Synthesis, Modification, and Characterization of a Family of Homologues of *exo*-Calix[4]arene: *exo*-[*n.m.n.m*]Metacyclophanes, *n,m* ≥ 3

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A general strategy for the preparation of the family of *exo*-[*n.m.n.m*]metacyclophanes (*n,m* ≥ 3) in 6-steps (starting from 2-bromoanisole) that utilizes a [2 + 2] approach to furnish the *exo*-metacyclophane ring in good to moderate yield is described. The soluble copper catalyst [CuBr−LiSPh−LiBr−THF] is used to efficiently couple Grignard and alkyl or ether tosylate reagents in several of the synthetic steps, including the ring construction in the final step. The *exo*-[*n.m.n.m*]-metacyclophane ring is conformationally mobile on the NMR time scale, and X-ray crystallography reveals that *exo*-[3.3.3.3]metacyclophane **2a** assumes a cone conformation, and that *exo*-[6.6.6.6]-metacyclophane **6a** assumes a chair conformation. Molecular mechanics calculations show that both conformations for each *exo*-metacyclophane are very similar in energy. Regiocontrol over the alkylation and acylation of the phenolic oxygens of **2b** is problematic, although the preparation of the tetraacetylated **18** and alkylation of **2b** with CH_2BrCl to furnish the methylene-linked mono- and bis-adducts **19** and **20** are straightforward.

Introduction

The development of molecular devices prepared from calix[4]arenes (tetrahydroxy[1.1.1.1]metacyclophane) is of current interest.[1] Applications of modified calix[4]-arenes as enzyme and antibody mimics,[2] metal-oxo surface mimics,[3] extractants for decontamination,[4] sensors and diagnostics,[5] molecular magnets,[6] photochemical and electron-transfer devicies,[7] porous surfactants,[8] and their use in ISEs[9] and nonlinear optical and liquid crystalline systems[10] have all been recently reported. Only a few examples of calix[*n*]arenes (*n* > 4) with a larger annulus have been utilized as building blocks for the fabrication of molecular systems with defined functions.[11] Due to the greater number of phenolic rings in the larger calixarenes, there has been an associated difficulty with regiochemical control in the chemical modification of the macrocycle's upper and lower rims. The larger calix[*n*]arenes (*n* > 4) possess a larger number of possible ring conformations,[12] (calix[6]arene has eight

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§ Responsible for X-ray crystal analysis.

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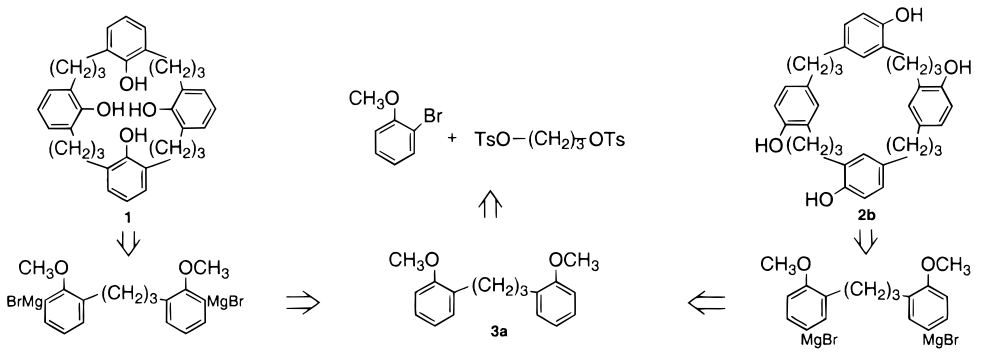
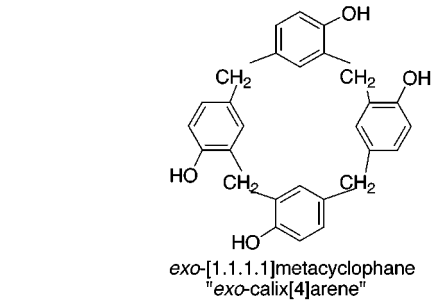
Scheme 1



possible conformations, for example), and when chemically modified the number of possible structures only increases. Both of these complications have limited their use in molecular devices. A way to increase the size of the annulus of a calixarene, and yet avoid the difficulties associated with an increase in the number of phenolic rings, is to prepare tetrahydroxy[*n.n.n.n*]metacyclophanes, $n > 1$. Little attention has been paid to these higher methylene homologues of calix[4]arenes, even though their larger cavity size and different shape makes their supramolecular structure a potential scaffolding for use in molecular devices.

Previous preparations of the higher methylene homologues of calixarenes are not general in scope and are limited in the number of methylene units connecting the aromatic rings. Additionally, their syntheses either require many steps to produce the macrocycle[13] or produce many macrocyclic products (individually in low yield) necessitating extensive purification.[14] For several years we have labored to develop a more general and efficient preparation of larger metacyclophanes and have communicated the synthesis of the *endo*-tetrahydroxy-[3.3.3.3]metacyclophane (**1**)[15] and the *exo*-tetrahydroxy-[3.3.3.3]metacyclophane (**2b**),[16] whose retrosynthetic analysis is shown in Scheme 1. The macrocyclic synthesis uses a common intermediate, bis-anisole **3a**, for the preparation of both *endo*- and *exo*-metacyclophanes. Unlike the synthesis[1] of the parent metacyclophane, calix[4]arene, no positional *tert*-butyl protecting group is needed during the synthetic scheme due to the inherent regioselectivity of organometallic coupling. We now report in full on a general preparation of a family of *exo*-[*n.m.n.m*]metacyclophanes, $n,m \geq 3$ ($n = m$, or $n \neq m$), including an *exo*-metacyclophane whose methylene bridges contain ether functional groups, and detail the necessary modifications to our earlier synthetic scheme that allow the efficient preparation of *exo*-[*n.m.n.m*]metacyclophanes where $n,m > 3$. Solution and solid-state characterization



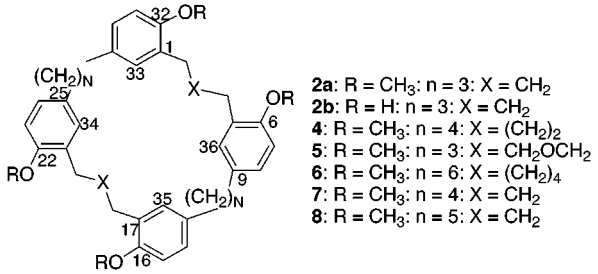


Figure 1. Structures of exo-metacyclophanes. Numbering system shown when $n = 3$ and X = CH_2.

of the metacyclophanes are described, along with initial results in the elaboration of the phenolic oxygens of *exo*-metacyclophane **2b**.

Results and Discussion

Synthesis of *exo*-Tetramethoxy[*n.m.n.m*]metacyclophanes. The preparation of the family of *exo*-[*n.m.n.m*]metacyclophanes **2** and **4**−**6** (Figure 1) was made possible by the co-development of our soluble copper catalyst, [CuBr−LiSPh−LiBr−THF].[17] The Cu(I) catalyst directs the high-yield coupling of 1 equiv of a Grignard reagent with 1 equiv of an alkyl sulfonate and is utilized in several steps of the *exo*-metacyclophane synthetic scheme (Scheme 2). The Cu(I) catalyst is highly reactive and proved to be much more efficient at coupling the stabilized anisole Grignard reagent with the bis-tosylate than other copper catalysts, such as Li_2CuCl_4 or CuBr/HMPA. Additionally, the coupling reaction is effective when the Grignard reagent concentration is as low as 0.05 M and the reaction temperature is 67 °C (refluxing THF). These properties of our soluble copper catalyst have enabled us to synthesize *exo*-metacyclophanes **2a**, **4**, and **6** routinely in 40−70% yields, for metacyclophane ring closure is promoted by elevated

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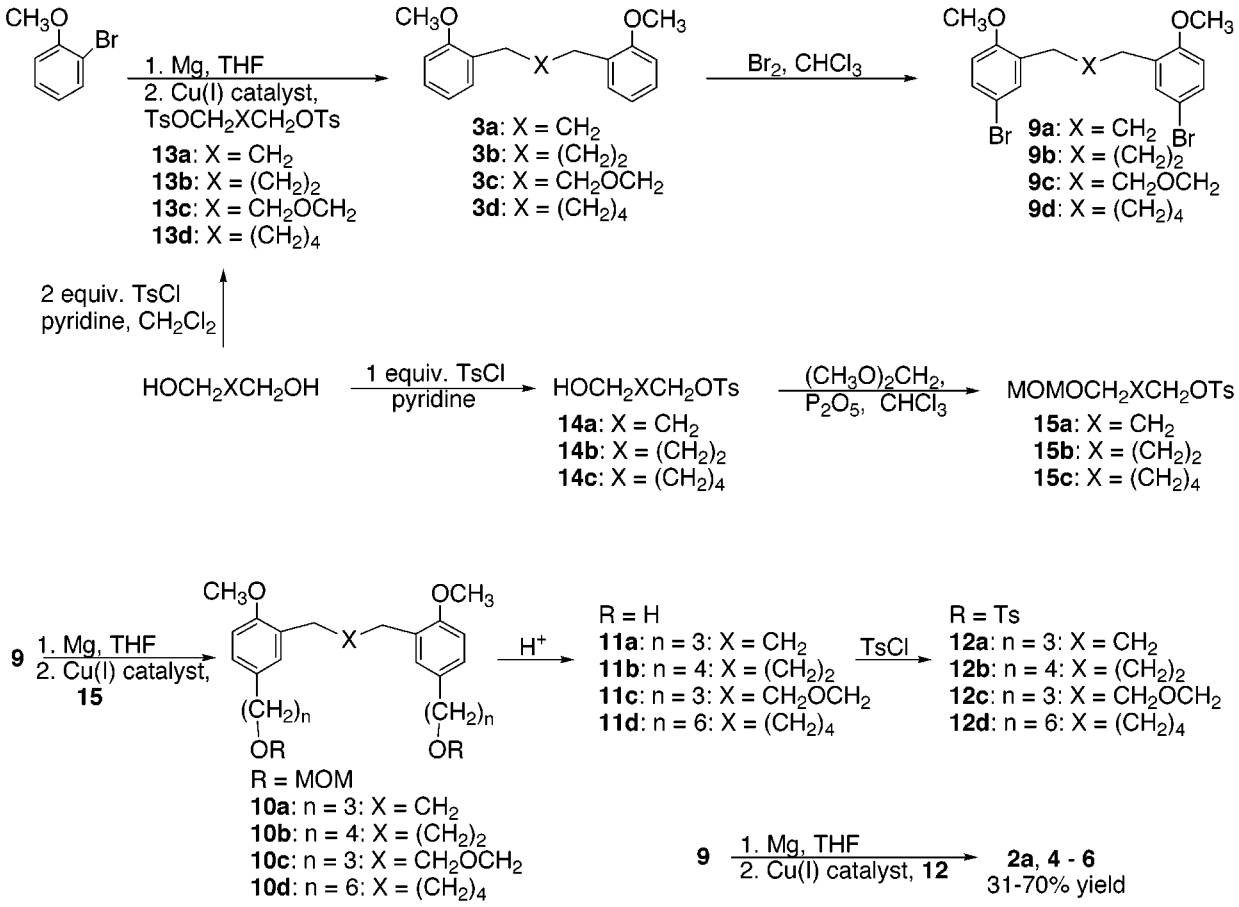
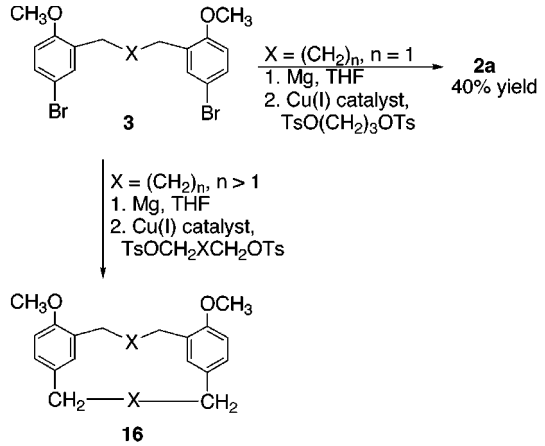
Scheme 2



temperatures, and polymer byproduct is minimized when the reaction is kept under concentrations < 0.1 M. The oxygen-containing *exo*-metacyclophane **5** was synthesized in 31% yield, but the lower yield was due primarily to the difficulty in drying the more highly oxygenated precursors **9c** and **12c** (as determined from IR spectroscopy).

