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Constitutional Isomers of Pentahydroxy-functionalized Pillar[5]arenes: Synthesis, Characterization, and Crystal Structures

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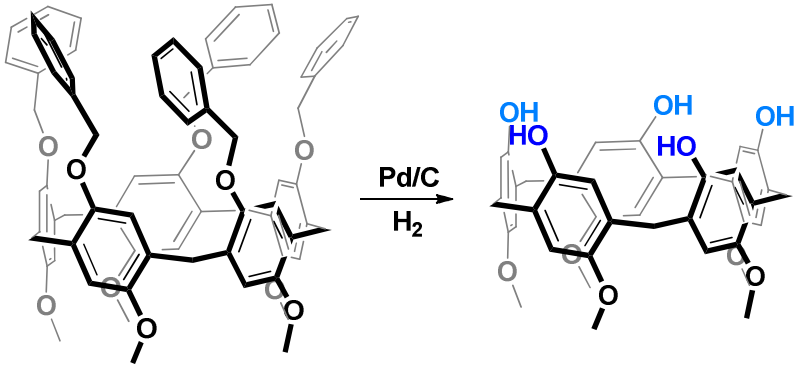


Abstract

We herein report the preparation of constitutional isomers of pentahydroxy-functionalized pillar[5]arenes via the deprotection of their benzylated derivatives by catalytic hydrogenation. The structures of the obtained isomers were then established using single crystal X-ray diffraction. We also found that the yield distribution of the different constitutional isomers was dependent on the nature of the substitution, as revealed by HPLC analysis of the crude mixture. Finally, further characterization of the separated constitutional isomers indicated that they possess different melting points, NMR spectra, crystal structures, and stacking patterns in the solid state.

Introduction

Macrocyclic oligomers such as crown ethers,[1–3] calixarenes,[4–7] cucurbiturils,[8,9] cyclodextrins,[10–12] and cyclophanenes[13–15] are attractive receptors that possess the ability to recognize non-covalently bound guest molecules through multipoint interactions. Recently, pillar[*n*]arenes, which are a relatively new class of macrocyclic compounds with unique structural features, have been reported to exhibit the exceptional ability to selectively encapsulate different kinds of guest molecules.[16–20] To date, a range of pillar[*n*]arenes composed of different ring sizes have been reported, including pillar[5]arenes (i.e., containing a 5-membered ring),[16,17] pillar[6]arenes,[18] and pillar[7]arenes.[19] In addition, larger pillar[n = 6–15]arenes have also been synthesized recently through the ring expansion of pillar[5]arenes.[21] Due to their ease of formation compared to larger pillararenes, pillar[5]arene and its derivatives have received the most attention to date. In addition, as the negatively charged pillar[5]arene cavity favors the binding of positively charged guests,[20] pillar[5]arene and its analogs have been demonstrated to act as hosts toward a range of organic compounds, including viologens,[22] alkanediamines,[23] dinitrobenzenes,[24] azobenzene derivatives,[25] and neutral molecules.[26–28]

The incorporation of functional groups into pillararenes also enables further modification of its macrocycle structure and expands the functionality of the system through alteration of its physical properties such as its solubility, optical response, and crystallinity. Indeed, many functionalized pillar[5]arenes bearing bromo,[29] amino,[30] alkyne,[31] and hydroxyl moieties[32–39] have been reported thus far. A range of different strategies has been developed for the synthesis of hydroxy-functionalized pillararenes. For example, monohydroxy pillar[5]arene has been synthesized by controlling the de-*O*-methylation of permethylated pillar[5]arene using 0.9 eq. of BBr_3.[32] In addition, an oxidation-reduction strategy has been employed to synthesize di- and

tetrahydroxy pillar[5]arenes.[35–37] Another approach involved the synthesis of mono- and A1/A2-dihydroxy-functionalized pillar[5]arenes through the co-cyclization of 1,4-dimethoxybenzene and 1,4-bis(3-bromopropoxy)benzene, followed by an elimination reaction to yield the diallyl ether and subsequent deprotection to give the desired product.[38–39]

Thus, we herein report the synthesis of pentahydroxy-functionalized pillar[5]arenes through the condensation of nonsymmetrical hydroquinone derivatives of 1-(benzyloxy)-4-alkoxybenzene followed by the removal of the benzyl groups through catalytic hydrogenation. Separation of the constitutional isomers and their resulting isomeric yield distributions are also investigated for the supramolecular system. In addition, the obtained constitutional isomers are characterized by NMR spectroscopy and X-ray single crystal diffraction studies. To the best of our knowledge, this is the first report on the synthesis of pentahydroxy-functionalized pillar[5]arenes through the deprotection of their benzylated equivalents using a catalytic hydrogenation strategy.

