Stepwise Construction of Some Hexahomooxacalix[3]arenes and Their Conformations in Solid State

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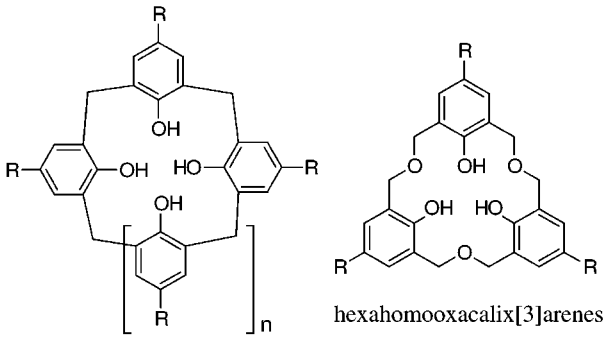
Hexahomooxacalix[3]arenes **1** bearing different substituents on their upper rim were synthesized from the corresponding linear trimers **2** by the acid-catalyzed cyclization. The X-ray crystallographic analyses of **1** ($R^1 = R^3 = H$, $R^2 = t$-Bu, and $R^1 = Et$, $R^2 = t$-Bu, $R^3 = i$-Pr) revealed that they adopt a cone conformation, owing to an intramolecular hydrogen-bonded network in the solid state.

Introduction

Since the pioneering work on the one-step synthesis of *p-tert*-butylcalix[4,6,8]arenes (Chart 1) by Gutsche and co-workers,[1] a considerable amount of attention has been paid to these molecules from the viewpoint of host−guest chemistry. Calixarenes were prepared by the base-induced condensation of 4-*tert*-butylphenol with 37% formaldehyde under strictly controlled conditions. Contrary to calixarenes, hexahomooxacalix[3]arenes have received little attention[2] despite their unique structural features such as a cavity composed of an 18-membered ring, C_3 symmetry, and a limited number of possible conformations (i.e., cone and partial cone). Only a few methods for the synthesis of hexahomooxacalix[3]arenes have been available so far. These include the methods reported by Gutsche et al.,[3] Vicens et al.,[4] and Hampton et al.[5] All involve cyclotrimerization using 2,6-bis(hydroxymethyl)phenols as a monomer unit. Consequently, these procedures can only give symmetrical hexahomooxacalix[3]arenes bearing the same substituents on the upper rim of the molecules. On the other hand, desymmetrization of the molecules by the introduction of different substituents into the upper rim leads to chiral host molecules, which realize enantioselective molecular recognition, if their conformation is fixed.

Chart 1



calix[4,6,8]arenes
n = 1, 3, 5

hexahomooxacalix[3]arenes

Calixarenes having para substituents other than *tert*-butyl have been synthesized by a reverse Friedel−Crafts reaction[6] of *tert*-butylcalixarenes followed by electrophilic substitution with a variety of electrophiles.[1e,g,i] However, this approach is not applicable to hexahomooxacalix[3]-arenes because it is difficult to selectively remove the para substituents by the reverse Friedel−Crafts reaction due to the presence of three dibenzyl ethereal linkages. Therefore, a prior introduction of the specified para substituents is necessary. In this paper, we report the

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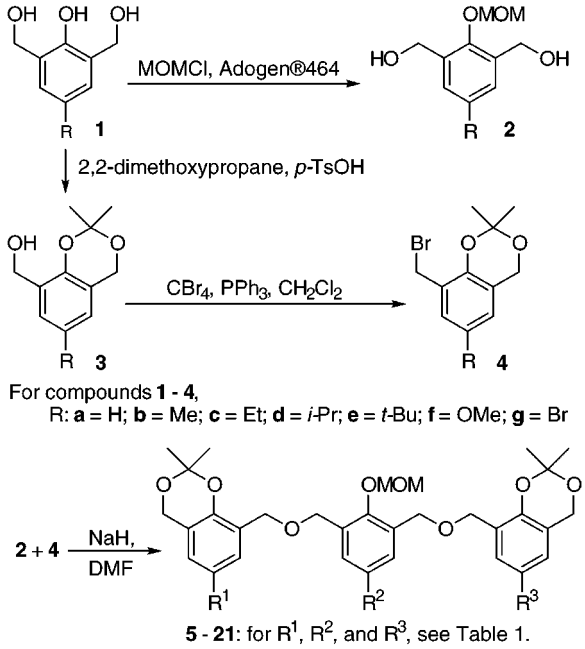
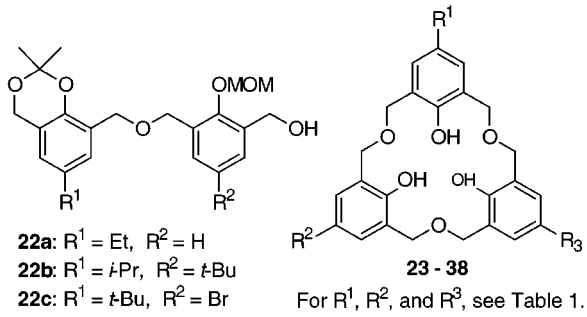
Scheme 1



first stepwise synthesis of a variety of hexahomooxacalix[3]arenes **23**−**38** having different substituents on their



upper rim. We report elucidation of their conformations in the solid state; the synthesis is based on the cyclization of the corresponding linear trimers under acidic high-dilution conditions.

