Synthesis B. Ingenfeld et al. Paper

Synthesis of Monofunctionalized Calix[5]arenes

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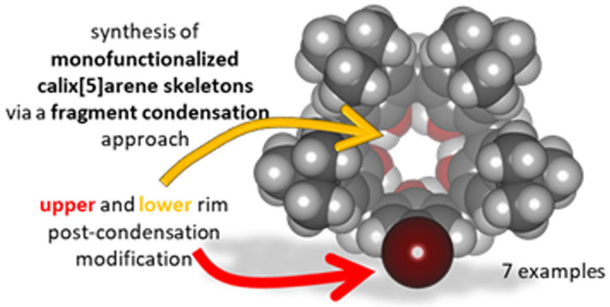

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Abstract Seven OH-free and *O*-permethylated monofunctionalized calix[5]arenes carrying either additional methyl or *tert*-butyl groups are prepared following fragment condensation protocols. This strategy proves to be superior to previous approaches. Calix[5]arenes with free OH groups all adopt a cone conformation stabilized by a seam of hydrogen bonds at the lower rim. Post-condensation modifications, i.e., methylation of phenolic OH groups or functional group interconversions can also be achieved. Bulky *tert*-butyl groups are also found to stabilize the cone conformations of *O*-methylated compounds. These compounds offer versatile functional groups that make these concave molecules interesting building blocks for the synthesis of more sophisticated molecular architectures.

Key words concave molecules, cyclophanes, calix[5]arenes, Duff reaction, fragment condensation strategy

Concave macrocyclic molecules bearing cavities,[1] for example, cyclodextrins,[2] resorcinarenes,[3] or calixarenes,[3,4] are important building blocks in supramolecular chemistry. Among these, the latter are arguably the best studied artificial cyclophane derivatives. This is definitely true for the tetrameric calix[4]arenes and the hexameric calix[6]arenes, which can be accessed rather easily. Unfortunately, the synthesis of calix[5]arenes is not as easy, although the pentamer has been reported to have some very interesting recognition properties toward cesium[5] and ammonium ions[6] and toward fullerenes.[7] One of these receptors could even be controlled by an allosteric effect,[7d] which, due to our interest in the development of artificial allosteric receptors,[8,9] is why calix[5]arenes caught our attention.

To be useful for this purpose it is necessary to prepare selectively (mostly mono-)functionalized derivatives. Up to now, however, there are only a few reports on selective O-alkylations at the phenolic OH functions[10] or on aryl substitutions.[6c,11] Hence, we decided to prepare monofunctionalized tetraalkyl calix[5]arenes to provide useful building blocks for the synthesis of more sophisticated (supra-) molecular architectures.

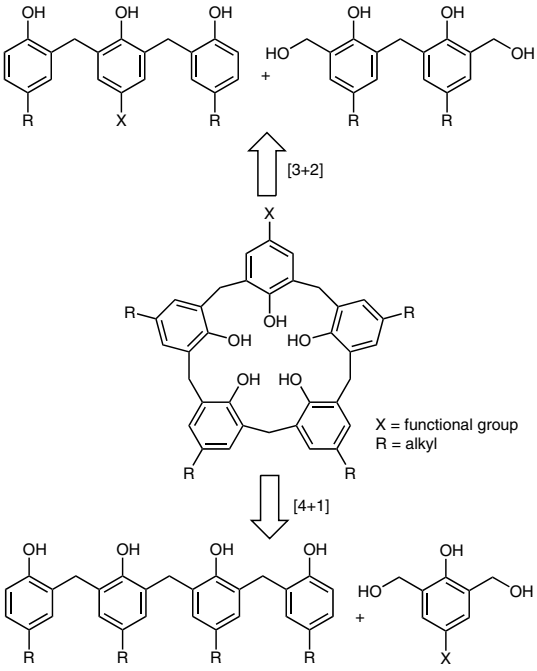
In principle, there are three strategies to prepare selectively functionalized calixarenes that have also been employed to synthesize calix[5]arene derivatives: (i) by preparing a calix[5]arene first and performing a post-cyclization modification,[6c,11] (ii) by preparing a functionalized linear oligomer and then cyclizing it,[12] or (iii) by fragment condensation of oligomeric building blocks, such as trimeric and dimeric or tetrameric and monomeric combinations, to prepare a calix[5]arene.[13]

Whereas approach (i) works nicely for calix[4]-, calix[6]-, and calix[8]arenes that carry *tert*-butyl groups in *para* positions relative to the hydroxy functions, which can be assembled in 50%,[14] 85%,[15] or 78% yield,[16] respectively, this does not really work well for calix[5]- or calix[7]arenes, which cannot really be prepared in yields higher than 10–15%.[17,18] Since this approach then includes a retro-Friedel–Crafts alkylation and an additional electrophilic aromatic substitution, the overall yields are usually way below 3%.[6c]

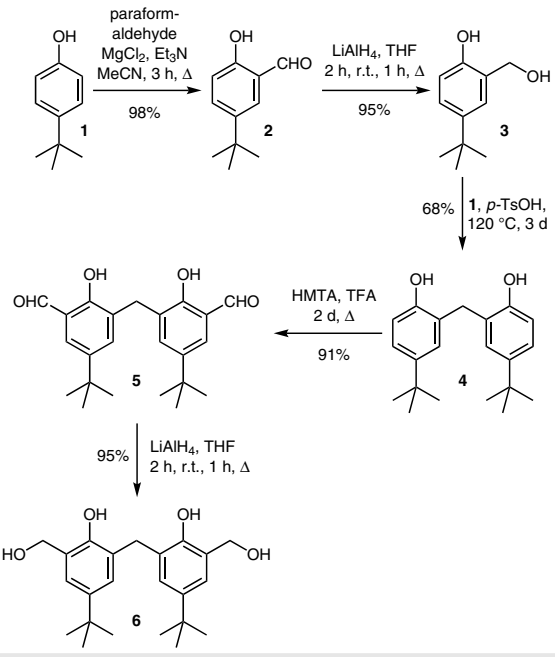
Although the second approach (ii) proved to be more versatile concerning the choice of the alkyl groups on the aromatic rings and the functionalization of the OH groups,[6d] it still suffers from similar low overall yields. Hence, we decided to follow the fragment condensation strategy as depicted schematically in Scheme 1, because it usually provides the desired functionalized calixarenes in the highest yields.[13a,19]

