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Modification of the Upper Rim of Homooxacalix[3]arenes and Complexation between a Nitrohomooxacalix[3]arene Derivative and *n*-Hexylamine†

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Several functional groups were introduced on the upper rim of (lower rim free) homooxacalix[3]-arene for the first time. The swinging nitrohomooxacalix[3]arene host **1** was fixed in the cone conformation by complexation with *n*-hexylamine.

Introduction

Homooxacalix[3]arene is related to calix[4]arene and 18-crown-6 ether with 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).[1] The most striking structural difference between homooxacalix[3]arene and 18-crown-6 ether is that homooxacalix[3]arene has a three-dimensional cavity. These features have awakened supramolecular chemists to make receptors for metal cations,[2] ammonium cations,[3] and fullerene derivatives.[4] Due to the presence of three fragile dibenzyl etheral linkages, many difficulties, however, arose in the transformation of functional groups on the upper rim. To the best of our knowledge, only two papers have been reported concerning the transformation of functional groups for lower rim (phenolic hydroxy group) protected homooxacalix[3]arenes.[2g,4f] We investigated a stepwise construction of homooxacalix[3]arenes based on the cyclization of the corresponding linear trimers to overcome those difficulties.[1e] Although this method is appropriate to construct homooxacalix[3]arenes bearing different substituents or functional groups on their upper rims, the types of functional groups on their upper rims are limited. Here, we report for the first time the transformation of functional groups on the upper rim in the presence of the phenolic hydroxy group on the lower rim of homooxacalix[3]arenes as well as functions of the chromogenic nitrohomooxacalix[3]arene receptor **1** (Figure 1).

Results and Discussion

Improved Synthetic Route for Linear Trimers. The synthetic route for key intermediates (**11a** and **11b**) is depicted in Scheme 1. **11a** and **11b** were prepared from the corresponding linear trimers **10a** and **10b** by the previously reported method.[1e] The synthetic routes of the linear trimers were modified as follows: (1) On the basis of recent work of Crisp et al.,[5] nitrobenzyl alcohol **5** was synthesized through the Mannich reaction. (2) Benzyl bromide **9** was afforded from benzyl alcohol **8** by methanesulfonylation and bromination instead of using PPh_3 and CBr_4.

† Dedicated to Emeritus Professor Soichi Misumi on the occasion of his 77th birthday.

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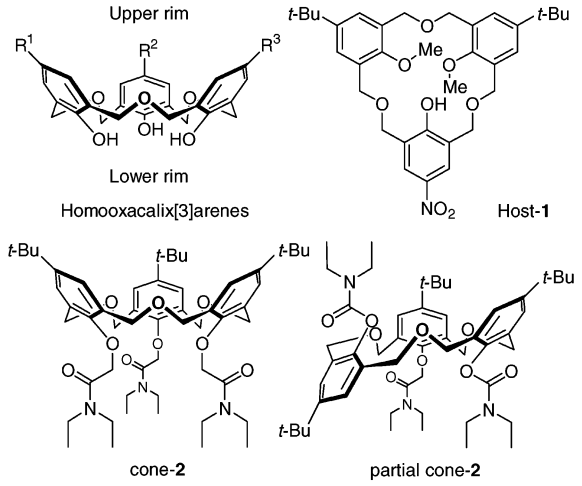
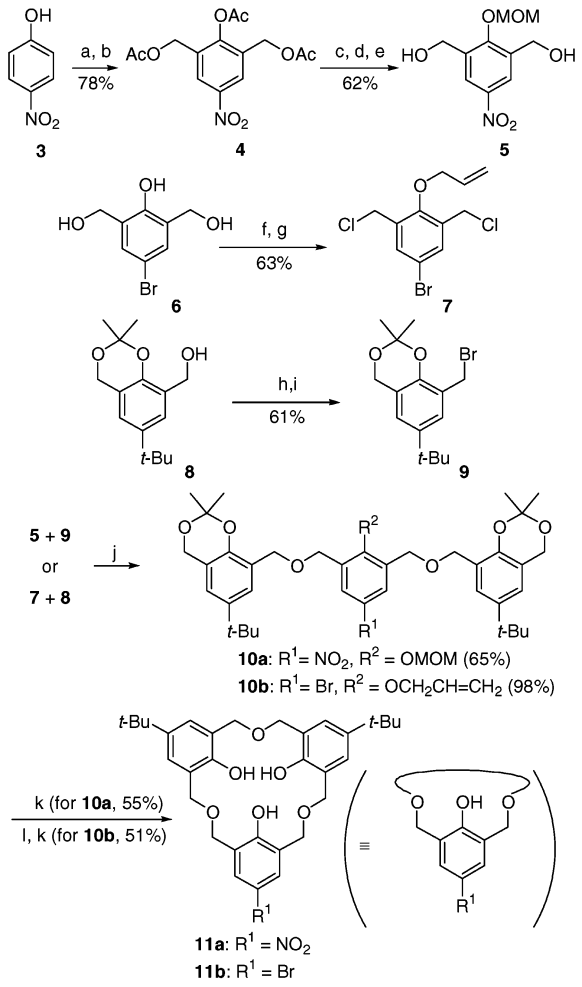


FIGURE 1. Homooxacalix[3]arenes and hosts **1** and **2**.

