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Mono- and Tri-Functionalization of Trimethylresorcin[4]arenes

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Abstract: Short and efficient syntheses of mono- and tris-functionalized resorcin[4]arenes were developed. The co-condensation of resorcinol and 2-methylresorcinol was optimized, targeting for the trimethylresorcin[4]arene, easy to isolate. Complementary regiospecific conditions for the mono- and tris-halogenation in almost quantitative yields are setting the stage for subsequent functionalizations: radicalic bromination leads to the trisbromomethyl compound, while the polar bromination and iodination via the mono-lithiated species leads to the aryl bromide and iodide in excellent yields.

Introduction

Resorcin[4]arenes in general are intensively studied tetrameric resorcinol-based structures with a broad range of useful applications in catalysis and especially in host-guest chemistry,[1] supramolecular containers,[2,3] or even molecular machines.[4] Resorcin[4]arenes offer a broad variety of bowl- or vase-like structural backbones on the road to specifically designed supramolecular structures.[5] Accordingly to the increasing knowledge of chemical reactions and catalysis in cavitands and enzymatic(-like) environments or chemistry in confinement in general the demand for chemically more specific supramolecular motifs has also increased.

Acetalized resorcin[4]arenes offer a rigid electron rich cavity, which can be used e.g. as multi- and mono-dentate bowl-shaped ligands in several transition metal catalysed cross-coupling reactions.[6,7] Furthermore, tri-dentate resorcinarene ligands with imidazole binding sites were used as biomimetic model-compounds to study various zinc and copper based enzymatic binding sites, reported by Reinaud et al.[8–10] Molecular resorcinarene-based capsules connected by three linkers have been reported,[11,12] some of them even with a photosensitive gate,[13] as well as dimers with only one covalent bond between the resorcinarene-units.[14,15]

All these examples derive from tri- or mono-functionalized resorcinarenes. The classical protocol for their synthesis is following a five step procedure; first the formation of the resorcin[4]arene backbone by condensation of resorcinol with an aldehyde and then the electrophilic fourfold halogenation, mostly bromination, prerequisite as steric control element to ensure a satisfying yield for the fourfold acetalization with $BrClCH_2$ or similar methylenating agents.[16] Finally, the selectivity of the mono-lithiation or the tris-lithiation of the tetrahalogeno-resorcin[4]arene is a main factor for the overall efficiency of the reaction sequence, facing statistical distribution

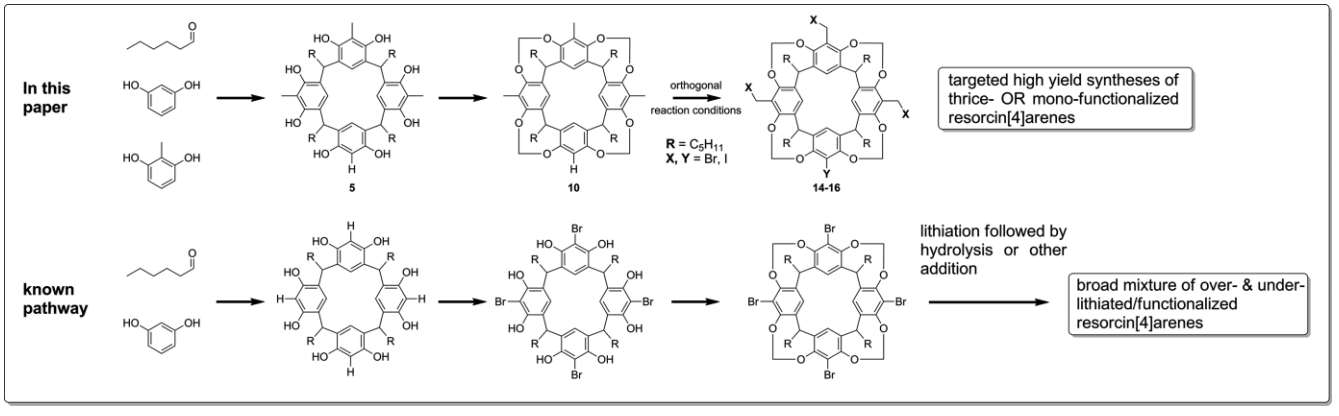

Figure 1. Selectively functionalized resorcin[4]arenes, the new and the classical approach.

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with under- or over-lithiated by-products as a yield diminishing problem.

For the further transformation of the lithiated resorcin[4]-arene various electrophiles are suitable, e.g. simple protolysis, or transmetalations such as the borylation, or for the direct CC-bond formations through acylations (with chloroformates) or alkylations (with methyl iodide).[17] However, for the latter example – the upper-rim methylation – the overall reaction sequence seems to be far from ideal and efficient. For instance, for the synthesis of the trimethyl-substituted resorcin[4]arene **10** we envisioned the straightforward introduction of the methyl groups already in the first step of the reaction sequence (Figure 1), applying an appropriate mixture of resorcinol and 2-methylresorcinol in the initial multiple condensation. The trimethyl-resorcin[4]arene **10** then offers the backbone for further complementary regiospecific upper-rim CH-transformations, either in the three benzylic positions or at the single remaining upper-rim aryl-CH.