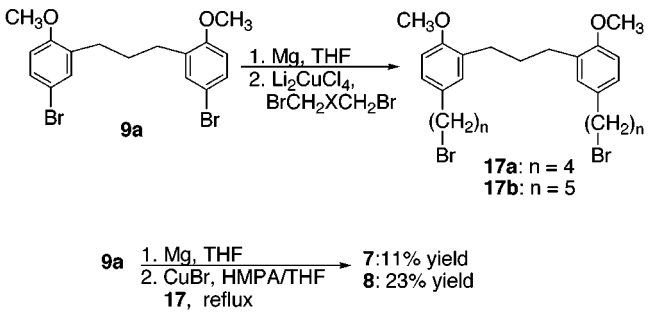
The synthetic pathway, detailed in Scheme 2, illustrates a [2 + 2] approach to the construction of the *exo*-[*n.m.n.m*]metacyclophane's macrocyclic ring from two bis-anisole precursors. The bis-anisole **3** was synthesized in one step by Cu(I) catalyzed coupling of the Grignard reagent, prepared from 2-bromoanisole, and an appropriate bis-tosylate in 75−95% yield. Ring synthesis was accomplished either in two additional steps, or with an additional 5-step route that included the elaboration of one of the bis-anisole precursors via a protection-deprotection sequence (compounds **9**−**12**, **14**, and **15**). While quick and easy, the overall 3-step *exo*-metacyclophane synthesis (starting from 2-bromoanisole) worked poorly when used to make the larger ring systems, primarily due to the formation of large quantities of byproduct [*n.n*]metacyclophane **16** (Scheme 3). For example, cyclophane **2a** was furnished in 40% yield when the bis-Grignard of **9a** and bis-tosylate **13a** were allowed to react under an inert atmosphere in the presence of 18 mol % of the Cu(I) catalyst for 72 h. On the other hand, little of the larger metacyclophanes **4** or **6** were produced by the same procedure; rather, cyclophane **16** was produced in the largest amount. An overall 6-step synthetic procedure, again starting from 2-bromoanisole, proved more fruitful by avoiding the difficulties associated with di-

Scheme 3

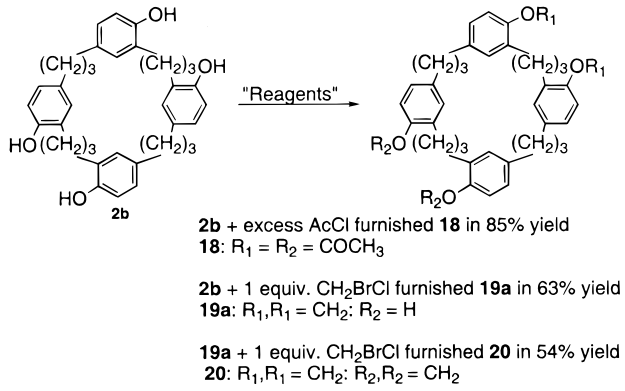


functional reactants. Thus, elaboration of the bis-Grignard of **9d** via coupling (catalyzed by the Cu(I) catalyst) with MOM-tosylate **15c**, followed by deprotection and tosylation, furnished the bis-tosylate **12d** in 42% overall yield. When the bis-Grignard of **9d** and bis-tosylate **12d** were allowed to react under an inert atmosphere in the presence of 18 mol % of the Cu(I) catalyst for 72 h, metacyclophane **6** was furnished in 45% yield. Under the same reaction conditions the bis-Grignard of **9a** and bis-tosylate **12a** furnished the smaller metacyclophane **2a** routinely in 70% yield. In contrast, prior to the development of our soluble copper catalyst and 6-step synthetic scheme (that utilizes MOM-tosylates), we used the (common) catalyst system Cu(I)Br−HMPA to prepare *exo*-metacyclophanes **7**,**8** from precursor bis-bromides **17a**,**17b**

Scheme 4



Scheme 5



in 23% yield or less (Scheme 4). Clearly the 6-step synthetic scheme, in which three of the steps utilize our Cu(I) catalyst as a coupling agent for Grignard and alkyl sulfonate reagents, is an efficient and general preparation of this family of *exo*-metacyclophanes. However, the sensitivity of the Grignard reactions toward moisture makes the preparation of *exo*-metacyclophane **5** (with a more highly coordinating oxygen-containing bridge that connects the anisole rings) more problematic than the preparation of the all-methylene carbon analogue due to the difficulty in drying the reactive tosylate precursors.

Solution and Solid-State Structure. The UV/vis spectra of the *exo*-metacyclophanes are unremarkable. The one methoxy resonance (3.75−3.79 ppm) in the ^{1}H NMR spectra of metacyclophanes **2a** and **4**−**8** demonstrates the symmetry of the macrocycles and indicates their methoxy groups are not shielded by the aromatic rings, i.e., they are directed outside of the rings, exhibiting a normal anisole methoxy resonance (unlike *endo*-metacyclophane **1**, whose upfield methoxy resonance of 3.45 ppm suggests shielding from the aromatic rings[15]). The ^{1}H NMR spectrum of **2a** at 323 K exhibits (besides the one methoxy resonance) a doublet (4H) at 6.74 and multiplet at 6.94−6.95 (8H) ppm in the aromatic region and a somewhat broadened pair of triplet resonances at 2.53 and 2.67 ppm that correspond to the set of eight ortho- and para-benzyl methylene protons. The straightforward proton resonances in the aromatic region, and the triplets corresponding to methylene protons (which demonstrates that equivalent methylene groups also carry equivalent hydrogens), indicate the macrocycle is conformationally mobile on the NMR time scale. That the ring is conformationally mobile is not surprising since the smaller *exo*-calix[4]arene ring is also conformationally flexible.[18] Indeed, the NMR spectra of **2a** exhibits no appreciable change in the appearance of its proton signals over the temperature range 323−228 K. Force field calculations[19] corroborate the flexibility of cyclophane **2a**, indicating no real global minimum energy conformation but rather several conformations with similar energy. Presumably, the ^{1}H NMR spectrum of **2a** is a set of averaged proton signals originating from several conformations (vide infra). The ^{1}H NMR spectra of the homologous metacyclophanes **4**−**8** exhibited similar aromatic, methoxy, and methylene proton resonances and as a group are conformationally mobile on the NMR time scale. Cyclophane **2b**[16] was furnished in 92% yield when cyclophane **2a** was subjected to BBr_3 in dichloromethane. It was not possible to determine the existence of internal hydrogen bonding between the phenolic hydrogens by ^{1}H NMR because **2b** was only soluble in solvents such as acetone or DMSO, but IR spectroscopy (KBr) exhibited no detectable hydrogen bonding.[16]

Table 1: Crystallographic Data

	2a	**6**
formula	$C_{40}H_{48}O_4$	$C_{52}H_{72}O_4$
fw (g/mol)	592.82	761.14
cryst dimens (mm)	0.20 × 0.20 × 0.15	0.60 × 0.50 × 0.25
cryst syst	monoclinic	monoclinic
space group	*C*2/*c*	$P2_1/c$
cryst color	colorless	colorless
a, Å	31.930(9)	16.00(2)
b, Å	4.623(3)	8.850(3)
c, Å	28.232(7)	16.80(2)
β, deg	117.63(3)	105.81(9)
V, Å^3	3692(3)	2289(4)
Z	4	2
ρ_{calc}, g/cm^3	1.066	1.10
T, °C	room temp.	room temp.
μ(Mo Kα), cm^{-1}	0.67	0.67
λ, Å	0.71069	0.71069
R^a ($I > 2\sigma(I)$)	0.085	0.064
$R_W{}^b$($I > 2\sigma(I)$)	0.080	0.062
GOF	2.19	2.06

^{a} $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. ^{b} $R_w = [\Sigma w(|F_0| - |F_c|)^2/\Sigma wF_o^2]^{1/2}$.

Crystals of **2a** and **6** suitable for X-ray crystallographic analysis were grown by slow evaporation of a CH_2Cl_2 solution. The crystal data and refinement results for **2a** and **6** are presented in Table 1. The smaller parent *exo*-calix[4]arene has been shown by X-ray crystallography to exist in a cone conformation,[18] and the crystal structure likewise shows **2a** to exist in a cone conformation (Figure 2). In contrast, the crystal structure of **6** is shown to assume a chair conformation (Figure 3). Although the two homologous metacyclophanes exhibit different conformations in the solid state, both cone and chair isomers have very similar conformational energies (approximately 1.0 kcal/mol) for each metacyclophane as determined from molecular mechanics calculations. Most likely these conformations (and probably others) are in equilibrium in solution.

Molecule **2a** crystallizes on a special position in the monoclinic space group *C*2/*c*. A crystallographically imposed 2-fold axis extends through the center of the molecule, perpendicular to the bowl. Molecule **6** crystallizes on a special position in the monoclinic space group $P2_1/c$, and the crystallographically imposed inversion symmetry leads to the chair conformation. Both molecules' bond angles and bond lengths are unexceptional.

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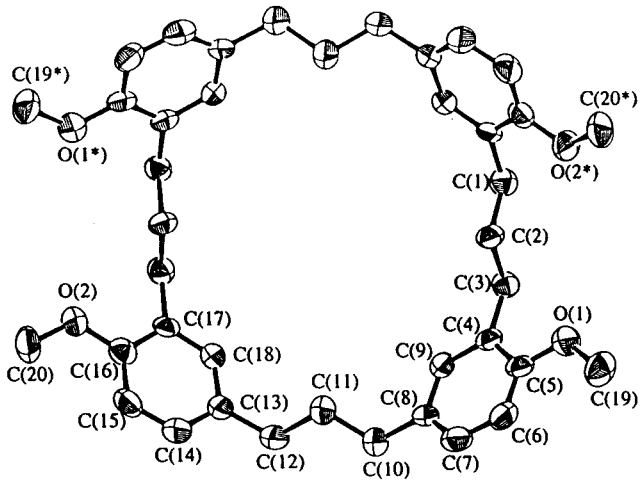

Figure 2. ORTEP diagram illustrating the cone conformation of **2a** (a disordered solvent molecule of water found in the cavity and hydrogens are omitted for reasons of clarity); 50% probability ellipsoids are displayed.

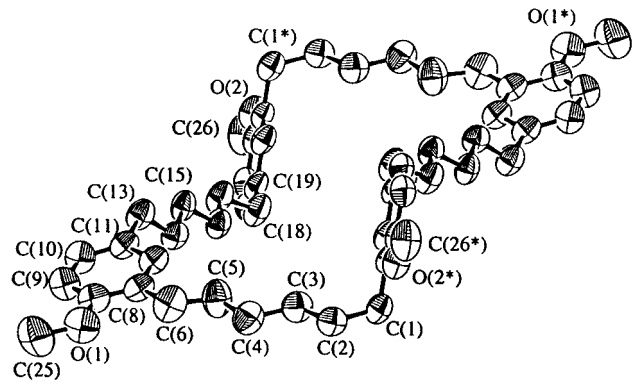

Figure 3. ORTEP diagram illustrating the chair conformation of **6** (hydrogens are omitted for reasons of clarity); 50% probability ellipsoids are displayed.