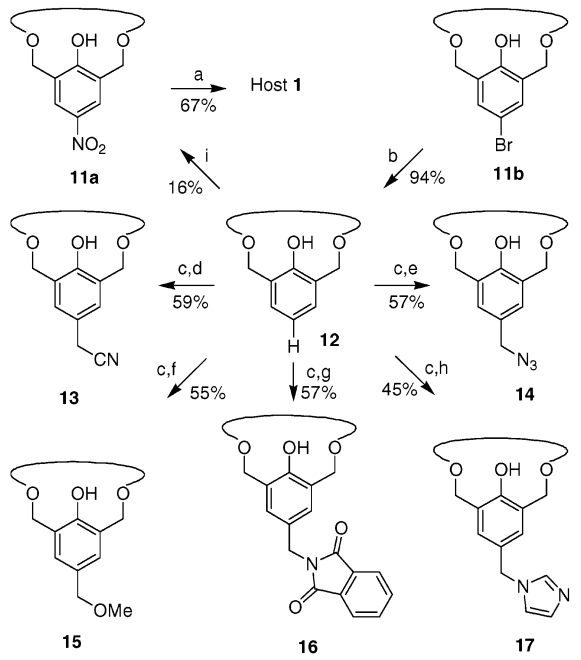
SCHEME 1[a]



[a] Reaction conditions: (a) formalin, morpholine; (b) acetic anhydride; (c) DMAP, MeOH; (d) K_2CO_3, MOMCl; (e) NaOH; (f) allyl bromide, K_2CO_3; (g) thionyl chloride; (h) MsCl, triethylamine; (i) LiBr; (j) NaH; (k) $HClO_4$; (l) $PdCl_2(PPh_3)_2$, $NaBH_4$.

4-Nitrophenol (**3**) was treated with morpholine and formalin in acetic acid to form bis(morpholinomethyl)-phenol, and then the crude Mannich base was converted to its triacetate **4** in 78% overall yield in two steps. The activated phenyl acetate part was selectively removed by DMAP and methanol followed by protection with a MOM group and hydrolysis of acetate on both sides with sodium hydroxide to give the nitrobenzyl alcohol **5** in 62% overall yield. The phenolic hydroxy group of bis(hydroxymethyl)-phenol **6**[1e] was protected by allyl bromide followed by chlorination of benzylic alcohols with thionyl chloride to produce dibenzyl chloride **7** in 63% yield in two steps. On the other hand, benzyl alcohol **8**[1e] was treated with methanesulfonyl chloride followed by bromination with lithium bromide to give benzyl bromide **9**[1e] in 61% yield. Reaction of **5** and benzyl bromide **9** provided the linear trimer **10a** in 65% yield. The key nitrohomooxacalix[3]-arene **11a** was synthesized from the linear trimer **10a** by a previously reported procedure in 55% yield.[1e] Benzyl alcohol **8** was treated with sodium hydride followed by condensation with dibenzyl chloride **7** to give the corresponding linear trimer **10b** in 98% yield. After deprotection of the allyl group in **10b** by palladium and sodium borohydride,[6] **10b** was converted to another key bromohomooxacalix[3]arene **11b**[1e] in 51% yield.

SCHEME 2[a]



[a] Reaction conditions: (a) NaH, MeI; (b) $Pd(OAc)_2$, PPh_3, HCO_2H, triethylamine; (c) dimethylamine, formalin, acetic acid then methyl iodide; (d) NaCN; (e) NaN_3; (f) sodium methoxide; (g) potassium phthalimide; (h) imidazole; (i) NH_4NO_3, acetic anhydride.

