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p-(Benzyloxy)calix[8]arene Synthesis Revisited: *p*-(Benzyloxy)calix[4]-, *p*-(Benzyloxy)calix[5]-, *p*-(Benzyloxy)calix[7]-, and *p*-(Benzyloxy)bis(homooxa)calix[4]arenes

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A detailed investigation of the 4-(benzyloxy)phenol/formaldehyde reaction shows that along with the previously described *p*-(benzyloxy)calix[8]arene and *p*-(benzyloxy)calix[6]arene, others calixarenes are observed and easily recovered on a preparative scale. All these new calixarenes are opening interesting perspectives for the synthesis of new supramolecular hosts, easily functionalized at the *para* position under very mild conditions and/or exhibiting a deep hydrophobic pocket.

Introduction

Calixarenes have received much attention during the last decades due to the tremendous possibilities offered by these easily accessible macrocycles.[1–4] Some of the most thoroughly studied properties include ion and/or molecule recognition phenomena,[5–14] supramolecular assemblies,[15,16] nanoparticles synthesis,[17–21] and so on. In most cases, these studies were performed with ubiquitous *p*-(*t*Bu)-functionalized calixarenes, as the synthesis of these derivatives is by far the most documented one since the pioneering work of Gutsche et al.[3,22] As a consequence, the use of other *p*-functionalized phenols for calixarene synthesis is to a large extent unexplored, even if some one-step syntheses of other *p*-(alkyl)-functionalized calixarenes are known.[23–27] In most cases, post-functionalization of the *p*-position of these calixarenes (not always possible) is a multistep process, requiring the use of reactive electrophilic de-*tert*-butylating reagents, not compatible with heavily functionalized calixarenic platforms.[28–37] The *p*-functionalization of calixarenes under mild conditions is thus still an open question. However, this is an important concern, as the control of the *p*-functionalization of calixarenes was shown to open very interesting possibilities for the synthesis of new receptors (Figure 1).[28,29,32–34,38–41]

Some years ago, we and others described the use of *p*-(benzyloxy)phenol (**1**) as a starting compound for the synthesis of the corresponding *p*-(benzyloxy)calix[8]arene and its derivatives (Scheme 1, **2**). This calixarene was shown to be easily debenzylated under mild and selective Pd-catalyzed hydrogenolysis conditions, opening the way to easy derivatization of the *p*-position by alkylation of the released hydroxy groups.[7,16,21,42]

Along with the *p*-(benzyloxy)calix[8]arene, the corresponding *p*-(benzyloxy)calix[6]- and *p*-(benzyloxy)calix[7]-arenes (compounds **3** and **4**, respectively) were also mentioned,[42] but detailed characterizations was provided only for the former.[7] To the best of our knowledge, these are the only known examples of one-step syntheses of *p*-(benzyloxy)calixarenes. We show here that along with these known compounds, the corresponding *p*-(benzyloxy)calix[4]arene (**5**), *p*-(benzyloxy)bis(homooxa)calix[4]arene (**6**), and *p*-(benzyloxy)calix[5]arene (**7**) are also present as by-products during the synthesis of *p*-(benzyloxy)calix[8]arene and are recovered on a preparative scale (Scheme 2a). Moreover, the corresponding calix[7]arene is directly recovered (and fully characterized) from the reaction mixture in a very simple way, without the need for any derivatization procedure. This last point contrasts its first description.[42] Along with an enrichment of the *p*-(benzyloxy)calixarene family, these results open the way to the one-step synthesis of new calixarenes with interesting *p*-functionalization, leading to new possibilities in the field of supramolecular chemistry and materials.

The synthesis of an ethyl bromoacetate alkylated derivative of all these new calixarenes was also undertaken. These derivatives were synthesized for two main reasons. First, some interesting functionalization and ion complexation opportunities are offered by these ester-functionalized com-