Since [3+2]-condensations tend to work slightly better than the [4+1]-condensations,[13a] we employed this strategy first. The necessary dimeric building block **6** was prepared in 5 steps in 55% overall yield starting from 4-*tert*-butylphenol (**1**) as shown in Scheme 2. Therefore, the starting material was formylated upon treatment with paraform-

aldehyde and $MgCl_2$ following a protocol reported by Knight,[20] before the resulting aldehyde **2** was reduced to the corresponding benzylic alcohol **3** employing conditions developed by Lee.[21] Acid-mediated condensation with **1** then gave **4**,[22] which was subsequently diformylated to give **5** in a two-fold Duff reaction.[23] Finally, two-fold reduction gave rise to the desired diol **6**.

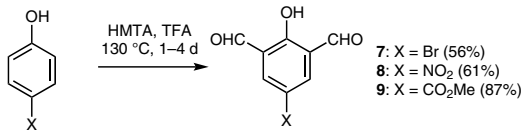


Scheme 1 [3+2]- and [4+1]-fragment condensation strategies for the synthesis of functionalized calix[5]arenes



Scheme 2 Synthesis of dimeric building block **6**

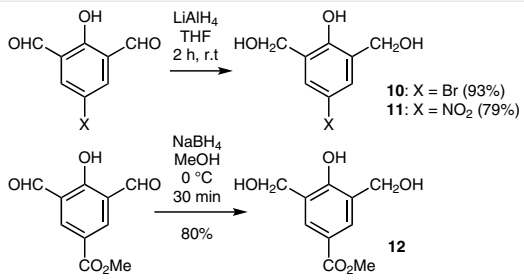
We then turned our attention to the synthesis of tetrafunctionalized phenols carrying a bromine atom, a nitro, or an ester group (Scheme 3). Therefore, *p*-functionalized phenols were subjected to a two-fold Duff reaction following protocols reported by Lindoy,[23] Hrynielwicka,[24] and Routasalo,[25] respectively.



Scheme 3 Synthesis of 2,6-diformylated *p*-functionalized phenols **7–9**

At this point temperature control turned out to be crucial to succeed: at temperatures in the range of 90–100 °C we mainly obtained monoformylated products, whereas we observed polymerization at temperatures >130 °C. It should also be noted that elongating the reaction time for the synthesis of the bromide **7**, unfortunately, did not lead to an increase in the yield.

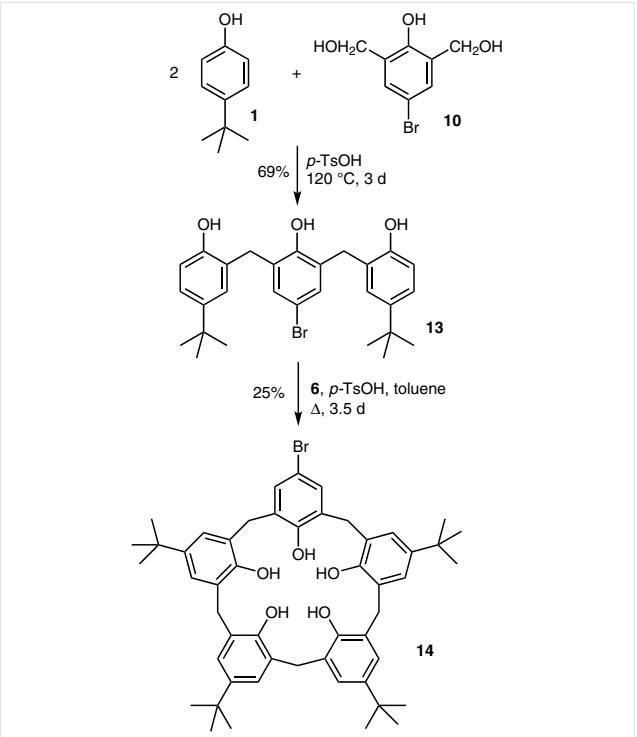
Subsequent reduction with either $LiAlH_4$ or $NaBH_4$ went smoothly to give the desired diols **10–12** in very good yields as shown in Scheme 4.



Scheme 4 Synthesis of diols **10–12**

Unfortunately, the two-fold condensation with two molecules of 4-*tert*-butylphenol (**1**) turned out to be unexpectedly difficult. We were only able to transfer **10** into the trimeric building block **13** (Scheme 5) needed for the [3+2]-condensation with **6** to afford the targeted monobromo-functionalized calix[5]arene **14** in 25% yield.[26]

This corresponds to an overall yield of 9% starting from 4-bromophenol or 14% starting from 4-*t*-butylphenol for this nine-step synthesis, which is significantly higher than is usually achieved by using any of the other strategies described above. However, we have to point out that the concentration of the building blocks turned out to be critical since, at higher concentrations, we observed the formation of calix[10]arene **15** (Figure 1) as a side product by mass spectrometric means.[27]



Scheme 5 Synthesis of bromine-functionalized calix[5]arene **14** via [3+2]-fragment condensation of building blocks **6** and **13**

