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Microwave-Assisted Synthesis of a Nitro-*m*-xylylenedioxycalix[6]arene Building Block Functionalized at the Upper Rim

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Microwave-assisted synthesis represents a new methodology to obtain calix[6]arene building blocks. The synthesis of compounds **1** and **2** is described. These compounds are A,D-*m*-xylylenedioxy-bridged calix[6]arenes in *cone* conformation, functionalized with potential amino groups in the lower rim spacer (5-position) and amino groups or their precursors in A,D-*para* positions at the upper rim. A conformational study has been performed for all newly synthesized compounds.

Introduction

The design of platforms such as calix[6]arenes for supramolecular chemistry requires both efficient control of their conformational flexibility[1] and the formation of multifunctionalized macrocycles at the upper and lower rims.

Although the *cone* conformation can be occasionally obtained for calix[6]arenes,[2] it is not the general case, as rotation of the rings can also take place by the passage of the *para* substituent (i.e., the *tert*-butyl group) through the cavity.[2c,3] A common way to prevent this rotation is to bridge two or three phenol rings with appropriate spacers.[4] Most often, the bridge links two opposite (A,D) rings.[5] Spacers such as *m*-xylylene or 2,6-lutidinedinyl can better keep the A and D rings in *syn* orientation, although the relative direction of the remaining four rings depends on their *O*-substituents.[6] It has been demonstrated that *O*-ethyl groups facilitate a *cone* conformation of A,D-*m*-xylylenedioxycalix[6]arenes.[6d,6f] Moreover, the use of the *m*-xylylene spacer allows the introduction of an additional function at the 5-position, thus enabling linkage of the calixarene to other platforms. Thus, these macrocycles may serve as molecular building blocks for the construction of more complex structures such as dendrimeric endoreceptors.[7]

Here we report on the benefits of using microwave (MW)-assisted synthesis to prepare branching units **1** and **2**, which are constituted by bridged A,D-*m*-xylylenedioxy-calix[6]arenes in a *cone* conformation, with ethyl groups in the remaining phenol groups and functionalized with amino group precursors at the 5-position of the spacer. To use these macrocycles as building blocks, a new methodology to introduce two new functional groups at the *para* positions of two opposite (A, D) rings was necessary (Figure 1).

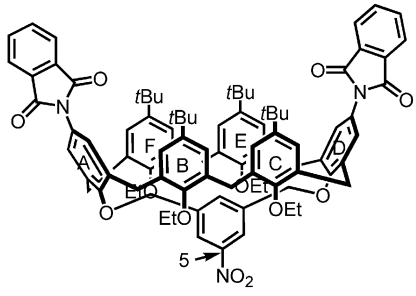

Figure 1. Compounds **1** and **2**.

The general strategy to selectively obtain *para*-functionalization in calix[6]arenes is based on the well-established differences in reactivity between anisole and phenol.[1] *O*-Benzylation of the A and D phenol rings, followed by methylation of the remaining rings and deprotection of the benzyl groups affords the desired substitution pattern.[2c,8,9a] However, to the best of our knowledge, only a few examples have been published for this reaction sequence.[9] In order to link the A and D rings, which are

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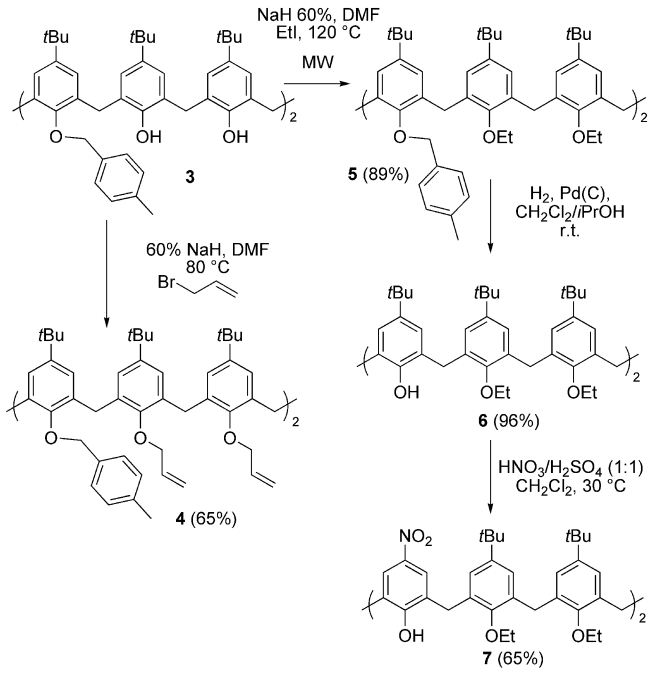
previously functionalized in the *para* positions, we have established a new strategy based on the use of MW irradiation.

Results and Discussion

Reaction of **3**[2b] with sodium hydride and ethyl or propyl iodide yielded complex reaction mixtures, and compound **4** was only obtained in a 65% yield when allyl bromide was employed (Scheme 1). These results suggest that the phenol groups are buried into the cavity, disabling *O*-alkylation, which is favored by a more reactive halogen derivative.[10]



Scheme 1. Synthesis of compounds **4**–**7**.