The inclination of the phenyl rings to the mean plane of the molecule (defined as the plane that contains the four benzyl methylene carbons either para or ortho to the methoxy group) is 41−42° for **2a** in the cone conformation. In the chair conformation of **6** one pair of diagonally placed phenyl rings is inclined 60−70° above or below the plane of the other pair, and each pair of parallel methylene bridges is roughly perpendicular to the other.[20] Perhaps the most intriguing structural feature common to both the *exo*-metacyclophanes is their large size. The distance between phenyl rings diagonal to each other in the cone conformation of **2a** is 8.6−8.7 Å and in the chair conformation of **6** is 11.9−13.0 Å (calculated distance between two carbons, each occupying a position between the two methylene bridges in a set of diagonal phenol rings).

Phenolic Oxygen Modification. The reactivity toward aromatic electrophilic substitution of the unsubstituted ortho-positions on the *exo*-metacyclophane's aromatic rings is dependent upon the nature of the substituent on the phenolic oxygen, i.e., the ring decreases in reactivity in the order PhOH > PhOR ≫ PhOCOR.[1] Therefore, regiocontrol over the modification of the phenolic oxygens is one way to control the elaboration of the aromatic ring, which is desirable for the controlled synthesis of more complex nanostructures of defined function. The *exo*-tetrahydroxymetacyclophanes contain two possible orientations of adjacent phenolic oxygens with respect to one another; either with a para or ortho connection via the methylenes that bridge two phenol rings. Accordingly, three (1,2-para, 1,2-ortho, and 1,3) possible di-*O*-substituted isomers can form upon the alkylation or acylation of the phenolic oxygens, as well as the mono-, tri-, and tetra-*O*-substituted isomers. Regiocontrol over such elaboration, starting from *exo*-tetrahydroxymetacyclophanes of various size, would seem a daunting task. Considering the stepwise approach to the design of the ring system, it may ultimately prove best to instead use several different "directed ortho metalation" functional groups that can be selectively unmasked to furnish a desired pattern of free phenols. As a starting point, however, we examined the acylation and alkylation of the *exo*-tetrahydroxy[3.3.3.3]metacyclophane **2b**.

Acylation of **2b** with acetyl chloride in THF and Et_3N at room temperature or below led to all possible substituted isomers, although the mono-, di-, tri-, and tetra-*O*-acylated isomers could be separated with chromatography. Only when **2b** and excess acetyl chloride were allowed to stir at reflux for 24 h did one isomer predominate, the tetra-*O*-acylated isomer, furnished in 85% yield along with small amounts of easily separated mono-, di- and tri-*O*-acylated isomers. Besides the experimental evidence cited above, structural properties intrinsic to the ring indicate there would be difficulty in the regioselective preparation of isomers other than the tetra-*O*-substituted isomer. CPK model analysis predicts that any attempt to use steric interactions between adjacent phenolic oxygen substituents (as can be done in calix[4]arene chemistry[1]) to direct acetylation or alkylation in a regioselective manner would most likely fail because of the large distance (approximately 9−13 Å) that separates the phenolic oxygens. Furthermore, the IR and ^{1}H NMR spectra of **2b** exhibit no intramolecular hydrogen bonding between phenols (vide supra). Any preferential formation of the three possible dianions (1,2-ortho, 1,2-para, or 1,3) due to stabilization via intramolecular hydrogen bonding, and therefore consequent regiocontrol of alkylation or acylation would seem unlikely.

Rather than address the above issues by experimenting further with larger acyl chlorides or different bases, we shifted our attention to the use of difunctional electrophiles in the expectation that fewer regioisomers would result from this type of modification to the *exo*-metacyclophane's phenolic oxygens. It seemed probable that 1 equiv of a small electrophile such as bromochloromethane might preferentially react with adjacent phenolic oxygens in a 1,2-ortho pattern since semiempirical calculations[21] showed that the heat of formation of the 1,2-ortho adduct **19a** (Figure 4) was 6 kcal more stable than the 1,3 adduct **19b** and that the 1,2-para adduct would be too high in energy to form. Reaction of **2b** with 1 equiv of bromochloromethane in DMSO and K_2CO_3 furnished a monoadduct in 63% purified yield. Due to the low boiling point

(20) The conformation of **6** allows the molecules to pack in an alternating fashion such that each cyclophane has a neighboring cyclophane above it and another below it with one methoxy group from each of the neighboring cyclophanes directed into the center of the cyclophane ring.

(21) CAChe 3.9 MOPAC/PM3 (James Stewart), CAChe Scientific (Oxford Molecular), Beaverton, OR 97076.

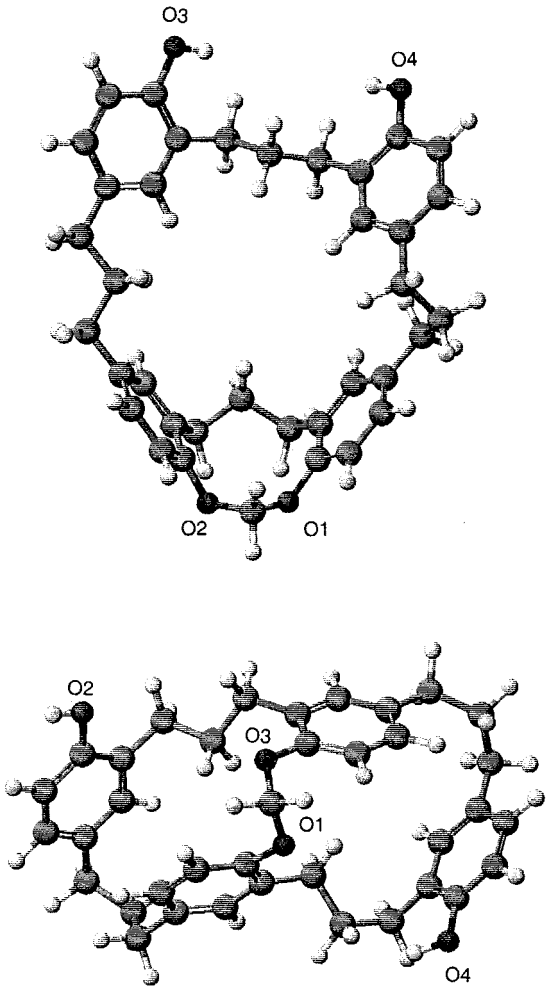

Figure 4. Minimized (PM3) structures of mono(methylene-linked) **19**. Top: 1,2-adduct **10a**. Bottom: 1,3-adduct **19b**.

of bromochloromethane, the reaction temperature was kept at 60 °C overnight, allowing the alkylation of one phenolic oxygen. The temperature was then raised to 120 °C, and the reaction mixture allowed to stir for an additional 48 h to complete the ring formation. While attempts to prepare a bis-adduct directly from **2b** proved problematic, the bis-adduct was furnished in 54% yield by reaction of the monoadduct **19** with bromochloromethane using the procedure discussed above.

Whereas the ^{1}H NMR spectrum of **2b** exhibits a pair of triplet resonances for the ortho and para-benzyl methylene protons (8H at 2.53 ppm and 8H at 2.67 ppm), the ^{1}H NMR spectrum of the monoadduct exhibits three triplets (8H at 2.50 ppm, 4H at 2.63 ppm, and 4H at 2.84 ppm). This spectrum is consistent with the optimized geometry of monoadduct **19a**, where the ortho-benzyl protons that occupy positions in the newly formed ring experience a different electronic environment from that of the ortho-benzyl protons associated with the remaining phenols (the 8 para-benzyl protons experience very similar electronic environments and it is not surprising that the ^{1}H NMR spectrum would exhibit only the one corresponding triplet). Examination of the optimized structure of **19b** shows that it contains a C_2 axis which cuts through the center of the molecule perpendicular to the methylene attached to the two phenol oxygens. In this structure, the ortho-benzyl methylene protons probably experience similar electronic environments, as do

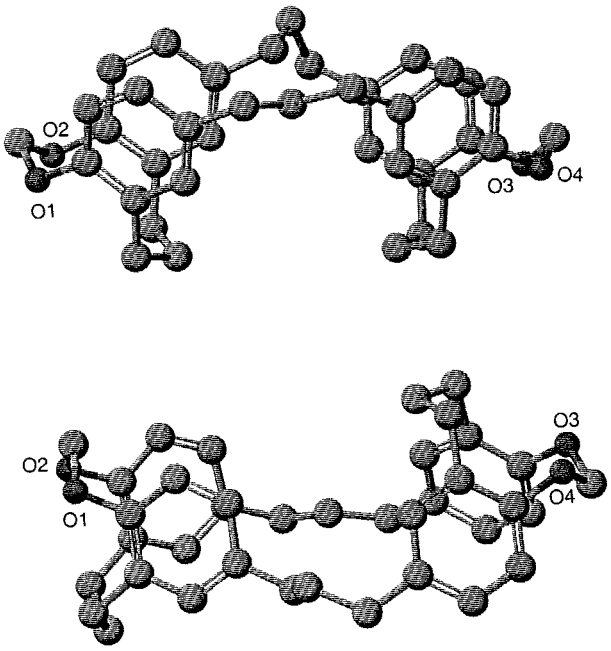

Figure 5. Minimized (PM3) structures of bis(methylene-linked) **20** (hydrogens are omitted for reasons of clarity). Top: cone conformation **20a**. Bottom: 1,2-alternate conformation **20b**.

the para-benzyl protons, leading to the expectation that two triplet proton resonances, each corresponding to 8 protons, would be observed in its spectrum. More diagnostic, however, is the aromatic region in the monoadduct's spectrum, which contains proton resonances nearly identical to those observed in the spectrum of **2b**. CPK model analysis indicates that, starting with the PM3 optimized structure of **19b**, it would take only very small phenol ring rotations to place the phenol's meta-proton on top of the π-system of an adjacent phenol ring. Each of these meta-protons should be shielded by the adjacent aromatic ring, and their resonances shifted upfield in comparison to those of **2b**. Since this type of aromatic ring shielding would not occur in **19a**, the upfield resonance shifts would not be expected to be present in its ^{1}H NMR spectrum. Thus, *exo*-metacyclophane **19a** would seem the more likely structure of the two monoadducts, given its more stable calculated heat of formation and that the aromatic region in the monoadducts ^{1}H NMR spectrum is so similar to that of **2b**.

An *exo*-metacyclophane with both sets of ortho-phenolic oxygens bridged by a methylene carbon is consistent with the spectral analysis of the bis-adduct prepared from **19a**. As in the case with the cone and 1,2-alternate conformation of the bis(methylene-linked) *exo*-calix[4]arene reported by Sorrel,[22] it is not possible to distinguish between the cone conformation of **20a** (Figure 5) and 1,2-alternate conformation of **20b** by their ^{1}H NMR spectra due to symmetry considerations. The NMR spectra of **20** exhibits only slight broadening of its protons signals over the temperature range 323−228 K (the largest change is seen in the triplets at 2.54 and 2.72 ppm, which coalesce into two broad singlets by 312 K). While this suggest **20** is less flexible than **2a**, it also shows that the bis(methylene-linked) adduct is also conformationally mobile on the NMR time scale like its parent *exo*-

(22) Sorrell, T. N.; Yuan, H. *J. Org. Chem.* **1997**, *62*, 1899−1902.

metacyclophane. The simple rt ^{1}H NMR spectrum and narrow melting point range of the bis-adduct **20** suggests it is likely one compound. Both molecular mechanics and semiempirical calculations show the two conformations **20a** and **20b**, which cannot interconvert into one another, are less than 1 kcal/mol apart in energy. Accordingly, absolute proof of the structure for both **19** and **20** will have to wait for the preparation of suitable crystals for X-ray diffraction.