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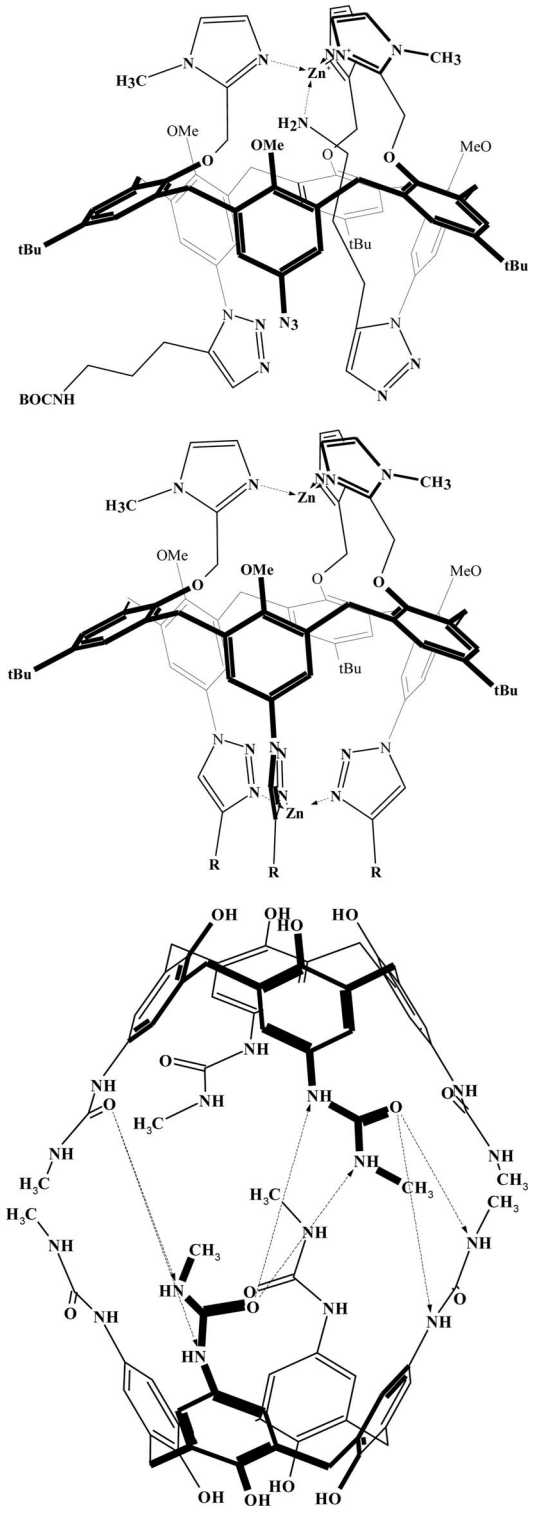
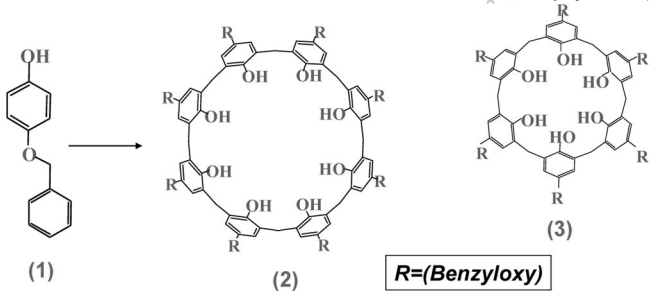
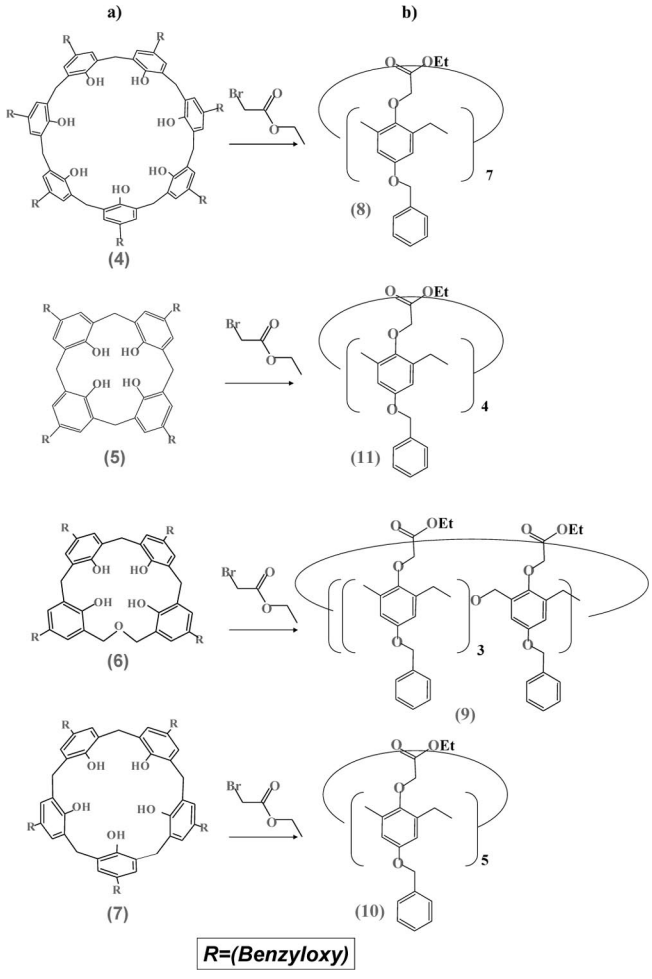


Figure 1. Some examples of *p*-functionalized calixarenes.

pounds.[2,3,43] Second, these alkylated derivatives also offer the possibility to compare their conformational behavior with the corresponding *p*-(*t*Bu)calixarenes. Indeed, the conformational behavior of a given calixarene strongly influences its complexation abilities. The study of this point for our new calixarenes is thus an important concern.



Scheme 1. Previously characterized *p*-(benzyloxy)calixarenes.



Scheme 2. (a) New calixarenes described in this work; (b) alkylation with ethyl bromoacetate.

Results and Discussion

The synthesis of *p*-(benzyloxy)calix[8]arene has already been described.[7,16,21,42] A modification of one procedure[16] (use of a mechanical stirrer) was used in this work (see the Experimental Section). Filtration of the xylene crude reaction media and washing with acetone led to quite pure *p*-(benzyloxy)calix[8]arene.

