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A Study on the Synthesis of Calix[4 and 6]arenes Using Alternately Arranged Phloroglucinols and *p-tert*-Butylphenols

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A method for the synthesis of calix[4 and 6]arenes with two or three alternately arranged phloroglucinols and *p-tert*-butylphenols was studied using "3+1" and "5+1" approaches, compared to a simple one-pot synthesis based on a "1+1" approach. By using Yb(OTf)$_3$ as a catalyst, each calix[4 and 6]arenes was afforded, in an overall yield of 20.7% and 11.8% in the "3+1" and "5+1" approaches, respectively, and 24.6% and 19.9% using a "1+1" approach with chlorobenzene and toluene as refluxing solvents, respectively.

Key words calix[4]arene; calix[6]arene; phloroglucinol; *p-tert*-butylphenol; 1+1 approach

Various calixarenes composed of phenol derivatives have been synthesized and their functionality such as inclusion property has been developed in molecular recognition and supramolecular chemistry.[1—5] However, to our knowledge, calixarenes including phloroglucinols (1,3,5-tri-hydroxybenzenes) have not been synthesized. Recently we have first synthesized a calix[4]arene (**1**) with two alternately arranged phloroglucinols and *p-tert*-butylphenols and explored its property such as determination of the pK_a-values by a potentiometric titration and a photometric pH titration methods, observation of the structure's change with the change of pH by NMR spectroscopy, solvent extraction of some alkali metal ions, and measurement of the cyclic voltammogram.[6] That is due to the property of phlorogrucinol which is easy to change into keto-form in alkaline solution. In the previous paper,[6] it was found that **1** showed pK_a values to be 3—4, 7.5, and the other chelated hydroxyls 11, and caused the structure-change over pH 11, and extracted only Li$^+$ among alkaline metals at pH 11.

We have been interested in the calix[6]arene (**2**) which is expected to be able to extract larger ions than Li$^+$, because **2** has a larger cavity than **1**. We have also been interested in the simple and effective synthetic method for the larger amount of supply of these calix[4 and 6]arenes (**1** and **2**) for the above study.[2]

Results and Discussion

The synthesis of calix[4]arene **6** was performed by "3+1" approach.[1—6] Trimer **5** could be prepared by the condensation of 2 eq of trimethoxybenzenes (**3**) and 1 eq of 2,6-di-hydroxymethyl-4-*tert*-butylphenol (**4**) in the presence of catalytic amounts (0.1 eq) of *p*-TsOH·H$_2$O, as shown in Table 1. The reaction was carried out by dropwise addition of a solution of **4** in toluene to a solution of **3** and *p*-TsOH·H$_2$O in toluene at room temperature for 10 min—1 h and an additional heating. Even when the temperature and time was changed, respectively, the yield was scarcely changed. The best yield of **5** was 56% with a linear pentamer **7** of 21% yield by stirring at 110 °C for 1 h after 20 min-stirring at room temperature (Table 1, Entry 3).

The next "3+1" approach, in which trimer **5** and equimolar amount of **4** were condensed by azeotropic refluxing in toluene under the conditions of high-dilute concentrations (0.59 mM) in the presence of 0.45 eq of *p*-TsOH·H$_2$O,[3—5] afforded a calix[4]arene **6** in the best yield of 37%,[6] as shown by Entry 2 in Table 2. When the concentration was either too dilute or too concentrated, the yield was not good. Scandium(III) trifluoromethanesulfonate [Sc(OTf)$_3$] or ytterbium (III) trifluoromethanesulfonate [Yb(OTf)$_3$] was used as a catalyst in the place of *p*-TsOH·H$_2$O, however, the yield was no improvement.