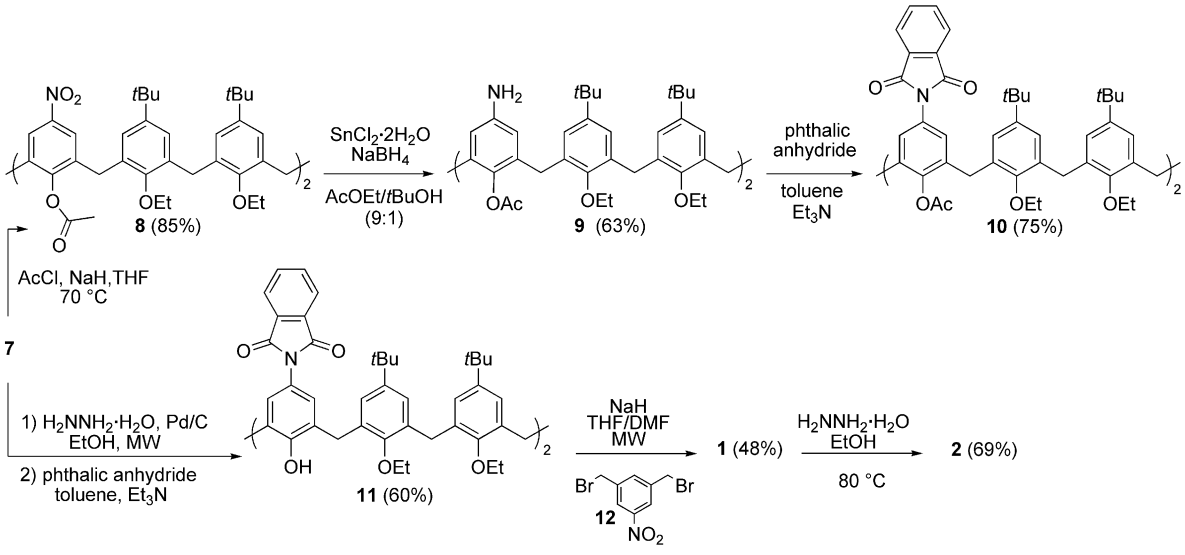
In fact, ethyl groups were only introduced successfully when MW irradiation was employed, and compound **5** was obtained almost pure in 89% yield. Debenzylation of **5** was carried out by hydrogenolysis. Treatment of **6** with a mixture of nitric and sulfuric acids (1:1) in dichloromethane afforded nitro derivative **7** in 65% yield (Scheme 1).

Before *O*-alkylation of **7** with bridging reagent **12**, it was necessary to differentiate the amino precursor of the upper rim from the one at the lower rim. Therefore, both nitro groups of compound **7** were converted into protected amino groups after protection of the phenol groups as a result of the easy oxidation of aminophenols. Acetylation of **7** and subsequent reduction of **8** with $SnCl_2{\cdot}2H_2O/NaBH_4$ in a mixture of AcOEt/*t*BuOH (9:1) gave diamine **9** in 54% overall yield. Finally, protection of these functional groups with phthalic anhydride gave derivative **10** in 75% yield (Scheme 2).

The selective hydrolysis of the acetyl groups under acidic or basic conditions resulted in complex reaction mixtures. Indeed, mass spectrometry showed that partial hydrolysis of the phthalimido groups had occurred.

Reduction of the nitro groups in compound **7** with $SnCl_2{\cdot}2H_2O/NaBH_4$, or with hydrazine and Pd/C in ethanol for prolonged reaction times, gave complex reaction mixtures in which only minor amounts of the amino derivatives were found, probably due to oxidation of the aminophenols, thus indicating that the amino groups should be protected in situ. Therefore, a fast and quantitative reduction method was necessary. Once again, after testing numerous experimental conditions and reduction reagents, only MW conditions gave satisfactory results. Compound **7** was reduced by using hydrazine and Pd/C in ethanol at 130 °C under pressure (6 bar) followed by treatment with phthalic anhydride to give **11** in 60% overall yield (Scheme 2).

Reaction of **11** with difunctional derivative **12** was again successful when MW irradiation was used, and **1** was ob-



Scheme 2. Synthesis of compounds **8**–**11**, **1**, and **2**.

tained in 48% yield. Deprotection of the amino groups in **1** was carried out with hydrazine in ethanol to give **2** in 69% yield (Scheme 2).

The ^{1}H NMR spectra of compounds **4**–**11** are broad at room temperature, revealing a flexible structure for all of them. In most cases, variable-temperature (188–298 K) studies showed complex spectra at 188 K. Ethyl or allyl signals appear at abnormally high fields, indicating that at least some of these substituents are inside the cavity. Nevertheless, some differences could be observed depending on the substitution at the A and D rings.

Compounds **4** and **5**, which have two *p*-methylbenzyl groups in opposite rings, displayed similar ^{1}H NMR (CD_2Cl_2, 238 K) behavior: three AB systems are observed for the calixarene methylene bridges ($ArCH_2Ar$) in a 1:1:1 ratio, as well as six signals for the aromatic calixarene protons. Remarkably, ethyl or allyl chains appeared as two well-separated groups of signals, one strongly shielded, indicating inclusion of the chain into the cavity. These results indicate that compounds **4** and **5** are in a conformation displaying only one element of symmetry (Figure 2).

To have better insight into the conformation of these calix[6]arenes, 2D NMR experiments (HSQC, COSY, and ROESY) were recorded at 238 K. In the HSQC spectrum of **4**, three signals are visible for the calixarene methylene bridges, which correspond to the three AB systems in the ^{1}H NMR spectrum, two at ca. 29 ppm and the other one at ca. 33 ppm. In compound **5**, two of these carbon signals are present at ca. 29 ppm (which correlates with the AB systems) and at ca. 34 ppm (which correlates with a singlet). Although the observed values (ca. 33 ppm) are away from the 37 ppm standard shift to confirm an *anti* arrangement of the bridged aromatic rings,[11] it has been reported (for calix[4]arenes) that large deviations from the usual 31 and 37 ppm values for "pure" *syn* or *anti* arrangements, respectively, may be interpreted either as a distorted conformation or as a fast equilibrium between *syn* and *anti* forms.[12]

A ROESY experiment of compounds **4** and **5** (238 K, CD_2Cl_2) revealed exchange peaks between similar protons. Considering the symmetry of the compound (inversion center) and the observed ROESY peaks, we conclude that an equilibrium between several 1,2,3-*alternate* conformations of lower symmetry operates, as a result of the inclusion of the two opposite rings carrying alkyl groups that are more shielded than the remaining rings. Similar results were previously reported by us for *p*-unsubstituted calix[6]arenes.[10]

Single crystals were obtained for **4** from tetrachloroethane. In the solid state, a *uudddu* conformation is displayed, with the allyl groups oriented inside the cavity and in agreement with low-temperature studies in solution (Figure 3).

