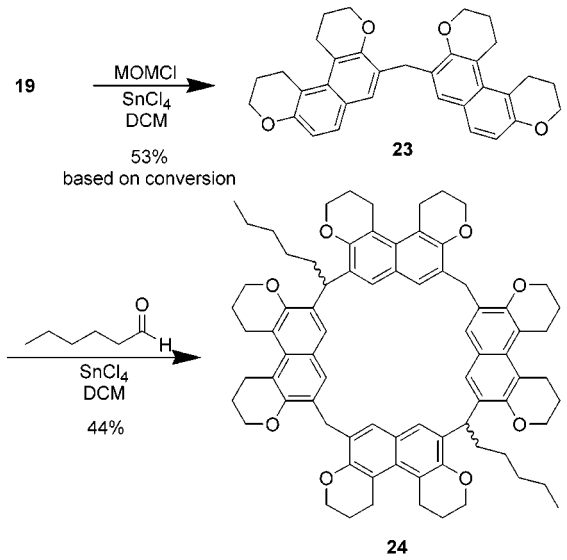


Figure 3. ORTEP diagram of the trans isomer of calix[4]-naphthalene **24**. Hydrogen atoms have been omitted for clarity.

Scheme 8



proceeded to afford the desired calixarene precursor **21**. Treatment of carbinol **21** with catalytic acid resulted in the formation of a mixture of cyclic oligomers (**22**) ranging from trimer to hexamer, as indicated by mass spectrometry. The regiochemistry of **22** is most likely a 3,6-linkage (vide infra); however, issues of insolubility hampered isolation and complete characterization of these products. The major product of this cyclization appeared to be the calix[5]naphthalene, independent of acid or reaction concentration.

To preferentially obtain the cyclic tetramer of compound **19**, a simple dimerization strategy was employed (Scheme 8).[6,9] Reaction of monomer **19** with a limiting amount of MOMCl and $SnCl_4$ gave linear dimer **23** linked at the C3 positions. Other combinations of formaldehyde equivalents and Lewis acids were inferior to these conditions. Compound **23** could be dimerized again under identical conditions to give cyclic tetramer **22** ($n = 4$) as a single compound; however, this tetramer is quite insoluble in most organic solvents. To avoid these solubility problems, hexanal was used for the cyclodimerization of **23** producing calix[4]naphthalene **24** in 44% as a 1:1.2 mixture of cis/trans isomers (Scheme 8). The pentyl side chains greatly increased the solubility of the final product. Thus, a soluble, expanded calix[4]naphthalene was easily prepared in two steps from the readily available precursor **19**.

The trans isomer of **24** crystallized from benzene. The single-crystal X-ray structure (Figure 3) confirmed the 3,6-linkage of the naphthalene rings and established the identity of the trans isomer. The structure is a flattened partial cone in which two opposing naphthalenes are approximately planar and the other naphthalenes are perpendicular to this plane. The pentyl chains are somewhat disordered in the crystal. Interestingly, the X-ray analysis indicates that the cyclic ethers of each naphthalene core are geared, similar to the calculated state of compound **18** (Figure 2).

Conclusions

In summary, two novel expanded calixarenes have been prepared from substituted dihydroxynaphthalene precursors. We observed an interesting change in regiochemistry from a 3,5-linkage to a 3,6-linkage based on the substitution pattern of the monomeric unit. Additionally, the preference for trimer versus pentamer varied as per the geometry of the linkage. A dimerization strategy served to prepare a 3,6-linked cyclic tetramer. Thus, the readily prepared bis-ether **19** was converted in two steps to calix[4]naphthalene **24**. Expanded cavitands (similar to compound **5**, Scheme 1) should be accessible from this class of calix[*n*]naphthalenes via dealkylation and subsequent bridging of the phenolic oxygens. Furthermore, possibilities for functionalization of these structures, both on the naphthalene core and on the aldehyde linking units, make these calix[*n*]naphthalenes promising subunits for receptor construction. The recognition properties of these calixarenes, as well as their conversion to cavitands, are currently under investigation.

Experimental Section

General Methods. All reagents and solvents employed are commercially available and were used without further purification unless otherwise stated. Anhydrous CH_2Cl_2 was obtained by distillation from CaH_2. Anhydrous THF was obtained by distillation from sodium benzophenone. All reactions were performed under Ar unless otherwise stated. ^{1}H NMR spectra were obtained at 400 MHz (unless otherwise indicated) in $CDCl_3$ on Bruker instruments and were referenced to tetramethylsilane (TMS). ^{13}C NMR spectra were also obtained on Bruker instruments at 100 MHz (unless otherwise indicated) and were referenced to $CDCl_3$ (77.0 ppm). Compounds **9**−**12** and **19** were prepared as previously reported.