We next examined the synthesis of calix[6]arene (**8**) by "5+1" approach applying the above "3+1" approach. Linear pentamer **7** was synthesized by condensation of trimer **5** and **3** with an equimolar amount of **4** in the yield of 31% along with **6** in a yield of 13% under the reaction conditions of stir-

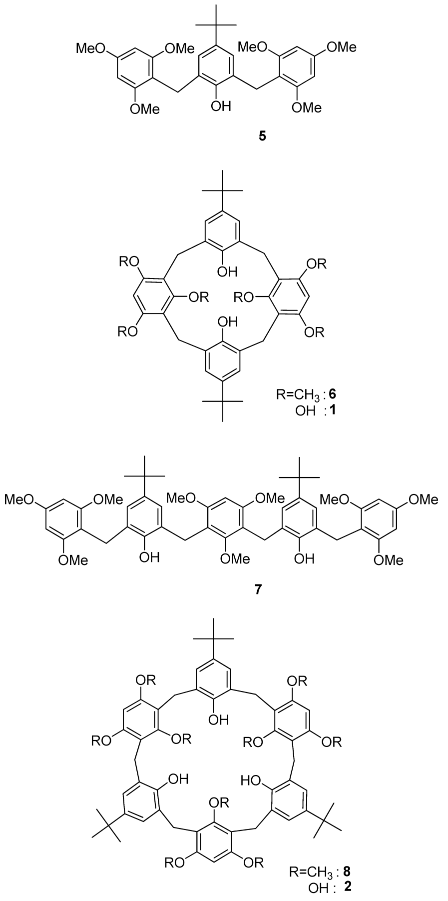

Fig. 1.

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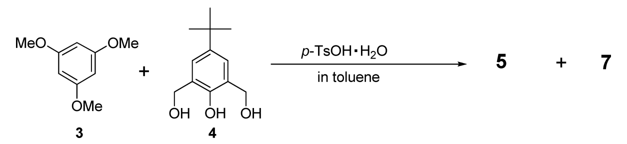
Table 1. Synthesis of Trimer **5**



Entry	p-TsOH·H_2O (eq)	Temp./Time	Yield (%)	
			5	**7**
1	0.1	rt, 1 h →60 °C, 5 h	47	18
2	0.1	rt, 30 min→100 °C, 1 h	52	22
3	0.1	rt, 20 min→110 °C, 1 h	56	21
4	0.2	rt, 10 min→100 °C, 40 min	47	23
5	0.05	rt, 10 min→100 °C, 40 min	44	21

Table 2. Synthesis of Calix[4]arene **6**

$$\mathbf{5} + \mathbf{4} \xrightarrow[\text{in toluene, reflux, 8 h}]{\text{Catalyst}} \mathbf{6}$$

Entry	Catalyst (eq)	Conc. (mM)	Yield of **6** (%)
1	p-TsOH·H_2O (0.45)	0.44	32
2	p-TsOH·H_2O (0.45)	0.59	37
3	p-TsOH·H_2O (0.45)	0.88	26
4	$Sc(OTf)_3$ (0.10)	3	11
5	$Yb(OTf)_3$ (0.10)	3	18
6	$Yb(OTf)_3$ (0.20)	0.44	22

$$\mathbf{5} + \mathbf{4} + \mathbf{3} \xrightarrow[\text{in toluene rt, 1 h, 60 °C 4 h}]{p\text{-TsOH}\cdot\text{H}_2\text{O (0.1 equiv)}} \mathbf{7}$$

Y: 31%

Chart 1. Synthesis of Linear Pentamer **7**

$$\mathbf{7} + \mathbf{4} \xrightarrow[\text{in toluene (1.29 mM) reflux 3 h}]{p\text{-TsOH}\cdot\text{H}_2\text{O (0.15 equiv)}} \mathbf{6}$$

Y: 21%

Chart 2. Synthetic Attempt of Calix[6]arene **8** Using “5+1” Approach under High-Dilution Conditions

Table 3. Synthesis of Calix[6]arene **8** Using “5+1” Approach under High-Dilution Conditions

$$\mathbf{7} + \mathbf{4} \xrightarrow[\text{in benzene reflux, for 7 h}]{\text{Yb(OTf)}_3\text{ (0.15 equiv)}} \mathbf{8}$$

Entry	Conc. (mM)	Yield of **8** (%)
1	0.408	28.8
2	0.815	30.7
3	1.63	28.2
4	3.26	16.9

