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Resorcinarenes

DISTAL Dibromoresorcin[4]arenes Through Selective Deactivation: A Practical Optimization

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Abstract: A simple and straightforward regioselective synthesis of distal disubstituted resorcin[4]arenes was developed, avoiding competing substitution patterns at an early stage via regioselective deactivation. Product limiting reaction steps were optimized by starting material recovery and by an improved protocol for ester cleavage while providing simple workup procedures throughout the synthesis without requiring column chromatography. The cyclizing acetalization of distal disubstituted resorcinarene octols proved to be a high yield process without oligomer formation, although less sterically controlled compared to the usual tetrabromo case.

Introduction

Resorcin[4]arenes, the tetrameric cyclic condensation products of resorcinol with an aldehyde, represent a versatile class of precursors en route to supramolecular hosts such as cavitands, carcerands, and hemicarcerands. Their applications spread from encapsulation of highly reactive compounds[1] and molecular recognition[2] to the experimental utilization in catalysis[3] and as stationary phases in chromatography.[4] While carcerands are composed of two four-fold interconnected resorcin[4]arene units, giving them an isolated inner shell, hemicarcerands offer portals for guest-exchange reactions, often implemented by the lack of at least one interhemispheric linker. Beyond mono- or trifunctionalization recently reported,[5] distal (or A,C-) difunctionalized resorcinarenes offer an interesting substitution pattern to provide a basis for hemicarcerand and cavitand synthesis.[6] Thus, a selective, high-yield access to these precursors is desirable.

Hitherto two approaches towards difunctionalized resorcinarenes are commonly used (Figure 1): Route A is performing a substoichiometric bromination of the resorcinarene backbone **1** (with regard to the four vacant aromatic upper rim positions), giving a vast statistical mixture of all possible upper-rim substitution patterns, including the desired A–C dibrominated resorcinarene **2**, followed by acetalization of the mixture. Due to the similar physical properties of the oligobrominated resorcinarenes, the acetalized dibromoresorcinarene **3** generally is not thoroughly purified, but used as a crude product, subsequently leading to unsatisfactory yields.[7]

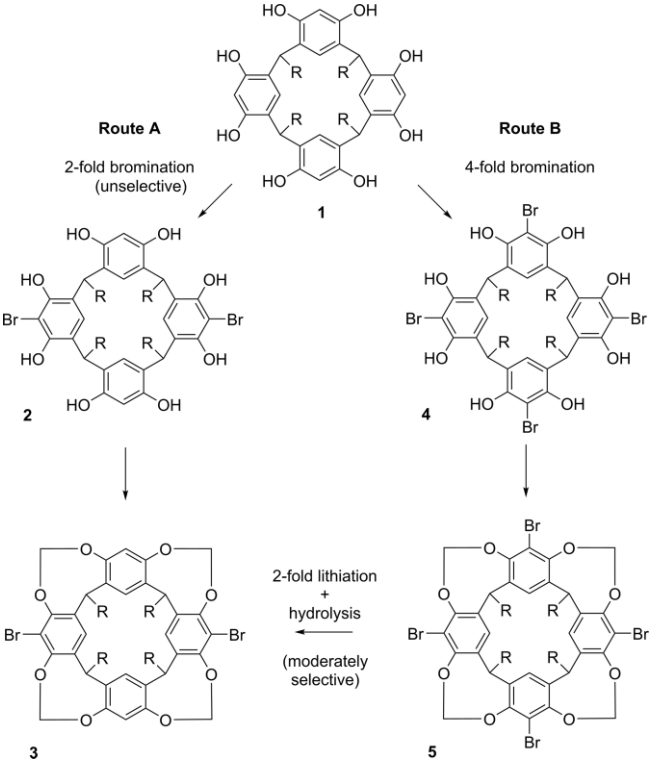

Figure 1. Previous approaches towards distal disubstituted resorcinarenes.

The other more prominent method (route B) allows for higher yields, however with a likewise low atom economy[8] since the resorcinarene backbone **1** is fourfold brominated (**4**) and acetalized (**5**), followed by debromination via lithiation and hydrolysis. Although target product yields of the latter reaction have been successfully pushed above the statistical expectancy

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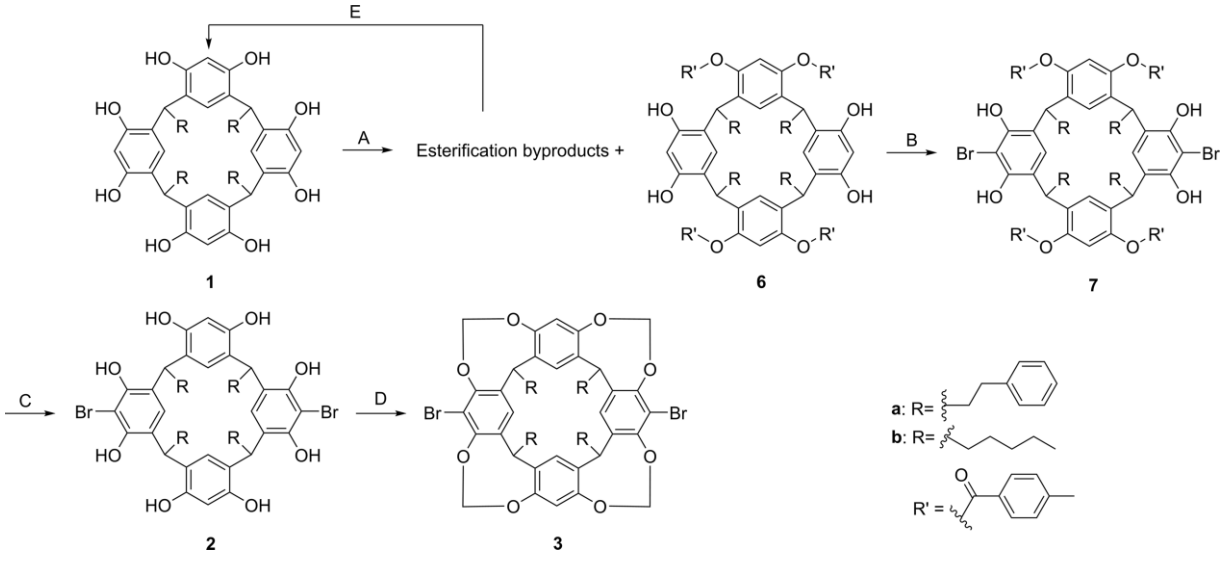