We then turned our attention to the corresponding acetone/xylene filtrate. The filtration/precipitation sequence used to completely analyze this filtrate is depicted in

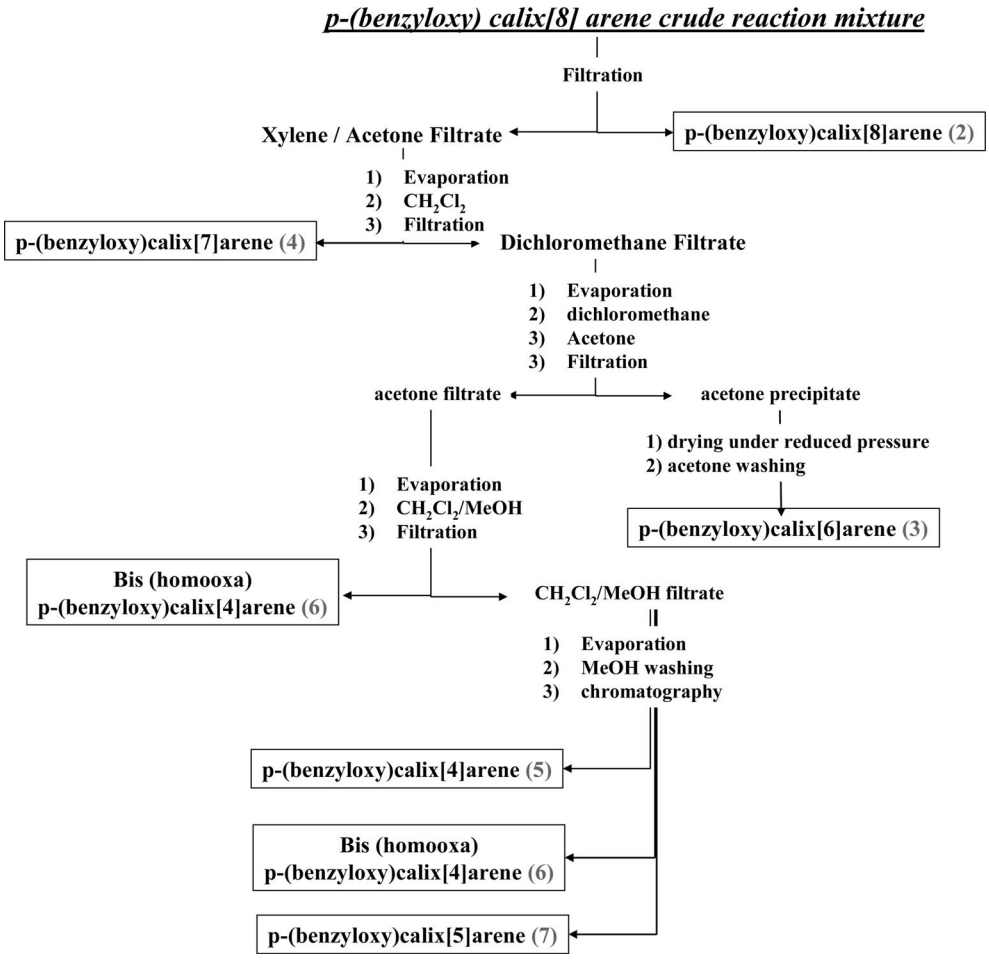


Figure 2. The purification sequence used in this work.

Figure 2. After complete evaporation of the xylene/acetone filtrate, we were surprised to observe that the resulting solid was not completely soluble in dichloromethane. Filtration and analysis of the corresponding precipitate showed that this precipitate was constituted by pure *p*-(benzyloxy)calix-[7]arene (Scheme 2a). This assignment was made on the basis of the very high symmetry of the ^1H and ^{13}C NMR spectra, along with electrospray and MALDI mass spectrometry analysis (see the Experimental Section and the Supporting Information, S2a, S2b). Calix[7]arene was recovered in 8% yield, and despite this low yield, its ease of recovery makes this calixarene readily available.

Corresponding alkylated product **8** (Scheme 2b) shows complete conformational flexibility at ambient temperature (Supporting Information, S3a→S3d). This is not surprising, as the size of the macrocycle is high enough to allow easy interconversion processes.

Analysis of the dichloromethane filtrate obtained after the recovery of **4** was then undertaken. Precipitation with acetone followed by acetone washing of this precipitate led to quite pure *p*-(benzyloxy)calix[6]arene (**3**; 1 g, 2% yield, spectroscopic characteristics in accordance with previously published ones[7]). The combined acetone filtrates were then evaporated, dissolved in CH_2Cl_2, and precipitated with methanol. $^1H/^{13}C$ NMR along with mass spectrometry analysis showed this precipitate to be constituted by quite pure *p*-(benzyloxy)(bishomooxa)calix[4]arene **6** (Scheme 2a; see also the Experimental Section and the Supporting Information, S4a→S4d). Although known for quite a long time in the *p*-(*t*Bu) series,[44–47] this is the first time that this compound is described in the (benzyloxy) series. Single crystals of **6**, suitable for X-ray diffraction, were grown by slow evaporation of a toluene solution.

Compound **6** crystallizes with two disordered toluene molecules per unit cell. Interestingly, two independent molecules are observed: both are in the cone conformation, but with a different orientation for the CH_2OCH_2 bridge (Figure 3). Compound **6** shows a restricted conformational flexibility at ambient temperature, as evidenced by the broadness of the resonances for the ($ArCH_2Ar$) and (CH_2OCH_2) bridging methylene groups. Variable-temperature NMR experiments showed that the coalescence temperature is about 290 K (see the Supporting Information, S4c). From this experiment, we were able to determine an interconversion barrier of 53.3 kJ mol^{-1}. This value compares with previously published ones.[48]