Conclusion

The general preparation of *exo*-tetramethoxy[*n.m.n.m*]-metacyclophanes in good to moderate yield is possible via a 6-step synthetic strategy that relies heavily on our soluble copper catalyst [CuBr−LiSPh−LiBr−THF] to efficiently couple Grignard and alkyl tosylate reagents. The *exo*-metacyclophane rings are flexible on the NMR time scale, and molecular mechanics calculations indicate the cone and chair conformations seen in the crystal structures of **2a** and **6** have very similar energies and are therefore most likely in equilibrium in solution. Regiocontrol over the alkylation and acylation of the phenolic oxygens of **2b** is problematic, although the preparation of the tetra-acylated **18**, and alkylated **19** and **20** is straightforward.

Experimental Section

Materials and Procedures. The following chemicals were obtained commercially and dried and/or purified according to literature procedures before use[23] (all solvents were dried unless otherwise noted): tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium and benzophenone; tetramethylethylenediamine (TMED), pyridine, and dimethoxymethane (MOM) were distilled from sodium; hexamethylphosphoramide (HMPA) was distilled from sodium under high vacuum; 2-bromoanisole was distilled from calcium hydride under vacuum; 1,3-propanediol, 1,4-butanediol, 1,6-hexanediol, and diethylene glycol were dried over sodium carbonate, filtered, and then fractionally distilled; 1,2-dichloroethane was predried over $CaCl_2$ and then distilled from P_2O_5; chloroform and CH_2Cl_2 were distilled from P_2O_5. Lithium bromide, cuprous bromide−dimethyl sulfide, *para*-toluenesulfonyl chloride, (dimethylamino)pyridine (DMAP), and 1,3-propanediol di-*para*-tosylate were used as received from Aldrich Chemical Co. Lithium reagents were assayed according to literature procedures.[24] All reactions were performed under a nitrogen atmosphere obtained by passing the nitrogen through a drying tower containing 3 Å molecular sieves, or were performed in a Vacuum Atmospheres glovebox under a nitrogen atmosphere.

All melting points (Mel-Temp) and boiling points (micro boiling point apparatus) are uncorrected. ^{1}H NMR spectra were recorded at either 400 or 300 MHz in $CDCl_3$ with Me_4Si as an internal reference unless otherwise specified. Low-resolution mass spectra were obtained at 70 eV using a Finnigan INCOS 50 direct inlet system, and HRMS were obtained on a VG ZAB system. Column chromatography was carried out on silica gel (Davisil 633), and analytical thin-layer chromatography was performed using precoated Analtech Uniplates (silica gel GF). Samples that were used for spectral and analytical analyses were purified by radial chromatography using a Chromatotron.[25] Analytical samples were dried under vacuum in a drying pistol at 120 °C for a minimum of 2 days. Elemental analysis was done by Desert Analytics, Tucson, AZ.

Structure Determinations. The crystal structures for *exo*-tetramethoxy[3.3.3.3]metacyclophane (**2a**) and *exo*-tetramethoxy[6.6.6.6]metacyclophane (**6**) were performed at room temperature using graphite-monochromated Mo Kα radiation on an Enraf-Nonius CAD4 diffractometer controlled by software running on an SGI O2 computer. The crystals were affixed with epoxy to the tip of a glass fiber which was mounted in the gonoiometer head on the diffractometer. The unit cells were determined from the setting angles of 24 reflections with $20° < 2\theta < 24°$ and confirmed by axial photographs. For **2a**, 2797 reflections were collected ($\omega - 2\theta$; $+h, +k, \pm l$; $2° \leq 2\theta \leq 45°$), giving a unique set of 2758 reflections ($R_{int} = 0.139$) and 1186 observed reflections ($I > 1\sigma(I)$). For **6**, 3366 reflections were collected (ω; $+h, +k, \pm l$; $2° \leq 2\theta \leq 45°$), giving a unique set of 3242 reflections ($R_{int} = 0.039$) and 1721 observed reflections ($I > 2\sigma(I)$). The data were processed, and the structures were solved and refined using the TeXsan package.[26] The data were corrected for Lorentz and polarization effects, an empirical absorption correction based on azimuthal scans of three intense reflections (transmission factors: **2a**; 0.9314−0.9910, **6**; 0.8840−0.9997), and secondary extinction (**2a**, 2.01212×10^{-7}; **6**, 1.03788×10^{-6}). No decay was detected by measurement of three intense reflections. The structures were solved by direct methods[27] and refined by full-matrix least-squares techniques with values for $\Delta f'$ and $\Delta f''$ from Creagh and McAuley.[28] The structure of **2a** includes extra electron density in the center of the molecule corresponding to a disordered solvent, which was modeled with three partially occupied oxygen atoms representing a disordered water of crystallization. These atoms were included with isotropic thermal parameters. All other non-hydrogen atoms were refined with anisotropic temperature factors, and the attached hydrogen atoms were included at idealized positions but were not refined. Pertinent details are given in Table 1.

General Procedure for the Preparation of bis-Anisole: 1,1′-(1,3-Propanediyl)bis[2-methoxybenzene] (3a). THF (160 mL) was added to magnesium turnings (10.84 g, 446 mmol), and the reaction mixture was heated to reflux. A solution of 2-bromoanisole (16.69 g, 89.2 mmol) in THF (18 mL) was added via syringe at a rate of 0.6 mL/min to the reaction mixture. The resulting Grignard reaction was allowed to stir at reflux for 20 h and then cooled to room temperature. A second solution consisting of 1,3-propanediol, bis(4-methylbenzenesulfonate) (**13a**) (17.15 g, 44.6 mmol) in THF (20 mL), 26.8 mL (6 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution, and HMPA (11.4 mL; 6% v/v based on the volume of the Grignard reaction) was heated to reflux. The cooled Grignard solution, decanted from excess magnesium, was then added to the refluxing reaction mixture with a cannulating needle. After 2 h, an additional 13.4 mL (3 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution was added, and the reaction mixture was stirred at reflux for an additional 20 h. The reaction was then cooled to room temperature, quenched with 1.5 M HCl (150 mL), and extracted with CH_2Cl_2 (4 × 50 mL). The combined organic layers were washed with another portion of 1.5 M HCl (150 mL), followed by brine (150 mL), dried over Na_2SO_4, and concentrated under vacuum to yield off-white crystals. Recrystallization from ethanol yielded 10.95 g of the title compound (42.9 mmol, 96%) as white crystals: mp 53−54 °C; ^{1}H NMR δ 1.86−1.95 (m, 2H), 2.67 (t, 4H, $J = 7.83$ Hz), 3.80 (s, 6H), 6.80−6.91 (m, 4H), 7.10−7.23 (m, 4H); ^{13}C NMR (100.5 MHz) δ 29.67, 30.08, 55.26, 110.26, 120.30, 126.76, 129.67, 131.11, 157.54; HRMS *m/z* calcd for 256.1463, found 256.1461. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.53; H, 8.01.

1,1′-(1,4-Butanediyl)bis[2-methoxybenzene] (3b). The reaction of a Grignard solution, made from magnesium turn-

(23) Perrin, D.: Armarego, W. *Purification of Laboratory Chemicals*; Pergamon Press: New York, 1988.

(24) (a) Watson, S.: Eastham, J. *J. Organomet. Chem.* **1967**, *9*, 165−168. (b) Kofron, W.; Baclawski, L. *J. Org. Chem.*, **1976**, *41*, 1879−1890.

(25) Harrison Research, 840 Moana Court, Palo Alto, CA.

(26) TeXsan: *Crystal Structure Analysis Package*, *Molecular Structure Corporation* (1985 and 1992).

(27) SIR92: Altomare, A.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A. *J. Appl. Crystallogr.* **1993**, *26*, 343.

(28) Creagh, D. C.; McAuley, W. J. *International Tables for Crystallography, Vol. C*; Wilson, A. J. C., Ed.; Kluwer Academic Publishers: Boston, MA, 1992.

ings (1.28 g, 52.7 mmol) and 2-bromoanisole (0.98 g, 5.26 mmol) in THF (10.5 mL), and a refluxing solution consisting of 1,4-butanediol, bis(4-methylbenzenesulfonate) (**13b**) (1.05 g, 2.63 mmol) in THF (6.7 mL), HMPA (1.8 mL), and a total of 6.6 mL of 0.1 M LiBr/CuBr·SMe_2/LiSPh/THF furnished 0.66 g of the title compound (2.44 mmol, 93%) as white crystals after recrystallization from ethanol: mp 65−66 °C; ^{1}H NMR δ 1.61−1.68 (m, 4H), 2.52−2.68 (m, 4H), 3.80 (s, 6H), 6.81−6.89 (m, 4H), 7.09−7.19 (m, 4H); ^{13}C NMR (100.5 MHz) δ 29.71, 29.96, 55.27, 110.26, 120.29, 126.72, 129.79, 131.26, 157.48; LRMS *m*/*z* 270 (M^+), 254, 163, 91. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.73; H, 8.21.

1,1′-(1,1′-(2,2′-Oxybisethane)diyl)bis[2-methoxybenzene] (3c). The reaction of a Grignard solution, made from magnesium turnings (1.87 g, 76.9 mmol) and 2-bromoanisole (1.43 g, 7.69 mmol) in THF (15.4 mL), and a refluxing solution consisting of 1,1′-(2,2′-oxybisethanol), bis(4-methylbenzenesulfonate) **13c** (1.59 g, 3.85 mmol) dissolved in THF (9.7 mL), HMPA (1.0 mL), and a total of 6.9 mL of 0.1 M LiBr/CuBr·SMe_2/LiSPh/THF furnished 1.03 g of the title compound (3.58 mmol, 93%) as white crystals after recrystallization from ethanol: mp 98−99 °C; ^{1}H NMR δ 2.65 (t, 4H, J = 7.92), 3.52−3.59 (m, 4H), 3.79 (s, 6H), 6.87−6.99 (m, 4H), 7.23−7.38 (m, 4H); ^{13}C NMR (100.5 MHz) δ 34.92, 56.83, 66.36, 110.63, 121.84, 128.01, 130.91, 132.25, 158.87; LRMS *m*/*z* 286 (M^+), 178, 151, 91. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.17; H, 8.06.

1,1′-(1,6-Hexanediyl)bis[2-methoxybenzene] (3d). The reaction of a Grignard solution, made from magnesium turnings (1.00 g, 41.1 mmol) and 2-bromoanisole (0.76 g, 4.11 mmol) in THF (8.2 mL), and a refluxing solution consisting of 1,6-hexanediol, bis(4-methylbenzenesulfonate) **13d** (0.88 g, 2.06 mmol) dissolved in THF (5.4 mL), HMPA (0.5 mL), and a total of 2.4 mL of 0.1 M LiBr/CuBr·SMe_2/LiSPh/THF furnished 0.45 g (1.5 mmol, 73%) of the title compound as white crystals after recrystallization from ethanol: mp 70−71 °C; ^{1}H NMR δ 1.35−1.42 (m, 4H), 1.51−1.65 (m, 4H), 2.57 (t, 4H, J = 7.8 Hz), 3.85 (s, 6H), 6.81−6.90 (m, 4H), 7.10−7.19 (m, 4H); ^{13}C NMR (100.5 MHz) δ 29.49, 29.85, 30.13, 55.23, 110.26, 120.30, 126.70, 129.72, 131.39, 157.47; LRMS *m*/*z* 298 (M^+), 191, 107, 91. Anal. Calcd for $C_{20}H_{26}O_2$: C, 80.50; H, 8.78. Found: C, 80.60; H, 8.77.