Figure 2. Distal dibromination via regioselective deactivation. A: MeCN, TEA, *p*-toluoyl chloride, RT, 16 h. B: THF, NBS, RT, 16 h. C: MeOH, NaOMe, RT, 5 h. D: DMF, K_2CO_3, $BrCH_2Cl$, 60 °C, 48 h, E: a) MeOH, NaOH, RT,16 h. b) MeOH, NaOMe, RT, 16 h.

up to 65 %,[9] this reaction pathway is still afflicted with the inefficiency of the wasteful late-stage derivatization and a time-consuming workup procedure. An overall yield between 36–55 % over four steps can be calculated.[10]

While route A depends on a statistical yield distribution in the product-determining step and is, therefore, neither selective to the number of introduced substituents nor to the predominant isomer with respect to the desired twofold functionalization, route B presents a procedure with a directing factor. After the first lithiation at one of the four equivalent positions, the second lithium–halogen exchange is electrostatically repelled from the statistically more probable adjacent positions to the opposing one. Nevertheless, under- and over-lithiation are not prevented by other means than stoichiometry.

To overcome the statistical mismatch of both routes, we developed a highly regioselective approach (Figure 2), utilizing a deactivation for electrophilic aromatic substitution. With the introduction of four ester functionalities at the resorcinarene scaffold, Shivanyuk et al. presented a method to predefine a distal substitution pattern at an early stage.[11,12] The resulting C_{2V}-symmetrical tetraesters have found application in the synthesis of chiral, resorcinarene based ligands for asymmetric catalysis[13] and the development of photo-switchable molecular capsules.[14] It is to be noted, however, that the selectivity of the fourfold esterification derives from the formation of a complex of **1** with triethylamine, used as a base in this reaction, locking the resorcinarene in a C_{2V}-symmetric boat configuration and the peculiar insolubility of the distal tetraester in acetonitrile, being the only isomer to precipitate from the reaction mixture with yields just below 40 %. A combination of C_{2V} symmetry and π–π-interaction favors this selective precipitation since this solubility effect fails to appear with aliphatic acid moieties like BOC and acetate.

The easy access to **6** provides an ideal basis for the directed synthesis of the distal disubstituted target compound **3**, as the two opposing ester-functionalized phenyls are deactivated for electrophilic aromatic substitution reactions, determining the substitution pattern for upcoming reactions. Hence the above-mentioned isolation problems of other routes can be avoided. A recently published one-step synthesis of distal difunctionalized resorcinarene tetraethers exhibits a similar selectivity, starting from a mixture of resorcinol and 1,3-dimethoxybenzene.[15] Though satisfying yields are achieved, ester cleavage is preferred for the benefit of milder reaction conditions and reagents.

Results and Discussion

Resorcinarene backbones with phenethyl (**1a**) and pentyl (**1b**) residues were synthesized according to modified procedures by Cram et al.[16] with yields of 78 % (**1a**) and 99 % (**1b**) respectively. To ensure early-stage product determination, *p*-toluoyl chloride was used as an acylating agent in the presence of triethylamine as a base under vigorous stirring. Since the regioselectivity is reported to strongly depend on reagents, stoichiometry, solvents, and the precise conditions applied, a strict protocol was followed.[12]

After the introduction of the four *p*-toluic acid esters, the two aromatic positions *ortho* to the free phenols remained to be active for electrophilic substitution. Thus, using NBS we achieved the twofold bromination in yields of > 99 % [R = $(CH_2)_2C_6H_5$, **7a**] and 95 % (R = C_5H_{11}, **7b**), well above the 90 % for the fourfold bromination in the classical route to target compound **3**.[10] We found a mild 1.5-fold excess of NBS per vacant aromatic upper-rim position is sufficient for the reaction, thereby minimizing the amount of unconverted reagent, which was easily removed by washing the solid raw product. The resulting crude product was sufficiently pure, since no by-products e.g. of a substoichiometric bromination were found by ^1H NMR spectroscopy, where the missing aromatic upper rim signals, *ortho* to OH served as diagnostic signals (**6a**: 6.11 ppm,

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6b: 6.55 ppm), along with the two remaining ones, *ortho* to the esters (**7a**: 6.90 ppm, **7b**: 6.92 ppm).

Next, the cleavage of the previously introduced ester groups was targeted, which turned out to be problematic under typical alkaline conditions as mentioned by Shivanyuk et al.[12] While the successful saponification was proven by ^{1}H NMR spectroscopy, using sodium hydroxide in methanol, the separation of the resulting resorcinarene octols **2** from the *p*-toluic acid was difficult, both, under basic and under neutral or acidic conditions, and led to significant loss of product during workup. We solved this problem by cleaving off the *p*-toluic moieties via transesterification with sodium methoxide since washing easily separates the methyl *p*-toluate from the resorcinarene octols **2**. Trace amounts of remaining methyl *p*-toluate were removed by drying at 125 °C under vacuum in a Kugelrohr oven but also showed to be tolerated in the final synthesis step. The cyclizing tetraacetalization was performed with bromochloromethane and potassium carbonate as a base. Due to the acetalizing reagents low boiling point (68 °C), the reaction was given two days at 60 °C to avoid reagent loss via volatilization. With up to 94 % [R = $(CH_2)_2C_6H_5$, **3a**] and 84 % (R = C_5H_{11}, **3b**), these yields showed to be well within the range of the reported tetraacetalization reactions, performed at tetrabromo resorcinarenes.[10,17] As in the previous steps only simple and conserving workup methods were required, such as filtration, trituration, and drying, to give the spectroscopically clean difunctionalized resorcinarene cavitands in overall yields of 26 % [R = $(CH_2)_2C_6H_5$, **3a**] and 18 % (R = C_5H_{11}, **3b**) over five steps. We wish to emphasize, that this tetraacetylization performs to such high yields without the formation of interbowl oligomerization or substoichiometric acetalization products since this selectivity has not yet been reported on distal disubstituted resorcinarenes and was commonly assumed to require three or more sterically demanding upper rim substituents. Only a few examples show the fourfold cyclizing acetalization at unsubstituted resorcinarenes with yields higher than 50 %.[18] Most of them require large solubilizing groups (R) to maintain enough steric hindrance, keeping sites for intermolecular reaction apart.