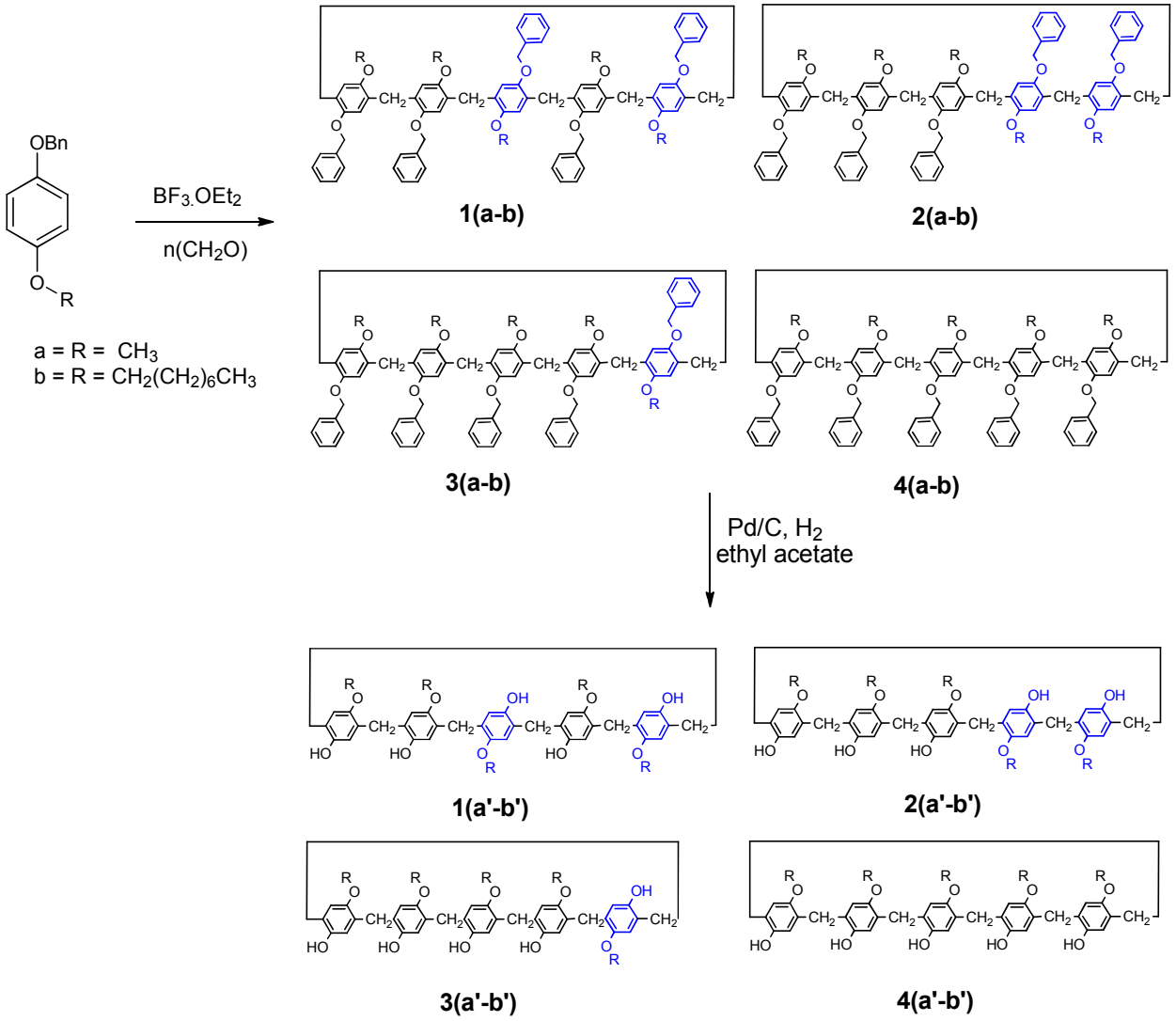
Results and discussion

Pillararenes synthesized using asymmetric hydroquinone derivatives are known to yield four constitutional isomers, namely the 1,3-alternate, 1,2-alternate, partial cone, and cone isomers, and the successful separation of these isomers depends on the nature of the substituents and the substitution pattern employed.[40] In addition, the introduction of functional groups into this macrocyclic system expand the functionality of the system, thereby enabling a wide range of chemical modifications, such as in the case of the propargyl-functionalized pillar[5]arene, which was previously prepared from the 1-decyloxy-4-propargyloxybenzene monomer.[31] In addition, this constitutional isomer with C_5 symmetry has also been further modified via the copper(I)-

catalyzed alkyne-azide 1,3-dipolar cycloaddition reaction to obtain the sugar-functionalized amphiphilic pillar[5]arene.

Based on such systems, we synthesized constitutional isomers of pentahydroxy-pillar[5]arenes using the strategy outlined in Scheme 1. Initially, the pillar[5]arene derivatives bearing benzyl groups (i.e., **Pillars 1a–1b**, **2a–2b**, **3a–3b**, and **4a–4b**) were synthesized by the condensation of asymmetric hydroquinone derivatives of 1-(benzyloxy)-4-alkoxybenzene and paraformaldehyde in the presence of $BF_3 \cdot OEt_2$. The hydroxylated pillar[5]arene analogs (i.e., **Pillars 1a′–1b′**, **2a′–2b′**, **3a′–3b′**, and **4a′–4b′**) were obtained following removal of the benzyl protecting groups under mild catalytic hydrogenation conditions.

SCHEME 1. Synthesis of the asymmetric pentahydroxy-functionalized pillar[5]arenes



The total yield of all benzyloxy-hydroxypillar[5]arene isomers (i.e., the yield of the isomeric mixture) prior to separation was 10%. As expected, TLC analysis of the asymmetric pillar[5]arenes synthesized using the 1-benzyloxy-4-methoxybenzene monomer produced four spots. Column chromatography using a dichloromethane/hexane mixture (60:40 v/v) was then employed to separate the isomeric mixture, and gave the four isomers (i.e., **Pillars 1a–4a**) as white solids (Scheme 1). Analysis by HRMS confirmed the presence of a signal at *m/z*

1153.4923 for all isomers, which corresponded to $[M+Na]^+$. However, the melting points of the four isomers differed significantly (i.e., **Pillar 1a** = 157 °C; **Pillar 2a** = 129 °C; **Pillar 3a** = 117 °C; and **Pillar 4a** = 114 °C), as did their ^{1}H NMR spectra, as shown in Figure 1. The signals corresponding to the benzyl methylene, phenyl, methylene, and methoxy protons for the **Pillar 1a–3a** isomers were observed as multiplets (Figures 1(a)–1(c)), due to the lack of symmetry, thereby rendering complete assignment of their structures from the ^{1}HNMR spectra particularly challenging. In contrast, the C_5 symmetrical isomer **Pillar 4a** was easily identified from its ^{1}H NMR spectrum (Figure 1(d)). Thus, the structures of the different isomers were assigned using single crystal X-ray diffraction, which clearly confirmed their corresponding substitution patterns (see the insets of Figure 1). To obtain suitable crystals for analysis, single crystals of **Pillars 1a**, **2a**, and **4a** were grown by the slow evaporation of a solution of each isomer in a mixture of dichloromethane/*n*-hexane, while a single crystal of **Pillar 3a** was obtained using a mixture of ethyl acetate and *n*-hexane. In the solid state, these four constitutional isomers were found to stack either in the edge-to-edge (registered) style (i.e., **Pillars 1a** and **4a**) or the corner-to-edge style (i.e., **Pillars 2a** and **3a**), which is a similar trend to the styles adopted by the asymmetric pillar[5]arene isomers prepared from the 1-butoxy-4-methoxybenzene monomer[40] (Figure S31).