Upper Rim Functionalization. Several functional group transformations on the upper rim of key homooxacalix[3]arenes **11a** and **11b** were examined (Scheme 2). Selective debromination of **11b** in the presence of the dibenzyl ether part was accomplished under formic acid reduction conditions to give **12** in 94% yield.[7] In the field of calixarene chemistry, the *p*-quinone methide or Mannich route is one of the most useful functionalization

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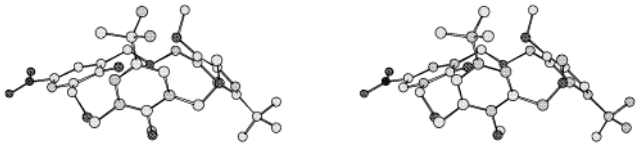

FIGURE 2. X-ray structure of host **1** (stereoview). Hydrogen atoms are excluded for clarity.

methods on the upper rim.[8] Thus, we investigated the Mannich reaction on homooxacalix[3]arene **12**. The corresponding Mannich base could be easily prepared by treatment of **12** with formalin and dimethylamine in acetic acid at 80 °C and then converted to the trimethyl quaternary ammonium salt followed by treatment with various nucleophiles to produce substituted homooxacalix[3]arenes **13**−**17**. Because of the difficulty of purification of the Mannich base due to its zwitterionic character, introduction of functional groups on the upper rim was achieved by successive reactions from **12** (i.e., the Mannich reaction, exhaustive methylation, *p*-quinone methide formation, and nucleophilic substitution). The transformations on the upper rim were adapted to *O*-, *N*-, and *C*-nucleophiles, and the desired products were obtained in moderate overall yields in four steps. The nucleophiles and yields of functional group transformations are as follows: sodium cyanide (**13**, 59% yield), sodium azide (**14**, 57% yield), sodium methoxide (**15**, 55% yield), potassium phthalimide (**16**, 57% yield), imidazole (**17**, 45% yield). Transformations other than the Mannich reaction route on the upper rim have not been effective. For example, nitration at the para position of **12** took place in very low yields (16% yield, from **12** to **11a**); therefore, we synthesized **11a** by a stepwise route vide supra.

Nitrohomooxacalix[3]arene **11a** is an especially attractive candidate compound from the perspective of host−guest chemistry because the nitrophenol part itself has chromogenic character and could potentially be converted to other chromogenic moieties such as an azophenol.[9] Due to their strong intramolecular hydrogen-bonding network,[1e,10] lower rim free homooxacalix[3]arenes have a negligible affinity for cations; therefore, we have designed host molecule **1** such that two methyl groups are selectively introduced on *p-tert* butylphenolic oxygens. Nitrohomooxacalix[3]arene **11a** was treated with methyl iodide (10 equiv) and sodium hydride (10 equiv) to produce host **1** in 67% yield. The structure of host **1** was confirmed by the results of X-ray analysis (Figure 2). On account of cutting off the intramolecular hydrogen-bonding network among three phenolic hydroxy groups by replacement of two methyl groups, the conformation of **1** should be predominantly inclined to the partial cone. This is the first example that swinging homooxacalix[3]arene is fixed in the partial cone conformation in the solid state.

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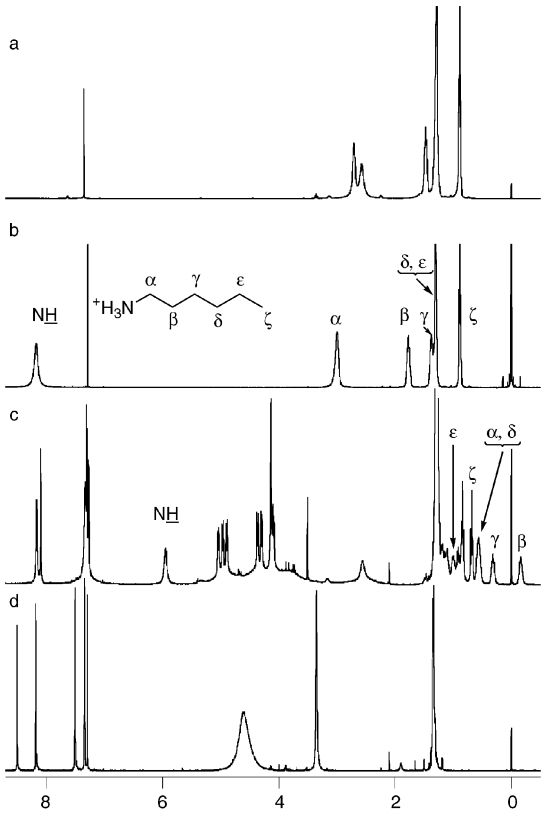

FIGURE 3. ^{1}H NMR (400 MHz) spectra of (a) *n*-hexylamine, (b) *n*-hexylamine hydrochloride, (c) 1:1 mixture of host **1** and *n*-hexylamine, [host **1**] = [*n*-hexylamine] = 6.6×10^{-2} M, and (d) host **1** in $CDCl_3$ at −20 °C (for b) or −40 °C (for a, c, and d).