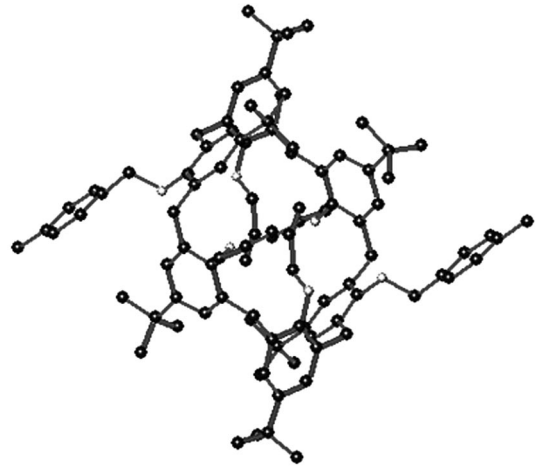


Figure 3. X-ray structure of compound **4**.

When variable-temperature (188–298 K) experiments were performed with compounds **6**, **7**, and **11**, which bear free OH groups, complex ^{1}H NMR spectra were observed. The spectrum of compound **6** was indeed too complex to conclude anything about its conformation. Compound **7** showed two nonsymmetrical conformers (CD_2Cl_2, hydrogen-bonding patterns at the 188 K), whereas for **11** only one could be observed (CD_2Cl_2, 188 K). These results could be explained by taking into account the lower rim and the nature of the substituent at the *para* position. For instance,

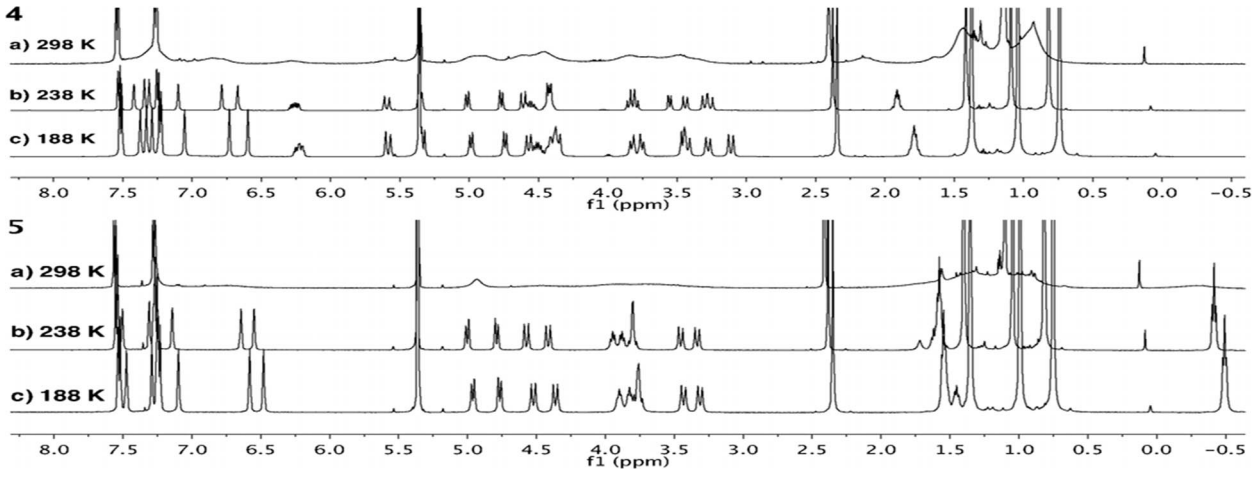


Figure 2. ^{1}H NMR spectra of compounds **4** and **5**.

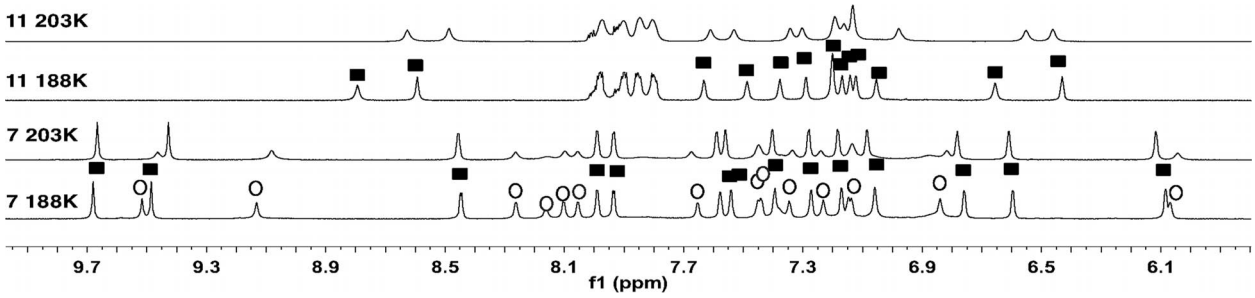


Figure 4. ^{1}H NMR spectra of compounds **7** and **11**. Signals for different conformations are highlighted.

compound **11**, which has stronger hydrogen bonds than **6**, and a bulkier group in the *para* position than **7**, shows the most defined conformation at 188 K (Figure 4).

COSY and ROESY experiments were performed at 188 K for **11**. Analysis of the COSY spectra proved the presence of four different ethyl groups, and at least two of them are diastereotopic. Nevertheless, its conformation could not be determined due to the large number of cross-peaks in the ROESY experiment.

Single crystals were obtained for **11** from CH_3CN/CH_2Cl_2. In the solid state, a *uudddu* conformation is displayed, with the phenol groups oriented inside the cavity (Figure 5).