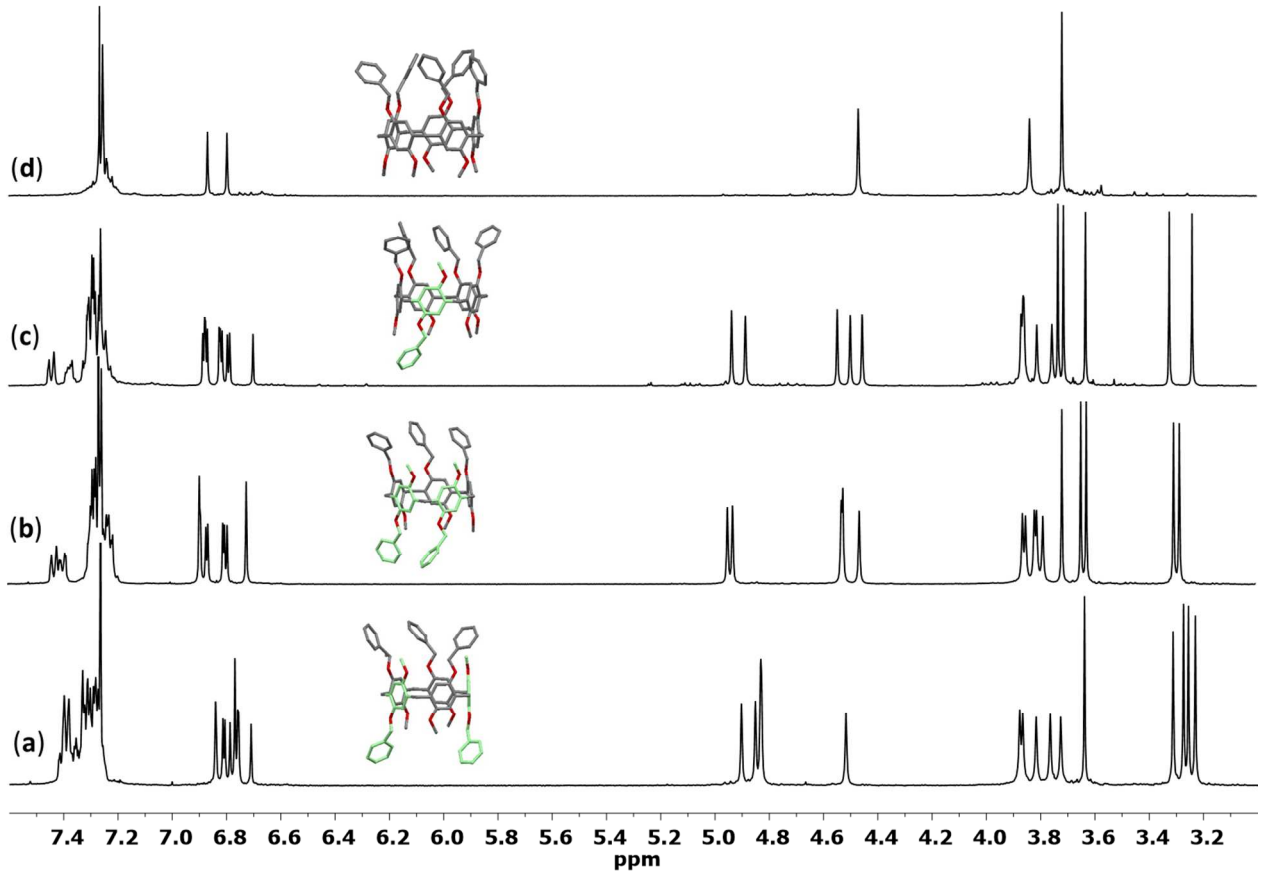


Figure 1. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of the four constitutional isomers of **Pillars 1a–4a** and insets showing the X-ray single crystal diffraction structures. (a) The 1,3-alternate isomer, **Pillar 1a**, (b) the 1,2-alternate isomer, **Pillar 2a**, (c) the partial-cone isomer, **Pillar 3a**, and (d) the cone isomer, **Pillar 4a**.

When 1-(benzyloxy)-4-(octyloxy)benzene was employed under the same reaction conditions, only three spots were detected by TLC analysis, and these were isolated by column chromatography using a mixture of dichloromethane/*n*-hexane (20:80 v/v). The ^{1}H NMR spectra of three isolated products are shown in Figure 2. As before, the C_5 symmetrical isomer (i.e., **Pillar 4b**) was easily identified by ^{1}H NMR spectroscopy (Figure 2(c)), and its structure was confirmed by single crystal X-ray diffraction (Figure 3). In addition, **Pillar 1b** exhibited a high

degree of multiplicity for the benzyl methylene, phenyl, methylene bridge, and methoxy hydrogen signals in its ^{1}H NMR spectrum (Figure 2(a)). The structure of the **Pillar 1b** isomer was also determined by single crystal X-ray diffraction following the growth of a suitable crystal by the slow evaporation method (Figure 3).

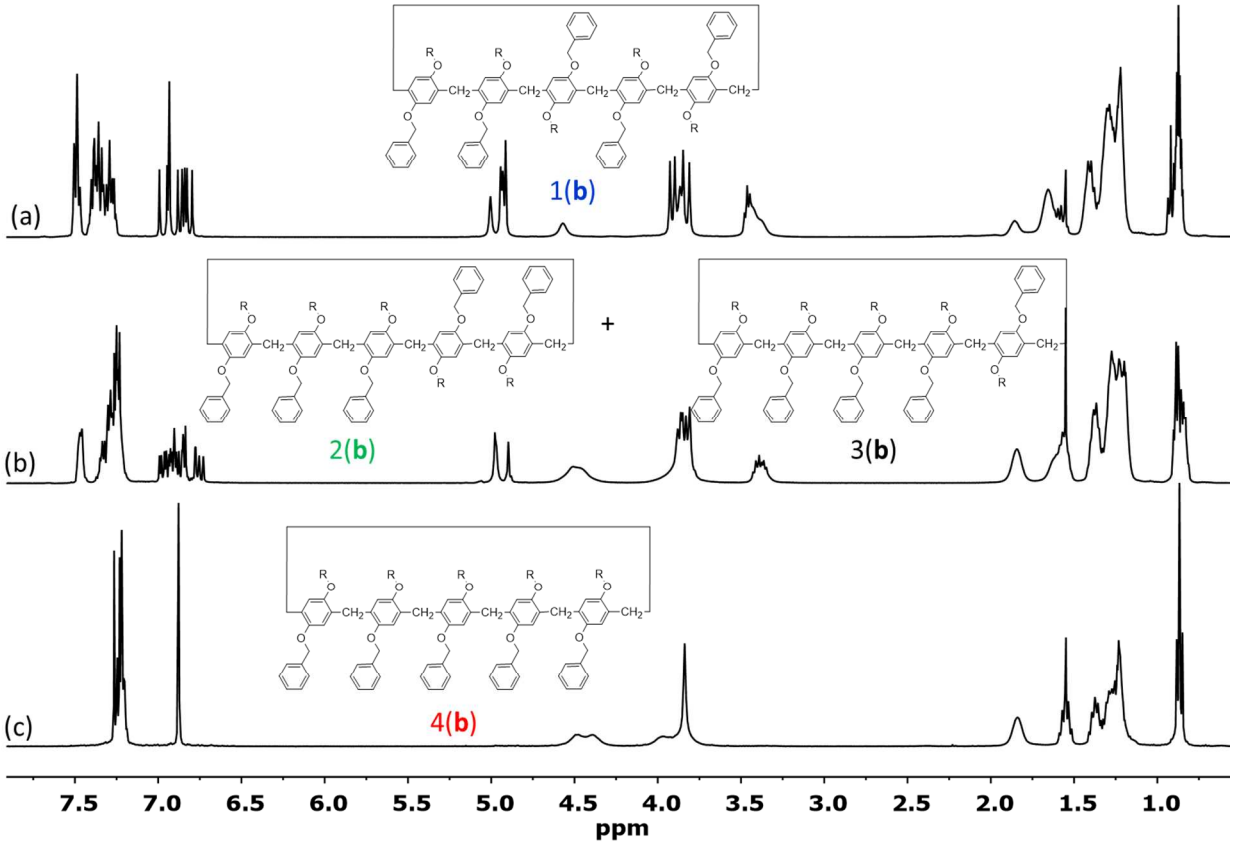


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_3$) and corresponding structures for the compounds present in the three fractions obtained following separation of the isomeric mixture by column chromatography. (a) The first fraction, isomer **1b**, (b) the second fraction, isomers **2b and 3b**, and (c) the third fraction, isomer **4b**.