Complexation with *n*-Hexylamine in Solution. Although some examples of the complexation between cone and/or partial cone fixed homooxacalix[3]arenes and ammonium ions have been reported,[3a,c,d] it is interesting to investigate the mode of complexation between swinging homooxacalix[3]arenes and amine/ammonium guest molecules. Therefore, we chose host **1** and *n*-hexylamine, and the complexation between them was investigated. With the addition of *n*-hexylamine to a solution of host **1** at 25.0 °C, the absorption at around 410 nm was gradually increased. Association constants (K_a) between host **1** and *n*-hexylamine in various solvents at 25 °C were determined by UV−vis titration and analyzed by the Rose−Drago method.[11] The association constants are: $K_a = 251 \pm 2$ (chloroform), $K_a = 1116 \pm 6$ (methanol), $K_a = 133 \pm 1$ (THF), $K_a = 627 \pm 17$ (acetonitrile), $K_a > 10^5$ (DMSO). Association constants are affected by the acidity of nitrophenolic OH of host **1** and by the degree of stabilization of the generated phenolate/ammonium ionic host−guest complex with solvents. With the exception of DMSO, it was actually observed that association constants roughly correlated to the $E_T(30)$ values that are used as empirical parameters of solvent polarities.[12]

To understand the mode of complexation, NMR studies of **1** and *n*-hexylamine were carried out (Figure 3).

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TABLE 1. ^{1}H-CIS Values (ppm) for *n*-hexylammonium Cation upon Complexation with Hosts 1 and 2[a]

host	N*H*	α-CH_2	β-CH_2	γ-CH_2	δ-CH_2	ϵ-CH_2	ζ-CH_3
1[b]	−2.23	−2.42	−1.93	−1.05	−0.72	−0.39	−0.21
cone-**2**[c]	−2.23	−2.82	−2.08	−1.06	−0.56	−0.38	−0.20
partial cone-**2**[c]	−1.24	−1.08	−0.62[d]	−0.37	−0.09[d]	−0.12[d]	−0.04

[a] 400 MHz ^{1}H NMR spectra in $CDCl_3$. ^{1}H-CIS (complexation-induced shifts) = δ (complex) − δ (guest)). [b] ^{1}H-CIS values were calculated based on a set of chemical shifts of *n*-hexylamine hydrochloride as guest.[13] [c] Association constant is estimated. See ref 13. [d] Peaks are not resolved; therefore, CIS values are estimated by cross-peaks of the corresponding COSY spectrum.

Shinkai and co-workers reported that ring inversion of homooxacalix[3]arene occurred through the oxygen-through-the-annulus rotation and that cone/partial cone ring inversion was allowed for *O*-trimethylated homooxacalix[3]arene.[2b] In fact, in the ^{1}H NMR spectrum of **1** even at −40 °C, the signals of the methoxy protons are a singlet and those of benzylic protons composed 18-membered ring are also a (broad) singlet. This result indicates that the ring inversion is faster than the NMR time scale (Figure 3d). In contrast, a drastic change was observed in the mixture of **1** and *n*-hexylamine in a 1:1 ratio, as the signals ascribed to *n*-hexylamine were dramatically shifted to higher magnetic field (Figure 3c). The ^{1}H-CIS (complexation-induced shifts = δ (complex) − δ (guest)) values of guest *n*-hexylamine are summarized in Table 1. The magnitude of higher magnetic shifts of guest signals grows fainter with increasing distance from the amino group. On the basis of these observations, it is clear that the amino group approaches the π-cavity composed of the aromatic rings of host **1**. Furthermore, the benzylic protons on the 18-membered ring of host **1** changed from a broad singlet to three (not six) AB quartets in a ratio of 1:1:1. Thus, the flexible homooxacalix[3]arene skeleton should be fixed to one symmetric conformation by complexation through *n*-hexylamine. Among the possible complexes, the following two candidates could be proposed. Complex A: the guest amine approaches the cone shape **1** from the upper rim side. Complex B: the guest amine approaches the inverted nitrophenol part of the partial cone shape **1** from the *tert*-butyl substituent side (Figure 4).

Since NOESY and ROESY spectra did not provide any useful information concerning the shape of the complex, the CIS values of host **1** and *n*-hexylamine were compared with those of the cone or partial cone fixed homooxacalix[3]arenes **2** and *n*-hexylamine hydrochloride.[2c,3a,d] The ^{1}H NMR charts between the cone and partial cone-**2** and *n*-hexylamine hydrochloride are shown in Figure 5, and the CIS values are also given in Table 1. Taking together, the behavior of host **1** and *n*-hexylamine is very similar to that of cone-**2** and *n*-hexylamine hydrochloride. Thus, these data clearly indicate that the guest amine approaches the cone shape **1** from the upper rim side (Figure 4, complex A).

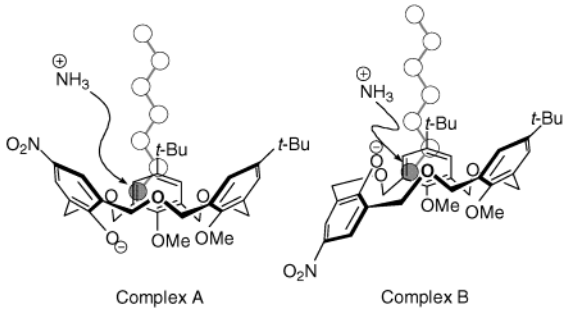

FIGURE 4. Proposed possible complex structures.