The protocol was crucially optimized by starting material recovery in the second stage of the synthesis. Besides the readily isolated distal tetraesters **6** an indistinctive fraction of by-products remained in the workups mother liquor. In order to understand the principles behind the product and by-product formation, several attempts to separate these by-products by column chromatography, crystallization, or solvent-antisolvent precipitation were undertaken but remained unsuccessful. However, the overall result was improved by developing a procedure for the recovery of **1** from the by-products mixture: Phenethyl resorcinarene (**1a**) was readily recovered by saponification of the by-products with sodium hydroxide in methanol. For the recovery of pentyl resorcinarene (**1b**) a transesterification with sodium methoxide was superior. As a notable convenience, the recycled starting materials required a mere filtration, washing, and drying as workup and were immediately used for the next batch. Based on the calculated amount of by-product, up to 85–88 % of **1** were recovered. Hence the initial yields of the tetraesters **6a** (39 %) and **6b** (26 %) were corrected to 84 % (**6a**) and 70 % (**6b**) as "based on recovered starting material", respectively, by considering the recovered starting material unreacted. The final products' overall yields are thus corrected to 57 % (**3a**) and 48 % (**3b**), as Table 1 displays. Further methods to increase conversion like pressure tube reactions,[17] or further increase of the reaction time[10] were not considered, in favor of a reliable and upscalable protocol.

Table 1. Yields in %.

	1	**6**	**7**	**2**	**3**	**3** Total[a]
a (Phenetyl)	78	39 (84)[b]	99.5	93	94	26 (57)[b]
b (Pentyl)	99	26 (70)[b]	95	86	84	18 (48)[b]

[a] Total yield over 5 steps. [b] Corrected yields based on recovered starting material.

Conclusion

Distal difunctionalized and tetraacetalized resorcinarenes **3a** and **3b** were successfully synthesized using a regioselective approach, deactivating two of four available sites for electrophilic aromatic substitution, with the introduction of the four ester groups as the product determining step. Special attention was turned towards the development of straightforward and upscalable syntheses and workups. Thus, time consuming and batch limiting protocols like column chromatography and pressure tube techniques were avoided. By successfully recovering the starting material from the by-products, yields of this step were increased from 26–39 % to 70–84 %. An alternative method for ester cleavage via transesterification under alkaline conditions was developed, enabling an efficient workup, where hitherto reported protocols suffer a significant loss of product. Furthermore, cyclizing tetraacetalization of distal disubstituted resorcinarenes was investigated and proven to be a highly selective process with yields well above 80 %.

Our methods have shown to significantly improve overall yields of a five-step synthesis in the range of 50 %, providing high-yield and high-selectivity access to two versatile precursors for cavitand and hemicarcerand syntheses.

Experimental Section

General

Dry THF was distilled from sodium-benzophenone prior to use. Ethanol, methanol, toluene, ethyl acetate, and *n*-hexane were purchased in technical grade purity and distilled prior to use. All other solvents were purchased in p.a. grade. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-200 (200 MHz), DPX-250 (250 MHz), and AVIII-300 (300 MHz) instruments and raw processed by Bruker TopSpin. Further analyses and fine processing were done using MestReNova version 14.0.1. Solvents for NMR spectroscopy were used in a 99.8 % deuteration grade and the residual undeuterated solvent was used as internal reference for calibration. All products were spectroscopically pure after the procedures given. Unpublished products (**2a**, **2b**, **3a**, **7a**, **7b**) were further purified for complete characterization via flash chromatography using silica as stationary phase and toluene, ethyl acetate, or ethanol as mobile phase.

Experimental Details

2,8,14,20-Tetra-(2-phenylethyl)resorc[4]arene (1a): To a solution of resorcinol (42.0 g, 381 mmol) in ethanol (300 mL) at 0 °C, concentrated HCl (84.0 mL) was added, followed by dropwise addition of 3-phenylpropionaldehyde (50.7 mL, 381 mmol) within 30 minutes. The mixture was stirred for 24 h at room temperature and 48 h at reflux before being poured onto ice water. The resulting precipitate was collected by filtration and washed with a 1:1 mixture of ethanol and water. Crystallization from methanol yielded 67.4 g (78 %) of **1a** as a colorless powder after vacuum drying at room temperature. Mp: 265 °C (decomp.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.45–2.53 ppm (m, 18 H, CH_2CH_2, DMSO), 4.30 (s, 4 H, C*H*), 6.23 (s, 4 H, Ar*H ortho* to OH), 7.10–7.27 (m, 20 H, C$_6H_5$), 7.46 (s, 4 H, Ar*H meta* to OH), 9.10 (s, 8 H, O*H*). ^{13}C NMR (75.0 MHz, [D$_6$]DMSO): δ = 33.3 ppm (s, *C*H), 34.4 (s, Ar-*C*H$_2$), 36.0 (s, CH-*C*H$_2$), 102.5 (s, Ar*C*H *ortho* to both OH), 123.5 (s, Ar*C*-CH), 125.0 (s, Ar*C*H *meta* to both OH), 125.6 (s, Ar*C*H *para* to CH$_2$), 128.2, 128.5 (both s, Ar*C ortho* and *meta* to CH$_2$), 142.3 (s, Ar*C*-CH$_2$), 151.7 (s, Ar*C*-OH).[16]