Further examination of the second (mixed) fraction by ESI-MS confirmed the presence of a peak at *m/z* 1644.2 $[M+Na]^{+}$, which was also observed for the other two fractions. However, upon

closer inspection of the aromatic region of the ^{1}H NMR spectrum (i.e., 6.70–7.1 ppm) shown in Figure 2(b), a significantly higher multiplicity was observed compared to that of isomer **1b**, thereby indicating that the second fraction is a mixture of two isomers, namely **Pillars 2b** and **3b** (Figure S27).

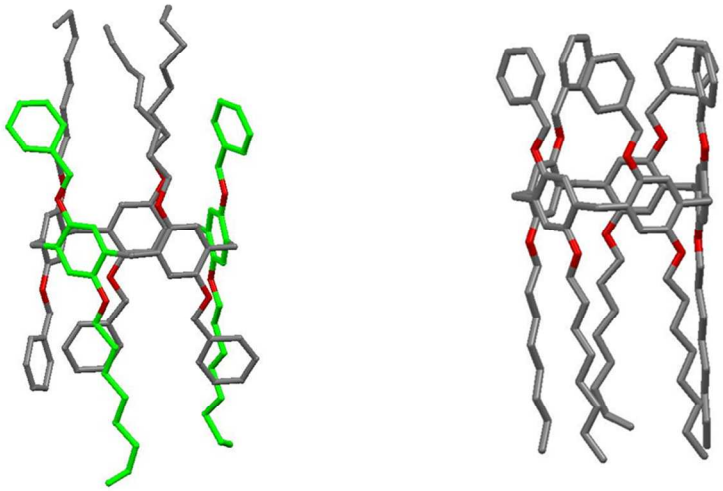


Figure 3. Crystal structures of the 1,3-alternate isomer (**Pillar 1b**) and the cone isomer (**Pillar 4b**) obtained from single crystal X-ray diffraction analysis.

The constitutional isomers of the asymmetrical pillar[5]arenes were then examined by HPLC, and their isomeric yield distribution was compared to the theoretical prediction of 5:5:5:1.[40] Due to small differences between the retention factors (R_f values) of the different constitutional isomers, the estimation of their distribution following separation by column chromatography is rather difficult. Control experiments were therefore conducted using both monomers (i.e., 1-(benzyloxy)-4-methoxybenzene and 1-(benzyloxy)-4-(octyloxy)benzene), and the crude reaction mixtures were passed through silica gel plugs and eluted with dichloromethane prior to HPLC analysis. For the asymmetrical pillar[5]arenes prepared using the 1-(benzyloxy)-4-

methoxybenzene monomer, the yield distribution obtained from HPLC analysis of the crude reaction mixture was in agreement with the theoretical yield distribution for the **Pillar 1a**, **2a**, **3a**, and **4a** isomers (Figure 4(a)). This peak assignment was based on a comparison with the retention times of the pure isomers (Figures S29 and S30). In contrast, HPLC analysis of the crude isomeric mixture obtained for the pillar[5]arenes prepared using 1-(benzyloxy)-4-(octyloxy)benzene produced three signals with an isomeric distribution of 2:4:1, which corresponded to the **Pillar 1b**, **2b+3b**, and **4b** isomers, respectively (Figure 4(b)). This result differs significantly from the predicted theoretical yield distribution, likely due to the isomeric distribution being dependent on the nature of the substituents present on the pillar[5]arene frame.[40]

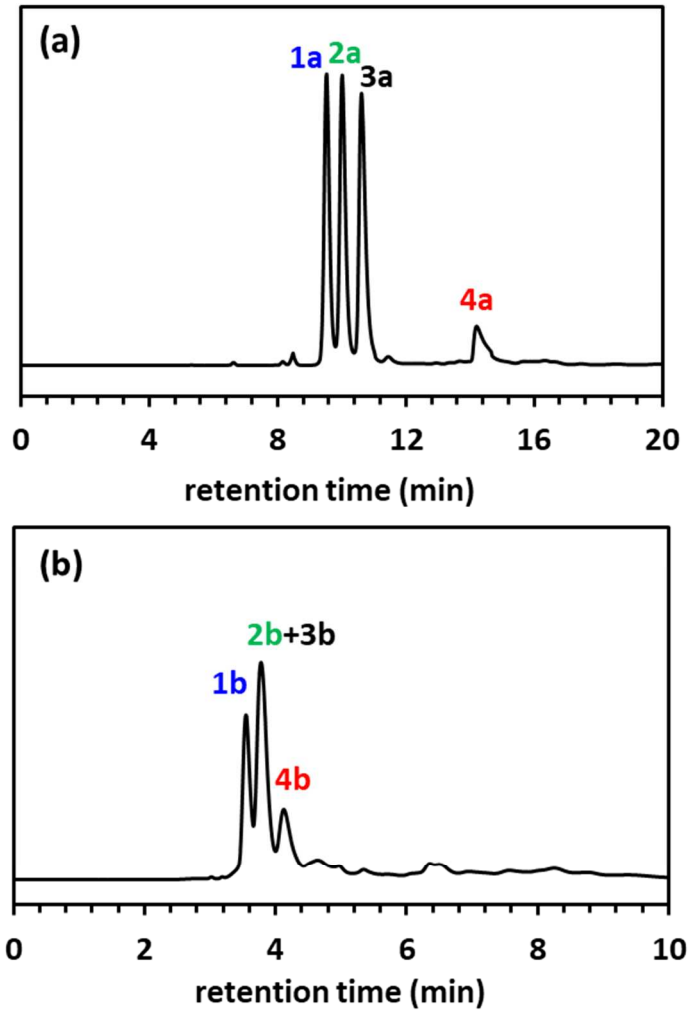


Figure 4. HPLC chromatograms for the crude reaction mixtures of the asymmetric pillar[5]arenes synthesized from (a) 1-(benzyloxy)-4-methoxybenzene, and (b) 1-(benzyloxy)-4-(octyloxy)benzene.