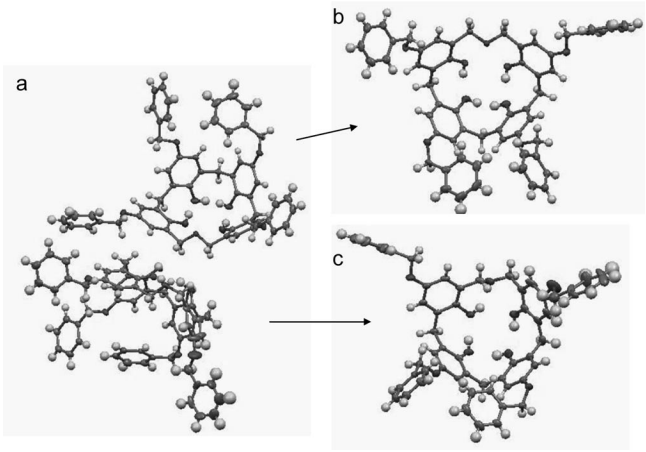


Figure 3. Solid-state structure of **6**: (a) orientations of the two independent molecules in the unit cell; (b) and (c) different views of the molecules, highlighting the orientations of the CH_2OCH_2 bridge.

A comparison between the ambient-temperature ^1H NMR spectra of compound **6** (Scheme 2a) and that of the corresponding peralkylated product **9** (Scheme 2b) is very interesting. As discussed above, compound **6** shows a restricted conformational flexibility at ambient temperature. However, the situation completely changes after alkylation with ethyl bromoacetate (compound **9**, Scheme 2b). The presence of four sharp doublets for the hydroquinone-type aromatic protons (^4J = 4 Hz) evidences a symmetry plane for this compound (see Supporting Information, S5b) Moreover, the bridging methylene signals now appear as sharp doublets, with characteristic ^2J coupling constants ranging from 10 to 15 Hz, evidencing a completely locked cone conformation for this compound. Such a conformational behavior has already been observed for others peralkylated dihomooxa derivatives in the *p*-(*t*Bu) series.[45]

Detailed examination of the spectra shows one extra AB quartet in the (CH_2OCH_2) bridging methylene resonances [confirmed by COSY and NOESY 2D analysis; see the Supporting Information, S4b (insert) and S4c). A possible interpretation is to be found in the symmetry-lowering effect associated with the presence of the bis(homooxa) bridge on the two hydrogen atoms of the benzyloxy-type methylene groups.

The same symmetry-lowering effect is also likely to affect the resonances of the other methylene groups on the small rim side of the molecule. However, overlapping of these signals with those of the bridging methylene groups (from the calixarene macrocycle) make this analysis difficult. The persistence of this compound in the cone conformation, along with the presence of the benzyloxy substituents, opens interesting perspectives for the formation of new ligands with a deep hydrophobic cavity.

Column chromatography of the remaining MeOH/CH_2Cl_2 filtrates obtained after the recovery of **6** allowed, first, the recovery of *p*-(benzyloxy)calix[4]arene (**5**; Scheme 2a, yield <1%), second, for a crop of compound **6** (final yield 10.4%), and last, of *p*-(benzyloxy)calix[5]arene (**7**; Scheme 2a; final yield 2.4%; see the Experimental Section).[55] Despite their low yields, **5** and **7** are described here for the first time. As in the other cases, compounds **5** and **7** were fully characterized by $^1H/^{13}C$ NMR spectroscopy along with mass spectrometry analysis. At ambient temperature, *p*-(benzyloxy)calix[5]arene shows a restricted conformational flexibility in $CDCl_3$ (broadness of the bridging methylene groups; see the Supporting Information, S6b). Variable-temperature NMR analysis showed that the coalescence temperature is close to the ambient one (about 290 K; see the Supporting Information, S6c).

From this experiment, we were able to obtain a value of 55.4 kJ mol^{-1} for the interconversion barrier. This value compares well with those in the literature.[48,49] However, alkylated derivative **10** (Scheme 2b) is conformationally locked at ambient temperature, as evidenced by ^1H and ^{13}C NMR spectroscopy, where several different conformations are observed (mass spectrometry analysis only showed the expected molecular peak, indicating that all the hydroxy groups from **7** were alkylated). The same alkylation experiment was repeated with methyl bromoacetate, resulting in the same mixture of conformations. This result contrasts previously published results with *p*-(*t*Bu)- and *p*-(*t*-octyl)-functionalized calix[5]arenes.[43] However, a mixture of conformations has already been observed in some examples of *p*-(*t*Bu)calix[5]arene alkylation experiments.[50]

The strongest signals around 6 ppm on the ^1H NMR spectra along with two sets of overlapping doublets (COSY analysis) indicate that the cone conformation is (at best) present only as a minor component (see the Supporting Information, S7d). Even heating at 400 K in DMSO (the limit of our experimental set up) did not allow recovery of full conformational flexibility (see the Supporting Information, S6c). These characteristics are quite similar to those observed in the case of the *p*-(*t*Bu)-functionalized calix[5]-arenes.[48]

p-(Benzyloxy)calix[4]arene shows at ambient temperature a locked cone conformation (in $CDCl_3$), as evidenced by the presence of the characteristic AX system with ^2J = 13 Hz. VT-NMR experiments (see the Supporting Information, S8d) allowed us to determine an activation barrier of 64 kJ mol^{-1}. Once again, this value agrees well with those in the literature.[47] Corresponding alkylated derivative **11** (Scheme 2b) was obtained in quantitative yield by using NaH as a base. The NMR spectra show that this derivative was obtained exclusively in the cone conformation, as observed in the case of the *p*-(*t*Bu)calix[4]arene when alkylation reactions are performed with sodium-containing bases.