General Procedure for the Preparation of 5,5′-Dibromo-bis-anisole: 1,1′-(1,3-Propanediyl)bis[5-bromo-2-methoxybenzene] (9a). Bis-anisole **3a** (3.08 g, 12.0 mmol) was dissolved in $CHCl_3$ (13.4 mL), the solution was cooled to 0 °C on an ice−water bath, and bromine (1.24 g, 48.06 mmol) was added dropwise ($CHCl_3$ with ethanol inhibitor was used directly from the bottle; HBr gas produced in the reaction was collected in two KOH traps cooled on dry ice/acetone baths). The reaction was stirred an additional 2 h, quenched with 1.5 M HCl (100 mL), extracted with Et_2O (3 × 50 mL), washed with brine (100 mL), and concentrated under vacuum. The crude solid was recrystallized from ethanol to yield 4.97 g (11.99 mmol, 99.9%) of the title compound as white crystals: mp 60−61 °C; ^{1}H NMR δ 1.79−1.90 (m, 2H), 2.61 (t, 4H, J = 7.7 Hz), 3.79 (s, 6H), 6.67−6.70 (m, 2H), 7.24−7.26 (m, 4H); ^{13}C NMR (100.5 MHz) δ 29.04, 29.62, 55.51, 111.87, 112.57, 129.46, 132.31, 133.09, 156.65; HRMS *m*/*z* calcd for $C_{17}H_{18}Br_2O_2$ 411.9676, found 411.9674. Anal. Calcd for $C_{17}H_{18}Br_2O_2$: C, 49.30; H, 4.39. Found: C, 49.43; H, 4.26.

1,1′-(1,4-Butanediyl)bis[5-bromo-2-methoxybenzene] (9b). The reaction of 1,1′-(1,4-butanediyl)bis[2-methoxybenzene] (**3b**) (4.27 g, 15.8 mmol) and bromine (1.63 g, 63.3 mmol) in $CHCl_3$ (17.6 mL) furnished 6.56 g (15.4 mmol, 97.5%) of the title compound as white crystals after recrystallization from ethanol: mp 78−79 °C; ^{1}H NMR δ 1.55−1.61 (m, 4H), 2.46−2.62 (m, 4H), 3.78 (s, 6H), 6.68−6.76 (m, 4H), 7.23−7.26 (m, 2H); ^{13}C NMR (100.5 MHz) δ 29.11, 29.56, 55.52, 111.87, 112.86, 129.22, 130.99, 133.16, 156.53; LRMS *m*/*z* 427 (M^+), 348, 269, 91. Anal. Calcd for $C_{18}H_{20}Br_2O_2$: C, 50.49; H, 4.71. Found: C, 50.61; H, 4.43.

1,1′-(1,1′-(2,2′-Oxybisethane)diyl)bis[5-bromo-2-methoxybenzene] (9c). The reaction of **3c** (5.72 g, 20.0 mmol) and bromine (6.39 mL, 80.0 mmol) in $CHCl_3$ (22.3 mL) furnished 7.88 g (17.8 mmol, 89.2%) of the title compound as white crystals after recrystallization from ethanol: mp 114−116 °C; ^{1}H NMR δ 2.59 (t, 4H, J = 7.92 Hz), 3.45−3.54 (m, 4H), 3.77 (s, 6H), 6.74−6.79 (m, 2H), 7.37−7.42 (m, 4H); ^{13}C NMR (100.5 MHz) δ 34.28, 57.05, 66.81, 112.23, 114.17, 129.82, 133.62, 134.29, 159.73. LRMS *m*/*z* 443 (M^+), 364, 286, 257, 229, 213, 178, 91. Anal. Calcd for $C_{18}H_{20}Br_2O_3$: C, 48.68; H, 4.54. Found: C, 48.39; H, 4.61.

1,1′-(1,6-Hexanediyl)bis[5-bromo-2-methoxybenzene] (9d). The reaction of 1,1′-(1,6-hexanediyl)bis[2-methoxybenzene] (**3d**) (5.47 g, 18.3 mmol) and bromine (5.86 mL, 73.4 mmol) in $CHCl_3$ (20.5 mL) furnished 7.82 g (17.2 mmol, 93.9%) of the title compound as white crystals after recrystallization from ethanol: mp 86−88 °C; ^{1}H NMR δ 1.31−1.41 (m, 4H), 1.49−1.63 (m, 4H), 2.56 (t, 4H, J = 7.9 Hz), 3.82 (s, 6H), 6.69 (d, 2H, J = 8.0 Hz), 7.22−7.26 (m, 4H); ^{13}C NMR (100.5 MHz) δ 28.86, 30.32, 30.68, 55.49, 111.86, 112.74, 129.42, 132.37, 133.36, 158.35; LRMS *m*/*z* 456 (M^+), 377, 297, 271, 185, 91. Anal. Calcd for $C_{20}H_{24}Br_2O_2$: C, 52.65; H, 5.30. Found: C, 52.67; H, 5.41.

General Procedure for the Preparation of MOM-Protected bis-Anisole: 1,1′-(1,3-Propanediyl)bis[5-(3-methoxymethoxypropyl)-2-methoxybenzene] (10a). THF (3 mL) was added to magnesium turnings (0.783 g, 32.2 mmol), and the reaction mixture was heated to reflux. The bis-anisole **9a** (1.33 g, 3.22 mmol) was dissolved in THF (3.4 mL) and transferred into the refluxing reaction mixture via syringe at a rate of 0.12 mL/min. The resulting Grignard solution was stirred at reflux for 20 h and then cooled to room temperature. A second solution consisting of MOM-protected tosylate **15a** (5.29 g, 19.3 mmol) dissolved in THF (2.2 mL), 3.8 mL (12 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/ THF) copper catalyst solution, and HMPA (0.41 mL; 6% v/v based on the volume of the Grignard reaction) was heated to reflux. The cooled Grignard solution, decanted from excess magnesium, was then added to the refluxing reaction mixture with a cannulating needle. After 2 h, an additional 1.9 mL (6 mol %) of 0.1 M LiBr/CuBr·SMe_2/LiSPh/THF was added. The reaction mixture was stirred at reflux for an additional 20 h, cooled to room temperature, quenched with 1.5 M HCl (50 mL), and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with another portion of 1.5 M HCl (50 mL), followed by brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to yield a yellowish oil. The crude product was purified by silica gel column chromatography (90:10 hexane/ethyl acetate) to yield 1.42 g (2.41 mmol, 75%) of the title compound as a clear oil: bp 125−126 °C; ^{1}H NMR δ 1.83−1.92 (m, 6H), 2.62−2.70 (m, 8H), 3.28 (s, 6H), 3.64−3.72 (m, 4H), 3.82 (s, 6H), 4.69 (s, 4H), 6.73 (d, 2H, J = 7.5 Hz), 6.91−7.02 (m, 4H); ^{13}C NMR (100.5 MHz) δ 30.85, 32.82, 33.62, 54.86, 56.31, 68.95, 99.07, 111.63, 127.97, 128.65, 130.74, 133.98, 154.89; LRMS *m*/*z* 460 (M^+), 416, 370, 359, 256, 91. Anal. Calcd for $C_{27}H_{40}O_6$: C, 70.41; H, 8.75. Found: C, 70.34; H, 8.82.

1,1′-(1,4-Butanediyl)bis[5-(4-methoxymethoxybutyl)-2-methoxybenzene] (10b). The reaction of a Grignard solution, made from magnesium turnings (2.06 g, 84.7 mmol) and bis-anisole **9b** (3.61 g, 8.47 mmol) in THF (15 mL), and a refluxing solution consisting of MOM-protected tosylate **15b** (13.08 g, 45.4 mmol) dissolved in THF (5.2 mL), HMPA (0.96 mL), and a total of 13.4 mL of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution furnished, after purification by silica gel column chromatography (90:10 hexane/ethyl acetate), 2.49 g (5.08 mmol, 60%) of the title compound as a clear oil: bp 188−190 °C; ^{1}H NMR δ 1.56−1.89 (m, 12H), 2.57−2.71 (m, 8H), 3.26 (s, 6H), 3.62−3.74 (m, 4H), 3.79 (s, 6H), 4.71 (s, 4H), 6.78 (d, 2H, J = 7.5 Hz), 6.87−6.97 (m, 4H); ^{13}C NMR (100.5 MHz) δ 30.85, 32.82, 33.05, 33.62, 54.86, 56.31, 68.95, 99.07, 111.63, 127.97, 128.65, 130.74, 133.98, 154.89; LRMS *m*/*z* 502 (M^+), 458, 412, 401, 256, 91. Anal. Calcd for $C_{30}H_{46}O_6$: C, 71.68; H, 9.22. Found: C, 71.83; H, 9.49.

1,1′-(1,1′-(2,2′-Oxybisethane)diyl)bis[5-(3-methoxymethoxypropyl)-2-methoxybenzene] (10c). The reaction of a Grignard solution, made from magnesium turnings (1.84 g, 75.7 mmol) and bis-anisole **9c** (3.40 g, 7.57 mmol) in THF (17 mL), and a refluxing solution consisting of MOM-protected

tosylate **15a** (13.92 g, 50.8 mmol) dissolved in THF (5.9 mL), HMPA (1.1 mL), and a total of 13.6 mL of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution furnished, after purification by silica gel column chromatography (90:10 hexane/ethyl acetate), 2.94 g (5.84 mmol, 69%) of the title compound as a clear oil: bp 139−141 °C; ^{1}H NMR δ 1.83−1.92 (m, 4H), 2.65 (t, 8H, J = 7.92 Hz), 3.28 (s, 6H), 3.52−3.59 (m, 4H), 3.64−3.72 (m, 4H), 3.79 (s, 6H), 4.69 (s, 4H), 6.73 (d, 2H, J = 7.5 Hz), 6.91−7.02 (m, 4H); ^{13}C NMR (100.5 MHz) δ 32.39, 34.65, 55.9, 56.71, 67.56, 69.17, 97.86, 110.57, 121.62, 127.60, 131.46, 132.75, 158.52; LRMS *m/z* 490 (M^+), 445, 400, 386, 341, 286, 253, 91. Anal. Calcd for $C_{28}H_{42}O_7$: C, 68.55; H, 8.63. Found: C, 68.29; H, 8.99.

1,1′-(1,6-Hexanediyl)bis[5-(6-methoxymethoxyhexyl)-2-methoxybenzene] (10d). The reaction of a Grignard solution, made from magnesium turnings (1.79 g, 73.8 mmol) and bis-anisole **9d** (3.35 g, 7.38 mmol) in THF (15 mL), and a refluxing solution consisting of MOM-protected tosylate **15c** (14.0 g, 44.3 mmol) dissolved in THF (5.1 mL), HMPA (0.94 mL), and a total of 13.2 mL of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution furnished, after purification by silica gel column chromatography (90:10 hexane/ethyl acetate), 3.16 g (5.39 mmol, 73%) of the title compound as a clear oil: bp 149−151 °C; ^{1}H NMR δ 1.31−1.44 (m, 12H), 1.50−1.67 (m, 12H), 2.48−2.61 (m, 8H), 3.36 (s, 6H), 3.52 (t, 4H, J = 11.7 Hz), 3.79 (s, 6H), 4.61 (s, 4H), 6.75 (d, 2H, J = 9.0 Hz), 6.94 (d, 4H, J = 10.5 Hz); ^{13}C NMR (100.5 MHz) δ 26.10, 29.11, 29.56, 29.69, 30.0, 30.24, 31.71, 55.07, 55.39, 67.84, 96.40, 110.14, 126.20, 129.88, 131.12, 134.45, 155.53; LRMS *m/z* 586 (M^+), 541, 496, 441, 335, 297, 271, 251, 91. Anal. Calcd for $C_{36}H_{58}O_6$: C, 73.68; H, 9.96. Found: C, 73.71; H, 9.78.