Results and Discussion

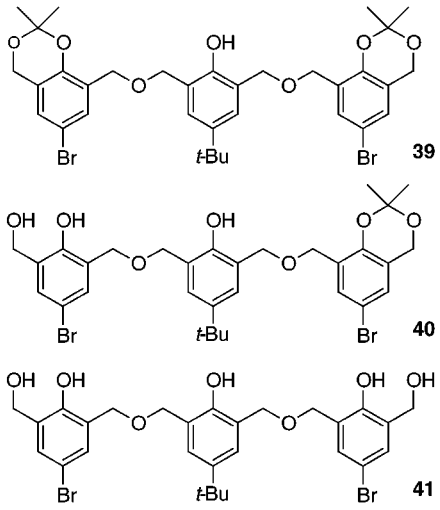
Synthesis of Hexahomooxacalix[3]arenes 23−38. The starting 2,6-bis-(hydroxymethyl)phenols **1**[5,7] were treated with 2,2-dimethoxypropane in the presence of *p*-TsOH to afford the acetonides **3**,[8] which were brominated with CBr_4−PPh_3, yielding the corresponding benzylbromides **4**. Separately, the coupling partners, diols **2**, were prepared by the reaction of **1** with MOMCl using Adogen464 as a phase-transfer catalyst.[9] Alkylation of **2** with 2.2 equiv of bromides **4** provided the linear trimers (**5**−**14**, **17**−**19**, and **21**) having the same substituent for R^1 and R^3 (Scheme 1). Monoalkylation of **2a**, **2e**, and **2g** with **4c**, **4d**, and **4e**, respectively, gave the dimers **22a**, **22b**, and **22c**. The second alkylation of the dimer **22a** with **4b** **22b** with **4c**, and **22c** with **4g**, gave the trimers **15**, **16**, and **20**, respectively.

Table 1. Cyclization of Linear Trimers to Hexahomooxacalix[3]arenes

entry	linear trimer	R^1	R^2	R^3	product	% yield[a]
1	**5**	H	H	H	**23**	22
2	**6**	Me	H	Me	**24**	44
3	**7**	Et	H	Et	**25**	42
4	**8**	*i*-Pr	H	*i*-Pr	**26**	42
5	**9**	*t*-Bu	H	*t*-Bu	**27**	54
6	**10**	H	*t*-Bu	H	**28**	22
7	**11**	Me	*t*-Bu	Me	**29**	43
8	**12**	Et	*t*-Bu	Et	**30**	50
9	**13**	*i*-Pr	*t*-Bu	*i*-Pr	**31**	54
10	**14**	*t*-Bu	*t*-Bu	*t*-Bu	**32**	48
11	**15**	Me	H	Et	**33**	45
12	**16**	Et	*t*-Bu	*i*-Pr	**34**	53
13	**17**	OMe	OMe	OMe	**35**	20
14	**18**	*t*-Bu	Br	*t*-Bu	**36**	51
15	**19**	Br	*t*-Bu	Bu	**37**	0
16	**20**	Br	Br	*t*-Bu	**37**	34[b]
17	**21**	Br	Br	Br	**38**	4

[a] Isolated yield. [b] 13 h for the reaction time.

Linear trimers **5**−**21** gave the desired hexahomooxacalix[3]arenes **23**−**38** after treatment with $HClO_4$[10] under high-dilution conditions in $CHCl_3$. Pretreatment of $CHCl_3$ with H_2O is indispensable for this cyclization. Thus, commercially available $CHCl_3$ was washed with water, allowed to stand for at least 6 h in a separatory funnel, and then separated. This process is required to supply H_2O for the deprotection as well as to remove trace amounts of ethanol added as a stabilizer. If nontreated $CHCl_3$ was used, byproducts originating from the addition of ethanol formed to some extent. No effective cyclization proceeded in $CHCl_3$ or CH_2Cl_2 containing amylene as a stabilizer. The additives $KClO_4$ and $NaClO_4$ did not exert any template effect on the reaction. The results of the cyclization to a variety of hexahomooxacalix[3]arenes **23**−**38** are summarized in Table 1. Constant and moderate chemical yields were observed, and among the R^2 substituents on the central ring of the linear trimers, *tert*-butyl, hydrogen, and bromine resulted in almost the same yield. In the case of $R^1 = R^3 = H$, somewhat lower yields were obtained (entries 1 and 6). Cyclization was extremely suppressed for trimers with $R^1 = R^3 = Br$ (entries 15 and 17). Thus, the attempted cyclization of a linear trimer **19** gave deprotected products **39**−**41** in 18%, 31%, and 40% yields, respectively.



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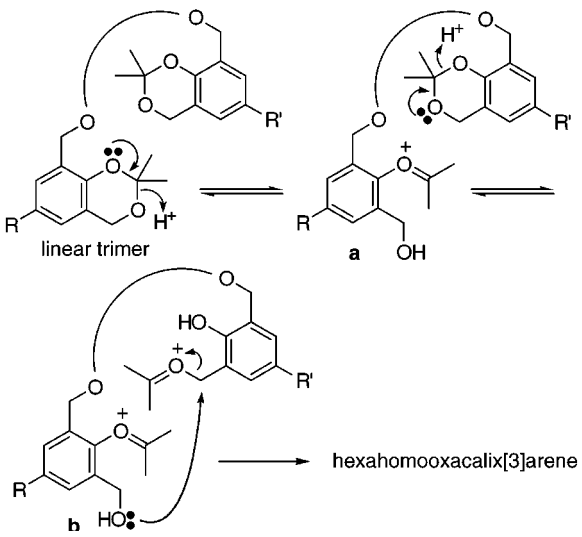
Scheme 2



Contrary to these results, the desired product **37** was obtained from **20** in 34% yield.