1,8-Diallyl-7-methoxy-1-methyl-1*H*-naphthalen-2-one (13). NaH (6.0 g, 150 mmol) was carefully added to a solution of 1,8-diallyl-2,7-dihydroxynaphthalene (**12**) (9.0 g, 37.5 mmol) in THF (130 mL). Following addition of CH_3I (9.3 mL, 150 mL), the mixture was heated to reflux overnight. After being cooled to room temperature, the reaction was quenched with saturated NH_4Cl. The mixture was extracted with CH_2Cl_2 (2 × 125 mL), and the combined organic layers were dried over $MgSO_4$. After removal of the solvents in vacuo, purification by chromatography (gradient eluent, 100% hexanes to 100% EtOAc) gave compound **13** (5.9 g, 59%) as an oil: ^{1}H NMR δ 7.35 (d, 1H, J = 9.8 Hz), 7.20 (d, 1H, J = 8.3 Hz), 6.86 (d, 1H, J = 8.4 Hz), 6.04 (d, 1H, J = 9.5 Hz), 5.93 (m, 1H), 5.24 (m, 1H), 5.02 (dd, 1H, J = 10.4, 1.8 Hz), 4.92 (dd, 1H, J = 17.4, 1.8 Hz), 4.82 (dd, 1H, J = 17.2, 1.8 Hz), 4.72 (dd, 1H, J = 10.4, 2.0 Hz), 3.85 (s, 3H), 3.72 (d, 2H, J = 4.0 Hz), 2.99 (dd, 1H, J = 13.9, 6.3 Hz), 2.87 (dd, 1H, J = 13.7, 8.0 Hz), 1.58 (s, 3H); ^{13}C NMR (100 MHz) δ 204.2, 160.3, 147.1, 144.4, 136.4, 133.4, 130.3, 128.1, 123.6, 121.7, 117.1, 114.9, 108.8, 55.4, 52.3, 44.8, 31.9, 25.8; IR (neat, cm^{-1}) 2977, 2936, 1651, 1564, 1262. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.59; H, 7.49.

2,7-Dimethoxy-1,8-dipropylnaphthalene (14). 1,8-Diallyl-2,7-dihydroxynaphthalene (**12**) was prepared as per ref 17

by heating 2,7-bisallyloxynaphthalene (8.00 g, 33.3 mmol) in *N*,*N*-diethylaniline (125 mL) to reflux for 1 h. The crude product was methylated by heating to 60 °C for 16 h with K_2CO_3 (18.43 g, 133 mmol) and CH_3I (8.30 mL, 133 mmol) in THF (135 mL). After cooling to room temperature, NaH (1.33 g, 33.3 mmol) was added and the resulting mixture was stirred for 2 h. The reaction was quenched with saturated ammonium chloride. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$. Solvents were then removed in vacuo, and the residue was purified by chromatography (4:6 Hexanes/CH_2Cl_2). Recrystallization from hexanes gave 1,8-diallyl-2,7-dimethoxynaphthalene (4.80 g, 54%, two steps) as white crystals (mp 189.4−194.0 °C): ^{1}H NMR δ 7.70 (d, 2H, J = 8.8 Hz), 7.16 (d, 2H, J = 8.5 Hz), 6.20 (ddt, 2H, J = 17.3, 10.8, 4.9 Hz), 5.06 (dd, 2 H, J = 9.8, 1.6 Hz), 4.82 (dd, 2 H, J = 17.3, 1.8 Hz), 4.11 (s, 6H), 3.89 (m, 4H); ^{13}C NMR (100 MHz) δ 157.2, 139.6, 135.5, 130.0, 126.8, 120.9, 115.0, 111.5, 57.2, 31.5; IR (neat, cm^{-1}) 3076, 2998, 2936, 2835, 1614, 1516; HRMS for M^+ calcd for $C_{18}H_{20}O_2$ 268.1463, found 268.1450.

