Synthesis of Bridged, Multifunctional Calixarenes via Ring Closing Metathesis

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Ring-closing metathesis catalyzed by $RuCl_2(CHPh)(PCy_3)_2$ has been used to synthesize calix[4]arenes in cone and 1,3-alternate conformations with upper and lower rim alkenyl bridges. Ester, methoxy, and hydroxy groups have been used to probe the effect of substituents on the mode of metathesis. With some substrates, intermolecular metathesis competes with the intramolecular process leading to oligocalix[4]arenes. X-ray diffraction has been used to reveal the molecular structures of two single-bridged calix[4]arenes and of a double-bridged calix[4]arene.

Introduction

Of the various functions associated with calixarenes,[1] their ability to act as platforms or core components for the construction of large, conformationally defined molecular receptors for neutral and ionic guests is considered to be the most significant.[2] Intramolecular cyclization leading to bridged-ring structures has been a key feature of the synthesis of many of these synthetic receptors.[3] For example, Lhotak and Shinkai[4] have applied the McMurry reaction to bridge formation in suitably constituted calix dialkenyl derivatives. It occurred to us that catalytic ring-closing metathesis (RCM) might have useful applications in this area.[5] Over the past few years, there have been major advances in applications of RCM, and new durable catalysts have emerged to expand the scope of the reaction to include the synthesis of common-, medium-, and large-ring carbocycles and heterocycles, many with multiple functionality.[6] One such catalyst is the alkylideneruthenium complex **1**.[7]

In seeking to apply RCM to the synthesis of bridged-ring calix[4]arenes, substrates with suitably positioned alkenyl groups were required. Calix[4]arenes have two well-defined rims, an upper rim defined by the *para* substituents of the phenolic rings and a lower rim defined by the phenolic hydroxy groups. Preliminary studies were conducted with lower rim dialkenylcalix[4]arene derivatives readily prepared from calix[4]arene **2** and its *p-tert*-butyl counterpart **3** via regioselective 1,3-(distal)-alkylation using the appropriate alkenyl bromide in acetone containing potassium carbonate to form the corresponding diphenol diethers. Further alkylation of these compounds with methyl iodide or methyl bromoacetate using sodium hydride as the base in THF afforded the fully substituted derivatives **4b** and **8a**−**c**, respectively. Interestingly, the *order* in which the two different sets of substituents were introduced had an effect on the conformations of the final product, which enables us to study the metathesis of derivatives in more than one conformation. This effect, which was discovered when the two alkylation steps were reversed, is examined in detail elsewhere.[8]

Results and Discussion

RCM reactions were conducted with 4−8 mol % of the ruthenium complex **1** in dry benzene under nitrogen at room temperature. Diphenol diether **4a** furnished a single product in 57% yield whose ^{1}H NMR and mass spectral features were fully consistent with the bridged structure **5a**. In the ^{1}H spectrum of **5a** the signals for the terminal vinyl groups of **4a** were replaced by those of a single disubstituted alkene, and the FAB mass spectrum ($M^+ = 756.7$) confirmed the loss of two methylene groups. The remaining NMR features of **5a** confirmed that the molecule retained the cone conformation of its precursor **4a**. The dimethyl ether **4b** of bisphenol **4a** was conformationally mobile. It also underwent intermolecular metathesis on the lower rim to furnish the bridged derivative **5b** in 62% yield. Again, the spectroscopic data were fully supportive of the bridged structure that, like its precursor, was conforma-

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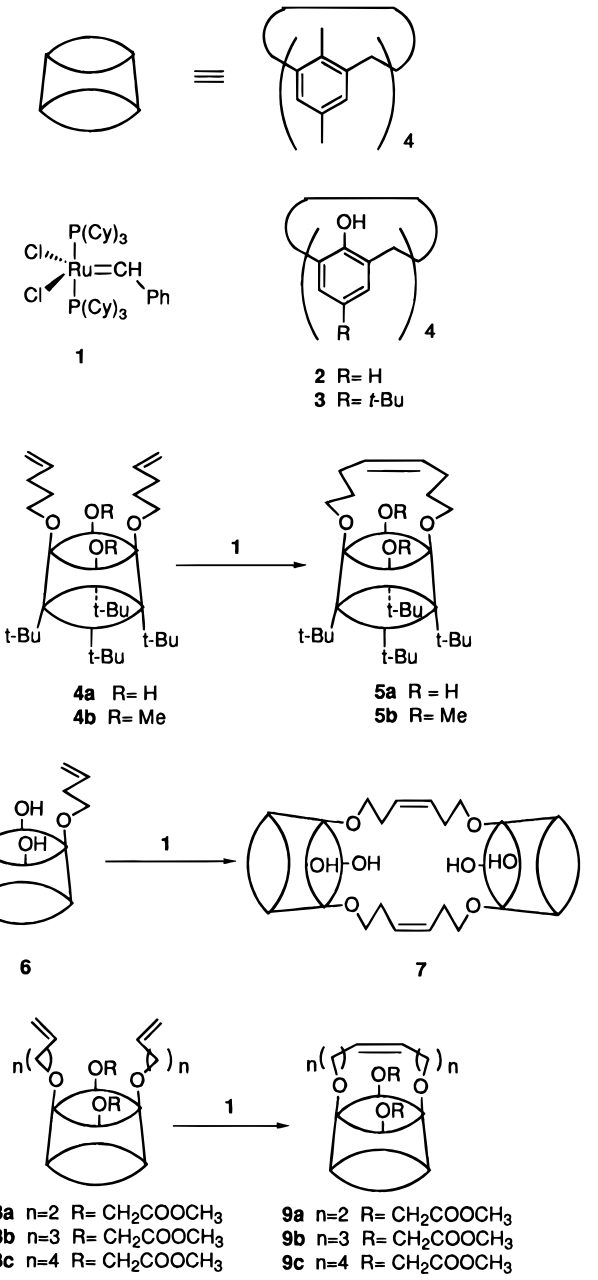
Scheme 1



tionally mobile, indicating that the presence of the bridge did not inhibit intraannular movement of the methoxy groups. Although both **5a** and **5b** are represented in Scheme 1 as having the *Z* geometry about the double bond, the NMR spectra indicated the presence of both *Z* and *E* isomers.