While modification at the methyl moieties of the upper-rim is normally achieved through radicalic halogenation, followed by simple S_N-reactions, the selectively mono-brominated, -iodinated or -lithiated upper-rim aryl-CHs provide manifold synthetic pathways for further derivatization, e.g. C–C-bond formation via Pd-catalysed coupling reaction[18] or the more sophisticated Rosenmund-von Braun synthesis for nitriles and their derivatives.[19]

Results and Discussion

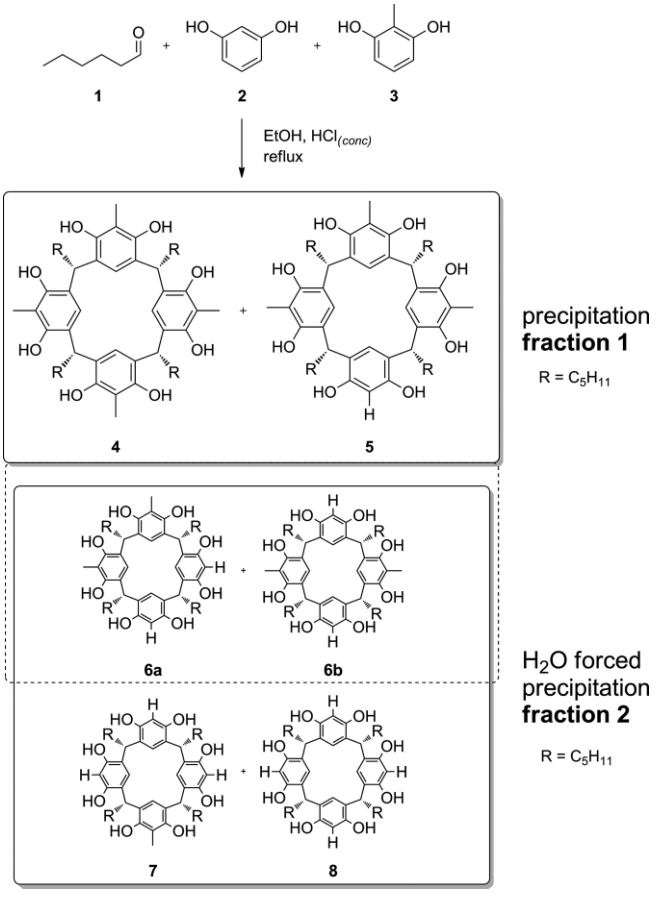
The first task was to develop a protocol that ensures higher yields of the designated product **10**. Two synthetic strategies are possible: Either to start with a well-known and easy to synthesize symmetric molecule, for example the tetrabrominated species, and to proceed in several synthetic steps via the mostly applied lithiation-protolysis-separation route, followed by a second lithiation and further derivatization. Of course, this procedure is again followed by chromatographic purification. As a result, the first definition of the (pre-)final substitution pattern takes place after five steps including at least two chromatographic separations, disadvantageously leading to lower overall yields.[8,11,17]

Or, how we proceeded, to set-up the targeted carbon-framework in an early stage, obtaining **10** in just two synthetic steps with only one separation required. It is remarkable that the preparation of partially methylated resorcinarenes at an early stage is hitherto only described for analytical amounts, probably due to separation and derivatization problems.[20]

A third, somewhat hypothetical pathway would utilize the well known tetramethyl resorcinarene[20] for subsequent demethylations, hitherto lacking short and efficient protocols.

Therefore, our process starts with the co-condensation of the aldehyde **1** and the two building blocks **2** and **3** for the macrocycle. Through adjusting the ratio between the resorcinols, we tried to increase the overall yield of **5**.

While using a starting concentration of 1.1 M of the resorcinols in a 1:1 mixture of aqueous $HCl_{(conc.)}$ and ethanol, followed by slow addition of a 2.9 M solution of hexanal in EtOH under elevated temperature, a smooth precipitation started. After refluxing overnight and cooling down to r.t., the separation of the two precipitated fractions (Scheme 1) is essential for the separability of **9** and **10** from the other isomers **6–8** later on at the next preparative step. The first fraction, which precipitates directly from the reaction mixture, mainly contains **4** and **5**, whereas the second precipitation fraction is obtained by adding water, largely consisting of less methylated homologues **6–8**. Reflux temperature as well as the chosen molarity were proven to be essential for a higher yield of **fraction 1**. A longer reaction time did not increase the yield upon precipitation, instead was leading to a higher amount of the unintentional dimethylated species in the raw **fraction 1**. Higher molarities lead to an even more complex compound mixture of **4–7** in **fraction 1**, while lower molarities inhibited, as expected, the precipitation of the desired product mixture of **4** and **5**. The changes in product distribution were monitored qualitatively by ^{1}H NMR. The diagnostic signals of the *ortho*-protons and the methyl-groups at the resorcinarene upper-rim were suitable.