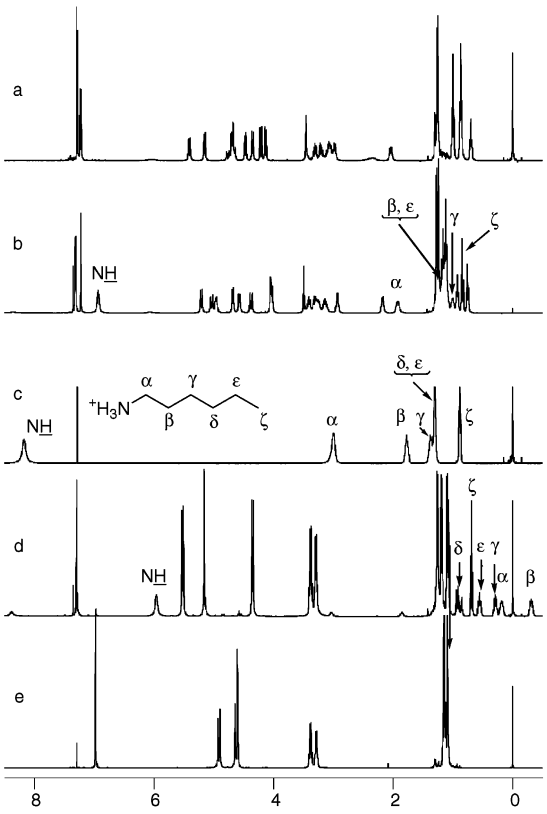

FIGURE 5. ^{1}H NMR (400 MHz) spectra of (a) partial cone **2**, (b) 1:1 mixture of partial cone **2** and *n*-hexylamine hydrochloride, [partial cone **2**] = [*n*-hexylamine hydrochloride] = 5.4×10^{-2} M (c) *n*-hexylamine hydrochloride, (d) 1:1 mixture of cone **2** and *n*-hexylamine hydrochloride, [cone **2**] = [*n*-hexylamine hydrochloride] = 7.1×10^{-2} M, and (e) cone **2** in $CDCl_3$ at −20 °C (for c, d, and e) or −40 °C (for a and b).

In this study, the upper rim functionalization of homooxacalix[3]arene was achieved through the Mannich route. This method should be suitable for synthesis of more functionalized homooxacalix[3]arene derivatives. Furthermore, the determination of the mode of complexation between host **1** and primary amines should be a base for the development of more complicated host−guest systems.

Experimental Section

General Methods. Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were taken at 200 MHz

(13) Due to the host−guest exchange rate is very slow compared to the NMR time scale, NMR spectrum of the mixture of host and guest gives peaks for host, guest, and complex separately. Therefore, the association constant can be estimated on the basis of the integration of the corresponding peaks. The association constants are: $K_a = 1.1 \times 10^4$ mol^{-1} (cone **2** and *n*-hexylamine hydrochloride, $CDCl_3$, −40 °C). $K_a > 9 \times 10^4$ mol^{-1} (partial cone **2** and *n*-hexylamine hydrochloride, $CDCl_3$, −40 °C, Even in the mixture of partial cone 2 (1.0×10^{-3} M) and *n*-hexylamine (1.0×10^{-3} M), only the peaks ascribed to the host−guest complex were observed).

with chemical shifts being reported as δ ppm from tetramethylsilane as an internal standard.

4. Mannich base was prepared from nitrophenol (**3**) according to the procedure of Crisp.[5] A solution of nitrophenol (**3**) (25.0 g, 180 mmol) and morpholine (36 mL, 413 mmol) in acetic acid (36 mL) and formalin (45 mL) was stirred for 18 h at 80 °C. Solvent was evaporated under reduced pressure to give a residue. The residue was dissolved in acetic anhydride (300 mL), and the mixture was stirred for 23 h at 100 °C. The solvent was evaporated in vacuo, and the residue was directly purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 2/1) followed by recrystallization from ethyl acetate and *n*-hexane to afford **4** as pale yellow needles (36.7 g, 63% yield). Additional **4** (8.5 g, 15% yield) was obtained from the mother liquors: mp 74−75 °C (from ethyl acetate/*n*-hexane); IR (KBr) 3071, 1740, 1539, 1352, 1242 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.13 (s, 6H), 2.41 (s, 3H), 5.10 (s, 4H), 8.33 (s, 2H); HRMS calcd for $C_{14}H_{15}NO_8$ (M^+) 325.0798, found 325.0802. Anal. Calcd for $C_{14}H_{15}NO_8$: C, 51.70; H, 4.65; N, 4.31. Found: C, 51.64; H, 4.60; N, 4.28