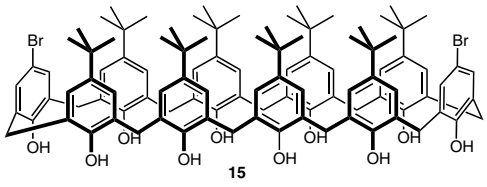
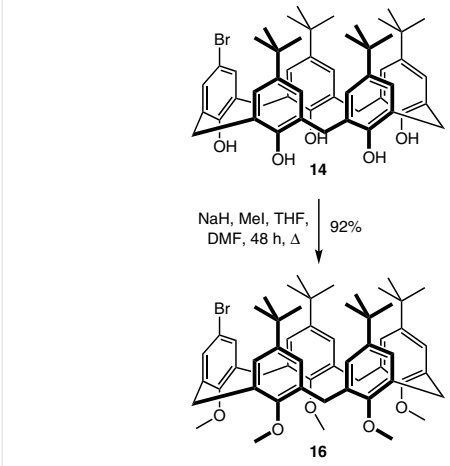


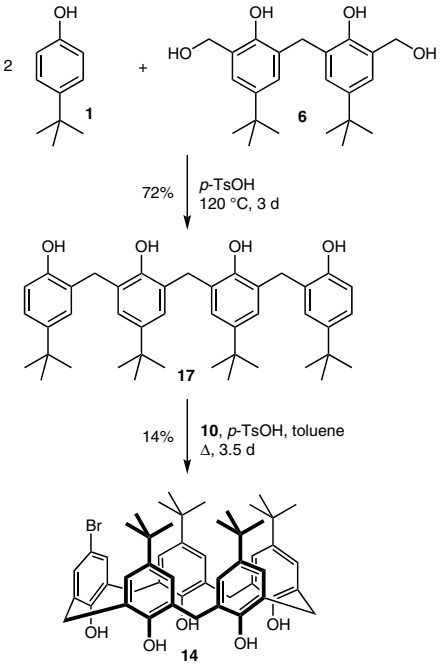
Figure 1 Difunctionalized calix[10]arene **15**

Calix[5]arene **14** adopts a cone conformation as revealed by analysis of the NMR spectra (see the Supporting Information). The same is true for its derivative **16**, obtained upon permethylation of the hydroxy functions according to the protocol of Gutsche (Scheme 6).[28]

We then decided also to explore the [4+1]-fragment condensation for comparison. Therefore, we first prepared tetrameric building block **17** in 72% yield from the two-fold condensation of **6** with 4-*t*-butylphenol (**1**) followed by a macrocyclization upon treatment of **17** with bromide **10** (Scheme 7). This sequence also gave target compound **14**, however, in only 14% yield, which corresponds to an overall yield of a little more than 7% starting from 4-bromophenol. Hence, this way proved slightly less efficient than the [3+2]-fragment condensation.

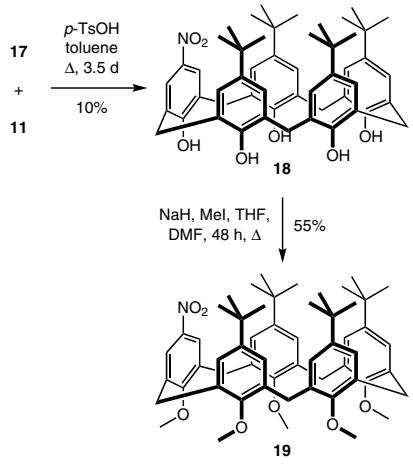


Scheme 6 Synthesis of hexamethyl ether **16**



Scheme 7 Synthesis of calix[5]arene **14** via [4+1]-fragment condensation of building blocks **10** and **17**

Nevertheless, it proved successful for the synthesis of the desired nitro-functionalized calix[5]arene **18**, which could be prepared in 10% yield upon reaction of **17** with **11**, corresponding to an overall yield of a little more than 4% starting from 4-nitrophenol. Again, calix[5]arene **18** could be successfully permethylated by Gutsche's protocol[28] to give the pentamethyl ether **19** (Scheme 8). Like the bromine-functionalized calix[5]arenes, the nitro-derivatives **18** and **19** also adopt cone conformations.



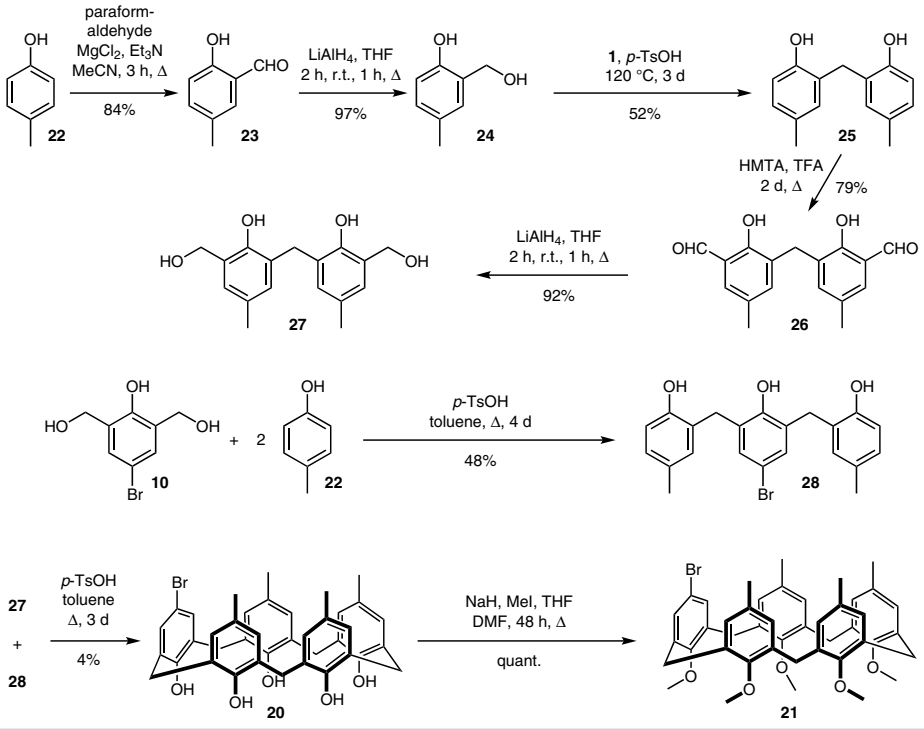
Scheme 8 Synthesis of nitro-functionalized calix[5]arenes **18** and **19**

Next, we followed a similar approach to prepare monobromo-tetramethylcalix[5]arene **20** as depicted in Scheme 9. Although all the formylation and reduction steps proceeded smoothly again, all three condensation steps gave significantly lower yields compared to the corresponding steps employing the respective *tert*-butyl derivatives. Nonetheless, **20** could be isolated and converted into its pentamethyl ether **21** in excellent yield.