Table 4. Synthesis of Calix[4 and 6]arenes (**6** and **8**) Using “1+1” Approach under High-Dilution Conditions

$$\mathbf{3} + \mathbf{4} \xrightarrow[\text{in benzene reflux, for 7 h}]{\text{Yb(OTf)}_3\text{ (0.15 equiv)}} \mathbf{5} + \mathbf{6} + \mathbf{7} + \mathbf{8}$$

Entry	Conc. (mM)	Yield (%)			
		5	**6**	**7**	**8**
1	1.63	8.7	22.3	2.9	8.5
2	2.45	4.7	20.2	6.1	9.1
3	3.26	2.7	17.9	5.2	9.7
4	6.52	3.5	13.5	1.4	1.7

ring in toluene in the presence of a 0.1 eq of p-TsOH·H_2O within a range of room temperature to 60 °C for 1 h (Chart 1). The “5+1” approach was performed in the same manner as the above “3+1” approach, however, these conditions gave no **8** and only a calix[4]arene **6** in the yield of 21% (Chart 2). Since these results suggested that scission of the **7** proceeded under these conditions, the reaction conditions were made to be milder, such as the use of benzene in the place of toluene as a refluxing solvent, and the use of $Yb(OTf)_3$ in the place of p-TsOH·H_2O as an acid catalyst (Table 3). The best condition was 7-h refluxing in benzene (concentration: 0.815 mM) in the presence of 0.15 eq of $Yb(OTf)_3$ and gave **8** in the yield of 30.7% (Table 3, Entry 2). When the concentration was either too dilute or too concentrated, the yield was not good.

Further, we tried a simpler one-step synthetic method, a “1+1” approach using the condensation reaction of equimolar amounts of **3** and **4** under high-dilution concentrations (Table 4).[2,8] Under the same conditions as the above that of **8**, the reaction was carried out using the four different concentrations to result in **5**, **6**, **7**, and **8** as a main product. The best yield of **8** was 9.7% with **6** of 17.9% in the concentration of 3.26 mM (Table 3, Entry 3), and the best yield of **6** was 22.3% with **8** of 8.5% in the concentration of 1.63 mM (Table 4, Entry 1). “1+1” Approach gave many products, however, purification of calix[4 and 6]arenes (**6** and **8**) was relatively easy because of ease of crystallization of the cyclic oligomers. After calix[4]arene **6** was firstly afforded by recrystallization from EtOAc, the filtrate was crude-separated by silica-gel column chromatography (n-hexane–EtOAc) and the resulted fractions including **8** afforded pure **8** as crystals by recrystallization from EtOAc. The production ratio of **3** and products (**5**, **6**, **7**, **8**) was measured at regular intervals from the start until 12 h, using sampling and HPLC analysis from some different refluxing solvents under a 3.26 mM concentration (Figs. 2a, b, c, d, e). The reaction was completed as follows: the dropwise-addition of a solution of equimolar **3** and **4** to a refluxing solution of $Yb(OTf)_3$ was continued during 6 h, with 6 h of additional refluxing. When benzene was used as a solvent, the formation of **6** was begun immediately, while the formation of **8** occurred at 4.5 h (Fig. 2a). The production ratios of **6** and **8** were 38 and 18%, respectively, and this ratio did not change from 6 to 12 h. The same reaction under the higher refluxing temperature using toluene (bp=118 °C) as a solvent was carried out (Fig. 2b). Both production ratios for **6** and **8** were the same, and gradually increased reaching the maximum of 32% after 5 h—beyond which the ratio did not change. The reaction was finished after 12 h and the each reaction product was isolated to afford **6** in 22.0% and **8** in 19.9% (Table 5). When xylenes (bp=138—145 °C) were used as a solvent, trimers **5′**, which were condensed between **4** and xylenes in the place of **3**, was produced as a main product (35—50%). Trimers **5′** may not be able to react further due to its own steric hindrance. Next, the same reaction using chlorobenzene (bp=132 °C) as a solvent which is the more polar and does not react itself, was