5. To a mixture of **4** (32.5 g, 100 mmol) and 4-(dimethylamino)pyridine (610 mg, 5 mmol) in DMF (150 mL) were added methanol (8.0 mL, 200 mmol) and potassium carbonate (27.6 g, 200 mmol), and the mixture was stirred for 4 h at room temperature. Chloromethyl methyl ether (15.2 mL, 200 mmol) was added to the reaction mixture and stirred for 39 h at room temperature. Chloromethyl methyl ether (8.0 mL, 107 mmol) and potassium carbonate (13.0 g, 94 mmol) were added, and the reaction mixture was stirred for a further 1.5 h. Aqueous sodium hydroxide solution (2.5 M, 300 mL) was added and the mixture stirred for 5 h. The precipitate was collected by filtration, washed with water, and air dried at room temperature to afford **5** (15.0 g, 62% yield): mp 125−126 °C (from toluene−ethanol); IR (KBr) 3385, 2933, 1523, 1439, 1349 cm^{-1}; ^1H NMR (200 MHz, DMSO) δ 3.51 (s, 3H), 4.63 (d, J = 5.2 Hz, 4H), 5.08 (s, 2H), 5.52 (t, J = 5.2 Hz, 2H), 8.23 (s, 2H); HRMS calcd for $C_{10}H_{13}NO_6$ (M^+) 246.0742, found 243.0742. Anal. Calcd for $C_{10}H_{13}NO_6$: C, 49.38; H, 5.39; N, 5.76. Found: C, 49.45; H, 5.42; N, 5.69.

7. Allyl bromide (10.3 mL, 119 mmol) was dropwise added to a mixture of **6** (25.0 g, 107 mmol) and potassium carbonate (22.0 g, 159 mmol) in DMF (120 mL) at 0 °C. The mixture was stirred for 24 h and poured into the mixed solvent of ethyl acetate and water. The organic layer was separated and washed successively with water (twice) and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo to give a residue as white powder. Thionyl chloride (23.0 mL, 315 mmol) was dropwise added to a solution of the residue in DMF (1 mL) and dichloromethane (200 mL) at 0 °C. The mixture was stirred for 17 h at room temperature. The solvent was evaporated in vacuo, and the residue was directly purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 10/1) to afford **7** as a white powder (21.0 g, 63% yield for two steps): mp 90−92 °C (white needle from *n*-hexane); IR ($CHCl_3$) 3155, 2253, 1793, 1466, 1381 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.55 (ddd, J = 5.3, 1.3,1.3 Hz, 2H), 4.59 (s, 4H), 5.34 (ddt, J = 10.5, 1.3, 1.3 Hz, 1H), 5.49 (ddt, J = 17.2, 1.3, 1.3 Hz, 1H), 6.12 (ddt, J = 17.2, 10.5, 5.3 Hz, 1H), 7.55 (s, 2H); HRMS calcd for $C_{11}H_{11}Br^{79}Cl^{35}{}_2O$ (M^+) 307.9371, found 307.9371; calcd for $C_{11}H_{11}Br^{79}Cl^{35}Cl^{37}O$ (M^+) 309.9341, found 309.9329; calcd for $C_{11}H_{11}Br^{81}Cl^{35}{}_2O$ (M^+) 309.9350, found 309.9368; calcd for $C_{11}H_{11}Br^{79}Cl^{35}{}_2O$ (M^+) 311.9312, found 311.9323; calcd for $C_{11}H_{11}Br^{81}Cl^{35}Cl^{37}O$ (M^+) 311.9321, found 311.9323. Anal. Calcd for $C_{11}H_{11}BrCl_2O$: C, 42.64; H, 3.58. Found: C, 42.80; H, 3.50.

9.[1e] To a solution of **8**[1e] (10.0 g, 39.9 mmol) and triethylamine (23 mL, 160 mmol) in ethyl acetate (300 mL) was added methanesulfonyl chloride (6.2 mL, 80 mmol) dropwise at 0 °C. After 2 h, white precipitate was filtered off, and $LiBr\cdot H_2O$ (42 g, 399 mmol) and DMF (100 mL) were added to the filtrate. The reaction mixture was stirred for 30 min at room temperature. The reaction mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated, washed successively with water, and brine. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 10/1) to afford **9** as a white powder (8.93 g, 61% yield). The characterization data are reported.[1e]