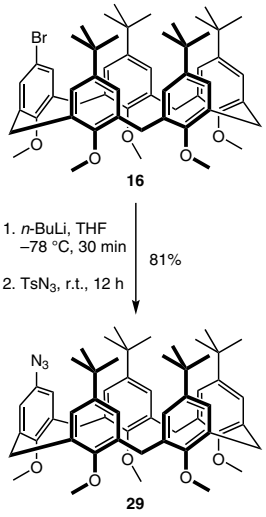
Whereas OH-free calix[5]arene **20** also adopts a cone conformation stabilized by a seam of hydrogen bonds, pentamethyl ether **21** behaves different. Due to the lack of stabilizing hydrogen bonds and the less bulky methyl groups instead of the *tert*-butyl groups in **16** and **19**, permethylated **21** is conformationally much more flexible and adopts at least two different conformations at room temperature, as revealed by rather complicated NMR spectra.

Finally, we explored the potential of **16** with regard to the synthesis of other functionalized calix[5]arenes via bromine–lithium exchange and subsequent quenching with an electrophile. Exemplarily, this was tested with tosyl azide as the electrophile and gave the corresponding azide **29** in very good yield (Scheme 10) that again adopted a single cone-shaped conformation.

In conclusion, we have successfully prepared a series of seven OH-free and *O*-permethylated monofunctionalized calix[5]arenes carrying either additional methyl or *tert*-butyl groups following fragment condensation protocols. In the case of mono-brominated calix[5]arene **14**, we tested a [3+2] strategy as well as a [4+1] strategy. Calix[5]arenes with free OH groups all adopt a cone conformation. Bulky *tert*-butyl groups were also found to stabilize the cone conformations of *O*-methylated compounds **16**, **19**, and **29**, but the methyl groups of **21** are obviously too small to prevent rotation of individual aryl groups, and hence **21** adopts at least two conformations at room temperature. All of these



Scheme 9 Synthesis of monobromo-tetramethylcalix[5]arenes **20** and **21**



Scheme 10 Synthesis of monoazide-functionalized calix[5]arene **29**

compounds offer versatile functional groups that make these concave molecules interesting building blocks for the synthesis of more sophisticated molecular architectures with potential applications as receptors in molecular recognition studies.

Solvents were dried, distilled and stored under argon according to standard procedures. Reactions with air and moisture-sensitive metalorganic compounds were performed under an argon atmosphere in oven-dried glassware using standard Schlenk techniques. Thin-layer chromatography was performed on aluminum TLC plates (silica gel 60 F_{254}) from Merck and the products were visualized under UV light (254 or 366 nm). Products were purified by column chromatography on Merck silica gel 60 (0.04–0.063 mm). ^{1}H and ^{13}C NMR spectra were recorded at 298 K using Bruker Avance 500 (500.1 MHz and 125.8 MHz), Bruker Avance 400 (400.1 MHz and 100.6 MHz), or Bruker Avance 300 (300.1 and 75.5 MHz) spectrometers, respectively. ^{1}H NMR chemical shifts are reported on the δ scale (ppm) relative to residual non-deuterated solvent as the internal standard. ^{13}C NMR chemical shifts are given in δ values (ppm) relative to the deuterated solvent as the internal standard. Signals were assigned on the basis of ^{1}H, ^{13}C, H,H-COSY, HMQC, and HMBC NMR experiments. For the numbering schemes of the nuclei of the individual compounds see the Supporting Information. Mass spectra were taken on a Finnigan MAT 212 with data system MMS-ICIS (EI) or a Bruker micrOTOF-Q (ESI). Elemental analyses were carried out with a Heraeus Vario EL. Like other calixarenes, all new calix[5]arenes and the linear tetramer **17** presented here melt or decompose at temperatures >250 °C. Chemicals and reagents obtained from commercial sources were used as received. 5-*tert*-Butyl-2-hydroxybenzaldehyde (**2**),[20] 4-*tert*-butyl-2-(hydroxymethyl)phenol (**3**),[21] 2,2′-methylenebis[4-(*tert*-butyl)phenol] (**4**),[22] 4-bromo-2,6-diformylphenol (**7**),[23] 4-nitro-2,6-diformylphenol (**8**),[24] methyl 3,5-diformyl-4-hydroxybenzoate (**9**),[25] methyl 4-hydroxy-3,5-di(hydroxymethyl)benzoate (**12**),[25] 2,2′-[(5-bromo-2-hydroxy-1,3-phenylene)bis(methylene)]bis(4-*tert*-butylphenol) (**13**),[13b] and 5-methyl-2-hydroxybenzaldehyde (**23**)[29] were prepared according to literature protocols.

3,3′-Methylenebis[(5-*tert*-butyl)-2-hydroxybenzaldehyde] (5)

2,2′-Methylenebis[4-(*tert*-butyl)phenol] (**4**) (3.60 g, 11.5 mmol) and hexamethylenetetramine (HMTA) (6.46 g, 67.9 mmol, 5.9 equiv) were dissolved in TFA (20 mL) and stirred for 2 d at 90 °C. After that time, water (60 mL) was added and the resulting mixture was stirred for 4 h at 80 °C. The product precipitated from solution, was collected by filtration, washed with water, and dried in vacuo. The product was obtained as a yellow solid.