It is especially worthwhile to note that the isolation of the products from the reaction mixture was quite easy in these reactions. The cyclized products **23**−**25**, **32**, and **33** were isolated from MeOH in an extremely pure form without any chromatographic separation. Simple purification by short column chromatography on silica gel with $CHCl_3$ as an eluent made it possible to isolate other products with a high degree of purity.

The formation of hexahomooxacalix[3]arenes from the corresponding linear trimers presumably involves the initial protonation at the aliphatic ethereal oxygen to give an oxonium species **a** (Scheme 2). The following protonation at the aromatic ethereal oxygen creates a dioxonium species **b**. The cyclic ether is formed by the intramolecular attack of the primary hydroxyl group to the benzylic position, as shown in **b**, or to the corresponding benzylic cation. According to this mechanism, both of the oxygen atoms in the ketal ring should be protonated. This explains why **37** was obtained from **20** but not from **19**. Protonation at the phenolic oxygen shown in **a** is less favorable for **19** due to an electron-withdrawing group on the phenyl ring, while this process occurs easily with **20**.

Conformation of Hexahomooxacalix[3]arenes in the Solid State. The X-ray crystallographic analysis of some hexahomooxacalix[3]arene derivatives such as metal complexes,[2a,b] *O*-alkylated[2i,j] or *O*-silylated[2k] compounds of the phenolic hydroxyl group, and **32**[2l] have been reported, and only two conformations had been observed to date. Among them, it was reported that **32** adopts a cone conformation owing to *three* intramolecular hydrogen bondings between each phenolic hydroxy group; however, the positions of the involving hydrogens are not specified.[2l]. It is interesting to investigate the conformation of the newly prepared hexahomooxacalix[3]arenes which have different substituents on their upper rim. Thus, the X-ray analyses of **28** and **34** were undertaken.

The crystals of hexahomooxacalix[3]arene **28** are trigonal and are classified as belonging to the space group $P3_1$. The compound **28** exists in two conformations, A and B, in the crystalline state (Figure 1a), and the both adopt the cone conformation in the solid state (Figure 1b). Of particular interest is that all the phenolic hydrogen atoms are geometrically fixed. Furthermore, it has become apparent from the X-ray analysis that **28** forms an extended network of *six* intramolecular hydrogen bondings. Each phenolic hydrogen atom is shared with two oxygen atoms (the phenolic oxygen and the dibenzyl ethereal oxygen); therefore the angles of O−H···O are not 180° (linear form) but between 102° and 163°. The pattern of the intramolecular hydrogen bonding in conformations A and B in terms of distances and angles is shown in Table 2. Thus, hexahomooxacalix[3]arenes adopt a cone conformation with a bifurcate-arranged intramolecular hydrogen bonds network, whose strong hydrogen bondings are supported by bond distances of approximately 2 Å. In addition, an astonishing feature is that **28** exists in an optically active form in the crystalline package despite being an achiral molecule.[11]

The crystals of hexahomooxacalix[3]arene **34** are orthorhombic and belong to the space group $Pna2_1$. The crystal structure of **34** is shown in Figure 2. It was also clarified

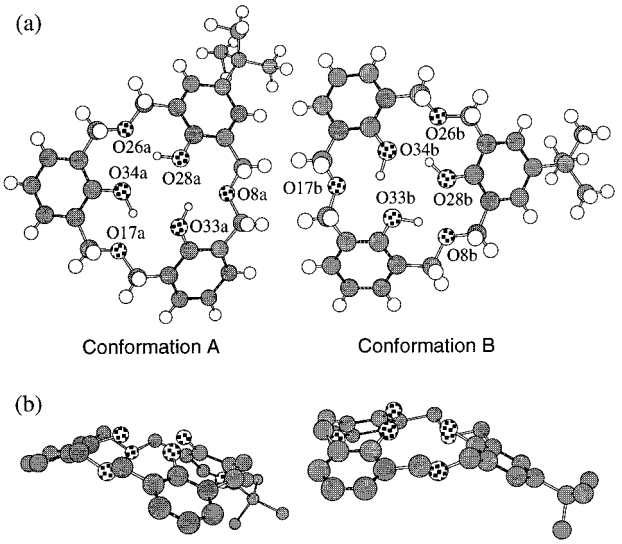


Figure 1. (a) Crystal structure of **28** in two conformations, A and B, showing the atom-labeling scheme for the oxygens. (b) Side view to emphasize their one conformation. Hydrogen atoms are excluded for clarity.