4,6,16,18-Tetrahydroxy-2,8,14,20-tetra-(2-phenylethyl)resorc[4]arene-10,12,22,24-tetra-*p*-toluate (6a): To a vigorously stirred suspension of **1a** (40.0 g, 44.2 mmol) in acetonitrile (400 mL), triethylamine (24.5 mL, 177 mmol) was added rapidly. The mixture was cooled down to 0 °C, stirred for 15 minutes and *p*-toluoyl chloride (23.4 mL, 177 mmol) was added in one portion. After stirring at room temperature overnight, the resulting precipitate was filtered off and the filtrate was preserved for starting material recovery. The filter cake was washed with acetonitrile and water successively and dried in vacuo to yield 23.9 g (39 %) of **6a** as a colorless powder. Mp: 220 °C (decomp.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.25–2.60 ppm (m, 47 H, Tol-CH_3, CH_2CH_2, DMSO), 4.56 (s, 4 H, C*H*), 6.11 (s, 2 H, Ar*H ortho* to OH), 6.96–7.18 (m, 22 H, C$_6H_5$, Ar*H ortho* to OCOTol), 7.38 (d, *J* = 8.1 Hz, 8 H, Tol*H*), 7.48 (s, 2 H, Ar*H meta* to OCOTol), 7.69 (s, 2 H, Ar*H meta* to OH), 8.02 (d, *J* = 8.1 Hz, 8 H, Tol*H*), 8.75 (s, 4 H, O*H*). ^{13}C NMR (75.0 MHz, [D$_6$]DMSO): δ = 21.3 ppm (s, Tol-*C*H$_3$, *C*H$_2$CH$_2$), 34.2 (s, *C*H), 101.9 (ws, Ar*C*H *ortho* to both OH), 116.2 (ws, Ar*C*H *ortho* to both OCOTol), 119.8 (s, Ar*C*-CH *ortho* and *para* to OH), 125.6 (s, Ar*C*H *meta* to both OH), 126.9 (s, Tol*C*-COO), 128.2, 128.3 (both s, Ar*C*H phenylethyl, Ar*C*H *meta* to both OCOTol), 129.4 (s, Tol*C*H *ortho* to CH$_3$), 129.9 (s, Tol*C*H *meta* to CH$_3$), 135.5 (s, Ar*C*-CH *ortho* and *para* to OCOTol), 142.0 (s, Ar*C*-CH$_2$ phenylethyl), 143.9 (s, Tol*C*-CH$_3$), 145.0 (s, Ar*C*-OCOTol), 153.7 (s, Ar*C*-OH), 164.2 (s, carbonyl *C*).[12]

Recovery of the Starting Material 1a: The solvent of the previous filtration was removed under reduced pressure to give the by-products (37.0 g, 26.9 mmol for average M = 1378 g/mol) as a red solid. Sodium hydroxide (17.1 g, 430 mmol) was dissolved in methanol (150 mL) and a solution of the by-products in methanol (200 mL) was added slowly. The mixture was stirred at room temperature overnight and poured onto 1 M HCl (430 mL). The precipitate was recovered by filtration and washed thoroughly with water and hexane to give 21.4 g (88 %) of **1a** as an off-white powder.

5,17-Dibromo-4,6,16,18-tetrahydroxy-2,8,14,20-tetra-(2-phenylethyl)resorc[4]arene-10,12,22,24-tetra-*p*-toluate (7a): A solution of **6a** (5.73 g, 4.16 mmol) in dry THF (90.0 mL) was cooled down to 0 °C under exclusion of light and an argon atmosphere. NBS (2.22 g, 12.5 mmol) was added, prior to stirring for 2 h at 0 °C and overnight at room temperature. Methanol (50.0 mL) and sodium sulfite (0.53 g) were added and the mixture was stirred for another 20 min before removing THF under reduced pressure. Water was added and the precipitate was collected by filtration, washed with water and dried in vacuo at 70 °C to yield 6.36 g (99.5 %) of **7a** as a spectroscopically pure off-white powder. Mp: 154 °C (decomp.). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 1.60 ppm (s, 4 H, H$_2$O), 2.15–2.35 (m, 8 H, CH_2CH_2), 2.46 (s, 12 H, Tol-CH_3), 2.53–2.70 (m, 8 H, CH_2CH_2), 4.47 (t, *J* = 7.34 Hz, 4 H, C*H*), 5.62–5.76 (m, 4 H, O*H*), 6.78–6.84 (m, 2 H, Ar*H ortho* to OCOTol), 6.97–7.10 (m, 20 H, C$_6H_5$), 7.15 (s, 4 H, Ar*H* lower rim), 7.18 (d, *J* = 8.1 Hz, 8 H, Tol*H*), 8.03 (d, *J* = 8.1 Hz, 8 H, Tol*H*). ^{13}C NMR (75.0 MHz, [D$_6$]DMSO): δ = 21.3 ppm (s, Tol-*C*H$_3$), 34.2 (s, *C*H$_2$CH$_2$), 35.7 (s, *C*H), 109.7 (s, Ar*C*-Br), 116.2 (ws observed in HSQC, Ar*C* lower rim), 122.6 (s, Ar*C ortho* and *para* to OH), 125.7 (s, Ar*C*H *ortho* to OCOTol), 126.5 (s, Tol*C*-CO), 128.2 (s, Ar*C*H phenylethyl), 129.4 (s, Tol*C*H *ortho* to CH$_3$), 130.4 (s, Tol*C*H *meta* to CH$_3$), 134.9 (s, Ar*C ortho* and *para* to both OCOTol), 141.7 (s, Ar*C*-CH$_2$), 144.6 (s, Tol*C*-CH$_3$), 145.7 (s, Ar*C*-OCOTol), 149.1 (s, Ar*C*-OH), 164.2 (s, carbonyl *C*). MS (MALDI-TOF): *m/z* (%) = 1573 (22) [M$^+$ + K], 1558 (14) [M$^+$ + Na], 1544 (10) [M$^+$ + K – C$_2$H$_2$], 1528 (63) [M$^+$ + Na – C$_2$H$_2$], 1485 (73) [M$^+$ + K – Tol], 1468 (45) [M$^+$ + Na – Tol]. IR: $\tilde{\nu}$ = 3516 cm^{-1} (w), 3023 (w), 2938 (w), 2859 (w), 1728 (s), 1609 (m), 1485 (m), 1452 (m), 1177 (s), 1242 (s), 1152 (s), 1076 (s), 1016 (s), 905 (m), 837 (m) 793 (m), 744 (s), 696 (s), 637 (m) EA: Calculated: [M + 2H$_2$O] C 70.32 %, H 5.26 %; found: C 70.51 %, H 5.21 %.