Alkenyl ether **6** differs from **4a** in that it does not have *tert*-butyl substituents on the upper rim and it has one fewer methylene spacer between calixarene and alkene. A distal bridge on the lower rim will thus be correspondingly shorter and may suffer greater steric strain, and the question arose as to whether intermolecular metathesis might now compete with intramolecular bridging. In the event, precursor **6** yielded a single product (53%) whose mass spectrum confirmed that it was the dimeric structure **7** resulting from intermolecular union of two calixarenes followed by metathetic macrocyclization. The preference for intermolecular reaction in the first union may reflect the higher steric strain associated with a shorter intramolecular bridge on the lower rim. The ^{1}H NMR spectrum of **7** was more complex than might have been anticipated (four AB systems for $ArCH_2Ar$ groups as compared with two for its precursor **6**), suggesting the presence of both *E* and *Z* geometrical isomers about the two alkenyl groups. Alternatively, **7** may be a single isomer of *E,Z* geometry. The above results demonstrate that intramolecular and intermolecular metathesis is possible on the lower rim of calix[4]arenes and that the catalyst can tolerate the presence of free phenolic groups.

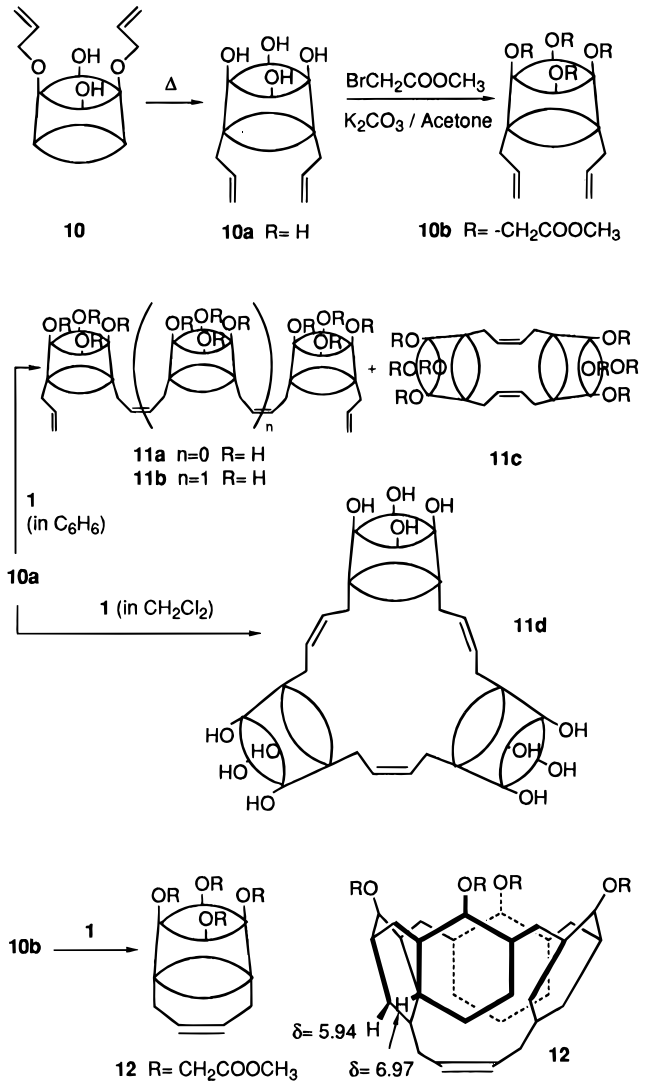
Precursors **8a**−**c** have two distal alkene and ester units, all in the cone conformation, and RCM proceeded intramolecularly to afford bridged products **9a** (79%), **9b** (35%), and **9c** (76%), respectively, each as a mixture of *E,Z* isomers. Precursor **8a** was chosen to explore the influence of substrate concentration on reaction pathway. At a concentration of 0.03 M the reaction was exclusively intramolecular, affording **9a** in 79% yield. With a much more concentrated solution (0.75 M), the product of intermolecular reaction could now be detected (5%), though the intramolecular reaction still dominated (42%) with a 45% recovery of unreacted starting material. Similar concentration effects in RCM have been reported by Grubbs and co-workers.[9]

We next turned our attention to the upper rim precursors starting with the simple distal *p*-allyl derivative of calix[4]arene **10a** (Scheme 2). This compound was readily prepared by Claisen rearrangement of its lower rim counterpart **10**, which in turn was obtained by allylation of **2**. Precursor **10a** on exposure to catalyst **1** in benzene showed no evidence of having undergone direct intramolecular reaction. Rather, three intermolecular reaction products were isolated, a dimer **11a** (25%), a trimer **11b** (20%), and a cyclodimer **11c** (5%), the last representing a subsequent cyclization of dimer **11a**. A significant solvent effect was observed in the metathesis of **10a**. When the reaction was repeated in dichloromethane the only product formed was the trimer **11d** arising from macrocyclization of the linear trimer **11b** formed in benzene. These structures are fully supported by ^{1}H NMR and FAB mass spectral data. The multiplicity of the ^{1}H NMR signals for the disubstituted alkene groups in **11a**−**d** suggested the presence of both *E* and *Z* isomers.