The isolated constitutional isomers were then subjected to catalytic hydrogenation over palladium on charcoal in anhydrous ethyl acetate under mild reaction conditions to conduct the debenzylation reaction and produce the corresponding pentahydroxy-functionalized pillar[5]arenes isomers. All products were isolated in quantitative yields as white solids (Scheme 1). In the ^{1}H NMR spectra ($CDCl_3$) of isomers **Pillar 1a′–4a′**, the absence of resonances

corresponding to the benzylic methylene protons (i.e., Ph-C$\underline{H}_2$) at 4.50–4.90 ppm and the phenyl groups (Ph) at 7.20–7.40 ppm indicated successful removal of the benzyl groups. A broad resonance centered at 8.40 ppm was also indicative of the newly formed free phenolic hydroxy groups (i.e., ArOH). In addition, the methoxy protons (OC$\underline{H}_3$) and the methylene bridge protons (-C$\underline{H}_2$-) were observed at 4.25 and 1.20 ppm, respectively. Furthermore, in the ^{13}C NMR spectra, the resonances corresponding to the aromatic carbon atoms of the benzyl groups at ~128 ppm were greatly reduced in intensity, while the absence of the benzylic methylene signal at ~70 ppm confirmed the successful deprotection. Similar results were observed when isomers **Pillar 1b** and **4b** were subjected to the catalytic hydrogenation protocol. However, even following the successful removal of the benzyl groups for the isomeric mixture of **Pillars 2b+3b**, separation of the individual isomers by column chromatography remained problematic. Furthermore, only three single crystals suitable for analysis by X-ray diffraction were obtained: **Pillars 1a′**, **2a′**, and **1b′** (Figure 5). Crystals of **1a′** and **1b′** were grown by slow evaporation of solutions of the individual isomers in mixtures of ethyl acetate/*n*-hexane, while single crystals of **2a′** were obtained by slow evaporation from a solution of the isomer in ethanol.

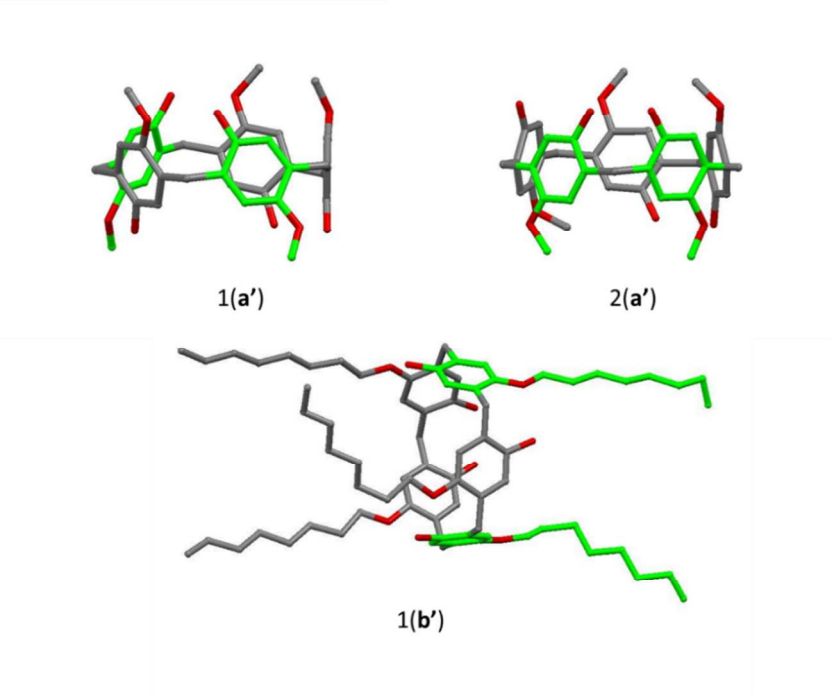


Figure 5. Crystal structures of three pentahydroxy-functionalized pillar[5]arene isomers, namely the 1,3-alternate isomer **Pillar 1a′**, the 1,2-alternate isomer **Pillar 2a′**, and the 1,3-alternate isomer **Pillar 1b′**.

We also found that the crystal packing of **2a′** is particularly unique, in that the unit cell is relatively large, and contains six ethanol molecules and six pillar[5]arene moieties (Figure S32). The four pillar[5]arene moieties containing ethanol encapsulated inside the cavity form two dimeric head-to-head assemblies induced by hydrogen-bonding interactions. In addition, two empty pillar[5]arene moieties are aligned perpendicularly to the supramolecular dimer in the crystal lattice. This dimer is hydrogen bonded to a free pillar[5]arene unit, and the presence of an ethanol molecule outside the cavity results in the formation of an interesting supramolecular assembly, which is depicted in Figure 6.

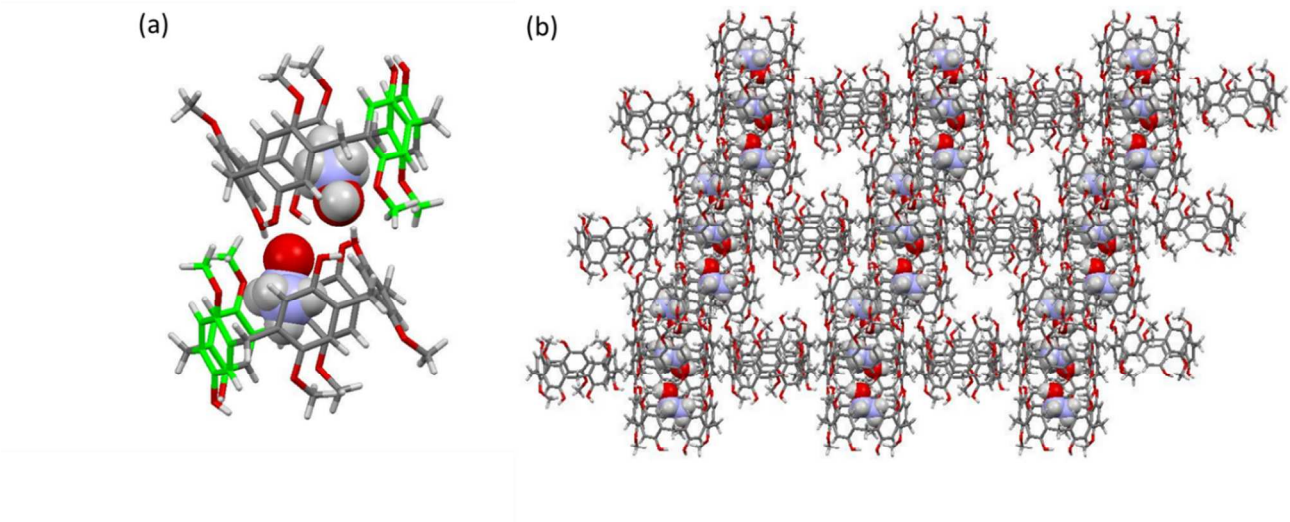


Figure 6. X-ray single crystal structure of the macrocyclic **Pillar 2a′** arrangement. (a) The supramolecular dimeric head-to-head assembly induced by hydrogen bonding, where ethanol is trapped inside the cavity, and (b) the supramolecular network crystal packing viewed along the crystallographic *b*-axis.