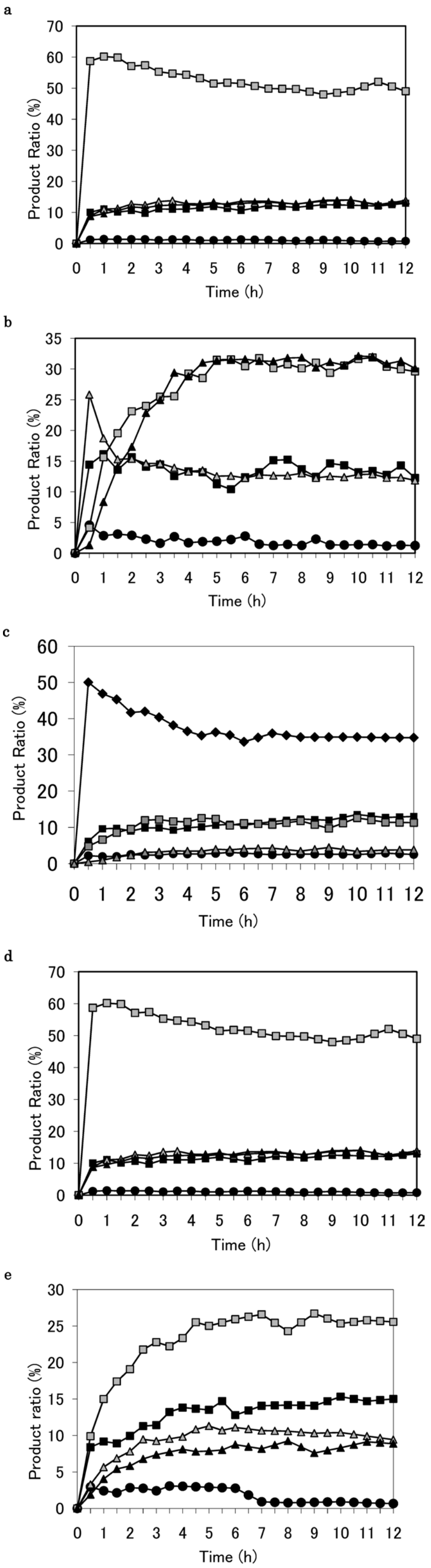
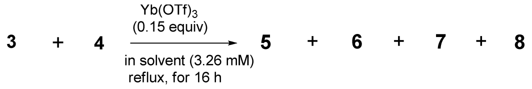


Fig. 2. Product Ratio *vs.* Reaction Time in the Condensation Reaction of Trimethoxybenzene (**3**) with Bis-hydroxymethyl-*tert*-butylphenol (**4**) in the Presence of Yb(OTf)$_3$ in Refluxing Solvent (**3**: ●, **5**: ■, **5′**: ◆, **6**: □, **7**: △, **8**: ▲)

Solvents: (a) benzene, (b) toluene, (c) xylenes, (d) chlorobenzene, (e) ethylbenzene.

Table 5. Synthetic Study of Calix[4 and 6]arenes (**6** and **8**) by "1+1" Approach under High-Dilution Reaction Conditions Using Some Refluxing Solvents



Solvent	Yield (%)			
	5	**6**	**7**	**8**
Benzene	2.8	17.9	5.2	9.7
Toluene	Trace	22.0	9.3	19.9
Chlorobenzene	Trace	24.6	14.0	12.8
Ethylbenzene	27.3	23.4	8.3	6.1