10a. To a solution of **5** (1.63 g, 6.7 mmol) in DMF (35 mL) and THF (10 mL) was added portionwise sodium hydride (60% mineral oil dispersion, 1.10 g, 26.7 mmol), and the reaction mixture was stirred for 15 min at 0 °C. A solution of **9** (4.4 g, 14 mmol) in THF (5 mL) was added dropwise to the reaction mixture. After being stirred for 1 h at room temperature, the mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated and washed successively with water and brine. The organic layer was dried over magnesium sulfate and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 10/1) to afford **10a** as a pale yellow oil (3.03 g, 65% yield): IR (neat) 2960, 2865, 1739, 1594, 1526 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.29 (s, 18H), 1.54 (s, 12H), 3.52 (s, 3H), 4.62 (s, 4H), 4.67 (s, 4H), 4.85 (s, 4H), 5.07 (s, 2H), 6.93 (d, J = 2.4 Hz, 2H), 7.31 (d, J = 2.4 Hz, 2H), 8.35 (s, 2H); HRMS calcd for $C_{40}H_{53}NO_{10}$ (M^+), 707.3670, found 707.3661. Anal. Calcd for $C_{40}H_{53}NO_{10}$: C, 67.87; H, 7.55; N, 1.98. Found: C, 67.58; H, 7.48; N, 1.79

10b. A solution of **8** (25.0 g, 100 mmol) in THF (100 mL) was added dropwise to a suspension of sodium hydride (60% mineral oil, 6.0 g, 150 mmol) in THF (50 mL) at 0 °C. A solution of **7** (35.5 g, 50 mmol) in DMF (150 mL) was added to the reaction mixture and stirred for 17 h. The mixture was poured into the mixed solvent of ethyl acetate and water. The organic layer was separated and washed successively with water (twice) and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 4/1) to afford **10b** as pale yellow oil (36.2 g, 98% yield): IR ($CHCl_3$) 2964, 2253, 1485, 1375 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (s, 18H), 1.54 (s, 12H), 4.35 (ddd, J = 5.6, 1.6, 1.6 Hz, 2H), 4.58 (s, 4H), 4.60 (s, 4H), 4.84 (s, 4H), 5.21 (ddt, J = 10.3, 1.6, 1.6 Hz, 1H), 5.33 (ddt, J = 17.2, 1.6, 1.6 Hz, 1H), 5.99 (ddt, J = 17.2, 10.3, 5.6 Hz, 1H), 6.92 (d, J = 2.2 Hz, 2H), 7.30 (d, J = 2.2 Hz, 2H), 7.57 (s, 2H); HRMS calcd for $C_{41}H_{53}Br^{79}O_7$ (M^+) 736.2975, found 736.2979; calcd for $C_{41}H_{53}Br^{81}O_7$ (M^+) 738.2954, found 738.2964.

11a. Starting from 10a. Compound **11a** was synthesized from the corresponding linear trimer **10a** by reported procedure (55% yield):[1e] mp 159−160 °C; IR (KBr) 3301, 2961, 1602, 1523, 1489 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (s, 18H), 4.75 (s, 12H), 7.14 (d, J = 2.6 Hz, 2H), 7.16 (d, J = 2.6 Hz, 2H), 8.07 (s, 2H), 8.39 (s, 2H), 9.83 (s, 1H); HRMS calcd for $C_{32}H_{39}NO_8$ (M^+) 565.2675, found 565.2673. Anal. Calcd for $C_{32}H_{39}NO_8$: C, 67.95; H, 6.95; N, 2.48. Found: C, 67.81; H, 6.96; N, 2.52

Starting from 12. To a solution of homooxacalix[3]arene **12** (97 mg, 0.19 mmol) in acetic anhydride (2.0 mL) was added ammonium nitrate (16 mg, 0.20 mmol) under nitrogen atmosphere and the mixture stirred for 5 h at 60 °C. Aqueous sodium hydrogen carbonate solution was carefully added to the reaction mixture at 0 °C and extracted with ethyl acetate (three times). The organic layers were collected and washed with brine and evaporated in vacuo. The residue was purified by PTLC (*n*-hexane/ethyl acetate = 9/1) to afford **11a** (17 mg, 16% yield).

11b.[1e] Sodium borohydride (1.8 g, 47.4 mmol) was added to a mixture of **10b** (35.0 g, 47.4 mmol) and dichlorobis(triphenylphosphine)palladium (350 mg, 0.7 mmol) in THF (150 mL) and stirred for 10 h at room temperature. The solvent was evaporated, and the residue was dissolved in ethyl acetate. The organic layer was washed successively with hydrochloric acid (twice), water, and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo to give crude deprotection of the allyl group derivative [ca. 34 g; ^1H NMR (200

MHz, $CDCl_3$) δ 1.28 (s, 18H), 1.56 (s, 12H), 4.58 (s, 4H), 4.66 (s, 4H), 4.85 (s, 4H), 6.93 (d, J = 2.6 Hz, 2H), 7.25 (d, J = 2.6 Hz, 2H), 7.30 (s, 2H), 7.89 (s, 1H)]. The residue (5.0 g) was converted to **11b** by reported procedure (51% yield).[1e] The characterization data were also reported.