General Method for the Removal of MOM-Protecting Group: 1,1′-(1,3-Propanediyl)bis[5-(3-hydroxypropyl)-2-methoxybenzene] (11a). MOM-protected bis-anisole **10a** (6.24 g, 13.56 mmol) was dissolved in methanol (67.8 mL), the solution was heated to reflux, and 12 M HCl (3.2 mL, 37.8 mmol) was added dropwise to the refluxing reaction mixture. The solution was allowed to stir at reflux for 20 min and then cooled to room temperature, and the solvent was removed under vacuum. Saturated $NaHCO_3$ solution (150 mL) was added to the remaining oil to quench the reaction (pH = 9). The resulting solution was extracted with CH_2Cl_2 (4 × 100 mL), and the combined organic layers were washed with 100 mL brine, dried over Na_2SO_4, and concentrated under vacuum. The crude solid was recrystallized from ethanol to yield 5.0 g (13.4 mmol, 99%) of the title compound as white crystals: mp 42−44 °C; ^{1}H NMR δ 1.34 (s, 2H), 1.81−1.93 (m, 6H), 2.56−2.72 (m, 8H), 3.60−3.70 (m, 4H), 3.80 (s, 6H), 6.77 (d, 2H, J = 10.5 Hz), 6.94−7.03 (m, 4H); ^{13}C NMR (100.5 MHz) δ 32.19, 33.17, 33.90, 55.03, 69.32, 111.84, 128.03, 128.89, 130.81, 133.78, 154.63; LRMS *m/z* 372 (M^+), 359, 256, 91. Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 73.94; H, 8.87.

1,1′-(1,4-Butanediyl)bis[5-(4-hydroxybutyl)-2-methoxybenzene] (11b). The reaction of MOM-protected bis-anisole **10b** (3.89 g, 7.74 mmol) in methanol (38.7 mL) and 12 M HCl (1.8 mL, 21.6 mmol) furnished 2.92 g (7.05 mmol, 91%) of the title compound as white crystals after recrystallization from ethanol: mp 52−54 °C; ^{1}H NMR δ 1.33 (s, 2H), 1.68−1.93 (m, 12H), 2.47−2.68 (m, 8H), 3.54−3.71 (m, 4H), 3.82 (s, 6H), 6.73 (d, 2H, J = 10.5 Hz), 6.86−6.95 (m, 4H); ^{13}C NMR (100.5 MHz) δ 31.65, 32.85, 33.16, 34.05, 55.38, 69.64, 112.28, 128.53, 128.53, 130.52, 133.81, 153.94; LRMS *m/z* 414 (M^+), 340, 256, 91. Anal. Calcd for $C_{26}H_{38}O_4$: C, 75.32; H, 9.24. Found: C, 75.08; H, 9.43.

1,1′-(1,1′-(2,2′-Oxybisethane)diyl)bis[5-(3-hydroxypropyl)-2-methoxybenzene] (11c). The reaction of MOM-protected bis-anisole **10c** (4.39 g, 8.95 mmol) in methanol (44.8 mL) and 18 M H_2SO_4 (0.7 mL, 13.8 mmol; H_2SO_4 was used in place of HCl to avoid the nucleophilic chloride counterion) furnished the crude product as an oil. Purification of the crude oil by silica gel column chromatography (50:50 hexane/ethyl acetate) yielded 3.10 g (7.70 mmol, 86%) of the title compound as white crystals: mp 131−133 °C; ^{1}H NMR δ 1.40 (s, 2H), 1.76−1.84 (m, 4H), 2.73 (t, 8H, J = 9.0 Hz), 3.48−3.56 (m, 4H), 3.67−3.76 (m, 4H), 3.81 (s, 6H), 6.69 (d, 2H, J = 7.5 Hz), 6.88−7.00 (m, 4H); ^{13}C NMR (100.5 MHz) δ 31.54, 34.39, 55.62, 67.81, 69.41, 111.07, 121.70, 127.34, 131.86, 132.73, 157.29; LRMS *m/z* 402 (M^+), 342, 286, 22, 209, 193, 91. Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.46; H, 8.63.

1,1′-(1,6-Hexanediyl)bis[5-(6-hydroxyhexyl)-2-methoxybenzene] (11d). The reaction of MOM-protected bis-anisole **10d** (5.10 g, 8.69 mmol) in methanol (43 mL) and 12 M HCl (2 mL, 24 mmol) furnished 4.25 g (8.52 mmol, 98%) of the title compound as white crystals after recrystallization from ethanol: mp 62−64 °C; ^{1}H NMR δ 1.34−1.45 (m, 14H), 1.52−1.69 (m, 12H), 2.48−2.60 (m, 8H), 3.61 (t, 4H, J = 9.0 Hz), 3.78 (s, 6H), 6.74 (d, 2H, J = 10.5 Hz), 6.90 (d, 4H, J = 10.5 Hz); ^{13}C NMR (100.5 MHz) δ 26.13, 29.12, 29.55, 29.72, 29.99, 30.26, 31.73, 55.06, 67.85, 110.16, 126.21, 129.89, 131.11, 134.47, 155.52; LRMS *m/z* 498 (M^+), 397, 297, 291, 207, 91. Anal. Calcd for $C_{32}H_{50}O_4$: C, 77.06; H, 10.10. Found: C, 76.69; H, 10.31.

General Procedure for the Preparation of bis-Tosylate-bis-anisole: 1,1′-(1,3-Propanediyl)bis[5-(3-(4-methylbenzenesulfonyloxy)propyl)-2-methoxybenzene] (12a). A solution of bis-anisole **11a** (1.85 g, 4.97 mmol) in CH_2Cl_2 (10 mL) and pyridine (3.22 mL, 39.8 mmol) was allowed to cool to 0 °C. *p*-Toluenesulfonyl chloride (2.82 g, 15.0 mmol) was added slowly over 5 min, and the reaction mixture was allowed to stir for 20 h and then quenched with 3 M HCl (100 mL). The resulting solution was extracted with CH_2Cl_2 (3 × 100 mL), and the organic layers were combined, dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by silica gel (plug) column chromatography (75:25 hexane/ethyl acetate) to yield 3.28 g (4.82 mmol, 97%) of the title compound as a clear oil: bp 143−144 °C; ^{1}H NMR δ 1.74−1.95 (m, 6H), 2.44 (s, 6H), 2.59−2.68 (m, 8H), 3.82 (s, 6H), 4.03 (t, 4H, J = 13.5 Hz), 6.72 (d, 2H, J = 7.5 Hz), 6.85 (d, 4H, J = 9.0 Hz), 7.34 (d, 4H, J = 9.0 Hz), 7.78 (d, 4H, J = 10.5 Hz); ^{13}C NMR (100.5 MHz) δ 27.54, 32.19, 33.17, 33.90, 55.03, 69.32, 110.19, 126.16, 127.75, 129.82, 129.92, 131.10, 133.21, 134.49, 144.72 155.54; LRMS *m/z* 680 (M^+), 525, 466, 368, 312, 256, 91. Anal. Calcd for $C_{37}H_{44}O_8S_2$: C, 65.27; H, 6.51. Found: C, 65.43; H, 6.29.

1,1′-(1,4-Butanediyl)bis[5-(4-(4-methylbenzenesulfonyloxy)butyl)-2-methoxybenzene] (12b). The reaction of bis-anisole **11b** (0.98 g, 2.37 mmol) with *p*-toluenesulfonyl chloride (1.34 g, 7.13 mmol) in CH_2Cl_2 (4.7 mL) and pyridine (1.5 mL, 19.0 mmol) furnished, after purification by silica gel column chromatography (75:25 hexane/ethyl acetate), 1.64 g (2.27 mmol, 96%) of the title compound as a clear oil: bp 156−157 °C; ^{1}H NMR δ 1.63−1.98 (m, 12H), 2.45 (s, 6H), 2.54−2.65 (m, 8H), 3.83 (s, 6H), 4.02 (t, 4H, J = 13.5 Hz), 6.73 (d, 2H, J = 7.5 Hz), 6.84 (d, 4H, J = 9.0 Hz), 7.36 (d, 4H, J = 9.0 Hz), 7.77 (d, 4H, J = 10.5 Hz); ^{13}C NMR (100.5 MHz) δ 26.94, 33.84, 34.32, 35.02, 56.48, 70.83, 111.32, 127.47, 129.23, 130.29, 131.65, 133.44, 135.83, 136.86, 146.30, 157.28; LRMS *m/z* 722 (M^+), 567, 412, 256, 91. Anal. Calcd for $C_{40}H_{50}O_8S_2$: C, 66.46; H, 6.97. Found: C, 66.54; H, 6.71.

1,1′-(1,1′-(2,2′-Oxybisethane)diyl)bis[5-(3-(4-methylbenzenesulfonyloxy)propyl)-2-methoxybenzene] (12c). The reaction of bis-anisole **11c** (1.62 g, 4.02 mmol) with *p*-toluenesulfonyl chloride (2.29 g, 12.1 mmol) in CH_2Cl_2 (8.1 mL) and pyridine (2.6 mL, 32.3 mmol) furnished, after purification by silica gel column chromatography (75:25 hexane/ethyl acetate), 2.40 g (3.38 mmol, 84%) of the title compound as a clear oil: bp 192−194 °C; ^{1}H NMR δ 1.71−1.79 (m, 4H), 2.46 (s, 6H), 2.69 (t, 8H, J = 9.0 Hz), 3.45−3.58 (m, 4H), 3.64−3.73 (m, 4H), 3.80 (s, 6H), 6.83 (d, 2H, J = 7.5 Hz), 6.91−7.04 (m, 4H), 7.31 (d, 4H, J = 9.0 Hz), 7.69 (d, 4H, J = 10.5 Hz); ^{13}C NMR (100.5 MHz) δ 26.82, 31.27, 34.35, 56.03, 66.38, 69.72, 111.11, 121.83, 126.83, 129.29, 130.48, 132.83, 133.37, 135.02, 143.98, 158.87; LRMS *m/z* 710 (M^+), 555, 496, 401, 363, 340, 286, 247, 91. Anal. Calcd for $C_{38}H_{46}O_9S_2$: C, 64.20; H, 6.52. Found: C, 64.05; H, 6.74.

1,1′-(1,6-Hexanediyl)bis[5-(6-(4-methylbenzenesulfonyloxy)hexyl)-2-methoxybenzene] (12d). The reaction of bis-anisole **11d** (0.37 g, 0.74 mmol) with *p*-toluenesulfonyl chloride (0.42 g, 2.23 mmol) in CH_2Cl_2 (1.5 mL) and pyridine (0.48 mL, 5.93 mmol) furnished, after purification by silica gel column chromatography (75:25 hexane/ethyl acetate), 0.55 g (0.69

mmol, 93%) of the title compound as a clear oil: bp 166−168 °C; ^{1}H NMR δ 1.20−1.41 (m, 12H), 1.47−1.64 (m, 12H), 2.41 (s, 6H), 2.44−2.62 (m, 8H), 3.77 (s, 6H), 3.99 (t, 4H, J = 10.5), 6.76 (d, 2H, J = 9.0 Hz), 6.90 (d, 4H, J = 10.5 Hz), 7.33 (d, 4H, J = 9.0 Hz), 7.79 (d, 4H, J = 9.0 Hz); ^{13}C NMR (100.5 MHz) δ 25.86, 26.16, 29.14, 29.53, 29.73, 30.01, 30.25, 31.76, 55.11, 71.28, 110.19, 126.16, 127.75, 129.82, 129.92, 131.10, 133.21, 134.49, 144.72, 155.54; LRMS m/z 807 (M^+), 652, 551, 498, 447, 359, 297, 91. Anal. Calcd for $C_{46}H_{62}O_8S_2$: C, 68.45; H, 7.74. Found: C, 68.52; H, 7.70.