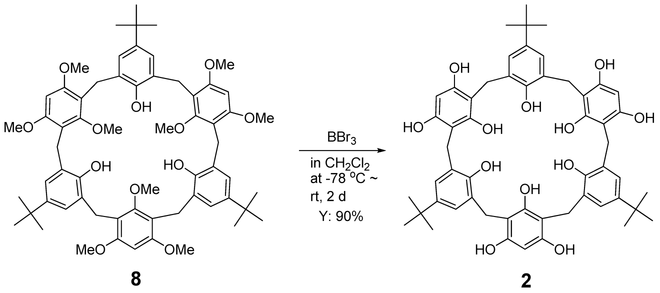


Chart 3

carried out (Fig. 2d). Under the condition of refluxing in chlorobenzene, the production ratio of **6** was immediately reached at a yield of 50—60% and the production ratio of **8** was low, at 10%. When the refluxing temperature was high, the starting material **3** almost reacted immediately. The reaction products after 12 h were isolated in the same manner. Cyclic tetramer **6** and hexamer **8** was afforded in 24.6% and 12.8% yield, respectively (Table 5). Finally ethylbenzene, having the high boiling point (bp=136 °C, Fig. 2e) was used as a refluxing solvent in the place of xylenes and chlorobenzene. However, unexpectedly the unreactive **5** and **7** were remained at the ratio of 14% and 9%, respectively, and the production ratio of **6** and **8** was low, at 25% and 8%, respectively. The isolated yield of **6** and **8** was 23.4% and 6.1%, respectively (Table 5). For the one-step synthesis using a "1+1" approach, when the more polar chlorobenzene was used as a refluxing solvent, the isolated yield of cyclic tetramer **6** reached the maximum of 24.6%. The maximum yield of the more unstable cyclic hexamer **8** was 19.9% when toluene was used as a refluxing solvent.

Deprotection of **8** was achieved, in the same manner as that of **6**,[6] by BBr$_3$ at −78 °C to room temperature to give **2** in the yield of 90%. Since ^{1}H- and ^{13}C-NMR spectra of **8** and **2** both gave a symmetry singlet peak for each proton and carbon of the *tert*-butylphenol, phloroglucinol, and methylene moieties, it was assumed that the structures of both **8** and **2** are symmetrical cyclic in analogy with **6** and **1**.

Conclusion

We studied on the simple and effective synthesis of the calix[4 and 6]arenes including two or three alternately arranged phloroglucinols and *p*-*tert*-butylphenols using either a "3+1" or a "5+1" approach, and a simple "1+1" approach for both using a refluxing solvent. The "3+1" approach requiring a two-step reaction gave the cyclic tetramer **6** in the overall yield of 20.7%, and the "5+1" approach requiring a three-step reaction gave the cyclic hexamer **8** in the overall yield of 11.8%. On the other hand, the simple "1+1" approach, by changing the reaction solvent, gave **6** and **8** in the maximum yield of 24.6% and 19.9%, respectively. Chlorobenzene and toluene were the most effective solvents in the one-pot synthesis of the calix[4 and 6]arenes using the "1+1" approach, respectively.

Experimental

$Sc(OTf)_3$ and $Yb(OTf)_3$, purchased from Taiheiyo Kinzoku Co., Ltd. and TOKYO KASEI Co., Ltd. respectively, and were directly used without any further manipuration. The solvents used in this reaction were purified by distillation. Reactions were monitored by TLC, on 0.25-mm Silica Gel F254 plates (E. Merck) using UV light, and a 7% ethanolic solution of phosphomolybdic acid with heat as a coloration agent. For separation and purification, flash column chromatography was performed on silica gel (230—400 mesh, Fuji-Silysia Co., Ltd., BW-300). Melting points were determined on a AS ONE ATM-01 melting point apparatus and are uncorrected. IR spectra were recorded on a Horiba FT-720 IR spectrometer in the form of KBr disks. NMR spectra were recorded on a Varian Inova 500 spectrometer using Me_4Si as the internal standard. Mass spectral data were obtained by fast-atom bombardment (FAB) using *m*-nitrobenzylalcohol as a matrix on a JEOL JMS-AX505HA instrument. Elemental analyses were performed on a Perkin-Elmer PE 2400 II instrument.

HPLC Analysis HPLC was performed on a Hitachi L-7100 and L-4200H system using the following conditions; column, GL Sciences Inc., Inertsil ODS-3 column (4.6×250 mm), solvent, methanol–H_2O=92 : 8: flow rate, 1 ml/min; and wavelength, UV 254 nm. Sampling (0.8 ml) for HPLC analysis was carried out at each 0.5 h from the reaction start time until the finish (12 h). After evaporation of the sample, the residue was dissolved in AcOEt (*ca.* 110 μl), and 10 μl was subjected to the HPLC analysis. Retention time (min) was as follows: **3**; 4.34, **5**; 7.76, **6**; 26.6, **7**; 16.6, **8**; 18.3.