Palladium on carbon (5%, 1.70 g) in EtOAc (120 mL) was purged with H_2 for 40 min. A solution of 1,8-diallyl-2,7-dimethoxynaphthalene (4.10 g, 16.0 mmol) in EtOAc (40 mL) was added via syringe, and the mixture was stirred for 3.5 h under an atmosphere of H_2. (The reaction was followed by TLC using SiO_2 plates pretreated with $AgNO_3$.) The mixture was then filtered through Celite, washing with EtOAc. Solvents were removed in vacuo to yield compound **14**, which was recrystallized from hexanes to give colorless crystals (4.10 g, 94%) (mp 68.0−69.6 °C): ^{1}H NMR δ 7.61 (d, 2H, J = 9.1 Hz), 7.17 (d, 2H, J = 9.1 Hz), 3.91 (s, 6H), 3.06 (m, 4H), 1.66 (m, 4H), 1.06 (t, 6H, J = 7.2 Hz); ^{13}C NMR (100 MHz) δ 156.2, 133.4, 128.8, 126.5, 124.7, 111.0, 56.7, 29.0, 24.6, 14.4; IR (neat, cm^{-1}) 2954, 2870, 2835, 1614, 1517, 1464; HRMS for M + H^+ calcd for $C_{18}H_{25}O_2$ 273.1855, found 273.1851.

3-Formyl-2,7-dimethoxy-1,8-dipropylnaphthalene (16). A mixture of compound **14** (2.00 g, 7.35 mmol) and TMEDA (2.77 mL, 18.4 mmol) in Et_2O (75 mL) was cooled to 0 °C. A solution of *n*-BuLi (1.6 M in hexanes) (9.19 mL, 14.7 mmol) was added dropwise over 12 min. The solution was allowed to warm to room temperature and was then brought to reflux for 13 h. The solution was cooled to 0 °C, and DMF (2.28 mL, 29.4 mmol) was added. The resulting mixture was stirred at 0 °C for 2 h and was quenched by slowly adding HCl (10 mL, 4 N). After extraction with CH_2Cl_2, the combined organic layers were washed consecutively with 5% HCl and saturated $NaHCO_3$ and were dried over $MgSO_4$. Solvents were removed in vacuo, and the resulting crude product was purified by chromatography (1:1 Hexanes/CH_2Cl_2) to yield compound **16** (1.26 g, 57%) as a colorless oil: ^{1}H NMR δ 10.35 (s, 1H), 8.18 (s, 1H), 7.77 (d, 1H, J = 9.1 Hz), 7.22 (d, 1H, J = 9.1 Hz), 3.94 (s, 3H), 3.90 (s, 3H), 3.09 (m, 4H), 1.61 (m, 4H), 1.06 (t, 3H, J = 7.3 Hz), 1.04 (t, 3H, J = 7.5); ^{13}C NMR (100 MHz) δ 190.3, 158.2, 156.9, 136.5, 132.5, 131.5, 130.9, 127.0, 125.5, 125.2, 112.2, 63.7, 56.2, 28.7, 28.2, 25.3, 24.3, 14.1 (one propyl carbon signal unresolved); IR (neat, cm^{-1}) 2956, 2870, 1688, 1606; HRMS for M + H^+ calcd for $C_{19}H_{25}O_3$ 301.1804, found 301.1791.

3-Hydroxymethyl-2,7-dimethoxy-1,8-dipropylnaphthalene (17). A mixture of compound **16** (0.918 g, 3.06 mmol) and $NaBH_4$ (0.289 g, 7.65 mmol) in absolute EtOH (30 mL) was stirred at room temperature for 16 h. The reaction was quenched with 10% HCl (13 mL) and extracted with CH_2Cl_2. The combined organic layers were washed consecutively with brine and 5% HCl and were dried over $MgSO_4$. Solvents were removed in vacuo, and the crude product was purified by chromatography, eluting with CH_2Cl_2, to give carbinol **17** (0.850 g, 92%) as an oil: ^{1}H NMR δ 7.57 (s, 1H), 7.57 (d, 1H, J = 8.9 Hz), 7.14 (d, 1H, J = 9.0 Hz), 4.79 (s, 2H), 3.79 (s, 3H), 3.72 (s, 3H), 3.09 (m, 4H), 2.72 (s, 1H), 1.55 (m, 4H), 1.01 (t, 6H, J = 7.4 Hz); ^{13}C NMR (100 MHz) δ 155.8, 155.5, 132.7, 130.4, 128.7, 128.1, 127.8, 125.3, 112.1, 61.8, 61.7, 56.6, 29.0, 28.2, 25.4, 24.6, 14.2 (one propyl carbon signal unresolved); IR (neat, cm^{-1}) 3600−3150, 2955, 2870, 2836, 1606, 1501, 1465; HRMS for M^+ calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1869.