Table 2. Distances (Å) and Angles (deg) of Intramolecular Hydrogen Bonding of 28[a]

donor	hydrogen	acceptor	D−A (Å)	D−H (Å)	H··A (Å)	∠D−H···A (deg)
O28a	H(O28a)	O26a	2.821(8)	0.86(5)	2.06(5)	147(6)
O28a	H(O28a)	O34a	2.828(8)	0.86(5)	2.27(8)	122(6)
O33a	H(O33a)	O8a	2.77(1)	0.8(1)	2.12(8)	135(6)
O33a	H(O33a)	O28a	2.920(9)	0.8(1)	2.2(1)	140(6)
O34a	H(O34a)	O17a	2.800(9)	0.81(8)	2.2(1)	136(7)
O34a	H(O34a)	O33a	2.890(5)	0.81(8)	2.22(5)	140(8)
O28b	H(O28b)	O26b	2.75(1)	1.09(7)	1.99(9)	123(5)
O28b	H(O28b)	O34b	2.828(4)	1.09(7)	1.90(6)	139(7)
O33b	H(O33b)	O8b	2.831(7)	1.02(8)	1.98(9)	139(9)
O33b	H(O33b)	O28b	2.832(8)	1.02(8)	2.4(1)	102(9)
O34b	H(O34b)	O17b	2.867(8)	1.09(9)	2.33(7)	108(3)
O34b	H(O34b)	O33b	2.879	1.09(9)	1.82(8)	163(5)

[a] 1. The symmetry operations are applied to the acceptors. 2. Estimated standard deviations (esd's) are shown in the parentheses. They are not calculated when one of the atoms has an esd = 0.0. 3. Estimated hydrogen positions are located at 1 Å away from the donors.

(10) Particular caution should be taken when handling perchloric acid and related compounds; it must, especially be kept in mind that heating the reaction mixture might cause a hazardous explosion.

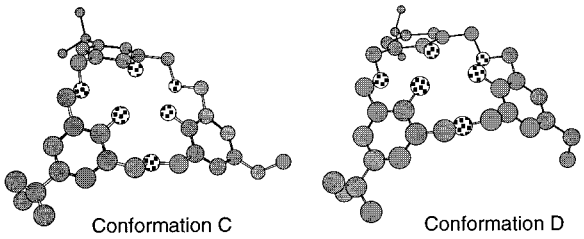


Figure 2. Crystal structure of **34** in two conformations, C and D. Hydrogen atoms are excluded for clarity.

that **34** consists of two individual cone conformations C and D in the crystalline state. The existence of a network due to hydrogen bondings in **34** in the solid state is strongly indicated by the distances both between each phenolic oxygen atom and between phenolic and dibenzyl ethereal oxygen atoms (2.70−2.98 Å), which are comparable to those of **28** (2.77−2.92 Å).

Conclusion

In the present study, the construction of a number of hexahomooxacalix[3]arene derivatives **23**−**38** was achieved by an acid-catalyzed cyclization of the corresponding linear trimers under high-dilution conditions in yields of 4−54%. It appeared that the newly prepared hexahomooxacalix[3]arenes adopt the cone conformation in the crystalline state by virtue of a network of bifurcated intramolecular hydrogen bonds. The present method not only is an alternative to previous methods but also has opened a new synthetic pathway to hexahomooxacalix[3]arenes bearing and a variety of substituents on their upper rim, which has been difficult to achieve by the previously available approach. We believe that this method is practical and useful, especially for the synthesis of unsymmetrical hexahomooxacalix[3]arenes, and might contribute to the field of host−guest chemistry. The interaction of **32** and **38** prepared by this method with fullerene has been examined,[12] and other complexations of these hexahomooxacalix[3]arenes with various guest molecules are now in progress.

Experimental Section

General. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken at 200 or 400 MHz in $CDCl_3$ with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard, and couplings are expressed in hertz. All extractive organic solutions were dried over anhydrous sodium sulfate. Flash column chromatography was carried out with silica gel 60 spherical (150−325 mesh).

General Procedure for the Preparation of Diols 2.[9] The preparation of the diol **2e** is typical. To a stirred solution of 4-*tert*-butyl-2,6-bis(hydroxymethyl)phenol (30.0 g) and Adogen464 (6.6 g) in CH_2Cl_2 (260 mL) and 2 N aqueous NaOH (130 mL) was added dropwise methoxymethyl chloride (13 mL) at room temperature. The resulting solution was stirred for 10 h, and then the organic layer was separated, washed with aqueous 0.5 N HCl, aqueous 0.5 N NaOH, water (two times), and brine. The extract was dried and concentrated under reduced pressure to afford the diol **2e** (24.7 g, 68%) as pale yellow powder, which was recrystallized from EtOAc (75%).

2a: 52% yield. **2f**: 38% yield. **2g**: 54% yield.

General Procedure for the Preparation of Acetonides 3. The acetonides **3** were prepared from the corresponding 2,6-bis-(hydroxymethyl)phenols **1**[5,7] according to the procedure of Nicolaou.[8] The preparation of the acetonide **3e** is typical. To a stirred solution of 4-*tert*-butyl-2,6-bis-(hydroxymethyl)-phenol (78.7 g) and 2,2-dimethoxypropane (160 mL) in acetone (80 mL) was added *p*-TsOH (0.5 g) at room temperature for 3 h. The solution was neutralized by the addition of excess solid sodium bicarbonate. The mixture was concentrated under reduced pressure, diluted with EtOAc, and washed with water (four times). The organic extract was evaporated under reduced pressure, and HOAc (60 mL, 50% v/v aqueous solution) was added to the residue. The mixture was allowed to stand for 0.5 h before being diluted with ethyl ether. The organic layer was washed successively with water (2 times), aqueous $NaHCO_3$ (two times), water (two times), and brine and dried. Evaporation under reduced pressure left the acetonide **3e** (80.3 g, 86%), which was directly used for the next step without further purification. A part of the sample was subjected to the further purification by PTLC to give an analytical sample.