Conclusions

A new set of *p*-(benzyloxy)-substituted calixarene derivatives was obtained on a preparative scale and was fully characterized. Along with completely new members of the *p*-(benzyloxy)calixarene family, the previously described[42] *p*-(benzyloxy)calix[7]arene is very easily obtained on a multigram scale and was fully characterized for the first time without the need for any derivatization procedure.

The very interesting *p*-(benzyloxy)calix[4]arene was obtained in very low yield after chromatographic analysis of the most polar fraction of the purification process. Despite the very low yield, this result is interesting, as it shows that the one-step formation of this compound is possible, in sharp contrast with previously reported results.[42] Studies are underway within our group to optimize the yield. Alkylation of this compound results in the formation of a rigid cone derivative. Moreover, the previously unknown *p*-(benzyloxy)(bishomooxa)calix[4]arene was easily obtained on a multigram scale. Alkylation of this product also results in the formation of a rigid cone derivative. In both cases, the formation of these alkylated calixarenes in the cone conformation opens interesting perspectives for the synthesis of new supramolecular hosts.

Clearly, significant differences are observed in the final compositions of the reaction media between this work and the previously described *p*-(benzyloxy)calix[8]arene synthesis.[42] The reason for this is unclear. One possible explanation may originate from differences in the refluxing periods [6 h (this work)/48 h[42]]. A shorter reflux time probably allows observation of the kinetic products, whereas a longer one may result in thermodynamic equilibrium between the different macrocycles.

More generally, this work demonstrates that the behavior of the *p*-(benzyloxy) system shows analogies with the well-known *p*-(*t*Bu) one. First, even a very complex mixture of several different calixarenic sizes is tractable and leads to pure compounds after conventional workup. The high similarity between the spectroscopic characteristics of some of these compounds may at first sight shed doubt on the real purity level of these calixarenes. However, some small (but significant and reproducible) differences are observed in the chemical shifts of some protons in the ^{1}H NMR spectra, especially the hydroquinone-type ones (Calix5: δ = 6.80 ppm; Calix6: δ = 6.61 ppm; Calix7: δ = 6.70 ppm; Calix8: δ = 6.58 ppm in DMSO). Careful calibration of the reference peak of the solvent thus allows easy analysis of a mixture of different calixarenic sizes [for this purpose, DMSO (calibrated at δ = 2.49 ppm) is the best choice, as all the calixarenes described in this work are soluble in this solvent]. Associated with both the very different mass spectrometric signals observed in each case and the synthesis of alkylated derivatives, this demonstrates the high level of purity of our calixarenes. Second, the conformational behavior of the alkylated derivatives of these new calixarenes is similar to that observed with *p*-(*t*Bu)-functionalized ones, with similar activation barriers for the cone-to-cone inversion. To the best of our knowledge, the *p*-(benzyloxy) and the *p*-(*t*Bu) systems are the only ones having demonstrated such versatility so far.

The results reported here (along with previous ones[7,16,21,42]) clearly demonstrate the potential of *p*-(benzyloxy)phenol for calixarene synthesis. The ease of removal of the benzyl groups under mild hydrogenolysis conditions, along with the possibility to easily convert these derivatives into calixquinones[51] opens very interesting perspectives for the formation of new ligands, easily derivatized at the *p*-position.

Experimental Section

Modified Procedure for the Preparation of *p*-(Benzyloxy)calix[8]-arene (2): In a 2-L, three-necked flask fitted with a Dean–Stark collector a suspension of 4-(benzyloxy)phenol (50.84 g, 0.254 mol), paraformaldehyde (19.92 g, 0.664 mol), and potassium *tert*-butoxide (1.87 g, 0.0167 mol) in xylene (960 mL) was heated under an atmosphere of argon at 120 °C for 18 h under strong magnetic stirring. The magnetic stirrer was removed, replaced by a mechanical one, and the pale-yellow suspension was then brought to moderate reflux for 6 h (using an oil bath). The resulting thick white suspension was then left overnight at ambient temperature. The white precipitate was filtered and washed with xylene (200 mL) and acetone (150 mL) to afford pure *p*-(benzyloxy)calix[8]arene as a bright-white solid (33.32 g, 65.5%). The spectroscopic characteristics were in accordance with those previously published.[7,16,21,42]

***p*-(Benzyloxy)calix[7]arene (4):** The above xylene/acetone filtrate was evaporated to dryness under reduced pressure. The resulting dark-brown solid was suspended in dichloromethane (200 mL) and filtered to yield **4** as a cream solid (4.3 g, 8%). ^{1}H NMR (250 MHz, DMSO, 20 °C): δ = 11.5 (OH), 7.7–7.2 (m, 5 H, ArH), 6.70 (s, 2 H, $Ar_{hydroquinone}H$), 4.92 (s, 2 H, $ArCH_2O$), 3.70 (br. s, 2 H, $ArCH_2Ar$) ppm. ^{13}C NMR (100 MHz, DMSO, 20 °C): δ = 72.4 [OCH_2(benzyl)], 117.26 ($Ar_{hydroquinone}$C-H), 130–132 (ArC-H), 131.6 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 140.3 ($ArC_{ipso}$-$CH_2$), 153.5 ($Ar_{hydroquinone}C_{ipso}$-OH) ppm. HRMS (MALDI): calcd. for $C_{98}H_{84}O_{14}$ [M + K]$^+$ 1523.54927; found 1523.55675.