Calix[3]naphthalene (18). A solution of compound **17** (0.321 g, 1.06 mmol) in CH_2Cl_2 (6.5 mL) was cooled to 0 °C. Trifluoromethanesulfonic acid (0.0095 mL, 0.106 mmol) was added. The mixture was warmed to room temperature for 5 h. Solvent was removed in vacuo, and the crude product was purified by chromatography (1:1 Hexanes/CH_2Cl_2) to give cyclic trimer **18** (0.069 g, 23%) as an oil: ^{1}H NMR (360 MHz) δ 7.70 (s, 1H), 7.27 (s, 1H), 4.25 (s, 2H), 3.88 (s, 3H), 3.60 (s, 3H), 3.07 (m, 4H), 1.48 (m, 4H), 0.90 (m, 6H); ^{13}C NMR (100 MHz) δ 156.0, 155.3, 136.5, 133.0, 130.6, 130.4, 127.0, 126.1, 123.9, 114.7, 61.2, 56.9, 36.0, 29.6, 28.2, 25.2, 24.4, 14.1 (one propyl carbon signal unresolved); IR (neat, cm^{-1}) 2954, 1595; HRMS for M + H^+ calcd for $C_{57}H_{73}O_6$ 853.5407, found 853.5404.

2,3,11,12-Tetrahydro-1*H*,10*H*-4,9-dioxabenzo[*c*]phenanthrene-5-carbaldehyde (20). A mixture of compound **19** (4.50 g, 19 mmol), DMF (2.44 mL, 31 mmol), and $POCl_3$ (20 mL) was heated to 100 °C overnight. The reaction was quenched by carefully pouring over ice. The mixture was extracted with CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$. Chromatography (CH_2Cl_2 as eluant) gave the purified carbaldehyde **20** (3.2 g, 64%) as a yellow solid (mp 189−193 °C): ^{1}H NMR (300 MHz) δ 10.45 (s, 1H), 8.05 (s, 1H), 7.54 (d, 1H, J = 8.8 Hz), 6.86 (d, 1H, J = 8.8 Hz), 4.33 (t, 2H, J = 4.9 Hz), 4.26 (t, 2H, J = 4.9 Hz), 3.26 (m, 4H), 1.99 (m, 4H); ^{13}C NMR (75 MHz) δ 190.5, 156.3, 154.0, 139.6, 131.1, 130.1, 123.9, 122.6, 117.7, 115.6, 114.6, 65.8, 65.8, 27.0, 26.9, 22.8, 22.5; IR (neat, cm^{-1}) 2871, 1674, 1600; HRMS for M + H^+ calcd for $C_{17}H_{17}O_3$ 269.1177, found 269.1166.

(2,3,11,12-Tetrahydro-1*H*,10*H*-4,9-dioxabenzo[*c*]phenanthren-5-yl)methanol (21). A mixture of aldehyde **20** (0.800 g, 3.0 mmol), $NaBH_4$ (0.282 g, 7.5 mmol), and absolute EtOH was stirred at room temperature overnight. The reaction was quenched with 10% HCl, and the mixture was extracted with CH_2Cl_2. After drying over $MgSO_4$, the solvents were removed in vacuo to give the desired carbinol **21** (0.800 g, 99%) as a white solid, which was used without purification. An analytically pure sample was obtained by chromatography (CH_2Cl_2 as eluent) (mp 159−163 °C): ^{1}H NMR δ 7.43 (d, 1H, J = 9.4 Hz), 7.42 (s, 1H), 6.84 (d, 1H, J = 8.9 Hz), 4.70 (d, 2H, J = 6.3 Hz), 4.29 (t, 2H, J = 5.0 Hz), 4.23 (t, 2H, J = 4.9 Hz), 3.29 (m, 4H), 2.52 (t, 1H, J = 6.5 Hz), 1.98 (m, 4H); ^{13}C NMR (100 MHz) δ 153.8, 152.0, 135.4, 128.7, 127.1, 126.9, 124.6, 116.6, 115.0, 114.6, 65.7, 65.5, 62.5, 26.9, 26.9, 22.9, 22.8; IR (neat, cm^{-1}) 3486, 2963, 1609, 1430, 1360; HRMS for M − OH^+ calcd for $C_{17}H_{17}O_2$ 253.1229, found 253.1225.