5,17-Dibromo-2,8,14,20-tetra-(2-phenylethyl)resorc[4]arene (2a): Under an argon atmosphere, sodium (0.53 g, 22.9 mmol) was placed in a thoroughly dried round-bottomed flask and methanol (10.0 mL) was added dropwise under ice bath cooling. A solution of **7a** (2.20 g, 1.43 mmol) in methanol (25.0 mL) was slowly added and the mixture was stirred for 5 h at room temperature before being poured onto 1 M HCl (23.0 mL). The precipitate was collected by filtration, washed with water and hexane and dried in vacuo at 125 °C to yield 1.42 g (93 %) of **2a** as a red powder. Mp: 156 °C (decomp.). ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.30 ppm (s, 3H, Toluene), 2.46–2.60 ppm (m, 34 H, CH_2CH_2, DMSO), 4.25 (s, 4 H, C*H*), 6.37 (s, 2 H, Ar*H ortho* to OH), 7.11–7.27 (m, 25 H, C$_6H_5$, Toluene), 7.41–7.57 (m, 4 H, Ar*H meta* to OH), 8.63 (bs, 4 H, O*H ortho* to Br), 10.23–10.67 (m, 4 H, O*H ortho* to H). ^{13}C NMR (75.0 MHz, [D$_6$]DMSO): δ = 33.9 ppm (s, *C*H), 34.7 (s, *C*H$_2$), 102.2 (ws observed in HSQC, Ar*C*H *ortho* to OH), 125.0 (s, Ar*C*-CH), 126.2 (s, Ar*C*-CH$_2$), 128.7, (s, Ar*C*H *ortho* and *meta* to CH$_2$), 129.0 (s, Ar*C*H *para* to CH$_2$), 129.6, 129.8 (both s, Ar*C*H lower rim), 142.5 (s, Ar*C*-Br), 148.9, 151.2 (both s, Ar*C*-OH). MS (MALDI-TOF): *m/z* (%) = 1101 (15) [M$^+$ + K], 1085(23) [M$^+$ + Na], 1075 (15) [M$^+$ + K – C$_2$H$_2$], 1056 (26) [M$^+$ + Na – C$_2$H$_2$], 1040 (75) [M$^+$ + Na – C$_2$H$_2$ – OH], 995 (100) [M$^+$ + K – (PhCH$_2$CH$_2$)]. IR:$\tilde{\nu}$ = 3360 cm^{-1} (m), 3024 (w), 2932 (w), 2860 (w), 1740 (m), 1719 (m), 1603 (m), 1495 (s), 1473 (s), 1452 (s), 1437 (s), 1350 (m), 1258 (s), 1165 (s), 1088 (s), 905 (w), 839 (m), 746 (s), 696 (s). EA: Calculated: [M + Toluene] C 69.67 %, H 5.41 %; found: C 69.80 %, H 5.32 %.

5,17-Dibromo-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-tetra-(2-phenylethyl)resorc[4]arene (3a): To a suspension of **2a** (7.67 g, 7.22 mmol) in DMF (200 mL), potassium carbonate (13.0 g, 93.8 mmol) was added and the mixture was heated to 60 °C. After the addition of bromochloromethane (7.25 mL, 108 mmol), the mixture was stirred for 48 h at 60 °C with another addition of bromochloromethane (7.25 mL, 108 mmol) after 24 h. The crude product was precipitated by pouring the reaction mixture onto 1 M HCl (95.0 mL), followed by filtration. The filtrate was triturated and thoroughly washed with water before vacuum drying at 120 °C to yield 7.50 g (94 %) of **3a** as a spectroscopically pure off-white powder. Mp: 286 °C (decomp.). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 2.37 ppm (s, 6 H, Toluene), 2.45–2.57 (m, 8 H, CH_2CH_2), 2.63–2.74 (m, 8 H, CH_2CH_2), 4.46 (d, *J* = 7.2 Hz, 4 H, OCH_2O), 4.90 (t, *J* = 7.9 Hz, 4 H, C*H*), 5.89 (d, *J* = 7.2 Hz, 4 H, OCH_2O), 6.60 (s, 2 H, Ar*H*, *ortho* to O), 7.04–7.29 (m, 37 H, C$_6$H$_5$, Ar*H meta* to O, Toluene, CHCl$_3$). ^{13}C NMR (75.0 MHz, CDCl$_3$): δ = 32.4 ppm (s, CH-CH$_2$), 34.4