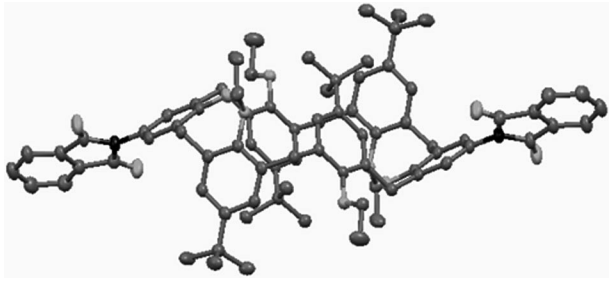


Figure 5. X-ray structure of compound **11**.

At 188 K, compounds **8**, **9**, and **10** (acetyl groups in the lower rim) still show complex NMR spectra, accounting for the importance of hydrogen bonding in the conformational rigidity.

Conformations of bridged calix[6]arenes **1** and **2** were established by a full set of 1D ^{1}H or ^{13}C NMR techniques. The NMR spectra of these compounds ($CDCl_3$, 298 K) showed signals corresponding to molecules with two planes of symmetry: two AX systems in a 2:1 ratio for the methylene protons ($ArCH_2Ar$) and the corresponding two signals in the ^{13}C NMR spectra at δ = 30.2 and 29.7 ppm, indicating that the macrocycles display *cone* conformations. A ROESY ($CDCl_3$, room temperature) experiment with **1** shows cross-peaks that are in agreement with those previously reported for bridged A,D-*m*-xylylenedioxycalix[6]-arenes, indicating that all of the aromatic rings are in a *syn* orientation.[7a]

Conclusions

The synthesis of A,D-*m*-xylylene-bridged calix[6]arenes **1** and **2**, functionalized in the 5-position of the spacer and in the upper rim with amino groups or amino precursors has been described. It was found that these compounds adopt a *cone* conformation. These building blocks contain functional groups that pave the way toward more complex branched structures. The new methodology described here is useful to obtain calix[6]arenes functionalized at both the lower and upper rims, and the use of microwave-assisted synthesis was the key in most cases to obtain the desired products.

Experimental Section

General: Unless otherwise reported, all reactions were carried out under a dry and deoxygenated argon atmosphere. Solvents were freshly distilled and dried before use by standard methods. All chemicals were used as purchased. Reported melting points were measured in open capillaries with a Gallenkamp Melting Point apparatus. NMR experiments (^{1}H,^{13}C{^{1}H}, and ROESY) were carried out at 500 (125) MHz and reported chemical shifts (δ) are externally referenced to solvent residual signal. Mass spectra were performed with a REFLEX spectrometer by using the MALDI-TOF method, with the use of dithranol as matrix and NaI as additive. Elemental analyses were performed with a LECO CHN 932 microanalyzer, indicated inclusion of solvent molecules for nearly all calixarene products and were supported by separate ^{1}H NMR spectroscopic studies. TLC was performed on silica gel Alugram Sil G/UV254 (Macherey-Nagel) sheets. Microwaves-assisted synthesis was performed with a Discover microwave (S-Class), cooling by nitrogen current. Reactions under ultrasound were performed with a Selecta "Ultrasons-H" (40 kHz).

37,38,40,41-Tetraallyloxy-5,11,17,23,29,35-hexa-*tert*-butyl-39,42-bis(4-methylbenzyloxy)calix[6]arene (4): A mixture of **3**[2b] (100.0 mg, 0.085 mmol) and NaH (60% suspension in mineral oil, 27.1 mg, 0.678 mmol) in dry DMF (5.0 mL) was heated at 80 °C under an argon atmosphere for 1 h. Then, allyl bromide (59.0 μL, 0.678 mmol) was added, and the mixture was kept under the same conditions for 24 h. Once cooled, MeOH was added, and the solvent was eliminated under reduced pressure. The residue obtained was partitioned between $CHCl_3$ and HCl (1 M). The organic phase was washed sequentially with brine (3 × 15 mL) and water, and then it was dried ($MgSO_4$). The solvent was eliminated under reduced pressure, and the residue obtained was triturated with