Scheme 1. Condensation reaction and separating by successive precipitation of resorcin[4]arenes.

While only minor amounts of precipitated **fraction 1** could be obtained from the starting material ratio of 3:1, consequently leading to inferior results in the overall yield after acetalization in this case (see Table 1, first line), in general the amount of **fraction 1** increased with the amount of resorcinol **3** applied.

Table 1. Isolated yields of resorcinarenes after condensation and bridging (following synthesis protocols 1 and 2, *see supporting information*), based on provided **3**.

Educt ratio **2** to **3**[a]	Yield **9**[b]	Yield **10**[b]	Yield **11**[b]	Statistical ratio[c]	Ratio[d] (diff. to statistics)
3:1	0	< 1	0	1:18:81	0:100:0 (–1):(82):(–81)
1:1	8	18	6	9:36:55	24:57:19 (15):(21):(–36)
2:3	13	18	< 1	16:42:42	41:56:3 (25):(14):(–39)
4:7	36	28	9	19:44:37	50:38:12 (31):(–6):(–25)
1:3	25	30	< 1	33:44:22	44:54:2 (11):(10):(–20)

[a] Applied ratio of starting materials for the condensation reaction, summarized molarity of resorcinols remained constant. [b] Yield in % over 2 steps after bridging reaction with $BrClCH_2$. [c] Anticipated statistical ratio was calculated based on **3** as limiting factor. [d] Ratios normalized to 100 for the three main products for better comparability. Yields of isomers, oligomers and partially acetalized by-products were not determined.

After separating **fraction 1** and **fraction 2** we first used the natural reactivity of the double *ortho*-activated position of the resorcinarene towards electrophilic bromination with NBS of both fractions, which worked with complete conversion as proven by complete disappearance of all proton signals in the ^1H NMR in the range of 6.0 to 6.4 ppm (see supporting information, *NMR spectra of reaction 1*).

Side-products like benzylic brominated resorcinarenes could only be found in traces.

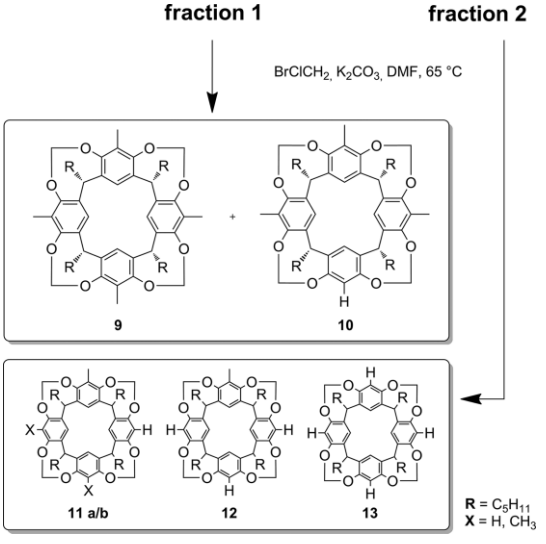
Since the separation into the individual components was unsuccessful on a preparative scale, both by crystallization and by chromatography, we performed the tetra-acetalization of the brominated **fraction 1**. However, the separation problems remained.

Fortunately, we noticed, that the bromination step is unnecessary for the selectivity of the cyclizing acetalization, since three methyl groups at the resorcinarene are already sufficient for sterically suppressing oligomerization. The direct acetalization of fraction 1 with **4** and **5** as main components by applying bromochloromethane as methylenating agent with K_2CO_3 as the base, both in excess, was successful (Scheme 2). We were able to isolate the fully bridged resorcinarenes **9** and **10** in good yields, depending on the ratio of **2** and **3**, used in the co-condensation step (see Table 1).

The obtained mixture of **9** and **10** with smaller amounts of the dimethylated **11** could be separated easily via column chromatography or an automated flash chromatography system if the solvent DMF was completely removed in advance. As by-products mainly three-times acetalized compounds could be identified in traces as well as resorcinarene-oligomers that were barely mobile at the column chromatography.

The cyclizing acetalization is sterically favored by substituents at the upper-rim,[16,21] suppressing intermolecular oligomerizations. Therefore components **4** and **5** from **fraction 1** react more selectively in the cyclizing acetalization than the minor congeners **6a** and **6b,** resulting in an additional overall simplification of the final product mixture.

This also explains the poor yields of **11–13** in our results for the cyclizing acetalization of **fraction 2** analogous to **fraction 1**. Especially **13** was isolable only in traces.