A contrasting picture emerged when we extended the study of upper rim metathesis to include calixarenes with two or four alkyl acetate residues on the phenolic groups on the lower rim. Calixarene esters of this type are of particular interest because of their extensive ionophoric properties.[2b] Diallyl derivative **10a** was readily transformed into tetraethyl ester **10b** on treatment with methyl bromoacetate and potassium carbonate in acetone. Whereas the free phenolic derivative **10a** underwent intermolecular metathesis to yield **11a**−**c**, the tetraester analogue **10b**, under similar conditions with catalyst **1**, yielded the product **12** of intramolecular bridging exclusively in 84% yield. The four-carbon bridge of **12** is a but-2-ene unit spanning two distal para positions on the upper rim, and as a result the molecule is constrained in an extreme rigidified form of a C_{2v} pinched cone conformation. This severe constraint is reflected in the ^{1}H NMR spectrum, which displays a

(9) Zuercher, W. J.; Hashimoo, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 634.

Scheme 2



signal at δ 5.94 for the four hydrogen atoms of the two distal aromatic rings directly attached to the bridge. The corresponding hydrogen atoms in the two unbridged aromatic rings appear at δ 6.97. The substantial shielding of the former is a direct consequence of the presence of an extreme pinched cone conformation. A similar ring current shielding effect was reported by Böhmer and coworkers,[10] who prepared a series of oligomethylene bridged calixarenes with bridge lengths of 5−16 carbon atoms. Although the ^{1}H NMR spectrum indicated that **12** was >90% one geometrical isomer, a distinction between *Z* and *E* was not possible.

X-ray diffraction analysis of a recrystallized sample of **12** was used to define the molecular conformation in the solid state (Figure 1). The data obtained for **12** were very weak (only 32% had $I > 2\sigma(I)$ in the range $4 < 2\sigma < 40°$), due to the small size of the crystals; despite this, the main features of the structure are clear. The calixarene takes up the pinched cone conformation; rings C(1a)−C(6a), C(1b)−C(6b), C(1c)−C(6c), and C(1d)−C(6d) are inclined to the mean plane of the four methylene carbon atoms by 38(1), 82(1), 37(1), and 98(1)°, respectively. This geometry is enforced by the short C−C═C−C bridge

(10) Goldman, H.; Vogt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811.

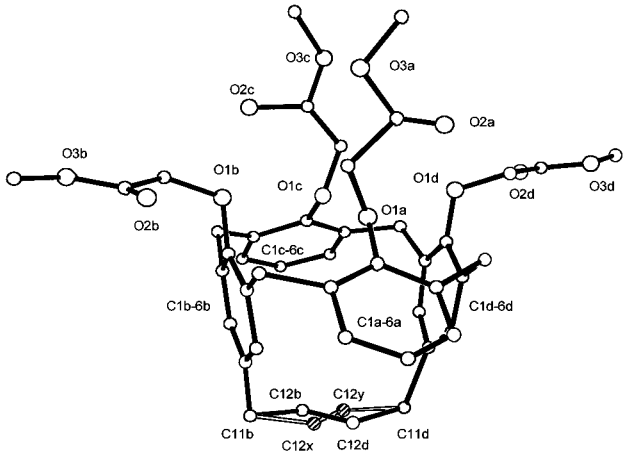


Figure 1. Molecular structure of **12** determined by X-ray crystallography.

linking rings C(1b)−C(6b) and C(1d)−C(6d). The bridge is disordered and has been modeled in the two alternate *E* geometries (55:45% occupancy for C11b, C12b, C12d, C11d and C11b, C12x, C12y, C11d, respectively). The *E* geometry was selected on the basis of the geometry of the link (bond lengths and angles) as well as the relative magnitudes of the atomic displacement parameters in the disordered group.

The distortion is also reflected in the fact that, unlike its precursor **10b** and many other unbridged calix[4]arene acetates,[2b] bridged tetraester **12** showed no evidence of complexation of sodium iodide: the rigidity and distortion of the bridged pinched cone prevent the molecule from adopting the approximate C_{4v} symmetrical arrangement of the four ester carbonyl and ether groups required for sodium ion encapsulation. Interestingly, the sodium iodide complex of **10b** when subjected to the metathesis conditions did not undergo either intermolecular or intramolecular reaction. One would not expect the latter reaction to occur with a kinetically stable complex since the presence of the sodium ion in the cavity would diminish skeletal mobility and thus prevent the conformational movement toward the pinched cone conformation that is needed to bring the two alkenyl groups within bonding distance. To confirm that the lack of reactivity of the **10b·NaI** complex was not due to low solubility in benzene, the reaction was repeated in dichloromethane, in which the complex is very soluble. Again, metathesis was not observed. That this was not simply a solvent effect could be demonstrated by showing that the rate of metathesis of **10b** alone in dichloromethane was comparable to that in benzene. The difference in behavior between **10a** and **10b** may also be conformational in origin. In the free phenolic form **10a**, tight intramolecular hydrogen bonding involving all four hydroxyl groups on the lower rim in a cyclic array results in a cone conformation of C_{4v}-like symmetry, which in turn increases the distance between the alkenyl groups on the upper rim. Intramolecular reaction, but not intermolecular reaction, is thereby inhibited. In **10b**, one would expect two rapidly interconverting C_{2v} structures, as is common with many derivatized calix[4]arenes, in one of which the two aryl rings will be approximately parallel, bringing the two alkenyl groups together in a more favorable relationship for intramolecular metathesis.