3a: 93% yield. **3b**: 90% yield. **3c**: 83% yield. **3d**: 99% yield. **3g**: 82% yield.

General Procedure for the Preparation of Benzylbromides 4. The conversion of the acetonide **3e** to the benzylbromide **4e** is typical. To a stirred solution of the acetonide **3e** (13.4 g) and triphenylphosphine (28.1 g) in CH_2Cl_2 (270 mL) was added portionwise carbon tetrabromide (26.6 g) at room temperature. The solution was stirred for 6.5 h and evaporated under reduced pressure. Hexane was added to the residue, and triphenylphosphineoxide was filtered off. The filtrate was evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel with hexane/EtOAc = 10:1 as an eluent to afford the benzylbromide **4e** (6.05 g, 36%).

4a: 65% yield. **4b**: 65% yield. **4c**: 56% yield. **4d**: 66% yield. **4f**: 43% yield. **4g**: 36% yield.

General Procedure for the Preparation of Linear Trimers 5−21. To a solution of the diol **2** in DMF (10 mL for 1.00 g of diol **2**) was added portionwise sodium hydride (2.5 equiv) at 0 °C, and the suspension was further stirred for 20 min at room temperature. A solution of the benzylbromide **4** (2.2 equiv) in DMF (10 mL for 1.00 g of diol **2**) was added dropwise to the suspension, and the resulting mixture was stirred for 10 h at ambient temperature. The reaction mixture was poured into ice-cold water and extracted with EtOAc. The organic layer was washed with water (four times) and brine and dried. Concentration of the extract under reduced pressure gave the residue, which was subjected to silica gel column chromatography with hexane/EtOAc = 5:1 to afford the linear trimer **5**−**21**.

5: 95% yield from **4a** and **2a**. **6**: 85% yield from **4b** and **2a**. **7**: 80% yield from **4c** and **2a**. **8**: 89% yield from **4d** and **2a**. **9**: 84% yield from **4e** and **2a**. **10**: 83% yield from **4a** and **2e**. **11**: 86% yield from **4b** and **2e**. **12**: 85% yield from **4c** and **2e**. **13**: 87% yield from **4d** and **2e**. **14**: 87% yield from **4e** and **2e**. **15**: 84% yield from **4b** and the dimer **22a**. **16**: 61% yield from **4c** and the dimer **22b**. **17**: 84% yield from **4f** and **2f**. **18**: 83% yield from **4e** and **2g**. **19**: 75% yield from **4g** and **2e**. **20**: 56% yield from **4g** and the dimer **22c**. **21**: 78% yield from **4g** and **2g**.

General Procedure for the Preparation of Dimers 22. To a stirred solution of the diol **2** in DMF (10 mL for 1.00 g of diol **2**) was added portionwise sodium hydride (1.1 equiv) at 0 °C, and the mixture was stirred for 20 min at room temperature. A solution of benzylbromide **4** (1.0 equiv) in DMF (10 mL for 1.00 g of diol **2**) was added dropwise to the above suspension, and the mixture was stirred at ambient temperature for 10 h. The reaction mixture was poured into ice-cold water and extracted with EtOAc. The organic layer was washed with water (4 times) and brine and dried. Evaporation under reduced pressure gave the residue, which was purified

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(12) The complexations of **32** and **28** with fullerene including their X-ray analyses will appear in a preliminary form in *J. Chem. Soc., Chem. Commun.*

by column chromatography on silica gel with a solvent system of hexane/EtOAc = 5/1 to afford the corresponding dimer **22**.

22a: 40% yield; **22b**: 34% yield; **22c**: 39% yield.

General Procedure for the Preparation of Hexahomooxacalix[3]arenes 23−38. To a stirred solution of the linear trimer in $CHCl_3$ saturated with H_2O (for the preparation, see text; 200 mL) was added 60% $HClO_4$[10] (0.20 mL for 1.00 g of the trimer). The reaction mixture was stirred at room temperature for 4 h, and then water was added to the solution. The organic layer was separated, dried, and evaporated under reduced pressure to leave the residue, which was triturated with MeOH (10 mL for 1.00 g of the linear trimer), and the mixture was allowed to stand overnight. When white solids were precipitated (**23**−**25**, **32**, and **33**), the precipitates were filtered off, washed with MeOH, and dried in vacuo to afford hexahomooxacalix[3]arenes. In the case of no precipitation, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel with chloroform to afford hexahomooxacalix[3]arenes. In this way, each hexahomooxacalix[3]arene was obtained from the corresponding linear trimer in the yield indicated in Table 1.

23: mp 135−136 °C (from $CHCl_3$−MeOH); IR (KBr) 3354, 3047, 2851, 1616, 1600, 1469, 1356, 1242, 1206, 1070, and 749 cm^{-1}; ^1H NMR δ 4.73 (s, 12H), 6.80 (t, J = 7.5, 3H), 7.13 (d, J = 7.5, 6H), 8.80 (s, 3H); HRMS calcd for $C_{24}H_{24}O_6$ (M^+) 408.1573, found 408.1565. Anal. Calcd for $C_{24}H_{24}O_6$•2/3 H_2O: C, 68.56; H,6.07. Found: C, 68.39; H, 6.04.