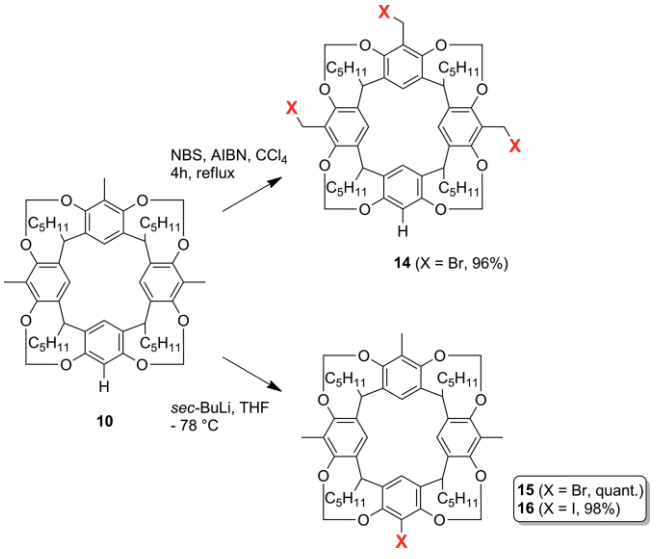


Scheme 2. Acetalization of **fraction 1** & **fraction 2** with main products.

For the condensation reaction, followed by full acetalization we obtained yields up to 30 % over two steps, based on the amount of methylresorcinol (**3**) as starting material. We tried to optimize the ratio of the two resorcinols **2** and **3** to find the highest yield for **10** at the ratio of 4:7. (see Table 1, entry *a* & *b*) There was a slightly better yield for **10** with the ratio of 1:3, but much higher amounts of the more expensive methyl resorcinol **3** had to be used. Also, the separation process lowered the yield for **9** and **10**. However, we wish to underline the simple, quick and cheap synthesis of the three times substituted resorcin[4]arene motif in only two preparative steps avoiding any synthetically demanding pathways such as Schlenk-techniques based protocols.

Having a preparatively simple access to the trimethylated resorcinarene **10** in hands we focused on the development of complementary regiospecific conditions for the halogenation in benzylic and in phenylic position at the molecules upper-rim (Scheme 3).

First, we tried to derivatize the methyl groups in order to create three positively polarized carbon atoms e.g. for S_N-type



Scheme 3. Orthogonal synthetic pathways towards tri- & mono-functionalized resorcinarenes.

reactions through radical bromination. Attempts to substitute the disputable CCl_4 as solvent for the radicalic bromination with several less problematic solvents unfortunately failed. Bromination was observed but in a quite unselective way. E.g. under use of eight eq of NBS and catalytic amounts of AIBN or benzoyl peroxide in various solvents a broad range of compounds could be identified via proton NMR. It contained a broad variety from starting material **10** up to overbrominated species. These mixtures unfortunately were inseparable on a preparative scale. Therefore we applied and modified the analogous procedure for tetra-methylated resorcinarenes like **9** with a yield of 96 % of **14**, staying with CCl_4 as the solvent of choice.[22] Further work on the derivatization of **14** is already in progress.

On the other hand, we also focused on the mono-derivatization of **10** at the phenylic position. Several attempts with highly active catalysts for the electrophilic aromatic substitution such as $FeCl_3$ or different Au(III) species failed, using NBS as well as elemental bromine. Only bromination at the methyl-groups could be observed. Radical bromination was indicated since the reaction rate decelerated under strict exclusion of light.

In contrast to a protocol in earlier literature,[23] reporting on the upper-rim lithiation of a parent tetra-protio methylene-bridged resorcinarene, the lithiation in phenylic position of **10** using *n*-butyllithium was unsuccessful. We suspected the steric hindrance of the methyl-groups at the upper-rim of the resorcinarene could influence the formation of a stable lithiated resorcinarene species, using *n*BuLi as the lithiating agent. In general, less rigid resorcinarenes seem to be more reactive towards lithiation agents.[24]

As a consequence, we changed to *sec*-butyllithium as a more reactive reagent towards a direct *ortho*-metalation of the phenylic position of **10.** This led, after refining the application modus, to quantitative lithiation at - 78 °C. As it turned out, the slow addition of the *sec*-butyllithium into the reaction mixture is quite important to avoid the deacetalization process, as occurs with *tert*-butyllithium which produces significant amounts of several deacetalization products of **10**. No lithiation of the methyl-groups was observed.

For further derivatization we aimed at the halogenation of the lithiated resorcinarenes, which worked in quantitative yield, so that chromatographical purification became obsolete. This could be monitored by the disappearance of any ^{1}H-signal in the NMR range of 6.4 to 6.6 ppm in the raw reaction mixture. To avoid side-reactions we chose the milder bromination reagent dibromotetrafluoroethane in a diluted form. However, applying elemental bromine instead is possible, resulting in slightly lower yield of **15**.