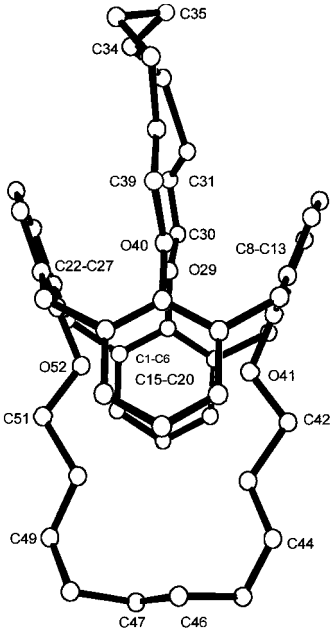
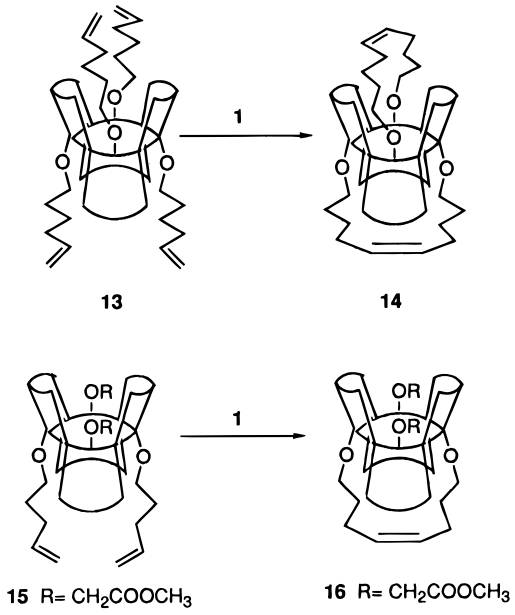


Figure 2. Molecular structure of **14** determined by X-ray crystallography.

Scheme 3



Precursor **13** is in the 1,3-alternate conformation but with two alkenyl groups on each rim. In the event this molecule produced the double cyclization product **14** (95% yield) as a 1:1 mixture of geometrical isomers (Scheme 3).

X-ray diffraction was also used to probe the effect of the alkenyl bridge on the calixarene conformation in **14**. The calix[4]arene core of **14** is defined by the angles made with the plane of the four methylene carbon atoms, C1−C6 110.0(2)°, C8−C13 112.3(2)°, C15−C20 112.0(2)°, and C22−C27 134.6(3)° (Figure 2). The two opposite rings C1−C6 and C15−C20 have an interplanar angle of 138.0(2)°. The other two rings C8−C13 and C22−C27 have an interplanar angle of 113.1(1)°. The two intramolecular carbon bridges show disorder over two positions, and this has been refined to 52:48 (1) for C44 to C49 and 56:44 (2) for C31 to C39. The geometry of the double bonds in these two disordered chains is modeled as being trans, although the possibility of cis isomers cannot be excluded.

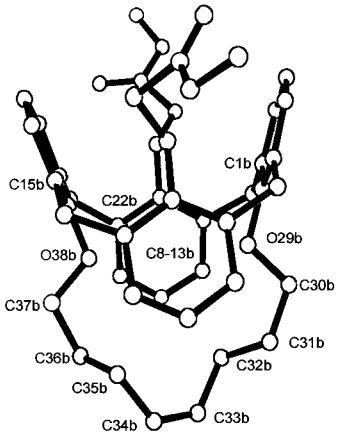


Figure 3. Molecular structure of **16** determined by X-ray crystallography.

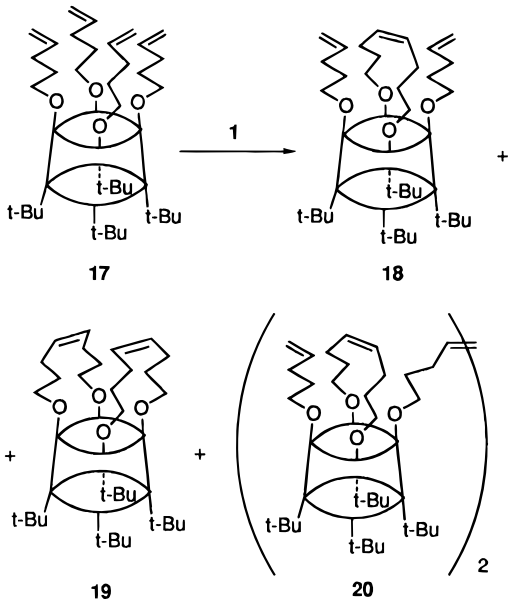
Precursor **15** is also a calix[4]arene in the 1,3-alternate conformation. Two alkenyl groups are distally located on one rim with two ester functions on the opposite rim. This compound underwent RCM smoothly to furnish the bridged product **16** in 76% yield. The structure of **16** is fully supported by ^{1}H NMR data which additionally indicated that it was a single geometrical isomer about the alkenyl bond.

X-ray analysis of a crystal of compound **16** revealed two calix[4]arene molecules A and B in the asymmetric unit that are arranged approximately about a noncrystallographic inversion center at the coordinates 0.25 0.25 0.25. The conformation of the calix[4]arene core for molecules **A** and **B** of **16** are defined by the angles made with the plane of the four methylene carbon atoms, for molecule **A**, C1−C6 110.7(1)°, C8−C13 112.2(2)°, C15−C20 107.6(1)°, and C22−C27 108.5(1)°, and for molecule **B**, C1−C6 108.0(2)°, C8−C13 115.0(2)°, C15−C20 109.3(1)°, and C22−C27 104.2(1)° (Figure 3). The two opposite rings C1−C6 and C15−C20 have interplanar angles of 141.3(3)° and 142.7(3)° for molecules **A** and **B**, respectively. The other two rings C8−C13 and C22−C27 have interplanar angles of 139.3(2)° and 140.0(2)° for molecules **A** and **B**, respectively. The conformation of the double bond for the intramolecular carbon bridge for both molecules is Z. In molecule **B**, one of the pendent methoxy groups was found to be disordered over two positions and the occupancy was allowed to refine to 58(1)% for the major position.

A final example illustrates the extension of RCM to **17**, a precursor in the cone conformation with four potential reaction sites on the same rim (Scheme 4). Several outcomes could be envisaged. Careful chromatography of the reaction product yielded two fractions, the first of which was found to contain two products, which were not separated but whose ^{1}H NMR and mass spectrometric data suggest structures **18** and **19**. The second fraction consisted of a single compound to which we have assigned the dimeric structure **20**. Product **18** is that of one intramolecular metathesis; product **19** is that of two intramolecular metathesis; and product **20** results from a combination of intermolecular and intramolecular metathesis.