MeOH. Finally, the precipitate obtained was purified by crystallization ($CHCl_3$/MeOH) to give **4** as a white solid (73.8 mg, 65%). M.p. 245–247 °C. ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 403 K): δ = 7.43 (d, $^3J_{H,H}$ = 7.6 Hz, 4 H, ArH), 7.19 (s, 4 H, ArH), 7.15 (d, $^3J_{H,H}$ = 7.7 Hz, 4 H, ArH), 7.07 (s, 4 H, ArH), 6.95 (s, 4 H, ArH), 5.55–5.35 (m, 4 H, CH=), 4.87 (s, 4 H, ArOCH$_2$Ph), 4.68–4.55 (m, 8 H, CH$_2$=), 4.53–4.44 (m, 8 H, ArOCH$_2$), 4.20 (d, $^2J_{H,H}$ = 13.1 Hz 4 H, ArCH$_2$Ar), 3.88–3.78 (m, 2 H, ArCH$_2$Ar), 3.62–3.42 (m, 6 H, ArCH$_2$Ar), 2.34 (s, 6 H, ArCH$_3$), 1.16 [s, 18 H, C(CH$_3$)$_3$], 1.10 [s, 36 H, C(CH$_3$)$_3$] ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 373 K, DEPT): δ = 153.5, 153.2, 145.9, 145.7, 137.7, 135.5 (Ar), 133.8 (*C*H=), 133.4, 133.3, 133.1 (Ar), 129.4, 128.5, 127.9, 126.3, 125.0 (ArH), 117.9 (*C*H$_2$=), 74.8, 74.2 (O*C*H$_2$), 34.4, 34.2 [*C*(CH$_3$)$_3$], 31.8, 31.7 [C(*C*H$_3$)$_3$], 30.0, 29.8 (Ar*C*H$_2$Ar), 21.3 (Ar*C*H$_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1363.6 (100) [M + Na]$^+$. $C_{94}H_{116}O_6$·MeOH (1374.0): calcd. C 83.05, H 8.80; found C 83.16, H 8.84.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40,41-tetraethoxy-39,42-bis(4-methylbenzyloxy)calix[6]arene (5): A suspension of **3**[2b] (500.0 mg, 0.421 mmol) and NaH (60% suspension in mineral oil, 118.5 mg, 2.947 mmol) in dry DMF (17.5 mL, 25 mM) was prepared in a 35-mL MW container. Ethyl iodide (550.0 μL, 6.876 mmol) was added, and the vessel was sealed and introduced into the MW oven. The reaction was programmed at 120 °C for 25 min by using a 5-min temperature ramp and a maximum power of 50 W. Then, H_2O and HCl (1 M) were added, and the mixture was stirred at room temperature for 40 min. The precipitate formed was filtered, and the solid obtained was triturated with MeOH to give **5** as a whitish solid (487.3 mg, 89%). M.p. 302–304 °C. ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 398 K): δ = 7.54 (d, $^3J_{H,H}$ = 7.9 Hz, 4 H, ArH), 7.30–7.20 (m, 8 H, ArH), 7.13 (s, 4 H, ArH), 6.97 (s, 4 H, ArH), 4.95 (s, 4 H, ArOCH$_2$), 4.27 (d, $^2J_{H,H}$ = 14.0 Hz, 4 H, ArCH$_2$Ar), 4.00–3.80 (m, 4 H, ArCH$_2$Ar), 3.64 (d, $^2J_{H,H}$ = 13.8 Hz, 4 H, ArCH$_2$Ar), 3.10–2.85 (m, 8 H, ArOC*H*$_2$CH$_3$), 2.42 (s, 6 H, ArCH$_3$), 1.22 [s, 36 H, C(CH$_3$)$_3$], 1.15 [s, 18 H, C(CH$_3$)$_3$], 0.80–0.55 (m, 12 H, CH$_3$) ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 373 K, DEPT): δ = 153.6, 152.8, 145.9, 145.5, 137.7, 135.6, 133.5, 133.4, 133.1 (Ar), 129.4, 128.5, 127.7 (ArH), 74.7, 68.6 (ArO*C*H$_2$), 34.3, 34.2 [*C*(CH$_3$)$_3$], 31.8, 31.7 [C(*C*H$_3$)$_3$], 30.1 (Ar*C*H$_2$Ar), 21.3 (Ar*C*H$_3$), 15.7 (ArOCH$_2$*C*H$_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1316.7 (100) [M + Na]$^+$. $C_{90}H_{116}O_6$·H$_2$O (1311.9): calcd. C 82.40, H 9.07; found C 82.23, H 8.98.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,40,41-tetraethoxy-39,42-dihydroxycalix[6]arene (6): To a mixture of **5** (3.800 g, 2.939 mmol) and 10% Pd/C (200.0 mg) in CH_2Cl_2/*i*PrOH (8.5:1.5, 220.0 mL) was passed a flow of hydrogen for 30 min, and the mixture was stirred under a hydrogen atmosphere at room temperature for 4 h. Then, the mixture was filtered through Celite, and the solvent was eliminated under reduced pressure. The residue obtained was triturated with MeOH to give **6** as a whitish solid (3.05 g, 96%). M.p. >280 °C (decomp.). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 403 K): δ = 7.25 (s, 4 H, ArH), 6.96 (s, 8 H, ArH), 6.84 (s, 2 H, ArOH), 3.87 (s, 4 H, ArCH$_2$Ar), 3.82 (s, 8 H, ArCH$_2$Ar), 3.57 (q, $^3J_{H,H}$ = 7.0 Hz, 8 H, ArO*C*H$_2$CH$_3$), 1.18 [s, 18 H, C(CH$_3$)$_3$], 1.10 [s, 36 H, C(CH$_3$)$_3$], 0.93 (t, $^3J_{H,H}$ = 7.0 Hz, 12 H, ArOCH$_2$*C*H$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K, DEPT): δ = 151.8, 149.9, 146.3, 141.7, 132.8, 132.2, 126.9 (Ar), 126.1, 125.9, 124.9 (ArH), 69.5 (ArO*C*H$_2$CH$_3$), 34.0, 33.8 [*C*(CH$_3$)$_3$], 31.5, 31.3 [C(*C*H$_3$)$_3$], 30.9 (Ar*C*H$_2$Ar), 14.9 (ArOCH$_2$*C*H$_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1107.7 (100) [M + Na]$^+$. $C_{74}H_{100}O_6$·H$_2$O (1103.6): calcd. C 80.54, H 9.32; found C 80.57, H 9.23.

5,17,23,35-Tetra-*tert*-butyl-37,38,40,41-tetraethoxy-39,42-dihydroxy-11,29-dinitrocalix[6]arene (7): To a solution of **6** (673.0 mg, 2.081 mmol) in dry CH_2Cl_2 (1.2 mL, 0.61 M) stirred at room temperature was added a freshly prepared mixture of 65% HNO_3 and concentrated H_2SO_4 (1:1, 260.0 μL). The mixture was heated at 30 °C for 3 h and, once cooled, water was added. The aqueous solution was extracted with CH_2Cl_2, and the organic phase was washed with water (until neutral pH) and then dried ($MgSO_4$). The solvent was eliminated under reduced pressure, and the residue obtained was triturated with acetonitrile/H_2O to give **7** as a yellowish solid (431.1 mg, 65%). M.p. >258 °C (decomp.). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 373 K): δ = 8.67 (s, 2 H, ArOH), 7.81 (s, 4 H, ArH), 6.94 (s, 4 H, ArH), 6.88 (s, 4 H, ArH), 3.75 (s, 4 H, ArCH$_2$Ar), 3.74 (s, 8 H, ArCH$_2$Ar), 3.55–3.45 (m, 8 H, ArO*C*H$_2$CH$_3$), 0.97 [s, 36 H, C(CH$_3$)$_3$], 0.99–0.96 (m, 12 H, ArOCH$_2$*C*H$_3$) ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 373 K, DEPT): δ = 158.5, 151.7, 147.3, 140.6, 133.8, 130.9, 128.8 (Ar), 127.1, 126.1, 124.0 (ArH), 69.8 (ArO*C*H$_2$CH$_3$), 34.0 [*C*(CH$_3$)$_3$], 31.6, 31.2 (Ar*C*H$_2$Ar), 31.1 [C(*C*H$_3$)$_3$], 14.7 (ArOCH$_2$*C*H$_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1085.6 (100) [M + Na]$^+$. $C_{66}H_{82}N_2O_{10}$·H$_2$O (1081.4): calcd. C 73.31, H 7.83, N 2.59; found C 73.54, H 7.74, N 2.60.