(s, CH_2-Ar), 37.1 (s, *C*H), 99.2 (s, OCH_2O), 117.7 (s, Ar*C*H *ortho* to OCH_2O), 120.9, 122.1 (both s, Ar*C* lower rim), 126.3 (s, Ar*C*H *para* to CH_2), 128.5, 128.8 (both s, Ar*C*H *ortho* and *meta* to CH_2), 133.6 (s, Ar*C*-Br), 138.3 (s, Ar*C*-CH *meta* to upper rim H), 139.3 (s, Ar*C*-CH *meta* to Br), 141.5 (s, Ar*C*-CH_2), 151.2 (s, Ar*C*-OCH_2O *ortho* to Br), 155.2 (s, Ar*C*-OCH_2O *ortho* to upper rim H). MS (MALDI-TOF): To enhance ionization, the substrate was doped with *N*-methylpyridinium iodide. *m/z* (%) = 1200 (14) [M^+ + *N*-Methylpyridinium], 1124 (21) [M^+ + *N*-Methylpyridinium – Ph], 1110 (80) [M^+], 1060 (63) [M^+ – C_4H_4], 1033 (23) [M^+ – Br]. IR: $\tilde{\nu}$ = 3024 cm^{-1} (w), 2934 (w), 2868 (w), 1736 (w), 1667 (w), 1603 (w), 1491 (m), 1452 (m), 1294 (m), 1229 (w), 1190 (w), 1092 (s), 1022 (m), 988 (m), 956 (s), 750 (m), 698 (s), 654 (m), 584 (m), 482 (m). EA: Calculated: [M + 2 Toluene] C 72.33 %, H 5.45 %; found: C 72.43 %, H 5.24 %.

2,8,14,20-Tetrapentylresorc[4]arene (1b): To a solution of resorcinol (39.6 g, 360 mmol) in a 1:1 mixture of ethanol and water (300 mL) at 0 °C, concentrated HCl (75.0 mL) was added, followed by dropwise addition of hexanal (44.5 mL, 360 mmol), diluted with ethanol (100 mL) within 2 h. The mixture was stirred for 3 d at 60 °C before water was added. The resulting precipitate was collected by filtration and washed with water to yield **1b** (68.2 g, 99 %) after vacuum drying as an off-white powder. Mp: 276 °C. ^{1}H NMR (200 MHz, [D_6]DMSO): δ = 0.83 ppm (t, *J* = 6.1 Hz, 12 H, CH_2CH_3), 1.18–1.36 (m, 24 H, $(CH_2)_3CH_3$), 1.84–2.13 (m, 8 H, CH-CH_2), 4.21 (t, *J* = 6.8 Hz, 4 H, C*H*), 6.14 (s, 4 H, Ar*H ortho* to OH), 7.15 (s, 4 H, Ar*H meta* to OH), 8.87 (s, 8 H, O*H*). ^{13}C NMR (75.0 MHz, [D_6]DMSO): δ = 14.0 ppm (s, CH_3), 22.3 (s, CH_2-CH_3), 27.5, 31.5 (both s, CH_2), 33.1 (s, CH-CH_2), 34.0 (CH-CH_2), 102.4 (s, Ar*C*H *ortho* to OH), 123.1 (s, Ar*C*), 125.0 (s, Ar*C*), 151.7 (s, Ar*C*OH).[16]

4,6,16,18-Tetrahydroxy-2,8,14,20-tetrapentylresorc[4]arene-10,12,22,24-tetra-*p*-toluate (6b): To a vigorously stirred suspension of **1b** (15.4 g, 20.0 mmol) in acetonitrile (200 mL), triethylamine (11.1 mL, 80.0 mmol) was added rapidly. The mixture was cooled down to 0 °C, stirred for 15 minutes and *p*-toluoyl chloride (10.6 mL, 80.0 mmol) was added in one portion. After stirring at room temperature overnight, the resulting precipitate was filtered off and the filtrate was preserved for starting material recovery. The filter cake was washed with acetonitrile and water successively and dried in vacuo to yield 6.50 g (26 %) of **6b** as a colorless powder. Mp: 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.66–0.78 ppm (m, 12 H, CH_2CH_3), 1.12–1.31 (m, 24 H, $(CH_2)_3CH_3$), 1.69–2.05 (m, 8 H, CH-CH_2), 2.41 (s, 12 H, Tol-CH_3), 4.39 (t, *J* = 6.4 Hz, 4 H, C*H*), 6.55 (s, 2 H, Ar*H ortho* to OH), 6.82 (s, 2 H, Ar*H ortho* to OCOTol), 7.07 (s, 2 H, Ar*H meta* to OCOTol), 7.19–7.28 (m, 10 H, Tol*H*, Ar*H meta* to OH), 8.08 (d, *J* = 8.2 Hz, 8 H, Tol*H*). ^{13}C NMR (75.0 MHz, [D_6]DMSO): δ = 14.1 ppm (s, CH_3), 21.9 (s, TolCH_3), 22.7, 27.7, 32.0, 35.8 (all s, CH_2), 36.1 (CH-CH_2), 103.4 (s, Ar*C*H *ortho* to both OH), 116.0 (s, Ar*C*H *ortho* to both OCOTol), 118.5 (s, Ar*C*-CH *ortho* and *para* to OH), 125.8 (s, Ar*C*H *meta* to both OH), 126.6 (s, Tol*C*-COO), 127.4 (s, Ar*C*H *meta* to both OCOTol), 129.5 (s, Tol*C*H *ortho* to CH_3), 130.4 (s, Tol*C*H *meta* to CH_3), 136.9 (s, Ar*C*-CH *ortho* and *para* to OCOTol), 144.7 (s, Tol*C*-CH_3), 146.0 (s, Ar*C*-OCOTol), 154.0 (s, Ar*C*-OH), 165.9 (s, carbonyl *C*).[12]

Recovery of the Starting Material 1b: The solvent of the previous filtration was removed under reduced pressure to give the by-products (21.0 g, 16.9 mmol for average M = 1241 g/mol) as a red solid. Under an argon atmosphere, sodium (6.22 g, 270 mmol) was placed in a thoroughly dried round-bottomed flask and methanol (150 mL) was added dropwise under ice-bath cooling. A solution of the by-products in methanol (150 mL) was slowly added and the mixture was stirred at room temperature overnight before being poured onto 1 M HCl (270 mL). The precipitate was collected by filtration, washed with hot water, and vacuum dried to give spectroscopically pure **1b** (11.0 g, 85 %) as an off-white powder.