Bis(2,3,11,12-tetrahydro-1*H*,10*H*-4,9-dioxabenzo[*c*]phenanthren-5-yl)methane (23). A solution of compound **19** (1.00 g, 4.2 mmol) and $MeOCHCl_2$ (0.079 mL, 1.0 mmol) in CH_2Cl_2 (84 mL) was cooled to 0 °C. $SnCl_4$ (1.7 mL of a 1.0 M solution in CH_2Cl_2, 1.7 mmol) was added. The reaction was warmed to room temperature for 50 min. After being quenched with saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by chromatography (1:1 hexanes/CH_2Cl_2) to give the starting material **19** (0.550 g, 55%) and dimer **23** (0.243 g, 26%) as a white solid (mp 267−269 °C dec): ^{1}H NMR δ 7.30 (d, 2H, J = 8.6 Hz), 7.12 (s, 2H), 6.77 (d, 2H, J = 8.6 Hz), 4.22 (m, 8H), 4.00 (s, 2H), 3.30 (m, 8H), 1.96 (m, 8H); ^{13}C NMR (100 MHz) δ 153.2, 152.8, 134.6, 128.4, 128.3, 127.2, 124.8, 116.0, 114.4, 114.3, 65.6, 65.5, 30.6, 27.3, 27.1, 23.1, 23.0; IR (neat, cm^{-1}) 2954, 1610, 1498, 1432. Anal. Calcd for $C_{33}H_{32}O_4$: C, 80.46; H, 6.55. Found: C, 80.70; H, 6.64.

Calix[4]naphthalene (24). A solution of dimer **23** (0.243 g, 0.49 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. Hexanal (0.065 mL, 0.52 mmol) was added. $SnCl_4$ (0.69 mL of a 1.0 M solution in CH_2Cl_2, 0.69 mmol) was added. The reaction was warmed to room temperature for 2.5 h. After being quenched with saturated $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and the solvents were removed in vacuo. The residue was purified by chromatography (7:3 hexanes/CH_2Cl_2) to give a mixture of the cis and trans isomers of **24**. Consecutive chromatography using 15% EtOAc/Hexanes and 20% Hexanes/Benzene gave analytically pure samples of each isomer as white solids. *trans*-

24 (0.068 g, 24%) (dec >300 °C): ^{1}H NMR δ 7.17 (s, 4H), 7.10 (s, 4H), 4.70 (t, 2H, J = 7.4 Hz), 4.14 (m, 16 H), 3.94 (s, 4H), 3.31 (dd, 16H, J = 9.5, 3.1 Hz), 1.88 (m, 20 H), 1.29 (m, 12 H), 0.82 (t, 3H, J = 6.9 Hz); ^{13}C NMR (125 MHz) δ 152.1, 152.0, 132.7, 132.6, 128.5, 127.1, 125.9, 124.2, 113.8, 113.8, 65.5, 65.4, 35.7, 35.1, 32.1, 30.1, 29.7, 27.6, 27.4, 23.3, 23.2, 22.6, 14.2; IR (neat, cm^{-1}) 2952, 2854, 1621, 1153; HRMS for M + H$^+$ calcd for $C_{78}H_{85}O_8$ 1149.6244, found 1149.6195. *cis*-**24** (0.054 g, 20%): ^{1}H NMR δ 7.16 (s, 4H), 7.08 (s, 4H), 4.67 (t, 2H, J = 7.3 Hz), 4.46 (d, 2H, J = 8.2 Hz), 4.16 (m, 16 H), 3.49 (d, 2H, J = 8.2 Hz), 3.31 (m, 16H), 1.88 (m, 20H), 1.30 (m, 12H), 0.84 (t, 6H, J = 6.7 Hz); ^{13}C NMR (90 MHz) δ 152.2, 152.1, 132.9, 131.9, 128.4, 126.9, 125.8, 124.3, 114.1, 114.0, 65.5, 65.4, 36.6, 34.5, 32.0, 29.7, 29.5, 27.7, 27.6, 27.5, 23.2, 22.6, 14.1; IR (neat, cm^{-1}) 2951, 2857, 1621, 1151; HRMS for M + H$^+$ calcd for $C_{78}H_{85}O_8$ 1149.6244, found 1149.6339.

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Supporting Information Available: ^{13}C NMR spectra for compounds **14**, **16**−**18**, **20**, **21**, **23**, and *cis*-**24**, as well as a ^{1}H NMR spectrum and crystallographic information for *trans*-calix[4]naphthalene **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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