***p*-(Benzyloxy)bis(homooxa)calix[4]arene (6):** The dichloromethane filtrate obtained after the recovery of **4** was evaporated to dryness and dissolved in dichloromethane (200 mL). Methanol (600 mL) was then added, and the resulting white precipitate was recovered by filtration to yield **6** (4 g). The corresponding filtrate was evaporated and washed with methanol. After column chromatography of the resulting MeOH insoluble residue (deactivated alumina, eluent CH_2Cl_2, R_f = 0,7), a second crop of **6** (1.8 g) was recovered. Final yield: 5.8 g, 10.4%. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 9.62 (s, 2 H, OH), 8.922 (s, 2 H, OH), 7.7–7.2 (m, 20 H, ArH), 6.87 (d, 2 H, ^4J = 3 Hz, $Ar_{hydroquinone}H$), 6.77 (d, 2 H, ^4J = 3 Hz, $Ar_{hydroquinone}H$), 6.70 (d, 2 H, ^4J = 3 Hz, $Ar_{hydroquinone}H$) 6.61 (d, 2 H, ^4J = 3 Hz, $Ar_{hydroquinone}H$), 4.98 (s, 4 H, $ArCH_2O$), 4.91 (s, 4 H, $ArCH_2O$), 4.57 (br. s, 4 H, $ArCH_2OCH_2Ar$), 3.83 (br. s, 6 H, $ArCH_2Ar$) ppm. ^{13}C NMR (100 MHz, DMSO, 20 °C): δ = 30–34 (br., $ArCH_2Ar$), 70.7 [OCH_2(benzyl)], 70.83 [OCH_2(benzyl)], 71 (br., $ArCH_2OCH_2Ar$), 114, 6 ($Ar_{hydroquinone}$C-H), 115.2 ($Ar_{hydroquinone}$C-H), 115.4 ($Ar_{hydroquinone}$C-H), 117.4 ($Ar_{hydroquinone}$C-H), 123.1 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 127–129 (ArC-H/$Ar_{hydroquinone}C_{ipso}$-$CH_2$/$ArC_{ipso}$-$CH_2$), 137.2 ($ArC_{ipso}$-$CH_2$), 143.5 ($Ar_{hydroquinone}C_{ipso}$-OH), 147.2 ($Ar_{hydroquinone}C_{ipso}$-OH), 152.1 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$), 153.4 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$) ppm. HRMS (MALDI): calcd. for $C_{57}H_{50}O_9$ [M + Na]$^+$ 901.33470; found 901.33119.

***p*-(Benzyloxy)calix[4]arene (5):** During the chromatographic recovery of the second crop of **6** (see above), **5** was eluted first and obtained as a white solid (deactivated alumina, eluent CH_2Cl_2, R_f = 0.8). Yield: 0.3 g, <1%. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 10.014 (s, 1 H, OH) 7.8–7 (m, 5 H, ArH), 6.66 (s, 2 H, $Ar_{hydroquinone}H$), 4.90 (s, 2 H, $ArCH_2O$), 4.26 (d, ^2J = 13 Hz, 1 H, $ArCH_2Ar$), 3.42(d, ^2J = 13 Hz, 1 H, $ArCH_2Ar$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 32.5 ($ArCH_2Ar$), 70.75 [OCH_2-(benzyl)], 115.26 ($Ar_{hydroquinone}$C-H), 127–130 (ArC-H), 137.3 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 143.14 ($ArC_{ipso}$-$CH_2$), 147.3 ($Ar_{hydroquinone}$-$C_{ipso}$-OH), 153.5 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$) ppm. HRMS (MALDI): calcd. for $C_{56}H_{48}O_8$ [M + Na]$^+$ 871.34701; found 871.34510.

***p*-(Benzyloxy)calix[5]arene (7):** After the chromatographic recovery of *p*-(benzyloxy)calix[4]arene and of the second crop of compound **6**, chromatography was continued (CH_2Cl_2/EtOH, 97:3). Compound **7** was recovered as a slightly yellow solid. Yield: 1.3 g, 2.4%. ^{1}H NMR (250 MHz, $CDCl_3$, 20 °C): δ = 8.47 (s, 1 H, OH) 7.5–7.2 (m, 5 H, ArH), 6.85 (s, 2 H, $Ar_{hydroquinone}H$), 4.95 (s, 2 H, Ar-CH_2O), 3.79 (br. s, 2 H, $ArCH_2Ar$) ppm. ^{13}C NMR (100 MHz, DMSO, 20 °C): δ = 33.5 (br., $ArCH_2Ar$), 72.3 [OCH_2(benzyl)], 117.9 ($Ar_{hydroquinone}$C-H), 130–132 (ArC-H), 131.6 ($Ar_{hydroquinone}$-C_{ipso}-CH_2), 140.2 (ArC_{ipso}-CH_2), 147.3 ($Ar_{hydroquinone}C_{ipso}$-OH), 154.7 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$) ppm. HRMS (MALDI): calcd. for $C_{70}H_{60}O_{10}$ [M + Na]$^+$ 1083.40787; found 1083.40425.