In conclusion, we have demonstrated that catalytic RCM is a very efficient route to a range of novel cage

Scheme 4



molecules with potential applications as selective receptors for ions and neutral molecules.

Experimental Section

^{1}H NMR spectra were recorded with General Electric QE 300 (^{1}H 300 MHz) and General Electric omega 500 (^{1}H 500 MHz) instruments with Me_4Si as internal standard. Spectrometric mass measurements (FAB) were carried out in a V.G. Organic Autospec mass spectrometer using a LSIMS source. Analytical TLC was performed on silica gel plates (SiO_2, Merck, 60 F_{254}), while silica gel 60 (SiO_2, Merck, flash chromatography) was used for preparative column chromatography. Microanalysis were carried out by the Service of Microanalysis of the School of Chemistry. Synthesis of compounds **4a**,**b**, **6**, **8a**−**c**, **15**, and **17** has been described in previous publications by our research group.[5,8] Melting points of mixtures of isomers are not stated.

25,27-Diallyl-26,28-dihydrocalix[4]arene, 10. To a stirring suspension of tetrahydroxycalix[4]arene **2** (10 g) and potassium carbonate (6.83 g, 2.1 equiv) was added allyl bromide (5.99 g, 2.1 equiv), and the mixture was refluxed for 18 h. After being cooled to rt, the suspension was filtered to remove inorganic salts. The filtrate was concentrated in a rotory evaporator, yielding the product as an off-white solid. Recrystallization from methanol−dichloromethane yielded **10** (10.1 g, 85%) as a white crystalline solid: mp = 105−109 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (s, 2H), 7.05 (d, 4H, J = 7.5 Hz), 6.90 (d, 4H, J = 7.6 Hz), 6.75 (t, 2H, J = 7.6 Hz), 6.65 (t, 2H, J = 7.5 Hz), 6.25 (m, 2H), 5.8 (d, 2H, J = 17.2 Hz), 5.4 (d, 2H, J = 10.5 Hz), 4.55 (d, 4H, J = 5.0 Hz), 4.30 (d, 4H, J = 13 Hz), 3.40 (d, 4H, J = 13 Hz). Anal. Calcd for $C_{34}H_{32}O_4$: C, 80.93; H, 6.39. Found: C, 80.57; H, 6.61.

5,17-Diallyl-25,26,27,28-tetrahydroxycalix[4]arene, 10a. A solution of 10 (6.5 g) in 30 mL of *N*,*N*-diethylaniline was refluxed for 2 h. After being cooled at rt, the reaction mixture reaction was dumped into an ice−water mixture (200 mL) and then shaken with concd HCl (150 mL). The solid obtained was filtered and washed with water. After recrystallization of this solid from methanol−dichloromethane, **10a** was obtained as a white solid (4.7 g, 73%): mp = 233−235 °C; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 2H), 7.05 (d, 4H, J = 7.5 Hz), 6.82 (s, 4H), 6.75 (t, 2H, J = 7.4 Hz), 5.85 (m, 2H), 5.0 (m, 4H), 4.25 (bd, 4H), 3.50 (bd, 4H), 3.20 (d, 4H, J = 5.2 Hz). Anal. Calcd for $C_{34}H_{32}O_4$: C, 80.93; H, 6.39. Found: C, 80.90; H, 6.29.

5,17-Diallyl-25,26,27,28-tetrakis[[(methoxycarbonyl)-methylene]oxy]calix[4]arene, 10b. 10a (4.5 g, 8.9 mmol) and 4.93 g of potassium carbonate (49 mmol) were suspended in 30 mL of dry acetone. To this suspension was added 8.19 g of methyl bromoacetate. The mixture was refluxed under nitrogen for 72 h. After the mixture was allowed to cool to room temperature, the inorganic salts were filtered off and the solution was concentrated in a rotory evaporator to yield an oil that was left for 12 h on a high-vacuum pump. The residue was purified by chromatographic column (flash silica, hexane−ethyl acetate 60:40), and the off-white solid obtained was recrystallized from ethanol to yield the product as a crystalline solid (82%): mp 192−194 °C; ^{1}H NMR ($CDCl_3$) δ 6.65 (s, 4H), 6.5 (m, 6H), 5.85 (m, 2H), 5 (m, 4H), 4.82 (d, 4H, J = 13.5 Hz), 4.8 (s, 4H), 4.7 (s, 4H), 3.77 (s, 6H), 3.75 (s, 6H), 3.2 (d, 4H), 3.17 (d, 4H, J = 5 Hz); MSFAB m/z 793 (M^+), 815 (M^+ + Na).

25,26,27,28-Tetrahex-1-enylcalix[4]arene, 13. To a suspension of 0.5 g of **2** (1.18 mmol) in 15 mL of dry THF and 1.5 mL of dry DMF containing 200 mg of NaH was added 0.81 mL of 6-bromopentene (5.9 mmol). The mixture was stirred and refluxed under nitrogen for 7 days. After the mixture was cooled, the inorganic solid that appeared was filtered off. The liquid phase was concentrated under vacuum and the semisolid obtained redissolved in CH_2Cl_2 (20 mL) and washed with water (2 × 15 mL). The organic phase was dried ($MgSO_4$) and the solvent removed under vacuum to afford a yellow semisolid. The ^{1}H NMR indicated that the product was a mixture of partial cone and 1,3-alternate conformers. Both isomers were separated by chromatographic column (flash silica, hexane−ethyl acetate 96:4).