For the iodination to **16** elemental iodine was used. The iodination is important in the light of potential palladium-catalyzed cross-coupling reactions, since at the electron-rich upper-rim positions iodinated resorcinarenes are far more reactive compared to brominated ones.[25]

Further functionalization reactions are already in progress and under investigation at our group, especially using tris-bromomethyl-substituted **14** for the construction of selectively coordinating bowls[26] and cavities[10] or even gated hemicarcerands.[13]

Conclusions

In this paper we reported the synthesis of the trimethyl-resorcinarene **10** in a simplified protocol, determining the substitution pattern at the upper-rim of the resorcinarene at an early stage. Through optimizing the reaction conditions and starting material ratios of **2** and **3** a rather selective precipitation of an almost binary product-mixture was obtained. An easy separation of the resulting product mixture was achieved after the acetalization step, obtaining the tri-methylated bowl **10** in yields up to 30 % after just two synthetic steps.

We demonstrated divergent halogenations to obtain mono- and tri-brominated trimethyl-substituted resorcinarenes **14**, **15** and **16** in almost quantitative yields while previous literature usually reported low yields at the late stage derivatization of resorcinarenes.[27] Our method is avoiding their dependency on statistics when targeting mono- or tri-functionalization. The synthesized resorcinarenes are useful building blocks towards partially substituted resorcinarene-based molecules. Based on the selectively halogenated upper-rim the stage is set for further derivatizations like S_N-type reactions or transition-metal catalyzed cross-coupling reactions.

Experimental Section

General: THF for reactions was freshly distilled from a sodium-benzophenone distillation apparatus. Solvents like ethanol *n*-hexane, DCM and EtOAc were distilled from technical grade purity prior to use. All other solvents were used in p.A. grade. For fast and automated flash chromatography a GRACE Reveleris X2 system was used with "*Flash Pure*" columns from Büchi in the sizes of 12, 24 and 40 g. Solvents were *n*-hexane, DCM and EtOAc, technical grade, distilled. ^{1}H- and ^{13}C-NMR spectra were recorded at a Bruker AVIII-300 (300 MHz) & AVIII-400 (400 MHz) spectrometer. Raw processing was done by Bruker TopSpin, for further analyses and detail

processing Mestrelab MNOVA v.12.0.4–22023 was used. Chemical shifts on the δ-scale are given in ppm. Detailed assignments are given under chapter "NMR Spectra". All ^{13}C assignments are included in the supplementary material for better clarity. Solvents for NMR spectroscopy were used in a 99.8 % deuteration grade. Compound **9** has already been reported in literature, but no full characterization was found, therefore complete spectroscopic data is given here.

Experimental Details:

5,11,17-Trimethyl-2,8,14,20-tetrapentylresorcin[4]arene (5) and 5,11,17,23-Tetramethyl-2,8,14,20-tetrapentylresorcin[4]arene (4): In a 500 mL three-neck flask $HCl_{conc.}$ (100 mL, 1200 mmol) was added slowly to a solution of 2-methylresorcinol (17.3 g, 140 mmol) and resorcinol (8.80 g, 79.7 mmol) in 100 mL of ethanol. The solution was heated up to 50 °C and hexanal (27.0 mL, 220 mmol) in 75 mL ethanol was added within 45 min under intensive stirring. The slowly red-coloring suspension was stirred for about 24 h under gentle reflux. The mixture was cooled down to r.t., a bright orange precipitate was filtered off and was resuspended in a mixture of 100 mL of MeCN and 100 mL of H_2O, followed by a second filtration (1st fraction).

100 mL of water were added to the mother liquor and the suspension was filtered. The orange-red residue was washed with water and resuspended in a mixture of 200 mL MeCN and 200 mL of H_2O, followed by further filtration (2nd fraction).

The first fraction contains mainly tetra- and trimethyl-resorcin[4]arene **4** and **5** in the ratio 9:7 with traces of **6a** and **6b** (dimethylated resorcin[4]arenes).

Both product mixtures were dried in a kugelrohr oven at 125 °C. 25.4 g of a light pale solid for **fraction 1** and 8.46 g of a light brownish solid for **fraction 2** were obtained.

5,11,17-Trimethyl-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorcin[4]arene (10) and 5,11,17,23-Tetramethyl-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorcin[4]arene (9): In a 250 mL two(three)-neck flask 6.02 g of the product mixture from synthesis 1 (1st fraction) and potassium carbonate (19.9 g, 0.14 mol) were dissolved in DMF (150 mL) and the mixture was heated up to 60 °C. After the addition of bromochloromethane (3.30 mL, 0.050 mmol) the mixture was stirred for about 24 h at 75 °C. After cooling to r.t., the solution was poured onto 400 mL of water and the precipitated solid was filtered off. The crude product was resuspended in 200 mL H_2O and filtered off. This washing process was repeated once more.