Heptakis(ethoxycarbonyl)methoxy *p*-(Benzyloxy)calix[7]arene (8): To a solution of **4** (216 mg, 0.145 mmol) in ethyl bromoacetate (6 mL) was added off-the-shelf DMF (0.3 mL) under an atmosphere of argon. 60% NaH (120 mg) was then added, and the resulting suspension was stirred overnight under an atmosphere of argon at 50 °C. 60% NaH (76 mg) was then added under an atmosphere of argon, and the suspension was left for 4 h at 50 °C. After cooling to ambient temperature, EtOH/CH_3COOH (90:10, 50 mL) was added. The resulting precipitate was filtered, washed with ethanol, dried under vacuum, and washed with pentane. Compound **8** was obtained in quantitative yield (0.3 g). ^{1}H NMR (400 MHz, CDCl3, 20 °C): δ = 7.25 (br., 5 H, ArH), 6.65 (s, 2 H, $Ar_{hydroquinone}$-H), 4.72 (s, 2 H, $ArCH_2O$), 4.25 (br. s, 2 H, $ArCH_2COO$), 4 (overlap: q, 2 H, O-CH_2-CH_3 + s, 2 H, $ArCH_2Ar$), 1 (t, 3 H, OCH_2-CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 13.9 (CH_3), 30.9 ($ArCH_2Ar$), 60.95 (OCH_2CH_3), 69.74 (CH_2OPh), 70.41 ($CH_2OCOOEt$), 115.3 ($Ar_{hydroquinone}$C-H), 127–129 (ArC-H), 134.5 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 137.2 ($ArC_{ipso}$-$CH_2$), 148.2 ($ArC_{ipso}$-OH), 148.7 ($ArC_{ipso}$-$OCH_2$), 155.15 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$), 169 (C=O) ppm. IR: $\tilde{\nu}$ = 1755 cm^{-1} (C=O). HRMS (MALDI): calcd. for $C_{126}H_{126}O_{28}$ [M + Na]$^+$ 2109.83279; found 2109.83614.

Tetrakis(ethoxycarbonyl)methoxy *p*-(Benzyloxy)(bishomooxa)calix-[4]arene (9): To a solution of **6** (290 mg, 0.233 mmol) in ethylbromoacetate (6 mL) was added off-the-shelf DMF (0.3 mL). 60% NaH (162 mg) was then added, and the resulting suspension was heated at 50 °C overnight under an atmosphere of argon. 60% NaH (60 mg) was then added, and the suspension was heated at 50 °C for 4 h. EtOH/CH_3COOH (90:10, 50 mL) was then added. The solvents were removed under vacuum. The resulting yellowish tar was then washed with pentane (100 mL), dried, and then washed with water (100 mL). After drying in vacuo, compound **6** was recovered as a white solid. Yield: 379 mg, 94%. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 7.5–7.2 (m, 20 H, ArH), 6.65 (d, ^4J = 3 Hz, 2 H, $Ar_{hydroquinone}H$, 6.59 (d, ^4J = 3 Hz, 2 H, $Ar_{hydroquinone}$-H), 6.53 (d, ^4J = 3 Hz, 2 H, $Ar_{hydroquinone}H$), 6.27 (d, ^4J = 3 Hz, 2 H, $Ar_{hydroquinone}H$), 4.95 (d, ^2J = 10 Hz), 4.856 (s, 4 H, CH_2OPh), 4.849 (s, 4 H, CH_2OPh),4.82 (d, ^2J = 12 Hz), 4.71 (d, ^2J = 16 Hz), 4.6 (d, ^2J = 15 Hz), 4.43 (d, ^2J = 16 Hz), 4.31 (t, 4 H, CH_2COOEt), 4.23 (t, 4 H, CH_2COOEt), 3.3 (d, 2 H, ^2J = 16 Hz), 3.28 (d, 1 H, ^2J = 12 Hz) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 14.2 (CH_3), 31.06 ($ArCH_2Ar$), 32.4 ($ArCH_2Ar$), 60.67 (OCH_2CH_3), 60.93 (OCH_2CH_3), 68.3 69.83 (CH_2OPh), 70.3 ($CH_2OCOOEt$), 71.2 (CH_2OCH_2), 112.37 ($Ar_{hydroquinone}$C-H), 114.34 ($Ar_{hydroquinone}$-C-H), 115.83 ($Ar_{hydroquinone}$C-H), 116.56 ($Ar_{hydroquinone}$C-H), 126–130 (ArC-H), 133 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 133.8 ($Ar_{hydroquinone}$-$C_{ipso}$-$CH_2$), 135.3 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 135.7 ($Ar_{hydroquinone}$-$C_{ipso}$-$CH_2$), 148.2 ($ArC_{ipso}$-OH), 148.8 ($ArC_{ipso}$-OH), 154.4 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$), 154.8 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$), 170 (C=O). IR: $\tilde{\nu}$ = 1754 cm^{-1} (C=O). HRMS (MALDI): calcd. for $C_{73}H_{74}O_{17}$ [M + Na]$^+$ 1245.48182; found 1245.48361.