24: mp 189−190 °C (from $CHCl_3$−MeOH); IR (KBr) 3343, 2858, 1602, 1488, and 1076 cm^{-1}; ^1H NMR δ 2.22 (s, 6H), 4.67 (s, 4H), 4.69 (s, 4H), 4.71 (s, 4H), 6.79 (t, J = 7.4, 1H), 6.93 (s, 4H), 7.12 (d, J = 7.4, 2H), 8.56 (s, 2H), 8.79 (s, 1H); HRMS calcd for $C_{26}H_{28}O_6$ (M^+) 436.1886, found 436.1876. Anal. Calcd for $C_{26}H_{28}O_6$•1/3$CHCl_3$: C, 66.41; H, 6.00. Found: C, 66.18; H, 6.02.

25: mp 158−160 °C (from $CHCl_3$−MeOH); IR (KBr) 3331, 2962, 2870, 1601, 1488, and 1077 cm^{-1}; ^1H NMR δ 1.15 (t, J = 7.6, 6H), 2.52 (q, J = 7.6, 4H), 4.70 (brs, 12H), 6.79 (t, J = 7.5, 1H), 6.95 (s, 4H), 7.12 (d, J = 7.5, 2H), 8.58 (s, 2H), 8.80 (s, 1H); HRMS calcd for $C_{28}H_{32}O_6$ (M^+) 464.2199, found 464.2187. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.18; H, 6.94.

26: mp 142−143 °C (from $CHCl_3$−MeOH); IR (KBr) 3348, 2955, 2866, 1604, 1487, 1359, 1207, 1178, 1079, 881, and 748 cm^{-1}; ^1H NMR δ 1.17 (d, J = 7.0, 12H), 2.79 (hep, J = 7.0, 2H), 4.72 (s, 12H), 6.78 (t, J = 7.6, 1H), 6.98 (s, 4H), 7.12 (d, J = 7.6, 2H), 8.58 (s, 2H), 8.81 (s, 1H); HRMS calcd for $C_{30}H_{36}O_6$ (M^+) 492.2512, found 492.2512. Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.15; H, 7.37. Found: C, 72.90; H, 7.34.

27: mp 178−179 °C (from $CHCl_3$−MeOH); IR (KBr) 3377, 2957, 2859, 1602, 1490, 1469, 1362, 1306, 1214, 1076, and 879 cm^{-1}; ^1H NMR δ 1.24 (s, 18H), 4.73 (brs, 12H), 6.78 (t, J = 7.4, 1H), 7.12 (d, J = 7.4, 2H), 7.14 (s, 4H), 8.59 (s, 2H), 8.81 (s, 1H); HRMS calcd for $C_{32}H_{40}O_6$ (M^+) 520.2825, found 520.2847. Anal. Calcd for $C_{32}H_{40}O_6$: C, 73.82; H,7.74. Found: C, 73.57; H, 7.83.

28: mp 183−185 °C (from $CHCl_3$−MeOH); IR (KBr) 3342, 2960, 2864, 1602, 1469, 1356, 1269, 1207, 1075, 1006, and 755 cm^{-1}; ^1H NMR δ 1.25 (s, 9H), 4.72 (brs, 12H), 6.79 (t, J = 7.5, 2H), 7.13 (d, J = 7.5, 4H), 7.15 (s, 2H), 8.58 (s, 1H), 8.81 (s, 2H); HRMS calcd for $C_{28}H_{32}O_6$ (M^+) 464.2198, found 464.2170. Anal. Calcd for $C_{28}H_{32}O_6$: C, 72.39; H, 6.94. Found: C, 72.40; H, 7.05.

29: mp 100−102 °C (from H_2O−MeOH); IR (KBr) 3352, 2954, 2859, 1612, 1488, 1357, 1306, 1210, 1159, 1078, 1000, 863, 824, 783, 756, 570, and 408 cm^{-1}; ^1H NMR δ 1.24 (s, 9H), 2.21 (s, 6H), 4.66 (s, 4H), 4.69 (s, 4H), 4.71 (s, 4H), 6.92 (s, 4H), 7.13 (s, 2H), 8.56 (s, 3H); HRMS calcd for $C_{30}H_{36}O_6$ (M^+) 492.2512, found 492.2540. Anal. Calcd for $C_{30}H_{36}O_6$: C, 73.15; H, 7.37. Found: C, 72.96; H, 7.45.

30: mp 153−154 °C (from $CHCl_3$−MeOH); IR (KBr) 3363, 2960, 1612, 1488, 1208, and 1082 cm^{-1}; ^1H NMR δ 1.14 (t, J = 7.6, 6H), 1.24 (s, 9H), 2.51 (q, J = 7.6, 4H), 4.69 (s, 4H), 4.70 (s, 4H), 4.72 (s, 4H), 6.95 (s, 4H), 7.13 (s, 2H), 8.58 (s, 3H); HRMS calcd for $C_{32}H_{40}O_6$ (M^+) 520.2825, found 520.2828. Anal. Calcd for $C_{32}H_{40}O_6$: C, 73.82; H, 7.74. Found: C, 73.63; H, 7.93.