The product mixture was purified by column chromatography (*n*-hexane/DCM 9:1 → 0:100), using a Reveleris ® X2 Flash chromatography. Two colorless solid products with melting points of 258 °C (**9**) ($R_{f\ (DCM)}$ = 0.60) and 199 °C (**10**) ($R_{f\ (DCM)}$ = 0.50) were obtained. ^1H NMR (300 MHz, $CDCl_3$) (**10**): δ = 7.13 ppm (s, 1 H, HAr*H*), 6.97 (s, 3 H, CH_3Ar*H*), 6.47 (s, 1 H, ArH_{upper}), 5.89 (d, *J* = 6.9 Hz, 2 H, O-$CH_{out,\ dis}$-O), 5.82 (d, *J* = 6.9 Hz, 2 H, O-$CH_{out,\ prox}$-O), 4.76 (t, *J* = 7.6 Hz, 2H, CH_{prox}), 4.74 (t, *J* = 7.6 Hz, 2 H, CH_{dis}), 4.32 (d, *J* = 6.9 Hz, 2 H, O-$CH_{in,\ prox}$-O), 4.28 (d, *J* = 6.9 Hz, 2 H, O-$CH_{in,\ dis}$-O), 2.21 (m, 8 H, CH-CH_2-), 1.99 (s, 3 H, $CH_{3,\ dis}$-Ar), 1.97(s, 9 H, $CH_{3,\ prox}$-Ar), 1.44 - 1.31 (m, 24 H, -CH_2-), 0.91 (m, 12 H, CH_3). *("prox" & "distal" are related to upper-rim H)*. ^{13}C NMR (75 MHz, $CDCl_3$) (**10**): δ = 154.87 ppm, 153.50, 153.40, 153.38, 138.78, 138.18, 138.09, 137.81, 123.87, 123.82, 121.20, 117.63, 117.52, 116.19, 99.21, 98.60, 37.15, 36.84, 32.22, 32.20, 31.74, 30.22, 30.09, 27.80, 27.76, 22.85, 22.80, 14.25, 10.52, 10.43. EA ($C_{55}H_{70}O_8$): calculated: C 76.89 %, H 8.21 %, O 14.90 %; EA ($C_{55}H_{70}O_8$·0.5H_2O): calculated: C 76.09 %, H 8.24 %, O 15.66 %; found C 75.95 %, H 8.26 %. IR (KBr) (**10**): $\tilde{\nu}$ = 3854 (vw) cm^{-1}, 2949 (w), 2926 (w), 2859 (w), 1491 (w), 1458 (w), 1431 (w), 1398 (vw), 1375 (vw), 1302 (w), 1273 (vw), 1236 (w), 1165 (vw), 1153 (w), 1070 (m), 1022 (w), 972 (s), 791 (w), 723 (w), 675 (w). MS (EI, 70 eV) (**10**): *m/z* (%) = 859 (100) $[M]^+$, 788 (12) $[M - C_5H_{11}]^+$. ^1H NMR (400 MHz, $CDCl_3$) (**9**): δ = 6.99 ppm (s, 4 H, Ar*H*), 5.90 (d, *J* = 6.9 Hz, 4 H, O-CH_{out}H-O), 4.77 (t, *J* = 8.1 Hz, 4 H, *CH*), 4.27 (d, *J* = 6.9 Hz, 4 H, -O-CHH_{in}-O), 2.21 (q, *J* = 7.8 Hz, 8 H, CH-CH_2-), 1.99 (s, 12H, CH_3-Ar), 1.53–1.28 (m, 24 H, -CH_2-), 0.92 (t, *J* = 7.1 Hz, 12 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (**9**): δ = 153.38, 138.10, 123.73, 117.70, 98.64, 37.15, 32.21, 30.22, 27.80, 22.84, 14.25, 10.46. EA ($C_{56}H_{70}O_8$): calculated: C 77.03 %, H 8.31 %, O 14.66 %; EA ($C_{56}H_{70}O_8$·0.5H_2O): calculated: C 76.24 %, H 8.34 %, O 15.42 %; found C 76.37 %, H 8.27 %. IR (ATR) (**9**): $\tilde{\nu}$ = 2926 (vw) cm^{-1}, 2859 (w), 1728 (w), 1458 (m), 1429 (w), 1396 (w), 1375 (vw), 1302 (w), 1233 (m), 1152 (w), 1092 (m), 1042 (vw), 1018 (w), 972 (s), 791 (w), 679 (w), 629 (vw). MS (EI, 70 eV) (**9**): *m/z* (%) = 873 (100) $[M]^+$, 843 (6) $[M - C_2H_6]^+$, 802 (12) $[M - C_5H_{11}]^+$.