Yield: 3.87 g (91%); $C_{23}H_{28}O_4$, *M* = 368.47 g/mol.

The analytical data are in accordance with those reported in the literature.[30]

6,6′-Methylenebis[(4-*tert*-butyl)-2-(hydroxymethyl)phenol] (6)

$LiAlH_4$ (2.16 g, 57 mmol, 3 equiv) was suspended in anhydrous THF (50 mL) under an argon atmosphere and stirred for 15 min. After that time, a solution of **5** (7.00 g, 19 mmol) dissolved in anhydrous THF (75 mL) was added dropwise over 1 h. The resulting mixture was stirred for 2 h at r.t. and then heated to reflux for 1 h. After cooling to r.t., the solution was carefully acidified by addition of 2 M HCl. Water (100 mL) was added and the resulting mixture stirred for 16 h. The mixture was extracted with EtOAc (5 × 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvents removed in vacuo to give the desired product as a white solid.

Yield: 6.71 g (95%); $C_{23}H_{32}O_4$, *M* = 372.51 g/mol.

The analytical data are in accordance with those reported in the literature.[31]

4-Bromo-2,6-di(hydroxymethyl)phenol (10)

$LiAlH_4$ (2.34 g, 61.7 mmol, 3 equiv) was suspended in anhydrous THF (50 mL) under an argon atmosphere and stirred for 15 min. After that time, a solution of **7** (4.68 g, 20.4 mmol) dissolved in anhydrous THF (40 mL) was added dropwise over 1 h. The resulting mixture was stirred for 2 h at r.t. and then heated to reflux for 1 h. After cooling the solution to 0 °C, it was carefully acidified by addition of 2 M HCl. Water (150 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvents removed in vacuo to give the desired product as a yellow solid.

Yield: 4.45 g (93%); $C_8H_9BrO_3$, *M* = 233.06 g/mol.

The analytical data are in accordance with those reported in the literature.[32]

4-Nitro-2,6-di(hydroxymethyl)phenol (11)

$LiAlH_4$ (1.00 g, 26.3 mmol, 2.6 equiv) was suspended in anhydrous THF (100 mL) under an argon atmosphere and stirred for 15 min. After that time, a solution of **8** (2.00 g, 10.2 mmol) dissolved in anhydrous THF (60 mL) was added dropwise over 1 h. The resulting mixture was stirred for 2 h at r.t. and then heated to reflux for 1 h. After cooling the solution to 0 °C, it was carefully acidified by addition of 2 M HCl. Water (150 mL) was added and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and the solvents removed in vacuo to give the desired product as a yellow solid.

Yield: 1.61 g (79%); $C_8H_9NO_5$, *M* = 199.16 g/mol.

The analytical data are in accordance with those reported in the literature.[33]

5-Bromo-31,32,33,34,35-pentahydroxy-11,17,23,29-tetra(*tert*-butyl)calix[5]arene (14)

[3+2]-Fragment condensation of **6** and **13**: compound **6** (1.65 g, 4.42 mmol), compound **13** (2.20 g, 4.42 mmol, 1 equiv), and *p*-TsOH (0.05 g, 0.29 mmol) were dissolved in toluene (400 mL) and stirred for 3 d at 120 °C. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (1:1) as eluent to give the product as a white solid.

Yield: 0.89 g (24%).

[4+1]-Fragment condensation of **10** and **17**: compound **10** (0.73 g, 3.14 mmol), compound **17** (2.00 g, 3.14 mmol), and *p*-TsOH (0.05 g, 0.29 mmol) were dissolved in toluene (400 mL) and stirred for 3 d at 120 °C. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (1:1) as eluent to give the product as a white solid.

Yield 0.37 g (14%); $C_{51}H_{61}BrO_5$, *M* = 833.95 g/mol; R_f = 0.82 (cyclohexane/CH_2Cl_2, 1:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 9.04 (s, 1 H, OH-1), 8.69 (s, 2 H, OH-3), 8.61 (s, 2 H, OH-2), 7.31 (s, 2 H, H-2), 7.22–7.25 (m, 4 H, H-7, H-11), 7.21 (d, $^4J_{14,18}$ = 2.4 Hz, 2 H, H-18*), 7.12 (d, $^4J_{14,18}$ = 2.4 Hz, 2 H, H-14*), 3.33–4.40 (br s, 10 H, H-5, H-12, H-19), 1.27 (s, 18 H, H-21*), 1.26 (s, 18 H, H-23*) (* assignment of the signals might be interchanged).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 149.6 (C-4), 147.7 (C-16), 147.6 (C-9), 144.4 (C-6*), 144.3 (C-13*), 131.6 (C-2), 129.1 (C-3), 126.5 (C-17*), 126.4 (C-10*), 126.4 (C-15*), 126.3 (C-8*), 125.9 (C-11*), 125.8 (C-7*), 125.8 (C-18*), 125.1 (C-14*), 115.5 (C-1), 34.1 (C-20*), 34.0 (C-22*), 31.7 (C-19*), 31.6 (C-12*), 31.6 (C-5*), 31.6 (C-23*), 31.5 (C-21*) (* assignment of the signals might be interchanged).

HRMS (ESI, –): *m*/*z* [M – H]$^-$ calcd for $C_{51}H_{60}{}^{81}BrO_5$: 833.3613; found: 833.3615.

Anal. Calcd for $C_{51}H_{61}BrO_5$·cyclohexane: C, 74.57; H, 8.01. Found: C, 74.55; H, 8.11.