5,17-Dibromo-4,6,16,18-tetrahydroxy-2,8,14,20-tetrapentylresorc[4]arene-10,12,22,24-tetra-*p*-toluate (7b): A solution of **6b** (4.00 g, 3.22 mmol) in dry THF (60.0 mL) was cooled down to 0 °C under exclusion of light and an argon atmosphere. NBS (1.72 g, 9.67 mmol) was added, prior to stirring for 2 h at 0 °C and overnight at room temperature. Methanol (30.0 mL) and sodium sulfite (0.20 g) were added and the mixture was stirred for another 20 min before removing THF under reduced pressure. Water was added and the precipitate was collected by filtration, washed with water and dried in vacuo to yield 4.28 g (95 %) of **7b** as a spectroscopically pure off-white powder. Mp: 152 °C (decomp.). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.59–0.78 ppm (m, 12 H, CH_2CH_3), 1.03–1.36 (m, 24 H, $(CH_2)_3CH_3$), 1.71–2.08 (m, 8 H, CH-CH_2), 2.43 (s, 12 H, Tol-CH_3), 4.29 (t, *J* = 6.9 Hz, 4 H, C*H*), 5.76 (s, 4H, OH), 6.55 (s, 2 H, Ar*H ortho* to OCOTol), 7.06 (s, 2 H, Ar*H* lower rim), 7.18 (s, 2 H, Ar*H* lower rim), 7.28 (d, *J* = 7.9 Hz, 8 H, Tol*H*), 8.10 (d, *J* = 7.9 Hz, 8 H, Tol*H*). ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 13.8 ppm (s, CH_3), 21.3 (s, TolCH_3), 22.1, 27.3, 31.3, 34.4 (all s, CH_2), 36.3 (CH-CH_2), 102.3 (s, Ar*C*-Br), 116.8, 118.0 (both s, Ar*C* lower rim), 123.6 (s, Ar*C ortho* and *para* to OH), 124.8 (s, Ar*C*H *ortho* to OCOTol), 126.4 (s, Tol*C*-CO), 129.3 (s, Tol*C*H *ortho* to CH_3), 129.8 (s, Tol*C*H *meta* to CH_3), 133.8 (s, Ar*C ortho* and *para* to both OCOTol), 144.0 (s, Tol*C*-CH_3), 146.0 (s, Ar*C*-OCOTol), 149.7 (s, Ar*C*-OH), 164.0 (s, carbonyl *C*). MS (FAB): *m/z* (%) = 1422 (100) [M^+ + Na], 1399 (40) [M^+], 1325 (73) [M^+ – C_5H_{11}]. IR: $\tilde{\nu}$ = 3510 cm^{-1} (w), 2953 (m), 2928 (m), 2859 (m), 1734 (s), 1611 (s), 1479 (s), 1429 (m), 1242 (s), 1177 (s), 1119 (s), 1072 (s), 1017 (s), 897 (w), 835 (m), 745 (s), 687 (m), 637 (w), 613 (w), 474 (w). EA: Calculated: [M + EtOH] C 65.17 %, H 5.94 %; found: C 65.44 %, H 5.80 %.

5,17-Dibromo-2,8,14,20-tetrapentylresorc[4]arene (2b): Under an argon atmosphere, sodium (0.49 g, 21.4 mmol) was placed in a thoroughly dried round-bottomed flask and methanol (10.0 mL) was added dropwise under ice bath cooling. A solution of **7b** (0.20 g, 0.14 mmol) in methanol (10.0 mL) was slowly added and the mixture was stirred for 5 h at room temperature before being poured onto 1 M HCl (23.0 mL). The precipitate was collected by filtration, washed with water and dried in vacuo at 50 °C to yield 0.11 g (86 %) of **2b** as a red powder. Mp: 250 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 0.84 ppm (t, *J* = 6.9 Hz, 12 H, CH_3), 1.17 (t, *J* = 7.11 Hz, EtOAc, overlaid), 1.20–1.38 (m, 24 H, $(CH_2)_3CH_3$), 1.99 (s, 3 H, EtOAc), 2.16–2.28 (m, 8 H, CH-CH_2), 4.03 (q, *J* = 7.11 Hz, 2H, EtOAc), 4.15 (t, *J* = 7.4 Hz, 4 H, C*H*), 6.32 (s, 2 H, Ar*H ortho* to OH), 7.35–7.44 (m, 4 H, Ar*H meta* to OH), 8.64 (s, 4 H, O*H ortho* to Br), 10.45 (s, 4 H, O*H ortho* to H). ^{13}C NMR (62 MHz, [D_6]DMSO): δ = 13.9 ppm (s, CH_3), 22.3 (s, CH_2-CH_3), 27.5, 31.3 (both s, CH_2), 32.7 (s, CH-CH_2), 34.0 (CH-CH_2), 99.8 (s, Ar*C*H *ortho* to OH), 101.5 (s, Ar*C*-Br), 122.4 (s, Ar*C*), 123.6 (s, Ar*C*), 124.5 (s, Ar*C*), 125.4 (s, Ar*C*), 149.3 (s, Ar*C*OH), 150.3 (s, Ar*C*OH). MS (FAB): *m/z* (%) = 949 (41) [M^+ + Na], 926 (25) [M^+], 855 (100) [M^+ – C_5H_{11}], 755 (20) [M^+ – C_5H_{11} – Br]. IR: $\tilde{\nu}$ = 3377 cm^{-1} (m), 2953 (m), 2926 (s), 2859 (m), 1614 (m), 1504 (w), 1468 (s), 1439(m), 1377 (w), 1344 (w), 1283 (m), 1186 (s), 1146 (s), 1107 (m), 1082 (s), 899 (w), 837 (m), 638 (w), 563 (w). EA: Calculated: [M + EtOAc] C 61.54 %, H 6.95 %; found: C 61.61 %, H 6.63 %.