5,11,17-Tris(bromomethyl)-4(24),6(10),12(16),18(22)-tetramethylene-dioxy-2,8,14,20-tetrapentylresorcin[4]arene (14): In a 250 mL round-bottom flask a solution of 751 mg (874 µmol) of **10**, 802 mg (4.51 mmol) NBS and catalytic amounts of AIBN (0.8 mg, 0.05 mmol) in 35 mL tetrachloromethane was heated up to reflux and stirred for four hours. The mixture was filtered, the solvent removed under vacuum, the residue dissolved in 35 mL of DCM and washed three times with 35 mL of water. The organic phase was dried with magnesium sulfate and the solvent was removed under vacuum. Purification by column chromatography (silica/DCM) gave 922 mg (841 µmol, 96 %) of the product **14** as colorless crystals with a m.p. 210 °C ($R_{f\ (n\text{-hexane/EtOAc, 9:1})}$ = 0.49). ^1H NMR (300 MHz, $CDCl_3$) (**14**): δ = 7.14 ppm (s, 4H), 6.51 (s, 1 H), 6.03 (d, *J* = 7.2 Hz, 2 H, O-$CH_{out,\ prox}$-O), 5.87 (d, *J* = 7.2 Hz, 2 H, O-$CH_{out,\ dis}$-O), 4.77 (m, 4 H, *CH*), 4.61 – 4.57 (dd, 4 H, O-CH_{in}-O), 4.49 (s, 4 H, $CH_{2,\ prox}$Br), 4.41 (s, 2 H, $CH_{2,\ dis}$Br), 2.26 – 2.17 (m, 8 H, CH-CH_2-), 1.43 – 1.34 (m, 24 H, -CH_2-), 0.91 (m, 12 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) (**14**): δ = 154.81 ppm, 153.81, 153.68, 153.58, 138.54, 138.12, 138.05, 137.86, 124.54, 124.50, 121.17, 120.99, 120.32, 117.44, 99.20, 36.97, 36.73, 32.10, 32.08, 30.14, 30.11, 27.66, 23.46, 23.27, 22.78, 22.77, 14.18. EA ($C_{55}H_{67}O_8Br_3$): calculated: C 60.28 %, H 6.16 %, O 11.68 %, Br 21.87 %; EA ($C_{55}H_{67}O_8Br_3$·DCM): calculated: C 56.96 %, H 6.24 %, O 10.57 %, Br 19.80 %; found C 56.86 %, H 5.58 %. IR (ATR) (**14**): $\tilde{\nu}$ = 2926 (m) cm^{-1}, 2859 (w), 1589 (vw), 1490 (w), 1472 (m), 1454 (m), 1246 (m), 1167 (vw), 1148 (m), 1111 (vw), 1055 (vw), 1017 (m), 1165 (vw), 966 (s), 935 (w), 725 (vw), 683 (w). MS (EI, 70 eV) (**14**): *m/z* (%) = 1097 (58) $[M]^+$, 1016 (100) $[M - Br]^+$, 938 (45) $[M - Br_2]$, 856 (23) $[M - H_2Br_3]^+$, 854 (18) $[M - Br_2\text{-}CH_2\text{-}C_5H_{11}]^+$ C_5H_{11}.

5-Bromo-11,17,23-trimethyl-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorcin[4]arene (15): Thoroughly dried reactant **10** (322 mg, 375 µmol) was dissolved in dry THF (15 mL) under an argon atmosphere and the solution was cooled down to –78 °C. *sec*-Butyllithium in cyclohexane (1.4 M, 0.40 mL, 0.56 mmol) was added within three minutes. After stirring for 30 minutes a solution of 1,2-dibromotetrafluoroethane (0.080 mL, 0.66 mmol) in 5 mL of dry THF was dropped to the reaction mixture within five minutes. The color changed from yellow over violet to colorless. After warming to r.t. over 2 h 1 mL of saturated NH_4Cl solution was added. The solvent was removed, and the crude product dissolved in 25 mL of $CHCl_3$ for washing three times with water and once with brine. After drying over $MgSO_4$ the solvent was removed to yield 350 mg (373 µmol, quant.) of the product **15** as a colorless solid with m.p. 256 °C ($R_{f\ (n\text{-hexane/EtOAc, 9:1})}$