The crystal structure of the 1,3-alternate isomer **Pillar 1b′** adopts the form of a supramolecular double-threaded dimer where one of the octyl chains is threaded inside the cavity of the adjacent pillar[5]arene unit (Figure 7). In this case, dimer formation is induced by C-H···π interactions between the octyl chain and the host. Indeed, similar pillar[5]arene supramolecular dimers have been reported in the solid state for copillar[5]arenes based on 1,4-dimethoxybenzene and 1-((10-bromodecyl)oxy)-4-methoxybenzene.[41]

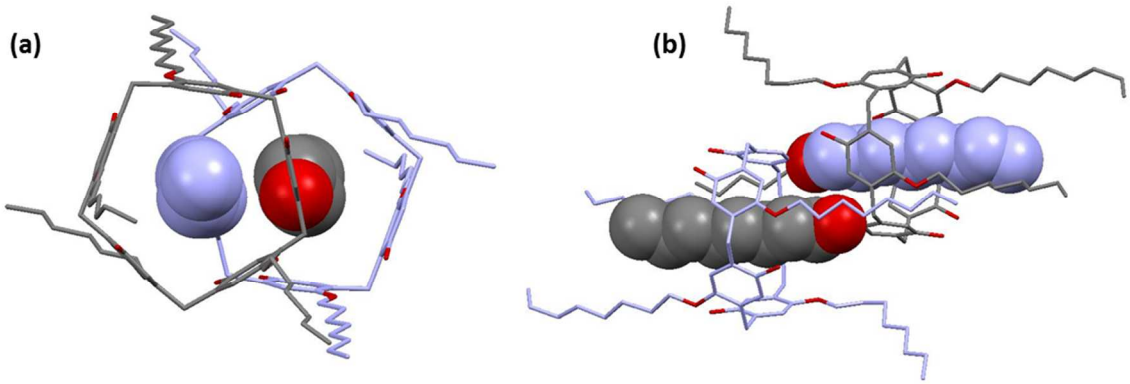


Figure 7. Supramolecular double-threaded dimer of the 1,3-alternate isomer **Pillar 1b′.** (a) The top view, and (b) the side view.

Conclusion

In conclusion, a series of pentahydroxy-functionalized pillar[5]arenes were synthesized through the simple benzylic deprotection of their corresponding asymmetric pillar[5]arenes, which were prepared from hydroquinone derivatives of 1-(benzyloxy)-4-alkoxybenzenes. A catalytic hydrogenation method was employed for the deprotection, which required only mild reaction conditions. Separation of the four constitutional asymmetric pillar[5]arene isomers by column chromatography was attempted, and its success was found to be dependent on the nature of the alkyl substitution, which also influenced the theoretical yield distribution of the constitutional isomers. HPLC analysis of the crude pillararene mixture prepared from 1-(benzyloxy)-4-methoxybenzene confirmed that the product distribution corresponded with the theoretical yield distribution, while the crude mixture prepared from 1-(benzyloxy)-4-(octyloxy)benzene produced a significantly different pattern due to the different alkyl substituents present and also because of the unsuccessful separation of two of the isomers. Characterization of the prepared

and isolated constitutional isomers revealed that they exhibited different melting points, NMR spectra, crystal structures, and stacking patterns in the solid state. Our future work will focus on the modification and application of the synthesized pentahydroxy-functionalized amphiphilic pillar[5]arenes.

Experimental section

Materials and methods

NMR spectroscopy was carried out by on Bruker Avance II 600 MHz and Bruker Avance DPX 400 spectrometers (Bruker, Germany). Electron impact (EI) mass spectrometry was performed using a DFS High Resolution GC/MS (Thermo Scientific, Germany). Electrospray ionization was carried out in high resolution mode using a Waters Xevo G2-S QTOF LC-MS/MS (Waters, Germany). As detailed later, single crystal X-ray diffraction was carried out using an R-AXIS RAPID II diffractometer (Rigaku, Japan), and the data were collected at −123 °C (Oxford Cryosystems, UK). LC was carried out using an instrument equipped with a photodiode array detector (LC-MS/MS, Thermo Scientific, Germany). Flash column chromatography was performed using silica gel (silica gel 60, 40–60 mesh ASTM, EMD Millipore, Merck KGaA, Germany). Dimethylformamide, dichloroethane, and ethyl acetate were employed in the hydrogenation reaction and were distilled prior to use. All other reagents and solvents were of reagent grade purity and were used without further purification. HPLC was carried out using a Waters HPLC system equipped with a 1525 binary pump, a 2487 dual absorbance detector, a 717 plus autosampler, and Breeze software (Waters, German). **Pillars 1a–4a** were separated using a Waters Spherisorb® 5 μm NH_2 column using hexane:chloroform (85:15 v/v) as the eluent, with a run time of 20 min and a flow rate of 1 mL/min. **Pillars 1b–4b** were separated using a Supelco

Astec Cellulose DMP column (5 μm) using hexane:isopropanol (99:1 v/v) as the eluent, with a run time of 10 min and a flow rate of 1 mL/min.

1-(Benzyloxy)-4-methoxybenzene: 4-Methoxyphenol (4.96 g, 40 mmol) was dissolved in acetone (100 mL) at room temperature, and potassium carbonate (8.28 g, 60 mmol) was added with stirring. The resulting solution was stirred for ~30 min then heated to reflux prior to the addition of benzyl bromide (4.76 mL, 40 mmol). The reaction was allowed to stir under reflux overnight, after which time the solvent was removed by evaporation under reduced pressure and the crude product was extracted with dichloromethane. Purification was by column chromatography using dichloromethane/*n*-hexane (60:40 v/v) to give the desired product as a white solid (7.80 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (s, 3H), 5.04 (s, 2H), 6.90 (m, 4H), 7.35 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 55.7, 70.7, 114.7, 115.9, 127.5, 127.9, 128.6, 137.3, 153.0, 154.0.

4-(Octyloxy)phenol: Hydroquinone (6.60 g, 60 mmol) was dissolved in acetone (120 mL) at room temperature, and potassium carbonate (12.42 g, 90 mmol) was added. The resulting solution was heated under reflux overnight following the addition of bromooctane (10.36 mL, 40 mmol). After this time, the solvent was removed by evaporation under reduced pressure and the crude product was extracted with dichloromethane. The obtained 4-(octyloxy)phenol was then purified by column chromatography using dichloromethane/*n*-hexane (80:20 v/v) to give the desired product as a white solid (9.45 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3H, J = 6.8 Hz), 1.33 (m, 8H), 1.45 (m, 2H), 1.77 (m, 2H), 3.92 (t, 2H, J = 6.8 Hz), 6.79 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.0, 29.2, 29.4, 31.8, 68.7, 115.6, 116.0, 149.3, 153.3.

1-(Benzyloxy)-4-(octyloxy)benzene: 4-(Octyloxy)phenol (8.9 g, 40 mmol) was dissolved in acetone (100 mL) at room temperature, and potassium carbonate (8.28 g, 60 mmol) was added.

After stirring the resulting solution for ~30 min, it was heated to reflux prior to the addition of benzyl bromide (4.76 mL, 40 mmol). The reaction system was then stirred under reflux overnight. After this time, the reaction solvent was removed by evaporation under reduced pressure and the crude product was extracted with dichloromethane. Purification was by column chromatography using dichloromethane/*n*-hexane (40:60 v/v) to give the desired product as a white solid (10.35 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, 3H, J = 7.2 Hz), 1.33 (m, 8H), 1.46 (m, 2H), 1.78 (m, 2H), 3.92 (t, 2H, J = 6.4 Hz), 5.04 (s, 2H), 6.88 (m, 4H), 7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.1, 29.2, 29.4, 31.8, 68.6, 70.1, 115.4, 115.8, 127.5, 127.8, 128.5, 137.3, 152.8, 153.5.