31: mp 191−192 °C (from $CHCl_3$−MeOH); IR (KBr) 3367, 2957, 2869, 1612, 1487, 1211, 1084, and 879 cm^{-1}; ^1H NMR δ 1.16 (d, J = 6.9, 12H), 1.24 (s, 9H), 2.78 (hep, J = 6.9, 2H), 4.71 (brs, 12H), 6.98 (s, 4H), 7.13 (s, 2H), 8.58 (s, 3H); HRMS calcd for $C_{34}H_{44}O_6$ (M^+) 548.3138, found 548.3129. Anal. Calcd for $C_{34}H_{44}O_6$: C, 74.42; H, 8.08. Found: C, 74.25; H, 8.17.

32:[3,4,5] This compound was identified by a comparison with the reported physical data.

33: mp 183−184 °C (from $CHCl_3$−MeOH); IR (KBr) 3341, 2961, 2855, 1602, 1488, 1358, 1205, 1158, 1077, 1011 867, 778, and 749 cm^{-1}; ^1H NMR δ 1.15 (t, J = 7.7, 3H), 2.22 (s, 3H), 2.52 (q, J = 7.7, 2H), 4.70 (brs, 12H), 6.79 (t, J = 7.6, 1H), 6.93 (s, 2H), 6.95 (s, 2H), 7.12 (d, J = 7.6, 2H), 8.56 (s, 1H), 8.57 (s, 1H), 8.80 (s, 1H); HRMS calcd for $C_{27}H_{30}O_6$ (M^+) 450.2043, found 450.2061. Anal. Calcd for $C_{27}H_{30}O_6$: C, 71.98; H, 6.71. Found: C, 71.82; H, 6.73.

34: mp 177−178 °C (from $CHCl_3$−MeOH); IR (KBr) 3366, 2957, 2868, 1613, 1488, 1209, 1084, and 877 cm^{-1}; ^1H NMR δ 1.10−1.25 (m, 3H), 1.16 (d, J = 6.9, 6H), 1.24 (s, 9H), 2.51 (q, J = 7.3, 2H), 2.79 (hep, J = 6.9, 1H), 4.70 (brs, 12H), 6.95 (s, 2H), 6.98 (s, 2H),7.13 (s, 2H), 8.58 (s, 3H); HRMS calcd for $C_{33}H_{42}O_6$ (M^+) 534.2981, found 534.3003. Anal. Calcd for $C_{33}H_{42}O_6$: C, 74.13; H, 7.92. Found: C, 73.79; H, 8.10.

35: mp 160 °C (from $CHCl_3$−MeOH); IR (KBr) 3358, 2838, 1611, 1489, 1359, 1320, 1252, 1193, 1156, 1082, 1053, 854, 778, and 750 cm^{-1}; ^1H NMR δ 3.73 (s, 9H), 4.68 (s, 12H), 6.72 (s, 6H), 8.39 (s, 3H); HRMS calcd for $C_{27}H_{30}O_9$ (M^+) 498.1890, found 498.1877. Anal. Calcd for $C_{27}H_{30}O_9$•1/2H_2O: C, 63.90; H, 6.16. Found: C, 63.92; H, 5.99.

36: mp 103−105 °C (from H_2O−MeOH); IR (KBr) 3364, 2956, 1614, 1489, 1362, 1213, 1079, 1011, 879, and 732 cm^{-1}; ^1H NMR δ 1.25 (s, 18H), 4.66 (s, 4H), 4.71 (s, 4H), 4.73 (s, 4H), 7.14 (brs, 4H), 7.24 (brs, 2H), 8.49 (s, 2H), 8.87 (s, 1H); HRMS calcd for $C_{32}H_{39}Br{*}O_6$ (M^+) 598.1930, found 598.1933, calcd for $C_{32}H_{39}Br{*}O_6$ (M^+) 600.1910, found 600.1902. Anal. Calcd for $C_{32}H_{39}BrO_6$•H_2O: C, 62.24; H, 6.69. Found: C, 62.42; H, 6.39.

37: mp 142−144 °C (from $CHCl_3$−MeOH); IR (KBr) 3346, 2959, 2860, 1471, 1353, 1242, 1200, 1079, 1010, 881, and 729 cm^{-1}; ^1H NMR δ 1.25 (s, 9H), 4.64 (s, 4H), 4.66 (s, 4H), 4.71 (s, 4H), 7.14 (s, 2H), 7.24 (s, 2H), 7.25 (s, 2H), 8.40 (s, 1H), 8.77 (s, 2H); HRMS calcd for $C_{28}H_{30}Br_2{*}O_6$ (M^+) 620.0409, found 620.0425, calcd for $C_{28}H_{30}Br_2{*}O_6$ (M^+) 622.0389, found 622.0409, calcd for $C_{28}H_{30}Br_2{*}O_6$ (M^+) 624.0369, found 624.0388. Anal. Calcd for $C_{28}H_{30}Br_2O_6$: C, 54.04; H, 4.86. Found: C, 54.30; H, 4.95.