Pentakis(ethoxycarbonyl)methoxy *p*-(Benzyloxy)calix[5]arene (10): To a solution of **7** (146 mg, 0.138 mmol) in ethylbromoacetate (6 mL) was added off-the-shelf DMF (0.3 mL). 60% NaH (162 mg) was then added, and the resulting suspension was heated at 50 °C overnight under an atmosphere of argon. 60% NaH (60 mg) was then added, and the suspension was heated at 50 °C for 4 h. EtOH/CH_3COOH (90:10, 50 mL) was then added. The solvents were removed under vacuum. The resulting yellowish tar was then washed with pentane (100 mL), dried, and then washed with water (100 mL). After drying in vacuo, compound **10** was recovered as a slightly yellow solid. Yield: 0.2 g, 97%. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 7.5–7.2 (m, 20 H, ArH), 7.2–6 (overlapping multiplets, 5 H, ArH), 5.2–3 (overlapping multiplets, 8 H, Ar-CH_2Ar, $ArOCH_2$, OCH_2Ph, OCH_2CH_3), 1.5–0.8 (overlapping triplets, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 14.2 (CH_3), 29–33 (br., $ArCH_2Ar$), 32.4 ($ArCH_2Ar$), 60–63 (OCH_2CH_3), 69–72 (CH_2OPh, $CH_2OCOOEt$), 113–118 ($Ar_{hydroquinone}$C-H), 126–130 (ArC-H), 133–140 ($Ar_{hydroquinone}$-C_{ipso}-CH_2), 147–150 (ArC_{ipso}-OH), 154–157 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$), 168–172 (C=O). IR: $\tilde{\nu}$ = 1755 cm^{-1} (C=O). HRMS (MALDI): calcd. for $C_{90}H_{90}O_{20}$ [M + Na]$^+$ 1513.59177; found 1513.58738.

Tetrakis(ethoxycarbonyl)methoxy *p*-(Benzyloxy)calix[4]arene (11): To a solution of **5** (200 mg, 0.179 mmol) in ethylbromoacetate (10 mL) was added off-the-shelf DMF (0.6 mL). 60% NaH (70 mg) was then added, and the resulting suspension was heated at 50 °C overnight under an atmosphere of argon. 60% NaH (115 mg) was then added, and the suspension was heated at 50 °C for 4 h. The product was then precipitated in pentane (200 mL) and filtered. The precipitate was recovered with CH_2Cl_2, and the solvents were evaporated. The product was then washed with pentane to remove any remaining paraffin. Compound **11** was recovered in nearly quantitative yield as a slightly yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$, 20 °C): δ = 7.5–7.2 (m, 20 H, ArH), 6.77 (s, 8 H, ArH), 5.90 (s, 8 H, OCH_2Ph), 4.44 (s, 8 H, $ArOCH_2$), 4.38 (q, 8 H, OCH_2CH_3), 4.23 (d, ^2J = 12 Hz), 4.37 (d, ^2J = 12 Hz), 1.42 (12 H, OCH_2CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 20 °C): δ = 14.2 (CH_3), 30.3 ($ArCH_2Ar$), 62 (OCH_2CH_3), 70.6 (CH_2OPh), 73.5 ($CH_2OCOOEt$), 115.3 ($Ar_{hydroquinone}$C-H), 127–129 (ArC-H), 135.5 ($Ar_{hydroquinone}C_{ipso}$-$CH_2$), 136.6 ($ArC_{ipso}$-$CH_2$), 146.2 ($ArC_{ipso}$-OH), 156.3 ($Ar_{hydroquinone}C_{ipso}$-$OCH_2$), 171.2 (C=O) ppm. IR: $\tilde{\nu}$ = 1755 cm^{-1} (C=O). MS (MALDI): calcd. for $C_{72}H_{72}O_{16}$ [M + Na]$^+$ 1215.472; found 1215.45.

X-ray Crystal-Structure Analysis of 6: Recrystallization from toluene at ambient temperature gave single crystals of **6** that were suitable for an X-ray crystal-structure analysis of the obtained product. X-ray diffraction data were collected with a Kappa X8 APPEX II Bruker diffractometer using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The temperature of the crystal was maintained at the selected value (100 K) to within an accuracy of ±1 K by means of a 700 series Cryostream cooling device. The data were corrected for Lorentz polarization, and absorption effects. The structures were solved by direct methods using SHELXS-97[52] and refined against F^2 by full-matrix least-squares techniques using SHELXL-97[53] with anisotropic displacement parameters for all non-hydrogen atoms. Hydrogen atoms were introduced into the calculations as a riding model with isotropic thermal parameters. The toluene solvent molecule is disordered. All calculations were performed by using the Crystal Structure crystallographic software package WINGX.[54] $C_{121}H_{100}O_{18}$, M = 1842.01, triclinic, a = 9.0983(8) Å, b = 16.3283(15) Å, c = 31.411(3) Å, α = 87.066(2)°, β = 89.637(2)°, γ = 87.784(3)°, V = 4656.7(8) Å^3, T = 100(1) K, space group $P\bar{1}$ (no. 2), Z = 2, μ(Mo-K_α) = 0.088 mm^{-1}, 64616 reflections

measured, 18504 unique (R_{int} = 0.1001), 9453 [$I > 2\sigma(I)$], which were used in all calculations; final $R(F^2)$ = 0.0812. CCDC-793733 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}NMR spectra and selected HSQC, HMBC, COSY, and NOESY spectra.

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[55] **Note Added in Proof** (September 21, 2010): By the time this manuscript was entering its final processing, one of us (C. M.) discovered that when this concentrated CH_2Cl_2/MeOH fraction is dissolved in ca. 20 mL of toluene (before the final chromatographic purification), *p*-(benzyloxy)calix[5]arene spontaneously precipitates out over a period of 24 h. This phenomenon greatly eases the final chromatographic purification of the remaining calixarenes.

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