5,17-Dibromo-4(24),6(10),12(16),18(22)-tetramethylenedioxy-2,8,14,20-pentylresorc[4]arene (3b): To a suspension of **2b** (0.67 g, 0.72 mmol) in DMF (125 mL), potassium carbonate (1.29 g, 9.35 mmol) was added and the mixture was heated to 60 °C. After the addition of bromochloromethane (0.73 mL, 10.8 mmol), the mixture was stirred for 48 h at 60 °C with another addition of bromochloromethane (0.73 mL, 10.8 mmol) after 24 h. The mixture was filtered and the filtrate was extracted with DCM and water. Organic phases were combined, washed with 1 M HCl and brine, and dried with magnesium sulfate. The solvent was removed and the resulting solid was vacuum dried to give **3b** as an off-white

powder (0.60 g, 85 %). Mp: 220 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.82–1.00 ppm (m, 12 H, CH_3), 1.24–1.49 (m, 24 H, (CH_2)$_3$CH$_3$), 2.07–2.38 (m, 8 H, CH-CH_2), 4.41 (d, J = 7.1 Hz, 4 H, OCH_2O), 4.79 (t, J = 7.3 Hz, 4 H, C*H*), 5.86 (d, J = 7.0 Hz, 4 H, OCH_2O), 6.53 (s, 2 H, Ar*H*, *ortho* to O), 6.88–7.18 (m, 4 H, Ar*H* *meta* to O). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 ppm (s, CH_3), 22.8 (s, CH_2-CH$_3$), 27.6, 30.0 (both s, CH_2), 32.1 (s, CH-CH_2), 37.2(C*H*-CH$_2$), 99.1 (s, OCH_2O), 113.3 (s, Ar*C*-Br),116.9 (s, Ar*C*H *ortho* to OCH$_2$O), 119.0, 121.0 (both s, Ar*C* lower rim), 126.3 (s, Ar*C*H *para* to CH$_2$), 128.5, 128.8 (both s, Ar*C*H *ortho* and *meta* to CH$_2$), 138.5 (s, Ar*C*-CH *meta* to upper rim H), 139.5 (s, Ar*C*-CH *meta* to Br), 152.2 (s, Ar*C*-OCH$_2$O *ortho* to Br), 155.0 (s, Ar*C*-OCH$_2$O *ortho* to upper rim H).[19]

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[1] D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024; *Angew. Chem.* **1991**, *103*, 1048.
[2] H.-J. Choi, Y. S. Park, J. Song, S. J. Youn, H.-S. Kim, S.-H. Kim, K. Koh, K. Paek, *J. Org. Chem.* **2005**, *70*, 5974.
[3] a) T. M. Bräuer, Q. Zhang, K. Tiefenbacher, *Angew. Chem. Int. Ed.* **2016**, *55*, 7698; *Angew. Chem.* **2016**, *128*, 7829; b) T. Chavagnan, D. Sémeril, D. Matt, L. Toupet, *Eur. J. Org. Chem.* **2017**, *2017*, 313.
[4] N. Li, R. G. Harrison, J. D. Lamb, *J. Inclusion Phenom. Macrocyclic Chem.* **2014**, *78*, 39.
[5] D. Loose, A. Aniol, M. Feigel, S. Röhling, G. Dyker, *Eur. J. Org. Chem.* **2020**, *2020*, 35.
[6] a) H. El Moll, D. Sémeril, D. Matt, L. Toupet, *Eur. J. Org. Chem.* **2010**, 1158; b) H. El Moll, D. Sémeril, D. Matt, L. Toupet, *Adv. Synth. Catal.* **2010**, *352*, 901; c) N. Natarajan, M. Pierrevelcin, D. Sémeril, C. Bauder, D. Matt, R. Ramesh, *Catal. Commun.* **2019**, *118*, 70.
[7] a) D. J. Cram, M. E. Tanner, C. B. Knobler, *J. Am. Chem. Soc.* **1991**, *113*, 7717; b) R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1998**, *120*, 9818.
[8] B. M. Trost, *Science* **1991**, *254*, 1471.
[9] a) E. S. Barrett, J. L. Irwin, P. Turner, M. S. Sherburn, *J. Org. Chem.* **2001**, *66*, 8227; b) A. Aniol, B. Mallick, M. Winter, M. Feigel, *J. Mol. Struct.* **2017**, *1144*, 451.
[10] X. Liu, R. Warmuth, *Nat. Protoc.* **2007**, *2*, 1288.
[11] O. Lukin, A. Shivanyuk, V. V. Pirozhenko, I. F. Tsymbal, V. I. Kalchenko, *J. Org. Chem.* **1998**, *63*, 9510.
[12] A. Shivanyuk, E. F. Paulus, V. Böhmer, W. Vogt, *J. Org. Chem.* **1998**, *63*, 6448.
[13] a) G. Arnott, H. Heaney, R. Hunter, P. Page, *Eur. J. Org. Chem.* **2004**, 5126; b) G. Arnott, R. Hunter, H. Su, *Tetrahedron* **2006**, *62*, 977.
[14] S. Bringmann, R. Brodbeck, R. Hartmann, C. Schäfer, J. Mattay, *Org. Biomol. Chem.* **2011**, *9*, 7491.
[15] J. N. Smith, T. K. Brind, S. B. Petrie, M. S. Grant, N. T. Lucas, *J. Org. Chem.* **2020**, *85*, 4574.
[16] L. M. Tunstad, J. A. Tucker, D. J. Cram, et al., *J. Org. Chem.* **1989**, *54*, 1305.
[17] E. Román, C. Peinador, S. Mendoza, A. E. Kaifer, *J. Org. Chem.* **1999**, *64*, 2577.
[18] a) F. Tancini, T. Gottschalk, W. B. Schweizer, F. Diederich, E. Dalcanale, *Chem. Eur. J.* **2010**, *16*, 7813; b) R. M. Yebeutchou, E. Dalcanale, *J. Am. Chem. Soc.* **2009**, *131*, 2452; c) L. Pirondini, D. Bonifazi, E. Menozzi, E. Dalcanale, *Eur. J. Org. Chem.* **2001**, 2311.
[19] T. M. Altamore, E. S. Barrett, P. J. Duggan, M. S. Sherburn, M. L. Szydzik, *Org. Lett.* **2002**, *4*, 3489.

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