Synthesis The syntheses and data of trimethoxybenzene (**1**), bis-hydroxymethyl-4-*tert*-butylphenol (**2**), and trimer (**5**) were showed in the previous paper.[6]

2,6-Bis[4-*tert*-butyl-2-hydroxy-3-(2,4,6-trimethoxybenzyl)]benzyl-1,3,5-trimethoxybenzene (7) A solution of **4** (420 mg, 2 mmol) in dry toluene (20 ml) was added dropwise for 1 h to a stirred solution of **5** (2.04 g, 4 mmol), **3** (672 mg, 4 mmol), and *p*-TsOH·H_2O (38 mg, 0.2 mmol) in dry toluene (10 ml) at room temperature under argon atmosphere, and then stirred at 60 °C for 4 h. After cooling, to the reaction mixture 5% aqueous $NaHCO_3$ solution was added until the reaction's pH to be 5. The resulting mixture was extracted with EtOAc twice. The organic layer was washed with water and brine, and dried with anhydrous Na_2SO_4, and then removed under vacuum. The residue was separated by silica-gel column chromatography (*n*-hexane–EtOAc=3 : 1) to give **7** (1063 mg, 31.2%) as a white powder.

Data for **7**: Colorless powder. mp 182 °C. IR (KBr) cm^{-1}: 3435, 2956, 2835, 1601, 1483, 1464, 1205, 1187, 1122. ^1H-NMR ($CDCl_3$) δ: 1.14 (18H, s, *tert*-Bu×2), 3.51 (3H, s, OMe×1), 3.77 (6H, s, OMe×2), 3.80 (6H, s, OMe×2), 3.84 (12H, s, OMe×4), 3.86 (4H, s, CH_2×2), 3.91 (4H, s, CH_2×2), 6.16 (4H, s, ArH×4), 6.35 (1H, s, ArH×1), 6.81 (2H, d, J=2.4 Hz, ArH×2), 7.02 (2H, d, J=2.4 Hz, ArH×2), 7.56 (2H, s, OH×2). FAB-MS *m*/*z*: 855 $(M+H)^+$. *Anal.* Calcd for $C_{51}H_{64}O_{11}$: C, 71.80; H, 7.56. Found: C, 71.52; H, 7.46.

11,23,35-Tri-*tert*-butyl-37,39,41-trihydroxy-4,6,16,18,28,30,38,40,42-nonamethoxycalix[6]arene (8). "5+1" Approach To a refluxing solution of $Yb(OTf)_3$ (55.8 mg, 0.09 mmol) in dry benzene (450 ml), a solution of **7** (512 mg, 0.6 mmol) and bis-hydroxymethyl-4-*tert*-butylphenol (**4**, 21 mg×6, 0.6 mmol) in dry benzene (50 ml×6) was added dropwise for 6 h. The resulting water was removed with a Dean–Stark trap. After additional refluxing for 1 h, the reaction mixture was cooled and then benzene was removed under vacuum until 100 ml. The residual benzene solution was washed with a 5% $NaHCO_3$ aqueous solution and water, and then dried over anhydrous Na_2SO_4. After removing the benzene under vacuum, the residue was recrystallized from EtOAc to give **8** (120 mg, 19.5%) as colorless powder. The filtrate was separated by silica-gel column chromatography (*n*-hexane–EtOAc=3 : 1) and recrystallized from $CHCl_3$ to give **8** (69 mg, 11.2%) as a colorless prism.

"1+1" Approach To a refluxed solution of $Yb(OTf)_3$ (446.4 mg, 0.72 mmol) in dry benzene (900 ml), a solution of trimethoxybenzene (**3**, 806 mg, 4.8 mmol) and bis-hydroxymethyl-4-*tert*-butylphenol (**4**, 1008 mg, 4.8 mmol) in dry benzene (600 ml) was added dropwise for 6 h, and additional 1-h refluxing. Na_2HPO_4 (102 mg, 0.72 mmol) was added to the cooled reaction mixture and benzene was removed under vacuum until 100 ml. The residual benzene solution was washed with water and brine, and then dried with anhydrous Na_2SO_4. Benzene was removed under vacuum and the residual solid was crystallized from EtOAc to afford **6** (588 mg, 17.9%). The filtrate was separated by silica gel column chromatography (*n*-hexane–EtOAc=3 : 1) to give fractions including **8**, along with **5** (66 mg, 2.7%) and **7** (213 mg, 5.2%), which were crystallized from EtOAc to give **8** (478 mg, 9.7%) as a white powder.