5-Bromo-31,32,33,34,35-pentamethoxy-11,17,23,29-tetra(*tert*-butyl)calix[5]arene (16)

Compound **14** (0.64 g, 0.77 mmol) was dissolved in anhydrous THF (40 mL) and anhydrous DMF (5 mL) and the solution was cooled to 0 °C. NaH (0.48 g, 20 mmol, 60% in mineral oil) was added, the mixture was stirred for 30 min at r.t. and MeI (5.00 g, 35 mmol) was added. After heating this mixture to reflux for 2 d, the solvents were removed in vacuo. Water (20 mL) was added to the residue. The precipitate was collected and subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (1:1) as eluent to give the desired product as a white solid.

Yield 0.64 g (92%); $C_{56}H_{71}BrO_5$, *M* = 904.08 g/mol; R_f = 0.55 (cyclohexane/CH_2Cl_2, 1:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 7.15 (d, $^4J_{7,11}$ = 2.4 Hz, 2 H, H-11), 7.09 (d, $^4J_{7,11}$ = 2.4 Hz, 2 H, H-7), 7.07 (d, $^4J_{14,18}$ = 2.5 Hz, 2 H, H-18), 7.02 (s, 2 H, H-2), 6.90 (d, $^4J_{14,18}$ = 2.5 Hz, 2 H, H-14), 3.83 (br s, 2 H, H-19), 3.81 (br s, 4 H, H-12), 3.77 (br s, 4 H, H-5), 3.29 (s, 3 H, OCH_3-1), 3.13 (s, 6 H, OCH_3-3), 2.86 (s, 6 H, OCH_3-2), 1.26 (s, 18 H, H-21), 1.15 (s, 18 H, H-23).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 155.4 (C-4), 154.4 (C-9), 154.1 (C-16), 145.6 (C-6), 145.4 (C-13), 137.0 (C-3), 134.0 (C-10), 133.8 (C-17), 133.6 (C-15), 133.0 (C-8), 131.2 (C-2), 127.0 (C-11), 126.3 (C-7), 126.3 (C-18), 125.7 (C-14), 115.9 (C-1), 60.6 (C-24), 60.3 (C-26), 60.2 (C-25), 34.2 (C-20), 34.1 (C-22), 33.3 (C-19), 31.8 (C-5), 31.6 (C-21), 31.6 (C-23), 30.9 (C-12).

HRMS (ESI, +): *m*/*z* [M + Na]$^+$ calcd for $C_{56}H_{71}{}^{81}BrO_5Na$: 927.4361; found: 927.4361.

Anal. Calcd for $C_{56}H_{71}BrO_5$·cyclohexane: C, 75.35; H, 8.47. Found: C, 75.40; H, 8.46.

6,6′-Methylenebis{4-(*tert*-butyl)-2-[5-(*tert*-butyl)-2-hydroxybenzyl]phenol} (17)

Compound **6** (5.00 g, 13.4 mmol), 4-*tert*-butylphenol (**1**) (12.00 g, 79.9 mmol, 6 equiv), and *p*-TsOH (0.30 g, 1.75 mmol) were dissolved in toluene (100 mL) and heated to reflux for 3 d. Excess **1** was removed by water–steam distillation. The reddish crude product was purified by column chromatography on silica gel using cyclohexane/EtOAc (1:1) as eluent. The product was obtained as a white solid.

Yield: 6.14 g (72%); $C_{43}H_{56}O_4$, *M* = 636.92 g/mol; R_f = 0.46 (cyclohexane/EtOAc, 1:1).

The analytical data are in accordance with those reported in the literature.[31]

5-Nitro-31,32,33,34,35-pentahydroxy-11,17,23,29-tetra(*tert*-butyl)calix[5]arene (18)

Compound **11** (0.35 g, 1.76 mmol), compound **17** (1.00 g, 1.57 mmol), and *p*-TsOH (0.05 g, 0.29 mmol) were dissolved in toluene (400 mL) and stirred for 3 d at 120 °C. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (1:1) as eluent to give the product as a yellow solid.

Yield 0.13 g (10%); $C_{51}H_{61}NO_7$, *M* = 800.05 g/mol; R_f = 0.78 (cyclohexane/CH_2Cl_2, 1:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 9.87 (s, 1 H, OH-1), 8.64 (s, 2 H, OH-3), 8.45 (s, 2 H, OH-2), 8.16 (s, 2 H, H-2), 6.97–7.25 (m, 8 H, H-7, H-11, H-14, H-18), 3.37–4.59 (br s, 10 H, H-5, H-12, H-19), 1.25 (s, 36 H, H-21, H-23).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 156.4 (C-4), 147.5 (C-16*), 147.4 (C-9*), 144.9 (C-6*), 144.4 (C-13*), 141.7 (C-1), 129.9 (C-2), 128.6 (C-3), 126.6 (C-17), 126.4 (C-10), 126.1 (C-15), 125.9 (C-8), 125.9 (C-11), 125.7 (C-7), 125.3 (C-18), 124.2 (C-14), 34.3 (C-20*), 34.2 (C-22*), 34.1 (C-19), 34.1 (C-12*), 34.0 (C-5*), 31.5 (C-21*), 31.5 (C-23*) (* assignment of the signals might be interchanged).

HRMS (ESI, +): *m*/*z* [M + Na]$^+$ calcd for $C_{51}H_{61}NO_7Na$: 822.4340; found: 822.4343.

5-Nitro-31,32,33,34,35-pentamethoxy-11,17,23,29-tetra(*tert*-butyl)calix[5]arene (19)

Compound **18** (0.10 g, 0.12 mmol) was dissolved in anhydrous THF (20 mL) and anhydrous DMF (2.5 mL) and the solution was cooled to 0 °C. NaH (0.24 g, 10 mmol, 60% in mineral oil) was added, the mixture was stirred for 30 min at r.t. and MeI (5.00 g, 35.2 mmol) was added. After heating this mixture to reflux for 2 d, the solvents were removed in vacuo. Water (20 mL) was added to the residue. The precipitate was collected and subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (1:1) as eluent to give the desired product as a yellow solid.