39,42-Diacetoxy-5,17,23,35-tetra-*tert*-butyl-37,38,40,41-tetraethoxy-11,29-dinitrocalix[6]arene (8): To a solution of **7** (1.495 g, 1.406 mmol) and NaH (60% suspension in mineral oil, 562.0 mg, 14.059 mmol) in dry THF (140 mL, 0.01 M) under an argon atmosphere at 60 °C was added acetyl chloride (1.40 mL, 19.7 mmol). The mixture was kept under the same conditions for 24 h. Solvent was eliminated under reduced pressure, and the residue obtained was partitioned between CH_2Cl_2/HCl (1 M). The organic phase was washed with water (until neutral pH) and dried ($MgSO_4$). The solvent was eliminated under reduced pressure, and the solid obtained was triturated with Et_2O to give **8** as a yellowish solid (1.4 g, 85%). M.p. >330 °C (decomp.). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 373 K): δ = 7.89 (s, 4 H, ArH), 7.02 (d, $^4J_{H,H}$ = 2.4 Hz, 4 H, ArH), 6.98 (d, $^4J_{H,H}$ = 2.4 Hz, 4 H, ArH), 3.92 (s, 4 H, ArCH$_2$Ar), 3.79 (s, 8 H, ArCH$_2$Ar), 3.38 (s, 8 H, ArO*C*H$_2$CH$_3$), 2.29 (s, 6 H, ArOCOCH$_3$), 1.20 [s, 36 H, C(CH$_3$)$_3$], 0.82 (t, $^3J_{H,H}$ = 6.8 Hz, 12 H, ArOCH$_2$*C*H$_3$) ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 373 K, DEPT): δ = 167.7 (CO), 153.1, 151.8, 146.5, 145.6, 136.3, 133.6, 130.5 (Ar), 127.2, 125.8, 123.3 (ArH), 68.6 (ArO*C*H$_2$CH$_3$), 34.1 [*C*(CH$_3$)$_3$], 31.7, 30.8 (Ar*C*H$_2$Ar), 31.3 [C(*C*H$_3$)$_3$], 20.5 (ArOCO*C*H$_3$), 15.1 (ArOCH$_2$*C*H$_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1169.7 (100) [M + Na]$^+$. $C_{70}H_{86}N_2O_{12}$·0.5CHCl$_3$ (1207.2): calcd. C 70.15, H 7.22, N 2.32; found C 69.70, H 7.30, N 2.56.

39,42-Diacetoxy-11,29-diamino-5,17,23,35-tetra-*tert*-butyl-37,38,40,41-tetraethoxycalix[6]arene (9): A mixture of **8** (651.0 mg, 0.567 mmol) and $SnCl_2$·2H$_2$O (1.456 g, 5.675 mmol) in AcOEt/*t*BuOH (9:1, 65.0 mL) under an argon atmosphere was heated at 80 °C for 1 h. Then, a suspension of $NaBH_4$ (21.6 mg, 0.567 mmol) in AcOEt (2.0 mL) was added in small portions. The mixture was kept at 70 °C for 2 h. The solvent was eliminated under reduced pressure and cold water was added. The solution was basified with 5% $NaHCO_3$ and extracted with AcOEt (2×20 mL). The organic phase was washed with water and dried ($MgSO_4$). The solvent was eliminated under reduced pressure, and the residue was triturated with hexane/Et_2O. The resulting precipitate was purified by column chromatography (silica gel; hexane/THF, 8:1) to give **9** as a white solid (389 mg, 63%). M.p. >280 °C (decomp.). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 408 K): δ = 7.15–7.10 (m, 4 H, ArH), 6.94 (d, $^4J_{H,H}$ = 2.5 Hz, 4 H, ArH), 5.70–5.60 (m, 4 H, ArH), 4.10–4.00 (m, 4 H, ArCH$_2$Ar) 3.73–3.69 (m, 8 H, ArO*C*H$_2$CH$_3$), 3.64 (s, 8 H, ArCH$_2$Ar), 2.32 (s, 6 H, ArOCOCH$_3$), 1.26 [s, 36 H, C(CH$_3$)$_3$], 1.15 (t, $^3J_{H,H}$ = 6.6 Hz, 12 H, ArOCH$_2$*C*H$_3$) ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 408 K, DEPT): δ = 169.2 (CO), 154.1,

146.2, 145.7, 138.1, 133.2, 131.8 (Ar), 126.8, 125.9, 114.3 (ArH), 68.7 (ArOCH_2CH_3), 34.0 [$C(CH_3)_3$], 31.5 [C(CH_3)$_3$], 30.7 (ArCH_2Ar), 20.4 (ArOCOCH_3), 15.7 (ArOCH$_2CH_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1109.7 (38) [M + Na]$^+$, 1087.7 (100) [M + H]$^+$. $C_{70}H_{90}N_2O_8$·0.5($CHCl_3$·H_2O) (1156.2): calcd. C 73.24, H 7.98, N 2.42; found C 73.16, H 8.17, N 2.50.