Data for **8**: Colorless prism ($CHCl_3$). mp >300 °C. IR (KBr) cm^{-1}: 3400, 2952, 2835, 1601, 1485, 1464, 1408, 1325, 1198, 1101. ^1H-NMR ($CDCl_3$) δ: 1.10 (278H, s, *tert*-Bu×3), 3.39 (9H, br s, OMe×3), 3.80 (12H, s, CH_2×3), 3.87 (18H, s, OMe×6), 6.36 (3H, s, OH×3), 6.84 (6H, s, ArH×6), 7.49 (6H, s, ArH×3). ^{13}C-NMR ($CDCl_3$, at 50 °C) δ: 23.8 (C-2, 8, 14, 20, 26, 32), 31.6 (*tert*-Butyl methyl C), 33.8 (*tert*-butyl quaternary C), 92.4 (C-11, 23, 35), 115.8 (C-1, 9, 13, 21, 25, 33), 124.4 (C-4, 6, 16, 18, 28, 30), 126.5 (C-3, 7, 15, 19, 27, 31), 141.31 (C-5, 17, 29), 149.56 (C-38, 40, 42), 157.26 (C-10, 12, 22, 24, 34, 36), 157.42 (C-37, 39, 41). FAB-MS *m*/*z*: 1027 $(M+H)^+$. *Anal.* Calcd for $C_{63}H_{78}O_{12}\cdot 0.6CHCl_3$: C, 69.51; H, 7.21. Found: C, 69.56; H, 7.15.

11,23,35-Tri-*tert*-butyl-4,6,16,18,28,30,37,38,39,40,42-dodecahydroxycalix[6]arene (2) To a solution of **8** (220 mg, 0.214 mmol) in dry CH_2Cl_2 (3 ml), BBr_3 (912 μl, 9.65 mmol) was added at −78 °C under argon. The reaction mixture was stirred at room temperature for 2 d, and then poured into ice-cold saturated $NaHCO_3$ aqueous solution, then extracted three times with AcOEt. The organic layer was washed with water and brine, and dried over anhydrous Na_2SO_4 and then evaporated under vacuum to give **2** (185 mg, 90%) as a pale-yellow powder.

Data for **2**: Pale-yellow powder (EtOAc–diethyl ether). mp >300 °C. IR (KBr) cm^{-1}: 3245, 2960, 2870, 1622, 1485, 1446, 1188, 1111. ^1H-NMR (DMSO-d_6, at 50 °C) δ: 1.07 (27H, s, *tert*-Bu×3), 3.64 (12H, br s, CH_2×6), 6.06 (3H, s, ArH×3), 6.95 (6H, br s, ArH×6), 8.86 (6H, br s, OH×6), 9.08 (6H, br s, OH×6). ^{13}C-NMR (DMSO-d_6+D_2O, at 50 °C) δ: 23.6 (C-2, 8, 14, 20, 26, 32), 31.3 (*tert*-butyl methyl C), 33.3 (*tert*-butyl quaternary C), 95.2 (C-11, 23, 35), 115.4 (C-1, 9, 13, 21, 25, 33), 124.5 (C-4, 6, 16, 18, 28, 30), 126.6 (C-3, 7, 15, 19, 27, 31), 141.1 (C-5, 17, 29), 148.5 (C-37, 39, 41), 153.1 (C-38, 40, 42). FAB-MS *m*/*z*: 901 $(M+H)^+$. *Anal.* Calcd for $C_{54}H_{60}O_{12}1.2B(OH)_3$: C, 66.50; H, 6.57. Found: C, 66.62; H, 6.83.

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