13: partial cone (39%); semisolid; ^{1}H NMR ($CDCl_3$) δ 7.2 (d, 2H, J = 7 Hz), 7.1 (d, 2H, J = 7 Hz), 6.95−6.8 (m, 4H), 6.42 (t, 2H, J = 6 Hz), 6.25 (d, 2H, J = 6 Hz), 6.0−5.75 (m, 4H), 5.1−4.9 (m, 8H), 4.1 (d, 2H, J = 13 Hz), 3.8 (m, 4H), 3.65 (s, 4H), 3.6 (dd, 2H, J = 15 Hz, J = 8 Hz), 3.35 (d, 2H, J = 8 Hz), 3.05 (d, 2H, J = 13 Hz), 2.2−1.2 (set of m, 24H). Anal. Calcd for $C_{52}H_{64}O_4$: C, 82.90; H, 8.56. Found: C, 82.67; H, 8.47.

13: 1,3-alternate (8.5%); mp 116 °C; ^{1}H NMR ($CDCl_3$) δ 7.0 (d, 8H, J = 8 Hz), 6.7 (t, 4H, J = 8 Hz), 5.9−5.85 (m, 4H), 5.1−4.9 (s+d, 8H), 3.7 (s, 8H), 3.5 (t, 8H, J = 7 Hz), 2.1 (m, 8H), 1.55 (m, 8H), 1.4 (m, 8H). Anal. Calcd for $C_{52}H_{64}O_4$: C, 82.90; H, 8.56. Found: C, 82.75; H, 8.48.

Synthesis of Compounds 5a−b, 7, 9a−c, 11a−c, 12, 14, 16, and 18−20. General Experimental Procedure. One hundred milligrams of the corresponding alkenylcalix[4]arene derivative was dissolved under nitrogen in 5 mL of dry benzene. To this solution was added 4−8% of catalyst **1**. The mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. When the reaction was completed, the solvent was removed at reduced pressure. Where a single product was obtained, the residue was taken up in hexane−ethyl acetate and a simple percolation through a small column of flash silica was enough to obtain a high-quality product. More complex mixtures were purified by column chromatography (flash silica, hexane−ethyl acetate 9:1). A microcrystalline powder could be obtained by recrystallization of the products from dichloromethane−methanol.

Synthesis of compound 11d. The experimental procedure was identical with that of compound **11a**−**c** but using CH_2Cl_2 as solvent. After the solvent was removed, the crude material was recrystallized from dichloromethane−methanol to afford **11d** in quantitative yield.

5a: 57%; ^{1}H NMR ($CDCl_3$) δ 8.99 (s, 2H), 7.06 (s, 4H), 7.01 (s, 4H), 5.66 (t, 2H, J = 4.4 Hz), 4.27 (d, 4H, J = 12.5 Hz), 4.02 (t, 4H, J = 4.5 Hz), 3.33 (d, 4H, J = 12.5 Hz), 2.83 (m, 4H), 2.02 (m, 4H), 1.22 (s, 18H), 1.18 (s, 18H); MSFAB m/z 756.2 (M^+). Anal. Calcd for $C_{52}H_{68}O_4$: C, 82.55; H, 9.14. Found: C, 82.32; H, 9.14.

5b: 62.2%; ^{1}H NMR ($CDCl_3$) the ^{1}H NMR of this compound at rt offers a set of broad signals of difficult assignation; MSFAB m/z 784.6 (M^+). Anal. Calcd for $C_{54}H_{72}O_4$: C, 82.60; H, 9.24. Found: C, 82.52; H 9.42.

7: 55%; ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 4H), 7.05−6.85 (m, 16H), 6.75 (t, 4H, J = 5 Hz), 6.62 (t, 4H, J = 5 Hz), 6.16 (t, 4H, J = 3 Hz), 6.02 (t, 4H, J = 4 Hz), 4.38 (d, 4H, J = 14 Hz), 4.18 (d, 4H, J = 14 Hz), 4.1 (m, 8H), 3.30 (d, 4H, J = 14 Hz), 3.21 (d, 4H, J = 14 Hz), 3.10 (m, 8H), 2.95 (m, 8H); MSFAB m/z 1009

(M^+). Anal. Calcd for $C_{68}H_{64}O_8$: C, 80.92; H, 6.93. Found: C, 79.18; H, 6.95.

9a: 79%; ^{1}H NMR (main isomer) ($CDCl_3$) δ 7.07 (d, 4H, J = 5 Hz), 6.86 (t, 2H, J = 5 Hz), 6.14 (m, 6H), 5.60 (t, 2H, J = 4 Hz), 4.34 (s, 4H), 4.32 (d, 4H, J = 14 Hz), 3.71 (s, 6H), 3.66 (t, 4H, J = 5 Hz), 3.10 (d, 4H, J = 14 Hz), 2.75 (d, 4H, J = 5 Hz). MSFAB m/z 649 (M^+), 672 (M^+ + Na). Anal. Calcd for $C_{40}H_{40}O_8$: C, 73.98; H, 6.21. Found: C, 73.00; H, 6.35.

9b: 35%; ^{1}H NMR (main isomer) ($CDCl_3$) δ 7.15 (d, 4H, J = 7 Hz), 6.96 (t, 2H, J = 7 Hz), 6.22 (t, 2H, J = 7 Hz), 6.10 (d, 4H, J = 7 Hz), 5.51 (t, 2H, J = 5 Hz), 4.48 (d, 4H, J = 12 Hz), 4.41 (s, 4H), 3.96 (t, 4H, J = 4.5), 3.76 (s, 6H), 3.19 (d, 4H, J = 12 Hz), 2.75 (m, 4H), 1.69 (m, 4H); MSFAB m/z 677 (M^+). Anal. Calcd for $C_{42}H_{44}O_8$: C, 74.53; H, 6.55. Found: C, 74.92; H, 6.59.