Yield 0.06 g (55%); $C_{56}H_{71}NO_7$, *M* = 870.18 g/mol; R_f = 0.15 (cyclohexane/CH_2Cl_2, 1:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 7.84 (s, 2 H, H-2), 7.18 (s, 2 H, H-11), 7.11 (s, 2 H, H-7), 7.00 (s, 2 H, H-18), 6.86 (s, 2 H, H-14), 3.87 (br s, 4 H, H-5), 3.83 (br s, 2 H, H-19), 3.81 (br s, 4 H, H-12), 3.33 (s, 3 H, OCH_3-1), 3.17 (s, 6 H, OCH_3-3), 2.93 (s, 6 H, OCH_3-2), 1.27 (s, 18 H, H-21), 1.09 (s, 18 H, H-23).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 162.0 (C-4), 154.4 (C-9), 154.0 (C-16), 146.0 (C-6), 145.4 (C-13), 143.3 (C-1), 136.3 (C-3), 134.2 (C-10), 133.8 (C-17), 133.4 (C-15), 132.3 (C-8), 127.4 (C-11), 126.2 (C-7), 126.2 (C-18), 125.4 (C-14), 124.0 (C-2), 61.0 (C-24), 60.4 (C-26), 60.3 (C-25), 34.3 (C-20), 34.0 (C-22), 32.5 (C-19), 31.8 (C-5), 31.6 (C-21), 31.3 (C-23), 31.0 (C-12).

HRMS (ESI, +): *m*/*z* [M + H]$^+$ calcd for $C_{56}H_{72}NO_7$: 870.5303; found: 870.5303.

5-Bromo-31,32,33,34,35-pentahydroxy-11,17,23,29-tetramethylcalix[5]arene (20)

Compound **27** (1.27 g, 4.40 mmol), compound **28** (1.82 g, 4.40 mmol, 1 equiv), and *p*-TsOH (0.1 g, 0.58 mmol) were dissolved in toluene (100 mL) and stirred for 3 d at 120 °C. The solvent was removed in vacuo and the residue was subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (2:1) as eluent to give the product as a white solid.

Yield 0.115 g (4%); $C_{39}H_{37}BrO_5$, *M* = 665.62 g/mol; R_f = 0.48 (cyclohexane/CH_2Cl_2, 2:1).

^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 9.09 (s, 1 H, OH-1), 8.75 (s, 2 H, OH-3), 8.68 (s, 2 H, OH-2), 7.30 (s, 2 H, H-2), 6.92–7.22 (m, 8 H, H-7, H-11, H-14, H-18), 3.33–4.40 (br s, 10 H, H-5, H-12, H-19), 2.22–2.25 (br s, 12 H, H-21, H-23).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 149.7 (C-4), 147.9 (C-16*), 147.8 (C-9*), 131.7 (C-2*), 131.0 (C-6*), 130.8 (C-13*), 130.2 (C-3*), 129.8 (C-17*), 129.7 (C-10*), 129.7 (C-15*), 129.1 (C-8*), 126.7 (C-11*), 126.6 (C-7*), 126.4 (C-18*), 125.6 (C-14*), 113.3 (C-1), 31.4 (C-19*), 31.3 (C-12*), 29.8 (C-5*), 20.5 (C-20*), 20.5 (C-21*) (* assignment of the signals might be interchanged).

MS (ESI, –): *m*/*z* (%) = 665.0 (100) [M – H]$^-$.

5-Bromo-31,32,33,34,35-pentamethoxy-11,17,23,29-tetramethylcalix[5]arene (21)

Compound **20** (0.06 g, 0.09 mmol) was dissolved in anhydrous THF (30 mL) and anhydrous DMF (3 mL) and the solution was cooled to 0 °C. NaH (0.04 g, 1.81 mmol, 60% in mineral oil) was added, the mixture was stirred for 30 min at r.t. and MeI (0.45 g, 3.16 mmol) was added. After heating this mixture to reflux for 2 d, the solvents were removed in vacuo. Water (30 mL) was added to the residue. The precipitate was collected and subjected to column chromatography on silica gel using EtOAc/CH_2Cl_2 (98:2) as eluent to give the desired product as a white solid.

Yield 0.07 g (quant.); $C_{44}H_{47}BrO_5$, *M* = 735.74 g/mol; R_f = 0.68 (EtOAc/CH_2Cl_2, 98:2).

The ^{1}H NMR and ^{13}C NMR ($CDCl_3$, 500.1 and 125.8 MHz, respectively, see the Supporting Information) spectra are rather complicated due to an equilibrium of different conformers at r.t. Unfortunately, assignment of individual peaks to individual conformers was not possible due to severe signal overlapping.

MS (ESI, +): *m*/*z* (%) = 759.2 (100) [M + Na]$^+$.

2-(Hydroxymethyl)-4-methylphenol (24)

$LiAlH_4$ (3.37 g, 89 mmol, 1.6 equiv) was suspended in anhydrous THF (100 mL) under an argon atmosphere and stirred for 15 min. After that time, a solution of compound **23** (7.50 g, 55.1 mmol) dissolved in anhydrous THF (60 mL) was added dropwise over 1 h. The resulting mixture was stirred for 2 h at r.t. and then heated to reflux for 1 h. After cooling down to r.t. again, the solution was carefully acidified by addition of 2 M HCl. Water (200 mL) was added and the resulting mixture stirred for 16 h. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents removed in vacuo to give the desired product as a white solid.

Yield: 7.41 g (97%); $C_8H_{10}O_2$, *M* = 138.17 g/mol.

The analytical data are in accordance with those reported in the literature.[34]

2,2′-Methylenebis(4-methylphenol) (25)

2-(Hydroxymethyl)-4-methylphenol (**24**) (7.41 g, 53.6 mmol), 4-methylphenol (**22**) (17.6 mL, 168 mmol, 3.1 equiv), and *p*-TsOH (0.30 g, 1.75 mmol) were dissolved in toluene (100 mL) and heated to reflux for 4 d. Excess **22** and toluene were removed by distillation under reduced pressure. The crude product was purified by column chromatography on silica gel using cyclohexane/EtOAc (7:1) as eluent. The product was obtained as a white solid.