Synthesis of the asymmetric benzoxymethoxypillar[5]arenes 1a–4a. Paraformaldehyde (1.86 g, 60.0 mmol) was added to a solution of 1-(benzyloxy)-4-methoxybenzene (4.28 g, 20.0 mmol) in dry dichloroethane (40 mL) under a nitrogen atmosphere. Boron trifluoride etherate [(BF_3·OEt_2), 2.5 mL, 20.0 mmol] was then added to the solution and the mixture was stirred at room temperature for 30 min. After this time, methanol (50 mL) was poured into the reaction mixture and the solution was concentrated then dissolved in dichloromethane (100 mL). The resulting organic solution was washed with aqueous $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), then dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and subjected to purification by silica gel chromatography (dichloromethane/hexanes (60:40 v/v)) to give a mixture of isomers **1a–4a** (0.490 g, 10%).

Isomer 1a: White solid (175 mg, 4%). Mp. 157-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.24 (s, 3H), 3.27 (s, 3H), 3.28 (s, 3H), 3.32 (s, 3H), 3.65 (s, 3H), 3.73 (s, 2H), 3.76 (s, 2H), 3.83 (s, 2H), 3.87 (d, 4H, J = 4.4 Hz), 4.53 (s, 2H), 4.84 (s, 4H), 4.86 (s, 2H), 4.91 (s, 2H), 6.76 (m, 10H), 7.31 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.7, 28.9, 30.1, 30.7, 31.0, 55.4, 55.9, 69.9,

70.4, 70.5, 114.2, 114.4, 114.5, 114.8, 114.9, 115.1, 127.5, 127.6, 127.6, 127.6, 127.8, 127.9, 128.0, 128.1, 128.1, 128.2, 128.4, 128.6, 128.6, 138.2, 138.2, 138.3, 149.9, 150.1, 150.1, 150.2, 150.2, 150.7, 150.8, 150.8. HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ Calcd for $C_{75}H_{70}O_{10}Na$ 1153.4867; Found 1153.4923.

Isomer 2a: White solid (120 mg, 3%). Mp. 129-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.29 (d, 6H, *J* = 8.4 Hz), 3.63 (s, 6H, *J* = 8.0 Hz), 3.71 (s, 3H), 3.81 (m, 10H), 4.46 (s, 2H), 4.52 (d, 4H, *J* = 2.4 Hz), 4.94 (d, 4H, *J* = 7.6 Hz), 6.72 (s, 2H), 6.80 (m, 3H), 8.88 (m, 5H), 7.25 (m, 20H), 7.39 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.1, 29.4, 29.8, 29.9, 30.1, 31.1, 55.4, 55.8, 55.8, 55.9, 69.8, 69.8, 69.9, 70.3, 70.3, 113.9, 114.1, 114.2, 114.9, 115.0, 115.1, 127.4, 127.4, 127.4, 127.5, 127.6, 127.6, 127.6, 127.7, 127.7, 127.8, 128.0, 128.1, 128.1, 128.2, 128.2, 128.4, 128.5, 128.5, 128.6, 128.6, 128.6, 138.2, 138.3, 138.3, 149.8, 149.8, 149.8, 150.0, 150.0, 150.8, 150.8, 150.9, 150.9, 151.0. HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ Calcd for $C_{75}H_{70}O_{10}Na$ 1153.4867; Found 1153.4910.

Isomer 3a: White solid (140 mg, 3%). Mp. 117-118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.24 (s, 3H), 3.32 (s, 3H), 3.63 (s, 3H), 3.71 (s, 3H), 3.73 (s, 3H), 3.76 (s, 2H), 3.81 (s, 2H), 3.87 (m, 6H), 4.45 (s, 2H), 4.50 (s, 2H), 4.55 (s, 2H), 4.88 (s, 2H), 4.94 (s, 2H), 6.70 (s, 1H), 6.81 (m, 5H), 6.87 (m, 4H), 7.28 (m, 21H), 7.37 (m, 2H), 7.44 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.7, 29.4, 29.5, 29.7, 30.0, 30.4, 55.2, 55.6, 55.7, 69.7, 70.2, 113.9, 114.0, 114.1, 114.2, 114.6, 114.7, 114.8, 114.9, 127.2, 127.3, 127.4, 127.5, 127,5, 127.5, 127.7, 127.8, 128.0, 128.2, 128.2, 128.3, 128.3, 128.4, 128.4, 128.4, 138.0, 138.0, 138.0, 138.1, 138.1, 149.7, 149.7, 149.7, 149.8, 149.9, 150.6, 150.7, 150.8, 150.9. HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ Calcd for $C_{75}H_{70}O_{10}Na$ 1153.4867; Found 1153.4918.

Isomer 4a: White solid (55 mg, 1%). Mp. 114-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (s, 15H), 3.84 (s, 10H), 4.47 (s, 10H), 6.80 (s, 5H), 6.87 (s, 5H), 7.23 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 29.8, 55.9, 69.8, 114.2, 115.0, 127.4, 127.6, 127.7, 128.3, 128.5, 138.2, 149.9, 151.0. HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ Calcd for $C_{75}H_{70}O_{10}Na$ 1153.4867; Found 1153.4924.

Synthesis of the asymmetric benzyloxyoctyloxypillar[5]arenes 1b–4b. Paraformaldehyde (1.86 g, 60.0 mmol) was added to a solution of 1-(benzyloxy)-4-(octyloxy)benzene (6.24 g, 20.0 mmol) in dry dichloroethane (50 mL) under a nitrogen atmosphere. $BF_3{\cdot}OEt_2$ (2.5 mL, 20.0 mmol) was then added to the solution and the mixture was stirred at room temperature for 30 min. After this time, MeOH (50 mL) was poured into the reaction mixture and the solution was concentrated then dissolved in dichloromethane (100 mL) prior to washing with aqueous $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL). The resulting organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and subjected to purification by silica gel column chromatography (hexanes/dichloromethane, 80:20) to give a mixture of isomers **1b–4b** (507 mg, 16%).