39,42-Diacetoxy-5,17,23,35-tetra-*tert*-butyl-37,38,40,41-tetraethoxy-11,29-bis(1,3-dioxo-1,3-dihydroisoindol-2-yl)calix[6]arene (10): To a suspension of **9** (210.0 mg, 0.193 mmol), phthalic anhydride (77.2 mg, 0.521 mmol), and molecular sieves (3 Å, powder) in dry toluene (5.2 mL) under an argon atmosphere was added Et_3N (150.0 μL). The mixture was heated at 100 °C for 20 h. After being filtered, the solvent was eliminated under reduced pressure. The residue was triturated with acetonitrile to give **10** as a white solid (194.0 mg, 75%). M.p. >296 °C (decomp.). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 403 K): δ = 7.93–7.90 (m, 4 H, ArH$_{phthal}$), 7.76–7.74 (m, 4 H, ArH$_{phthal}$), 7.35 (s, 4 H, ArH), 7.00 (d, $^4J_{H,H}$ = 2.3 Hz, 4 H, ArH), 6.97 (d, $^4J_{H,H}$ = 2.3 Hz, 4 H, ArH), 3.94 (s, 4 H, ArCH_2Ar), 3.82 (s, 8 H, ArCH_2Ar), 3.47 (q, $^3J_{H,H}$ = 6.9 Hz, 8 H, ArOCH_2CH_3), 2.08 (s, 6 H, ArOCOCH_3), 1.16 [s, 36 H, C(CH_3)$_3$], 0.96 (t, $^3J_{H,H}$ = 6.9 Hz, 12 H, ArOCH$_2CH_3$) ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 373 K, DEPT): δ = 168.5, 166.5 (CO), 153.2, 145.7, 134.9, 133.1 (Ar), 134.1 (ArH), 132.1, 131.3, 129.3 (Ar), 126.5, 126.1, 125.7, 123.5 (ArH), 68.7 (ArOCH_2CH_3), 34.0 [$C(CH_3)_3$], 31.4 [C(CH_3)$_3$], 31.0 (ArCH_2Ar), 20.6 (ArOCOCH_3), 15.3 (ArOCH$_2CH_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1369.7 (100) [M + Na]$^+$. $C_{86}H_{94}N_2O_{12}$·0.5H_2O (1356.7): calcd. C 76.14, H 7.06, N 2.06; found C 75.86, H 7.17, N 2.14.

5,17,23,35-Tetra-*tert*-butyl-37,38,40,41-tetraethoxy-39,42-dihydroxy-11,29-bis(1,3-dioxo-1,3-dihydroisoindol-2-yl)calix[6]arene (11): A suspension of **7** (343.0 mg, 0.323 mmol) and Pd/C (10%, 20.0 mg) in EtOH (13.5 mL) was prepared in a 35-mL MW vessel. Hydrazine monohydrate was added (630.0 μL, 6.450 mmol), and the vessel was sealed and introduced in the MW oven. The reaction was programmed at 120 °C for 20 min by using a 5-min temperature ramp and a maximum power of 125 W.

CAUTION! HIGH PRESSURE, OPEN CAREFULLY AFTER COOLING.

The mixture was filtered through Celite, and the solvent was eliminated under reduced pressure. A suspension of the solid obtained without further purification, phthalic anhydride (143.4 mg, 0.967 mmol), and molecular sieves (4 Å, in powder) in dry toluene (16.0 mL) was prepared under an argon atmosphere. Et_3N (300.0 μL) was added, and the mixture was heated at 90 °C for 20 h. After being filtered, the solvent was eliminated under reduced pressure. The residue obtained was purified by column chromatography (silica gel; CH_2Cl_2/hexane, 5:1) and finally triturated with Et_2O to give **11** as a white solid (240.0 mg, 60%). M.p. >340 °C. ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 388 K): δ = 8.00–7.98 (m, 2 H, ArH$_{phthal}$), 7.90–7.88 (m, 2 H, ArH$_{phthal}$), 7.87–7.84 (m, 2 H, ArH$_{phthal}$), 7.74–7.72 (m, 2 H, ArH$_{phthal}$), 7.56 (s, 2 H, ArOH), 7.10 (s, 4 H, ArH), 7.03 (d, $^4J_{H,H}$ = 2.0 Hz, 4 H, ArH), 6.98 (d, $^4J_{H,H}$ = 2.1 Hz, 4 H, ArH), 3.91 (s, 12 H, ArCH_2Ar), 3.68 (q, $^3J_{H,H}$ = 6.8 Hz, 8 H, ArOCH_2CH_3), 1.13 [s, 36 H, C(CH_3)$_3$], 1.01 (t, $^3J_{H,H}$ = 6.8 Hz, 12 H, ArOCH$_2CH_3$) ppm. ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 388 K): δ = 167.1, 163.3 (CO), 152.3, 152.1, 146.7 (Ar), 135.0, 133.8 (ArH), 133.4, 132.4, 131.9, 130.3, 128.4 (Ar), 126.4, 126.2, 126.0, 124.3, 123.2 (ArH), 69.5 (ArOCH_2CH_3), 34.0 [$C(CH_3)_3$], 31.5, 31.4 (ArCH_2Ar), 31.3 [C(CH_3)$_3$], 14.9 (ArOCH$_2CH_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1301.6 (20) [M + K]$^+$, 1285.6 (100) [M + Na]$^+$. $C_{82}H_{90}N_2O_{10}$·0.5H_2O (1272.6): calcd. C 77.39, H 7.21, N 2.20; found C 77.23, H 7.22, N 2.40.