Yield: 6.36 g (52%); $C_{15}H_{16}O_2$, *M* = 228.29 g/mol; R_f = 0.22 (cyclohexane/CH_2Cl_2, 7:1).

The analytical data are in accordance with those reported in the literature.[35]

3,3′-Methylenebis(2-hydroxy-5-methylbenzaldehyde) (26)

2,2′-Methylenebis(4-methylphenol) (**25**) (3.00 g, 13.1 mmol) and hexamethylenetetramine (HMTA) (5.52 g, 39.4 mmol, 3 equiv) were dissolved in TFA (20 mL) and stirred for 2 d at 90 °C. After that time, water (60 mL) was added to the orange solution and the resulting mixture was heated to reflux for 2 h. The product precipitated from solution, was collected by filtration, washed with water, and dried in vacuo. The product was recrystallized from a mixture of EtOH and water (1:1) and obtained as a white solid.

Yield: 2.95 g (79%); $C_{17}H_{16}O_4$, *M* = 284.31 g/mol.

The analytical data are in accordance with those reported in the literature.[36]

6,6′-Methylenebis[4-methyl-2-(hydroxymethyl)phenol] (27)

$LiAlH_4$ (0.87 g, 22.9 mmol, 3 equiv) was suspended in anhydrous THF (40 mL) under an argon atmosphere and stirred for 15 min. After that time, a solution of **26** (2.18 g, 7.67 mmol) dissolved in anhydrous THF (60 mL) was added dropwise over 1 h. The resulting mixture was stirred for 2 h at r.t. and then heated to reflux for 1 h. After cooling down to r.t. again, the solution was carefully acidified by addition of 2 M HCl. Water (200 mL) was added and the resulting mixture stirred for 16 h. The mixture was extracted with EtOAc (5 × 50 mL). The combined organic layers were dried over $MgSO_4$ and the solvents removed in vacuo to give the desired product as a white solid.

Yield: 2.04 g (92%); $C_{17}H_{20}O_4$, *M* = 288.34 g/mol.

The analytical data are in accordance with those reported in the literature.[37]

2,2′-(5-Bromo-2-hydroxy-1,3-phenylene)bis(4-methylphenol) (28)

Compound **10** (1.65 g, 7.08 mmol), 4-methylphenol (**22**) (3.82 g, 35.3 mmol, 5 equiv), and *p*-TsOH (0.10 g, 0.58 mmol) were dissolved in toluene (100 mL) and stirred for 4 d at 120 °C. The solvent and excess **22** were removed in vacuo and the residue was subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (6:1) as eluent to give the product as a white solid.

Yield 1.39 g (48%); $C_{22}H_{21}BrO_3$, *M* = 413.13 g/mol; R_f = 0.15 (cyclohexane/CH_2Cl_2, 6:1).

The analytical data are in accordance with those reported in the literature.[13b]

5-Azido-31,32,33,34,35-pentamethoxy-11,17,23,29-tetra(*tert*-butyl)calix[5]arene (29)

Under an argon atmosphere, compound **16** (0.130 g, 0.14 mmol) was dissolved in anhydrous THF (10 mL). After cooling to –78 °C, *n*-BuLi (0.2 mL, 2.5 M in hexane, 0.5 mmol, 3.6 equiv) was added dropwise. After 30 min, tosyl azide (0.07 mL, 0.47 mmol, 3.4 equiv) mixed with anhydrous THF (10 mL) was added dropwise. The resulting mixture was stirred overnight at r.t. Water (10 mL) was added and the aqueous phase extracted with EtOAc (3 × 25 mL). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and the organic residue subjected to column chromatography on silica gel using cyclohexane/CH_2Cl_2 (1:1) as eluent to give the product as a yellowish solid.

Yield: 0.10 g (81%); $C_{56}H_{71}N_3O_5$, *M* = 866.20 g/mol; R_f = 050 (cyclohexane/CH_2Cl_2, 1:1).

^{1}H NMR (400.1 MHz, $CDCl_3$): δ = 7.17 (d, $^4J_{7,11}$ = 2.4 Hz, 2 H, H-11), 7.13 (d, $^4J_{7,11}$ = 2.4 Hz, 2 H, H-7), 7.05 (d, $^4J_{14,18}$ = 2.5 Hz, 2 H, H-18), 6.86 (d, $^4J_{14,18}$ = 2.5 Hz, 2 H, H-14), 6.54 (s, 2 H, H-2), 3.83 (br s, 2 H, H-19), 3.82 (br s, 4 H, H-12), 3.79 (br s, 4 H, H-5), 3.39 (s, 3 H, OCH_3-1), 3.20 (s, 6 H, OCH_3-3), 2.82 (s, 6 H, OCH_3-2), 1.30 (s, 18 H, H-21), 1.15 (s, 18 H, H-23).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 154.5 (C-9), 154.2 (C-16), 153.7 (C-4), 145.6 (C-6), 145.3 (C-13), 136.4 (C-3), 134.2 (C-1), 134.1 (C-10), 133.7 (C-17), 133.6 (C-15), 133.1 (C-8), 127.1 (C-11), 126.5 (C-7), 126.3 (C-18), 125.4 (C-14), 118.7 (C-2), 60.8 (C-24), 60.4 (C-25), 60.3 (C-26), 34.2 (C-20), 34.1 (C-22), 32.8 (C-19), 31.8 (C-5), 31.6 (C-23), 31.4 (C-21), 30.9 (C-12).

HRMS (ESI, +): *m*/*z* [M + Na]$^+$ calcd for $C_{56}H_{71}N_3O_5Na$: 888.5286; found: 888.5303.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1589127.

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