9c: 68%; ^{1}H NMR ($CDCl_3$) δ 7.18 (d, 4H, J = 6 Hz), 6.95 (t, 2H, J = 6 Hz), 6.2 (m, 6H), 5.55 (t, 2H, J = 3 Hz), 5.40 (t, 2H, J = 3 Hz), 4.50 (d, 4H, J = 12 Hz), 4.40 (s, 4H), 4.0 (m, 4H), 3.81 (s, 6H), 3.16 (d, 4H, J = 12 Hz), 2.3−2.1 (m, 4H), 2.05−1.95 (m, 4H), 1.55−1.35 (m, 4H); MSFAB m/z 705 (M^+). Anal. Calcd for $C_{44}H_{48}O_8$: C, 74.97; H, 6.86. Found: C, 75.02; H, 6.59.

11a: 25%; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 8H), 7.03 (m, 8H), 5.85 (d, 8H), 6.73 (m, 4H), 5.86 (m, 2H), 5.58 (t, 2H), 5.50 (t, 2H), 5.01−5.05 (s+d, 4H), 4.23 (bd, 8H), 3.50 (bd, 8H), 3.23 (d, 4H, J = 6.6 Hz), 3.16 (d, 4H, J = 8.3 Hz), 3.13 (d, 4H J = 6.6 Hz); MSFAB m/z 981(M^+). Anal. Calcd for: $C_{66}H_{60}O_8$: C 80.79; H, 6.16. Found: C 80.72; H, 6.20.

11b: 20%; ^{1}H NMR ($CDCl_3$) δ 10.20 (s, 12H), 7.05 (m, 12H), 6.85 (m, 12H), 6.70 (m, 6H), 5.85 (m, 2H), 6.1−5.9 (3t, 4H), 5.05 (d + s, 4H), 4.25 (bd, 12H, J = 14 Hz), 3.50 (bd, 12H, J = 14 Hz), 3.3−3.05 (3d, 12H); MSFAB m/z 1457 (M^+).

11c: 5%; ^{1}H NMR ($CDCl_3$) δ 9.95 (s, 8H), 9.80 (s, 8H), 7.0 (d, 4H, J = 4 Hz), 6.75 (t 8H, J = 4 Hz), 6.65 (s, 8H), 5.8 (t, 4H, J = 5 Hz), 5.45 (t, 4H, J = 5 Hz), 4.2 (d, 8H, J = 13.6 Hz), 3.45 (d, 8H, J = 13.6 Hz), 3.0 (d, 8H, J = 5 Hz), 2.95 (d, 8H, J = 5 Hz); MSFAB m/z 953 (M^+). Anal. Calcd for $C_{64}H_{56}O_8$: C, 80.79; H, 6.18. Found: C, 80.75; H, 5.98.

11d: 99%; ^{1}H NMR ($CDCl_3$) δ 10.2 (s, OH), 7.0 (d, 12H), 6.85 (s, 12H), 6.7 (t, 6H), 5.6−5.5 (2t, 6H), 4.2 (bs, 12H), 3.5 (bs, 12H), 3.3−3.0 (2d, 12H); MSFAB m/z 1431 (M^+ + 1).

12: 83%; ^{1}H NMR ($CDCl_3$) δ 7.12 (d, 4H, J = 7.5 Hz), 6.97 (t, 2H, J = 7.5 Hz), 5.94 (s, 4H), 4.98 (s, 4H), 4.81 (d, 4H, J = 13 Hz), 4.74 (t, 2H, J = 4.5 Hz), 4.47 (s, 4H), 3.77 (s, 6H), 3.70 (s, 6H), 3.30 (d, 4H, J = 13 Hz), 2.60 (d, 4H, J = 4.5 Hz); MSFAB m/z 764 (M^+), 787 (M^+ + Na). Anal. Calcd for $C_{44}H_{44}O_{12}$: C, 69.10; H, 5.80. Found: C, 69.54; H, 5.96.

14: 95%; ^{1}H NMR ($CDCl_3$) δ 6.96 (m, 8H), 6.78 (m, 4H), 5.35 (t, 2H, J = 4.5 Hz), 5.11 (t, 2H, J = 4.5 Hz), 3.80 (s, 8H), 3.41 (m, 8H), 1.96 (m, 8H), 1.88 (m, 8H), 1.2−0.65 (set of m, 16H); MSFAB m/z 697 (M^+). Anal. Calcd for $C_{48}H_{56}O_4$: C, 82.72; H, 8.09. Found: C, 82.47; H, 8.42.

16: 76%; mp 198−200 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 4H, J = 8 Hz), 7.05 (d, 4H, J = 8 Hz), 6.82 (m, 4H), 5.28 (t, 2H, J = 5 Hz), 4.11 (d, 4H, J = 15 Hz), 3.88 (d, 4H, J = 15 Hz), 3.60 (t, 4H, J = 5 Hz), 3.59 (s, 6H), 3.28 (s, 4H), 1.44 (m, 4H), 1.32 (m, 4H); MSFAB m/z 677 (M^+), 700 (M^+ + Na). Anal. Calcd for $C_{42}H_{44}O_8$: C, 69.10; H, 5.80. Found: C, 74.14; H, 6.60.

18 + **19**: 9% + 9%; ^{1}H NMR ($CDCl_3$) δ 7.12 (s, 4H), 6.75 (s, 8H), 6.46 (s, 4H), 5.82 (m, 2H), 5.56 (m, 6H), 5.0−4.9 (2d, 4H, J = 14 Hz), 4.41 (d, 4 + 4 H, J = 13 Hz), 4.05 (m, 4H), 3.90 (m, 8H), 3.71 (t, 4H, J = 7 Hz), 3.12 (d, 4 + 4 H, J = 13 Hz), 3.05 (m, 4H), 2.82 (m, 4H), 2.25 (m, 4H), 2.16 (m, 4H), 2.0 (m, 4H), 1.89 (m, 4H), 1.80 (m, 4H), 1.70 (m, 4H), 1.33 (s, 18H), 1.09 (s, 9H), 1.08 (s, 18H), 1.06 (s, 9H), 0.82 (s, 18H). **18**: MSFAB m/z 893 (M^+). **19**: MSFAB m/z 865 (M^+).