5,17,23,35-Tetra-*tert*-butyl-37,38,40,41-tetraethoxy-39,42-[5-nitro-1,3-phenylenebis(methyleneoxy)]-11,29-bis(1,3-dioxo-1,3-dihydroisoindol-2-yl)calix[6]arene (1): A solution of **11** (15.0 mg, 0.012 mmol) and NaH (60% suspension in mineral oil, 2.0 mg, 0.047 mmol) in dry THF/DMF (9:1, 2.0 mL, 5×10^{-3} M) was prepared in a 10-mL MW vessel and stirred for 5 min under an argon atmosphere. Then, a solution of **12** (4.6 mg, 0.015 mmol) in THF/DMF (9:1, 0.5 mL, 5×10^{-3} M) was added, and the vessel was sealed and introduced in the MW oven. The reaction was programmed at 130 °C for 30 min by using a 5-min temperature ramp and a maximum power of 180 W. Then, H_2O and HCl (1 M) were added, and the mixture was stirred at room temperature for 30 min. The solvent was eliminated under reduced pressure, and the solid obtained was filtered, triturated with MeOH, and purified by thin-layer chromatography (silica gel; CH_2Cl_2/hexane, 3:1→5:1). Finally, the solid was triturated with MeOH to give **1** as a white solid (8.0 mg, 48%). M.p. >300 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 8.26 (s, 2 H, ArH$_{m\text{-xylylenyl}}$), 8.09–8.05 (m, 4 H, ArH$_{phthal}$), 7.89–7.86 (m, 4 H, ArH$_{phthal}$), 7.53 (s, 4 H, ArH), 7.00 (s, 4 H, ArH), 6.99 (s, 4 H, ArH), 5.70 (s, 1 H, ArH$_{m\text{-xylylenyl}}$), 4.59 (d, $^2J_{H,H}$ = 15.3 Hz, 4 H, ArCH_2Ar), 4.37 (d, $^2J_{H,H}$ = 14.8 Hz, 2 H, ArCH_2Ar), 4.32 (s, 4 H, ArOCH$_2$Ar), 3.75–3.66 (m, 8 H, ArOCH_2CH_3), 3.55 (d, $^2J_{H,H}$ = 15.0 Hz, 4 H, ArCH_2Ar), 3.29 (d, $^2J_{H,H}$ = 14.0 Hz, 2 H, ArCH_2Ar), 1.14 (t, $^3J_{H,H}$ = 7.0 Hz, 12 H, ArOCH$_2CH_3$), 1.03 [s, 36 H, C(CH_3)$_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K, DEPT): δ = 167.4 (CO), 152.1, 145.7, 135.2 (Ar), 134.3 (ArH), 132.7, 132.1, 132.0 (Ar), 129.2, 129.0 (ArH), 127.0 (Ar), 125.2, 124.3, 123.8, 118.6 (ArH), 70.9 (ArOCH_2Ar), 68.7 (ArOCH_2CH_3), 34.2 [$C(CH_3)_3$], 31.3 [C(CH_3)$_3$], 30.2, 29.7 (ArCH_2Ar), 15.4 (ArOCH$_2CH_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1433.8 (100) [M + Na]$^+$. $C_{90}H_{95}N_3O_{12}$·0.5$CHCl_3$ (1470.4): calcd. C 73.92, H 6.55, N 2.86; found C 73.66, H 7.31, N 2.60.

11,29-Diamino-5,17,23,35-tetra-*tert*-butyl-37,38,40,41-tetraethoxy-39,42-[5-nitro-1,3-phenylenebis(methyleneoxy)]calix[6]arene (2): To a sonicated suspension of **1** (55.0 mg, 0.039 mmol) in EtOH (3.0 mL) was added hydrazine monohydrate (300.0 μL, 3.899 mmol), and the mixture was heated at 80 °C for 48 h. The solvent was eliminated under reduced pressure, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with water and dried ($MgSO_4$). The solvent was eliminated under reduced pressure. The resulting solid was dissolved in $CHCl_3$/MeOH (2:1), and the solvent was again removed in vacuo (the procedure was repeated several times) to give **2** as a white solid (31.0 mg, 69%). M.p. >215 °C (decomp.). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ = 8.18 (s, 2 H, ArH$_{m\text{-xylylenyl}}$), 6.96 (s, 4 H, ArH), 6.94 (s, 4 H, ArH), 6.76 (s, 4 H, ArH), 5.70 (s, 1 H, ArH$_{m\text{-xylylenyl}}$), 4.44 (d, $^2J_{H,H}$ = 15.5 Hz, 4 H, ArCH_2Ar), 4.32 (d, $^2J_{H,H}$ = 14.6 Hz, 2 H, ArCH_2Ar), 4.20 (s, 4 H, ArOCH$_2$Ar), 3.66–3.63 (m, 8 H, ArOCH_2CH_3), 3.37 (d, $^2J_{H,H}$ = 14.7 Hz, 4 H, ArCH_2Ar), 3.27 (d, $^2J_{H,H}$ = 13.5 Hz, 2 H, ArCH_2Ar), 1.17–1.05 (m, 12 H, ArCH$_2CH_3$), 1.00 [s, 36 H, C(CH_3)$_3$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 298 K, DEPT): δ = 152.1, 147.4, 145.2, 142.1, 135.0, 132.6 (Ar), 129.0, 125.0, 124.2, 118.3, 117.7 (ArH), 71.0 (ArOCH_2Ar), 68.6 (ArOCH_2CH_3), 34.1 [$C(CH_3)_3$], 31.4 [C(CH_3)$_3$], 30.2, 29.7 (ArCH_2Ar), 15.4 (ArOCH$_2CH_3$) ppm. MS (MALDI-TOF+, NaI): *m*/*z* (%) = 1150. 8 (100) [M + H]$^+$, 1172.7 (60) [M + Na]$^+$. HRMS (MALDI): calcd. for $C_{74}H_{91}N_3O_8$ [M]$^+$ 1149.68007; found 1149.67810. $C_{74}H_{91}N_3O_8$·2($CHCl_3$·H_2O) (1425.3): calcd. C 64.04, H 6.86, N 2.95; found C 64.03, H 6.95, N 3.04.

CCDC-777050 (for **4**) and -777051 (for **11**) contain 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): Spectral characterization data (**1**, **2**, **4**–**11**) and VT-^{1}H NMR spectra (188–298 K) and 2D NMR experiments at low temperature.

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