12. A mixture of bromohomooxacalix[3]arene **11b** (7.0 g, 11.7 mmol), palladium acetate (50 mg, 0.2 mmol), triphenylphosphine (125 mg, 0.5 mmol), and formic acid (0.95 mL, 25.2 mmol) in triethylamine (5.0 mL) and DMF (25.0 mL) was stirred for 7.5 h at 50 °C under nitrogen atmosphere. The mixture was poured into ethyl acetate and washed successively with hydrochloric acid, water (twice), and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 6/1) to afford **12** (5.71 g, 94% yield). The characterization data were reported.[1e]

Functionalization on Upper Rim through Mannich Reaction. The preparation of **13** is typical. A solution of dimethylamine (40% in water, 13.0 mL) and formalin (37% in water, 8.0 mL) in acetic acid (7.0 mL) was stored for overnight as a stock solution. A solution of **12** (1.0 g, 1.92 mmol) and the stock solution (4.0 mL) in acetic acid (6.0 mL) was stirred for 17 h at 80 °C. The mixture was poured into ethyl acetate and washed successively with aqueous sodium hydrogen carbonate solution, water (twice), and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo to give a residue (1.4 g). Methyl iodide (179 μL) was added to a solution of the residue (1.4 g) in DMSO (10 mL) and stirred for 40 min at room temperature. Sodium cyanide (470 mg) was added to the solution and stirred for 4 h at 50 °C. The mixture was poured into ethyl acetate and washed successively with sodium hydrogen carbonate solution, water (twice), and brine. The organic layer was dried over sodium sulfate and evaporated in vacuo. The residue was purified by column chromatography (SiO_2, *n*-hexane/ethyl acetate = 4/1) to afford **13** as pale yellow powder (680 mg, 59% yield): mp 198−199 °C (white powder from Et_2O); IR ($CHCl_3$) 3358, 1488, 1220, 1209, 1076 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.25 (s, 18H), 3.62 (s, 2H), 4.70 (s, 4H), 4.72 (s, 4H), 4.73 (s, 4H), 7.07 (s, 2H), 7.13 (d, J = 2.4 Hz, 2H), 7.14 (d, J = 2.4 Hz, 2H), 8.50 (s, 2H), 8.92 (s, 1H); HRMS calcd for $C_{34}H_{41}NO_6$ (M^+), 559.2933 found 559.2939. Anal. Calcd for $C_{34}H_{41}NO_6$: C, 72.96; H, 7.38; N, 2.50. Found: C, 72.80; H, 7.46; N, 2.47.

14: 57% yield from **12** and sodium azide. **15**: 55% yield from **12** and sodium methoxide. **16**: 57% yield from **12** and potassium phthalimide. **17**: 45% yield from **12** and imidazole.

Host 1. To a solution of homooxacalix[3]arene **11a** (100 mg, 0.18 mmol) in DMF (1.0 mL) was added sodium hydride (60% mineral oil dispersion, 77 mg, 1.8 mmol) and the mixture stirred for 10 min at 0 °C. Methyl iodide (0.11 mL, 1.8 mmol) was added to the reaction mixture, and the reaction mixture was stirred for 40 min at 0 °C. The mixture was poured into the mixed solvent of ethyl acetate and hydrochloric acid. The organic layer was separated and washed successively with water (twice) and brine. The organic layer was dried over magnesium sulfate, and evaporated in vacuo. The residue was purified by PTLC (*n*-hexane/ethyl acetate = 5/1) to afford **1** (70 mg, 67% yield) as a white powder: mp 205−209 °C (from ethyl acetate); IR (KBr) 3334, 1600, 1521 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.33 (s, 18H), 3.33 (s, 6H), 4.52 (s, 4H), 4.56 (s, 4H), 4.58 (s, 4H), 7.30 (d, J = 2.4 Hz, 2H), 7.46 (d, J = 2.4 Hz, 2H), 8.12 (s, 2H) 8.36 (s, 1H); HRMS calcd for $C_{34}H_{43}NO_8$ (M^+) 593.2988, found 593.2969. Anal. Calcd for $C_{34}H_{43}NO_8$: C, 68.78; H, 7.30; N, 2.36. Found: C, 68.76; H, 7.41; N, 2.27

Supporting Information Available: Characterization data for **14**−**17**. ^1H NMR spectra for compounds **10b**, **11a**, **13**−**17**, and Figures 3a−d and 5a−e. COSY spectra for *n*-hexylamine hydrochloride, host **1** + *n*-hexylamine, cone **2** + *n*-hexylamine hydrochloride, and partial cone **2** + *n*-hexylamine hydrochloride. Crystallographic information file (CIF) of host **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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