20: 65%; ^{1}H NMR ($CDCl_3$) δ 7.10 (s, 8H), 6.78 (3s, 4H), 6.46 (s, 4H), 5.80 (m, 2H), 5.7−5.3 (m, 6H), 5.1−4.8 (m, 4H), 4.41 (d, 8H, J = 13 Hz), 3.91 (m, 8H), 3.70 (m, 8H), 3.11 (d, 8H, J = 13 Hz), 2.30−1.80 (m, 32H), 1.32 (s, 18H), 1.05 (s, 36H), 0.81 (s, 18H); MSFAB m/z 1759 (M^+). Anal. Calcd. for $C_{122}H_{164}O_8$: C, 83.30; H, 9.35. Found: C, 82.85; H, 9.50.

Crystallographic Studies. Crystal data for $C_{44}H_{44}O_{12}$ (**12**): M= 764.79, monoclinic, space group Cc, a = 15.645(7) Å, b = 13.510(7) Å, c = 18.560(9) Å, β = 103.59(2)°, U = 3813(3) Å^{-3}, Z = 4, D_c = 1.332 Mg m^{-3}, $F(000)$ = 1616, μ = 0.097 mm^{-1}, crystal dimensions = 0.20 × 0.12 × 0.10 mm. A total of 2853 reflections were measured for 4 < 2θ < 45°, and 2602 independent reflections were used in the refinement. The final parameters were $wR2$ = 0.3037 (all data) and $R1$ = 0.1031 (I > 2σI), S = 1.026, 233 parameters, 53 restraints, weighting scheme g_1 = 0.0958, g_2 = 0, $(\Delta/\sigma)_{max}$ = 0.004, $(\Delta\rho)_{max,min}$ = 0.405, −0.336 e Å^{-3}.

Crystal data for $C_{48}H_{54}O_4 \cdot 0.5(CH_2Cl_2)$ (**14**): M = 737.38, monoclinic, space group $P2_1/n$, a = 17.278(2) Å, b = 10.927(2) Å, c = 22.896(6) Å, β = 106.79(1)°, U = 4133(1) Å^{-3}, Z = 4, D_c = 1.185 Mg m^{-3}, $F(000)$ = 1580, μ = 0.135 mm^{-1}, crystal dimensions = 0.62 × 0.44 × 0.38 mm. A total of 7501 reflections were measured for 4 < 2θ < 50, and 7247 independent reflections were used in the refinement. The final parameters were $wR2$ = 0.3522 and $R1$ = 0.1145 [I > 2σI] (3351 reflections), S = 1.042, 483 parameters, 55 restraints, weighting scheme g_1 = 0.1304, g_2 = 11.114, $(\Delta/\sigma)_{max}$ = −0.003, $(\Delta\rho)_{max,min}$ = 0.800, −0.377 e Å^{-3}.

Crystal data for $C_{42}H_{44}O_8$ (**16**): M = 676.77, monoclinic, space group $P2_1/c$, a = 15.390(4) Å, b = 15.278(4) Å, c = 30.221(12) Å, β = 103.11(2)°, U = 6920(4) Å^{-3}, Z = 8, D_c = 1.299 Mg m^{-3}, $F(000)$ = 2880, μ = 0.089 mm^{-1}, crystal dimensions = 0.81 × 0.40 × 0.28 mm. A total of 11 174 reflections were measured for 4 < 2θ < 45, and 9039 independent reflections were used in the refinement. The final parameters were $wR2$ = 0.2483 and $R1$ = 0.0883 [I > 2σI] (4924 reflections), S = 1.095, 900 parameters, weighting scheme g_1 = 0.1032, g_2 = 7.886, $(\Delta/\sigma)_{max}$ < 0.001, $(\Delta\rho)_{max,min}$ = 0.507, −0.381 e Å^{-3}.

Data were collected using a Siemens P4 four-circle diffractometer with graphite-monochromated Mo $K\alpha$ radiation. Crystal stabilities were monitored every 100 reflections, and there were no significant variations (±1%). Cell parameters were obtained from 18, 38, and 25 accurately centered reflections in the 2θ range 10°−25° and 10°−20° for compounds **12**, **14**, and **16**, respectively. Data were collected at 153(2) K using ω scans; Lorentz and polarization corrections were applied.

All three structures were solved by direct methods. Due to the very weak data set obtained for **12**, all atoms were refined isotropically; FLAT restraints have been applied to rings C(1b)−C(6b) and C(1d)−C(6d), and SAME restraints were applied to the two orientations of disordered bridge. The non-hydrogen atoms in compounds **14** and **16** (except the disordered atoms) were refined with anisotropic atomic displacement parameters. Hydrogen atoms were added at idealized positions, and a riding model with fixed displacement parameters (U_{iso} = 1.2U_{ij}(equiv), 1.5U_{ij}(equiv) for methyl hydrogen atoms) was used for subsequent refinement. The dichloromethane moiety is disordered in compound **14**, and an occupancy factor for the two positions in the asymmetric unit was fixed at 25%.

The function minimized was $\Sigma[w(|F_o|^2 - |F_o|^2)]$ with reflection weights $w^{-1} = [\sigma^2|F_o|^2 + (g_1P)^2 + g_2P]$ where $P = [\max |F_o|^2 + 2|F_o|^2]/3$. The XSCANS, SHELXTL PC,[11] and SHELXL-93[12] packages were used for data collection, reduction and structure solution, and refinement. Additional material, available from the Cambridge Crystallographic Data Centre, includes all atom coordinates, bond lengths and angles, atomic displacement parameters and hydrogen atom coordinates.

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Supporting Information Available: X-ray data for **14** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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