38: mp 220−221 °C (from $CHCl_3$−MeOH); IR (KBr) 3328, 2856, 1471, 1352, 1241, 1077, 1010, 866, and 728 cm^{-1}; ^1H NMR δ 4.64 (s, 12H), 7.25 (s, 6H), 8.68 (s, 3H); HRMS calcd for $C_{24}H_{21}Br_3{*}O_6$ (M^+) 641.8888, found 641.8936, calcd for $C_{24}H_{21}Br_3{*}O_6$ (M^+) 643.8868, found 643.8906, calcd for $C_{24}H_{21}Br_3{*}O_6$ (M^+) 645.8847, found 645.8845, calcd for $C_{24}H_{21}Br_3{*}O_6$ (M^+) 647.8826, found 647.8854. Anal. Calcd for $C_{24}H_{21}Br_3O_6$: C, 44.68; H, 3.28. Found: C, 44.44; H, 3.24.

Attempted Cyclization of 19. To a stirred solution of the linear trimer **19** (145.5 mg) in $CHCl_3$ saturated with H_2O (for the preparation, see text; 29.1 mL) was added 60% $HClO_4$ (29 μL). The reaction mixture was stirred at room temperature for 4 h, and then water was added to the solution. The organic layer was separated, dried, and evaporated under reduced pressure. The residue was purified by PTLC with a solvent system of hexane/EtOAc = 1:1 to afford **39** (24.3 mg, 18%), **40** (39.6 mg, 31%), and **41** (48.1 mg, 40%), respectively.

39: IR ($CHCl_3$) 3386, 3014, 2963, 2846, 1463, 1376, 1245, and 1137 cm^{-1}; ^1H NMR δ 1.29 (s, 9H), 1.54 (s, 12H), 4.57 (s, 4H), 4.70 (s, 4H), 4.81 (s, 4H), 7.05 (brs, 2H), 7.18 (s, 2H), 7.41 (brs, 2H), 7.53 (s, 1H); HRMS calcd for $C_{34}H_{40}Br_2{*}O_7$ (M^+) 718.1141, found 718.1151, calcd for $C_{34}H_{40}Br_2{*}O_7$ (M^+) 720.1121, found 720.1124, calcd for $C_{34}H_{40}Br_2{*}O_7$ (M^+) 722.1100, found 722.1077.

40: IR ($CHCl_3$) 3386, 2964, 1466, 1376, 1247, and 1065 cm^{-1}; ^1H NMR δ 1.27 (s, 9H), 1.57 (s, 6H), 4.59 (s, 2H), 4.68 (brs, 6H), 4.74 (s, 2H), 4.83 (s, 2H), 7.07 (d, J = 2.4, 1H), 7.10 (d, J = 2.4, 1H), 7.14 (d, J = 2.4, 1H), 7.18 (d, J = 2.4, 1H), 7.27 (d, J = 2.4, 1H), 7.34 (d, J = 2.4, 1H), 7.72 (s, 1H), 8.15 (s, 1H); HRMS calcd for $C_{31}H_{36}Br_2{*}O_7$ (M^+) 678.0828, found 678.0808, calcd for $C_{31}H_{36}Br_2{*}O_7$ (M^+) 680.0807, found 680.0814, calcd for $C_{31}H_{36}Br_2{*}O_7$ (M^+) 682.0787, found 682.0843.

41: IR ($CHCl_3$) 3369, 3013, 2964, 1611, 1488, 1470, 1364, 1255, 1072, and 870 cm^{-1}; ^1H NMR δ 1.26 (s, 9H), 4.64 (s, 4H), 4.68 (s, 4H), 4.69 (s, 4H), 7.11 (s, 2H), 7.17 (d, J = 2.4, 2H), 7.21 (d, J = 2.4, 2H), 8.08 (s, 1H), 8.59 (s, 2H); HRMS calcd for $C_{28}H_{32}Br_2{*}O_7$ (M^+) 638.0515, found 638.0551, calcd for $C_{28}H_{32}Br_2{*}O_7$ (M^+) 640.0494, found 640.0509.

X-ray Crystallographic Analyses of 28 and 34. Crystal data for **28** ($C_{28}H_{32}O_6$): trigonal, space group $P3_1$, a = 18.6231(7) Å, c = 12.142(1) Å, V = 3646.9(4) $Å^3$, Z = 6, D_{calcd} = 1.269 g cm^{-3}, λ (Cu Kα) = 1.541 78 Å, T = 298 K, R = 0.061, R_w = 0.088 for 4588 reflections. Crystal data for **34** ($C_{33}H_{42}O_6$): orthorhombic, space group $Pna2_1$, a = 12.986(1) Å, b = 28.047(2) Å, c = 17.130(4) Å, V = 6238(2) $Å^3$, Z = 8, D_{calcd} = 1.138 g cm^{-3}, λ (Cu Kα) = 1.541 78 Å, T = 298 K, R = 0.098, R_w = 0.086 for 5601 reflections. Further details of the crystal structure investigation are available on request from the Director of the Cambridge Crystallographic Data Center.

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Supporting Information Available: The X-ray crystallographic analysis data for **28** and **34**, ^1H NMR, IR, MS spectral, and elemental analysis data of intermediates, **2a**,**e**−**g**, **3a**−**e**,**g**, **4a**−**g**, **5**−**21**, and **22a**−**c**, and ^1H NMR spectra of **3a**,**b**, **4c**,**d**, **8**, **10**, **18**−**21**, **22b**, and **39**−**41** lacking elemental analyses (21 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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