General Procedure for the Preparation of *exo*-Tetramethoxy[*n.m.n.m*]metacyclophane: *exo*-6,16,22,32-Tetramethoxy[3.3.3.3]metacyclophane (2a). (a) The reaction was performed under a nitrogen atmosphere in a Vacuum Atmosphere glovebox. THF (4.6 mL) was added to magnesium turnings (1.19 g, 49.0 mmol), and the reaction mixture was heated to 60 °C. A solution of 1,1′-(1,3-propanediyl)bis[5-bromo-2-methoxybenzene] (**9a**) (2.03 g, 4.90 mmol) dissolved in THF (5.2 mL) was transferred into the reaction mixture via a syringe at a rate of 0.17 mL/min, and the resulting Grignard solution was stirred at 60 °C for 20 h and then cooled to room temperature. A solution consisting of 1,1′-(1,3-propanediyl)-bis[5-(3-(4-methylbenzenesulfonyloxy)propyl)-2-methoxybenzene] (**12a**) (3.33 g, 4.90 mmol) dissolved in THF (32.7 mL), HMPA (0.62 mL, 6% v/v based on the volume of the Grignard solution), and 5.9 mL (12 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution was heated to 60 °C. The Grignard solution, decanted from excess magnesium turnings, was added into the reaction mixture via a syringe at a rate of 0.33 mL/min. After 2 h, an additional 3.0 mL (6 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution was added, and the reaction mixture was allowed to stir at 60 °C for an additional 72 h. The mixture was then cooled to room temperature, removed from the glovebox, quenched with 1.5 M HCl (50 mL), and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with a second portion of 1.5 HCl (50 mL), followed by brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to yield an yellowish oil. The crude product was purified by radial chromatography (silica gel, 50:50 hexanes/CH_2Cl_2) to yield 2.03 g (3.43 mmol, 70%) of the title compound as a white solid.

(b) The following procedure is not a general preparation of tetramethoxy[*n.n.n.n*]metacyclophanes, but is limited to n = 3 due to constraints on the macrocyclic yield when n > 3. THF (3.7 mL) was added to magnesium turnings (0.96 g, 39.3 mmol) and the reaction mixture heated to reflux. A solution of 1,1′-(1,3-propanediyl)bis[5-bromo-2-methoxybenzene] (**9a**) (1.62 g, 3.93 mmol) dissolved in of THF (4.20 mL) was transferred into the reaction mixture via a syringe at a rate of 0.14 mL/min, and the resulting Grignard solution was stirred at reflux for 20 h and then cooled to room temperature. A second solution consisting of 1,3-propanediol, bis(4-methylbenzenesulfonate) (**13a**) (1.51 g, 3.93 mmol) dissolved in THF (26.2 mL), HMPA (0.50 mL, 6% v/v based on the volume of the Grignard solution), and 4.7 mL (12 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution was heated to reflux. The Grignard solution, decanted from excess magnesium turnings, was added to the refluxing solution with a cannulating needle. After 2 h, an additional 2.4 mL (6 mol %) of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution was added, and the reaction mixture was allowed to stir at reflux for an additional 72 h. The reaction was then cooled to room temperature, quenched with 1.5 M HCl (50 mL), and extracted with CH_2Cl_2 (4 × 30 mL). The combined organic layers were washed with a second portion of 1.5 HCl (50 mL), followed by brine (50 mL), dried over Na_2SO_4, and concentrated under vacuum to yield a yellowish oil. The crude product was purified by radial chromatography (silica gel, 50:50 hexanes/CH_2Cl_2) to yield 0.93 g (1.57 mmol, 40%) of the title compound as a white solid: mp 120−122 °C; ^{1}H NMR δ 1.77−1.88 (m, 8H), 2.53−2.58 (m, 8H), 2.61−2.67 (m, 8H), 3.78 (s, 12 H), 6.72−6.75 (m, 4H), 6.92−6.95 (m, 8H); ^{13}C NMR (100.5 MHz) δ 30.07, 30.34, 34.41, 35.30, 55.44, 110.14, 126.45, 129.40, 130.99, 134.36, 155.57; LRMS m/z 592 (M^+), 336, 256, 91. Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16. Found: C, 80.82; H, 8.23.

***exo*-7,18,25,36-Tetramethoxy[4.4.4.4]metacyclophane (4).** The reaction of a Grignard solution, made from magnesium turnings (0.78 g, 32.0 mmol) and 1,1′-(1,4-butanediyl)bis[5-bromo-2-methoxybenzene] **9b** (1.37 g, 3.20 mmol) in THF (6.4 mL), and a heated (60 °C) solution consisting of 1,1′-(1,4-butanediyl)bis[5-(4-(4- methylbenzenesulfonyloxy)butyl)-2-methoxybenzene] **12b** (2.31 g, 3.20 mmol) dissolved in THF (21.4 mL), HMPA (0.41 mL), and a total of 5.7 mL of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution furnished, after purification by radial chromatography (silica gel, 50:50 hexanes/CH_2Cl_2), 0.89 g (1.38 mmol, 43%) of the title compound as a white solid: mp 134−136 °C; ^{1}H NMR δ 1.65−1.91 (m, 16H), 2.51−2.59 (m, 8H), 2.63−2.70 (m, 8H), 3.79 (s, 12 H), 6.71−6.77 (m, 4H), 6.88−6.97 (m, 8H); ^{13}C NMR (100.5 MHz) δ 31.16, 32.03, 33.20, 34.87, 55.21, 110.37, 126.64, 128.92, 131.25, 134.83, 155.48; LRMS m/z 648 (M^+), 394, 256, 91. Anal. Calcd for $C_{44}H_{56}O_4$: C, 81.44; H, 8.70. Found: C, 81.38; H, 8.80.

***exo*-8,18,26,36-Tetramethoxy[5.3.5.3]-4,22-dioxametacyclophane (5).** The reaction of a Grignard solution, made from magnesium turnings (0.76 g, 31.3 mmol) and 1,1′-(1,1′-(2,2′-oxybisethane)diyl)bis[5-bromo-2-methoxybenzene] **9c** (1.39 g, 3.13 mmol) in THF (6.3 mL), and a heated (60 °C) solution consisting of 1,1′-(1,1′-(2,2′-oxybisethane)diyl)bis[5-(3-(4-methylbenzenesulfonyloxy)propyl)-2-methoxybenzene] **12c** (2.23 g, 3.13 mmol) dissolved in THF (20.8 mL), HMPA (0.4 mL), and a total of 5.7 mL of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution furnished, after purification by radial chromatography (silica gel, 50:50 hexanes/CH_2Cl_2, 0.63 g (0.97 mmol, 31%) of the title compound as a white solid: mp 167−169 °C; ^{1}H NMR δ 1.62−1.77 (m, 4H), 2.42−2.71 (m, 16H), 3.48−3.56 (m, 8H), 3.77 (s, 12H), 6.75−6.91 (m, 4H), 7.21−7.35 (m, 8H); ^{13}C NMR (100.5 MHz) δ 32.81, 35.94, 55.48, 67.47, 111.37, 122.93, 128.25, 131.38, 133.84, 159.35; LRMS m/z 652 (M^+), 368, 286, 91. Anal. Calcd for $C_{42}H_{52}O_6$: C, 77.27; H, 8.03. Found: C, 77.29; H, 7.95.

***exo*-9,22,31,44-Tetramethoxy[6.6.6.6]metacyclophane (6).** The reaction of a Grignard solution, made from magnesium turnings (0.96 g, 39.3 mmol) and 1,1′-(1,6-hexanediyl)bis[5-bromo-2-methoxybenzene] **9d** (1.62 g, 3.93 mmol) in THF (7.9 mL), and a heated (60 °C) solution consisting of 1,1′-(1,6-hexanediyl)bis[5-(6-(4-methylbenzenesulfonyloxy)hexyl)-2-methoxybenzene] (**12d**) (1.51 g, 3.93 mmol) dissolved in THF (26.2 mL), HMPA (0.5 mL), and a total of 7.1 mL of 0.1 M (LiBr/CuBr·SMe_2/LiSPh/THF) copper catalyst solution furnished, after purification by radial chromatography (silica gel, 50:50 hexanes/CH_2Cl_2), 0.95 g (1.25 mmol, 40%) of the title compound as a white solid: mp 146−147 °C; ^{1}H NMR δ 1.34−1.42 (m, 16H), 1.49−1.67 (m, 16H), 2.46−2.62 (m, 16H), 3.75 (s, 12H), 6.81−6.90 (m, 4H), 7.10−7.19 (m, 8H); ^{13}C NMR (100.5 MHz) δ 29.16, 29.55, 29.80, 29.97, 31.69, 35.08, 55.29, 110.05, 126.16, 130.98, 131.03, 134.46, 155.42; LRMS m/z 760 (M^+), 464, 297, 91. Anal. Calcd for $C_{52}H_{72}O_4$: C, 82.06; H, 9.53. Found: C, 82.11; H, 9.49.

***exo*-6,16,22,32-Tetrahydroxy[3.3.3.3]metacyclophane (2b).** To a solution of tetramethoxy[3.3.3.3]metacyclophane **2a** (0.070 g, 0.118 mmol) in $ClCH_2CH_2Cl$ (3.0 mL), cooled to 0 °C in an ice-bath, was added a solution of BBr_3·SMe_2 (0.592 g, 2.36 mmol) in $ClCH_2CH_2Cl$ (5 mL) at a rate of 0.17 mL/min via a syringe. After the addition was complete, the reaction mixture was allowed to gradually warm to room temperature and stirred for 16 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with Et_2O (2 × 50 mL), and the combined ether layers were extracted with 10% $NaHCO_3$ (100 mL) and then were further extracted with 1 M NaOH (3 × 25 mL). The combined aqueous layers were acidified with 3 M HCl and extracted with Et_2O (3 × 50 mL). The combined organic layers were then dried over Na_2SO_4 and concentrated under vacuum. The crude solid was purified by radial chromatography (silica gel, 60:40 hexanes/ethyl acetate) to yield 0.0585 g (0.108 mmol, 92%) of the title compound as a white solid: mp 170−172 °C; ^{1}H NMR (acetone-d_6) δ 1.73−1.92 (m, 8H), 2.53 (t, 8H, J = 8.0 Hz), 2.67 (t, 8H, J = 7.9 Hz), 6.69−6.71 (m, 4H), 6.81−6.85 (m, 8H), 6.90−6.92 (s, 4H); ^{13}C NMR

(DMSO-d_6, 75.43 MHz) δ 29.56, 30.20, 34.27, 34.47, 114.60, 126.27, 128.08, 129.09, 132.19, 152.82; LRMS *m/z* 536 (M^+), 280, 256, 91. Anal. Calcd for $C_{36}H_{40}O_4$: C, 80.56; H, 7.51. Found: C, 80.19; H, 7.72.