= 0.36). Further purification can be achieved by column chromatography (silica/*n*-hexane/EtOAc/CH_3COOH (19:1:0.01)). ^1H NMR (400 MHz, $CDCl_3$) (**15**): δ = 7.09 ppm (s, 1 H, BrAr*H*), 6.95 (s, 3 H, CH_3Ar*H*), 5.92 (d, *J* = 7.1 Hz, 2 H, O-$CH_{out,\ prox}$-O), 5.88 (d, *J* = 6.9 Hz, 2 H, O-$CH_{out,\ dis}$-O), 4.80 (t, 2 H, CH_{prox}), 4.76 (t, 2 H, CH_{dis}), 4.296 (d, *J* = 7.1 Hz, 2 H, O-$CH_{in,\ prox}$-O), 4.292 (d, *J* = 6.9 Hz, 2 H, O-$CH_{in,\ dis}$-O), 2.26–2.14 (m, 8 H, CH-CH_2-), 1.99 (s, 3 H, Ar$CH_{3,\ dis}$), 1.98 (s, 6 H, Ar$CH_{3,\ prox}$), 1.44–1.30 (m, 24 H, -CH_2-), 0.96–0.88 (m, 12 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (**15**): δ = 153.65 ppm, 153.42, 153.22, 151.95, 139.85, 138.42, 138.00, 137.50, 124.10, 123.96, 119.50, 117.62, 117.49, 112.75, 98.55, 37.50, 37.13, 32.20, 32.12, 30.22, 30.08, 27.78, 27.69, 22.83, 14.24, 10.51, 10.41. EA ($C_{55}H_{69}O_8Br$): calculated: C 70.42 %, H 7.41 %, O 13.64 %, Br 8.52 %, EA ($C_{55}H_{69}O_8Br \cdot 0.5CH_3COOH$): calculated: C 69.48 %, H 7.39 %, O 14.87 %, Br 8.25 %; found C 69.39 %, H 7.30 %. IR (KBr) (**15**): $\tilde{\nu}$ = 2926 (m) cm^{-1}, 2859 (w), 1602 (vw), 1402 (m), 1234 (w), 1150 (w), 1090 (m), 1022 (vw), 970 (s), 1144 (w), 1084 (m), 1048 (m), 1010 (m), 973 (s). MS (EI) (**15**): *m/z* (%) = 939 (100) $[M]^+$, 868 (10) $[M - C_5H_{11} - H]^+$, 859 (8) $[M - Br]^+$.

5-Iodo-11,17,23-trimethyl-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetrapentylresorcin[4]arene (16): Thoroughly dried reactant **10** (344 mg, 384 μmol) was dissolved in dry THF (16 mL) under an argon atmosphere and the solution was cooled down to –78 °C. *sec*-Butyllithium in cyclohexane (1.4 M, 0.40 mL, 0.56 mmol) was added within three minutes. After stirring for 30 minutes Iodine (480 mg, 1.89 mmol) was added, followed by 10 minutes of stirring. After warming to r.t. over 2 h sodium thiosulfate (470 mg, 1.89 mmol), dissolved in 10 mL of water, was added. 25 mL of $CHCl_3$ were added for washing once with saturated NH_4Cl solution, three times with water and once with brine. After drying over $MgSO_4$ the solvent was removed to yield 372 mg (377 μmol, 98 %) of **16** as a colorless solid with m.p. 218 °C (decomp.) ($R_{f\ (n\text{-hexane/EtOAc, 9:1})}$ = 0.37). Further purification can be achieved by column chromatography (silica/*n*-hexane/EtOAc (19:1). ^1H NMR (400 MHz, $CDCl_3$) (**16**): δ = 7.13 ppm (s, 1 H, IAr*H*), 6.97 (s, 3 H, CH_3Ar*H*), 5.94 (d, *J* = 7.2 Hz, 2 H, O-$CH_{out,\ prox}$-O), 5.89 (d, *J* = 6.9 Hz, 2 H, O-$CH_{out,\ dis}$-O), 4.89 – 4.73 (m, 4 H, C*H*), 4.30 (d, *J* = 6.9 Hz, 2 H, O-$CH_{in,\ dis}$-O), 4.27 (d, *J* = 7.1 Hz, 2 H, O-$CH_{in,\ prox}$-O), 2.26–2.18 (m, 8 H, CH-CH_2-), 2.00 (s, 3 H, Ar$CH_{3,\ dis}$), 1.99 (s, 6 H, Ar$CH_{3,\ prox}$), 1.49–1.31 (m, 24 H, -CH_2-), 0.96–0.90 (m, 12 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) (**16**): δ = 154.80 ppm, 153.64, 153.42, 153.20, 139.32, 138.40, 137.98, 137.49, 124.09, 123.96, 121.19, 117.59, 117.47, 98.84, 98.54, 92.33, 37.64, 37.13, 32.19, 32.11, 30.22, 30.18, 27.78, 27.69, 22.83, 14.24, 10.51, 10.40. EA ($C_{55}H_{69}O_8I$): calculated: C 67.06 %, H 7.06 %, O 12.99 %, I 12.88 %; found C 66.65 %, H 6.96 %. IR (KBr) (**16**): $\tilde{\nu}$ = 2926 (m) cm^{-1}, 2856 (w), 1760 (w), 1458 (vw), 1397 (w), 1302 (w), 1234 (m), 1150 (w), 1090 (m), 1023 (w), 970 (s), 727 (vw), 587 (m). MS (EI) (**16**): *m/z* (%) = 985 (100) $[M]^+$, 954 (5) $[M - CH_3O]^+$, 914 (8) $[M - C_5H_{11} - H]^+$.

Keywords: Resorcinarenes · Mono-functionalization · Tri-functionalization · Molecular bowls · Supramolecular chemistry · Synthesis design

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