***exo*-6,16,22,32-Tetraacetoxy[3.3.3.3]metacyclophane (18).** A solution of *exo*-tetrahydroxy[3.3.3.3]metacyclophane **2b** (0.311 g, 0.579 mmol) and triethylamine (0.16 mL, 1.157 mmol) in THF (2.90 mL, 0.20 M) was heated to reflux, and acetyl chloride (0.11 mL, 1.45 mmol) was added dropwise to the refluxing solution. The reaction was allowed to stir for 24 h before being cooled to room temperature and quenched with 10 mL of $NaHCO_3$. The reaction mixture was then extracted with CH_2Cl_2 (4 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum to yield a clear oil. The crude product was purified by radial chromatography (silica gel, 45:55 hexanes/CH_2Cl_2) to yield 0.345 g (0.49 mmol, 85%) of the title compound as a white solid: mp 137−139 °C; ^{1}H NMR δ 1.64−1.91 (m, 8H), 2.09 (s, 12H), 2.56 (t, 8H, J = 8.0 Hz), 2.70 (t, 8H, J = 7.9 Hz), 6.64−6.68 (m, 4H), 6.82−6.87 (m, 4H), 6.92−7.05 (m, 4H); ^{13}C NMR (100.5 MHz) δ 29.77, 30.54, 35.04, 35.18, 58.57, 115.12, 125.68, 127.84, 129.35, 133.31, 153.87, 172.93; LRMS *m/z* 704 (M^+), 644, 585, 328, 256, 91. Anal. Calcd for $C_{44}H_{48}O_8$: C, 74.98; H, 6.86. Found: C, 74.71; H, 6.99.

Mono-(methylene-linked)-*exo*-6,16,22,32-tetrahydroxy-[3.3.3.3]metacyclophane (19). A reaction mixture consisting of *exo*-tetrahydroxy[3.3.3.3]metacyclophane **2b** (0.167 g, 0.310 mmol), K_2CO_3 (0.0902 g, 0.653 mmol), and bromochloromethane (20 μL, 0.310 mmol) in DMSO (14.4 mL) was heated to 60 °C for 20 h (the course of the reaction was followed by TLC to confirm the attachment of the chloromethane moiety). At this point, the reaction mixture was then heated to 120 °C and stirred for 48 h to complete the ring formation. The reaction was then allowed to cool to room temperature, quenched with a saturated solution of $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers dried over Na_2SO_4 and concentrated under vacuum to yield a clear oil. The crude product was purified by radial chromatography (silica gel, 45:55 hexanes/CH_2Cl_2) to yield 0.107 g (0.0196 mmol, 63%) of compound **19** as a white solid: mp 155−157 °C; ^{1}H NMR (acetone-d_6) δ 1.74−1.94 (m, 8H), 2.50 (t, 8H, J = 10.5 Hz), 2.63 (t, 4H, J = 10.5 Hz), 2.84 (t, 4H, J = 7.5 Hz), 5.98 (s, 2H), 6.60 (d, 2H, J = 7.5 Hz), 6.72 (d, 2H, J = 7.5 Hz), 6.82−6.96 (m, 10 H); ^{13}C NMR (100.5 MHz) δ 28.08, 31.41, 36.10, 36.96, 96.54, 115.63, 116.84, 123.49, 124.67, 126.37, 127.84, 128.52, 131.54, 132.98, 149.76, 151.31; LRMS *m/z* 548 (M^+), 534, 292, 256, 91. Anal. Calcd for $C_{37}H_{40}O_4$: C, 80.99; H, 7.35. Found: C, 80.61; H, 7.54.

Bis-(methylene-linked)-*exo*-6,16,22,32-tetrahydroxy-[3.3.3.3]metacyclophane (20). A reaction mixture consisting of *exo*-metacyclophane **19** (0.100 g, 0.18 mmol), K_2CO_3 (0.0530 g, 0.382 mmol), and bromochloromethane (12 μL, 0.18 mmol) in DMSO (8.47 mL) was heated to 60 °C for 20 h (the course of the reaction was followed by TLC to confirm the attachment of the chloromethane moiety). The reaction was then heated to 160 °C and allowed to stir for 168 h to complete the ring formation. The reaction was then allowed to cool to room temperature, quenched with a saturated solution of $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to yield a clear oil. The crude product was purified by radial chromatography (silica gel, 55:45 hexanes/CH_2Cl_2) to yield 0.055 g (0.098 mmol, 54%) of compound **20** as a white solid: mp 137−139 °C; ^{1}H NMR δ 1.70−1.98 (m, 8H), 2.54 (t, 8H, J = 8.0 Hz), 2.72 (t, 8H, J = 7.9 Hz), 5.91 (s, 4H), 6.69−6.71 (m, 4H), 6.81−6.85 (m, 8H); ^{13}C NMR (100.5 MHz) δ 28.64, 31.08, 35.25, 36.58, 96.74, 116.96, 124.30, 126.14, 128.64, 132.89, 151.31; LRMS *m/z* 560 (M^+), 549, 535, 304, 256, 91. Anal. Calcd for $C_{38}H_{40}O_4$: C, 81.40; H, 7.19. Found: C, 81.61; H, 7.08.

The following experimentals are examples of our previous methods used to prepare *exo*-metacyclophane **7** and **8** before the development of the soluble copper catalyst and the routine use of tosylate-MOM electrophiles and are included for purposes of comparison.

1,1′-(1,3-Propanediyl)bis[5-(3-bromobutyl)-2-methoxybenzene] (17a). Bis-anisole **9a** (1.12 g, 2.70 mmol) dissolved in THF (3 mL) was added at a rate of 0.33 mL/min to a solution of magnesium turnings (0.27 g, 11.13 mmol) in THF (8 mL). The resulting bis-Grignard was stirred at reflux for 16 h and then cooled to room temperature. The Grignard solution was cannulated into another solution containing 1,4-dibromopropane (5.84 g, 27.0 mmol) and 0.83 mL (3 mol %) of 0.1 M Li_2CuBr_4/THF copper catalyst solution maintained at 0 °C. The mixture was allowed to gradually warm to room temperature, and after 3 h another 0.83 mL of 0.1 M Li_2CuBr_4/THF was added. After 6 h a third portion of 0.83 mL of 0.1 M Li_2CuBr_4/THF was added. After 48 h the reaction was quenched with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with 10% HCl (100 mL), H_2O (100 mL), brine (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by radial chromatography (silica gel, 98:2 hexanes/ethyl acetate) to yield 0.636 g (1.22 mmol, 45%) of the title compound as a clear oil: bp > 300 °C; ^{1}H NMR δ 1.69−1.80 (m, 4H), 1.81−1.95 (m, 6H), 2.56 (t, 4H, J = 7.3 Hz), 2.65 (t, 4H, J = 7.7 Hz), 3.40 (t, 4H, J = 6.6 Hz), 3.79 (s, 6H), 6.73−6.77 (m, 2H), 6.94−6.95 (m, 4H); ^{13}C NMR (75.43 MHz) δ 29.86, 30.15, 32.33, 33.69, 34.19, 55.45, 110.29, 126.35, 129.81, 131.04, 133.49, 155.85. Anal. Calcd for $C_{25}H_{34}Br_2O_2$: C, 57.05; H, 6.51. Found: C, 57.08; H, 6.53.

1,1′-(1,3-Propanediyl)bis[5-(5-bromopentyl)-2-methoxybenzene] (17b). The procedure is the same as above. Thus, a Grignard solution made from bis-anisole **9a** (1.01 g, 2.43 mmol) and magnesium turnings (0.236 g, 9.73 mmol) in THF (10 mL) was added to a solution containing 1,5-dibromopentane (5.60 g, 24.3 mmol) and a total of 2.25 mL 0.1 M Li_2CuBr_4/THF copper catalyst solution to yield, after purification by radial chromatography (silica gel, 98:2 hexanes/ethyl acetate), 0.80 g (1.46 mmol, 60%) of the title compound as a clear oil: bp > 300 °C; ^{1}H NMR δ 1.40−1.52 (m, 4H), 1.55−1.68 (m, 4H), 1.82−1.97 (m, 6H), 2.53 (t, 4H, J = 7.4 Hz), 2.65 (t, 4H, J = 7.8 Hz), 3.39 (t, 4H, J = 6.9 Hz), 3.79 (s, 6H), 6.75−6.77 (m, 2H), 6.90−6.95 (m, 4H); ^{13}C NMR (75.43 MHz) δ 27.99, 29.97, 30.32, 31.06, 32.89, 33.94, 35.06, 55.57, 110.33, 126.43, 129.93, 131.04, 134.12, 155.84. Anal. Calcd for $C_{27}H_{38}Br_2O_2$: C, 58.49; H, 6.91. Found: C, 58.38; H, 6.93.

***exo*-6,17,23,33-Tetramethoxy[3.4.3.4]metacyclophane (7).** Bis-anisole **9a** (0.897 g, 2.16 mmol) dissolved in THF (4 mL) was added at a rate of 0.33 mL/min to a solution of magnesium turnings (0.210 g, 8.66 mmol) in THF (8 mL). The resulting bis-Grignard was stirred at reflux for 16 h and then cooled to room temperature. A second solution consisting of bis-anisole **17a** (0.570 g, 1.08 mmol) dissolved in THF (10 mL) and the bis-Grignard solution were both added simultaneously to a third refluxing solution containing CuBr·SMe_2 (0.25 g, 1.12 mmol), HMPA (2.0 mL), and THF (10.0 mL). After 40 h of stirring at reflux, the reaction was cooled to room temperature and quenched with 10% NH_4Cl (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with 3 M HCl (3 × 100 mL), water (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was purified by radial chromatography (silica gel, 50:50 hexanes/CH_2Cl_2) to yield 0.073 g (0.24 mmol, 11%) of the title compound as a white solid: mp 184−185 °C; ^{1}H NMR δ 1.60−1.67 (m, 8H), 1.85−1.95 (m, 4H), 2.53−2.61 (m, 8H), 2.61 (t, 8H, J = 7.8 Hz), 3.78 (s, 12H), 6.72−6.75 (m, 4H), 6.93−6.98 (m, 8H); ^{13}C NMR (75.43 MHz) δ 29.03, 29.50, 31.39, 35.13, 55.43, 110.15, 126.26, 129.86, 130.68, 134.31, 155.67;; LRMS *m/z* 621 (M^+), 592, 508, 429, 349, 323, 310. Anal. Calcd for $C_{42}H_{52}O_4$: C, 81.25; H, 8.44, Found: C, 80.32; H, 8.71.

***exo*-6,18,24,36-Tetramethoxy[3.5.3.5]metacyclophane (8).** The procedure is the same as that above. Thus, a Grignard solution made from bis-anisole **9a** (0.53 g, 1.28 mmol) and magnesium turnings (0.125 g, 5.14 mmol) in THF (6.5 mL) was added to a solution consisting of bis-anisole **17b** (0.32 g, 0.58 mmol), HMPA (1.5 mL), CuBr·SMe_2 (0.13 g, 0.64 mmol), and THF (17.5 mL) to yield, after purification by radial

chromatography (silica gel, 50:50 hexanes/CH_2Cl_2), 0.088 g (0.29 mmol, 23%) of the title compound as a white solid: mp 131−134 °C; ^{1}H NMR δ 1.30−1.45 (m, 4H), 1.53−1.66 (m, 8H), 1.79−1.93 (m, 4H), 2.50 (t, 8H, J = 7.8 Hz), 2.60−2.68 (m, 8H), 3.78 (s, 12H), 6.72 (d, 4H, J = 6.0 Hz), 6.93 (m, 8H); ^{13}C NMR (75.43 MHz) δ 29.27, 29.87, 29.95, 32.02, 35.24, 55.45, 110.16, 126.32, 129.58, 130.88, 134.68, 155.60. Anal. Calcd for $C_{44}H_{56}O_4$: C, 81.44; H, 8.70. Found: C, 81.33; H, 8.53.

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Supporting Information Available: Copies of ^{1}H NMR, ^{13}C NMR, and LRMS spectra of **2a**, **4**−**8**, and **18**−**20** and, an X-ray crystallographic report for **2a** and **6** and, experimentals and characterizations for compounds **13b**−**13d**, **14a**−**14c**, and **15a**−**15c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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