Isomer 1b: Yield (145 mg, 4%). Mp. 117-118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.94 (m, 15H), 1.25 (m, 40H), 1.38 (m, 10H), 1.55 (m, 8H), 1.86 (m, 2H), 3.46 (m, 8H), 3.87 (m, 12H), 4.57 (s, 2H), 4.93 (m, 6H), 5.01 (s, 2H), 6.89 (m, 10H), 7.28 (m, 17H), 7.34 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 14.3, 14.3, 22.8, 22.9. 26.5, 26.5, 26.5, 26.6, 28.6, 28.8, 29.5, 29.7, 29.8, 29.8, 30.0, 30.0, 30.0, 30.1, 30.4, 30.8, 32.0, 32.0 67.9, 67.9, 68.0, 68.5, 69.6, 70.2, 70.2, 70.3,70.3, 114.6, 114.7, 114.7, 114.8, 114.9, 115.1, 115.2, 127.4, 127.5, 127.6, 127.6, 127.7, 127.7, 127.8. 128.0, 128.1, 128.2, 128.3. 128.5, 128.5, 128.6, 128.6, 128.7, 138.3, 138.3, 149.6,

149.7, 149.8, 149.8, 150.1, 150.1. HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ Calcd for $C_{110}H_{140}O_{10}Na$ 1644.0344; Found 1644.0388.

Isomers 2b and 3b: Yield (305 mg, 4%). ^1H NMR (400 MHz, $CDCl_3$) δ: 0.88 (m, 15H), 1.23 (m, 46H), 1.56 (m, 8H), 1.84 (m, 6H), 3.39 (m, 4H), 3.84 (m, 16H), 4.51 (m, 6H), 4.89 (m, 4H), 6.86 (m, 10H), 7.27 (m, 25H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 14.3, 14.3, 22.8, 22.8, 22.9, 22.9, 26.4, 26.5, 26.6, 26.6, 26.7, 29.4, 29.5, 29.5, 29.7, 29.8, 29.8, 29.9, 30.0, 30.0, 30.1, 30.2, 32.0, 32.0, 67.8, 67.9, 68.0, 68.5, 68.5, 69.5, 69.5, 69.6, 70.0,70.0, 70.1, 70.1, 114.6, 114.7, 114.8, 114.9. 115.0, 115.1, 127.2, 127.3, 127.3, 127.3, 127.4, 127.4, 127.5, 127.5, 127.7, 127.8, 128.0, 128.0, 128.1, 128.1, 128.1, 128.2, 128.2, 128.2, 128.3, 128.4, 128.4, 128.5, 128.5, 128.6, 128.7, 128.7, 128.8, 138.3, 138.3, 138.3, 149.5, 149.5, 149.6, 149.6, 149.7, 149.7, 149.8, 150.0, 150.1, 150.1, 150.2, 150.2, 150.2. ESI-MS: *m/z*: 1644.2 ($C_{110}H_{140}O_{10}Na$).

Isomer 4b: Yield (60 mg, 4%). Mp. 160-161 °C. ^1H NMR (400 MHz, DMSO-d_6) δ: 0.88 (m, 15H), 1.33 (m, 40H), 1.47 (m, 10H), 1.74 (m, 10H), 3.52 (m, 10H), 3.91 (m, 6H), 4.13 (m, 4H), 6.62 (s, 5H), 6.79 (s, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 10.8, 13.8, 13.9, 22.2, 22.4, 23.3, 25.9, 28.4, 28.9, 29.3, 29.6, 29.8,32.0, 33.2, 38.1, 67.4, 67.5, 113.5, 114.6, 115.2, 117.6, 126.0, 127.8, 128.7, 131.6, 131.7, 138.8, 147.2, 148.2, 167.0. HRMS (ESI/QTOF) *m/z*: $[M + Na]^+$ Calcd for $C_{110}H_{140}O_{10}Na$ 1644.0344; Found 1644.0375.

General debenzylation procedure. Isomers **1–4(a–b)** (40 mg, 0.42 mmol) were dissolved in anhydrous ethyl acetate (30 mL) to which Pd/C (25 wt%) (10 mg) was added. The reaction apparatus for the catalytic hydrogenation process was evacuated then filled with H_2. Following absorption of the theoretical quantity of hydrogen by the isomers, the Pd/C catalyst was removed by filtration, then carefully washed with ethyl acetate and methanol. The combined filtrate was subsequently evaporated to yield the deprotected pillar[5]arene isomers as white solids in

quantitative yields. Finally, the isomers were dried to constant weight under reduced pressure, and dissolved in a suitable deuterated solvent for NMR analysis.

Isomer 1a′: Yield (28 mg, 97%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.79 (m, 22H), 3.90 (s, 3H), 6.63 (m, 3H), 6.70 (s, 1H), 6.80 (s, 2H), 6.83 (s, 1H), 6.85 (s, 1H), 6.87 (s, 1H), 6.92 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.9, 27.2, 30.3, 31.7, 31.8, 56.3, 56.6, 56.8, 56.8, 59.5, 113.4, 113.6, 113.7, 114.0, 117.4, 118.0, 118.1, 118.3, 118.5, 119.2. HRMS (ESI/QTOF) *m/z*: $[M]^+$ Calcd for $C_{40}H_{39}O_{10}$ 679.2543; Found 679.2537.

Isomer 2a′: Yield (27 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.72 (m, 19H), 3.93 (d, 6H, J = 11.2 Hz), 6.53 (s, 1H), 6.56 (s, 1H), 6.67 (m, 6H), 6.78 (s, 1H), 6.80 (s, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 27.2, 30.7, 30.7, 30.8, 31.6, 56.2, 56.3, 56.7, 56.9, 56.9, 112.8, 112.8, 113.2, 113.7, 115.6, 118.7, 118.8, 119.0, 119.1, 119.4, 124.9, 125.1, 126.2, 126.4, 126.5, 128.4, 128.5, 128.9, 130.8, 131.0, 147.1, 147.2, 147.2, 147.5, 148.4, 148.8, 149.1, 149.1, 150.7, 150.8. HRMS (ESI/QTOF) *m/z*: $[M]^+$ Calcd for $C_{40}H_{39}O_{10}$ 679.2543; Found 679.2540.

Isomer 3a′ Yield (26 mg, 90%).: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.71 (m, 20H), 3.86 (s, 5H), 6.55 (m, 3H), 6.62 (s, 1H), 6.72 (m, 3H), 6.76 (s, 1H), 6.79 (s, 1H), 6.82 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 28.0, 28.4, 28.9, 29.1, 29.3, 30.6, 30.8, 31.5, 32.0, 33.0, 34.3, 38.9, 56.2, 56.6, 56.8, 57.0, 112.8, 113.1, 113.5, 113.7, 118.3, 118.6, 119.1, 119.2, 119.3, 125.4, 126.2, 126.9, 127.9, 128.1, 128.6, 130.0, 130.4, 131.1, 144.9, 147.5, 148.2, 148.4, 148.6, 149.0, 150.9. HRMS (ESI/QTOF) *m/z*: $[M]^+$ Calcd for $C_{40}H_{39}O_{10}$ 679.2543; Found 679.2533.

Isomer 4a′ Yield (25 mg, 86%).: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (s, 10H), 3.876 (s, 15H), 6.66 (s, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 30.5, 56.6, 113.4, 118.7, 126.6, 128.0, 148.4, 148.7. HRMS (ESI/QTOF) *m/z*: $[M]^+$ Calcd for $C_{40}H_{39}O_{10}$ 679.2543; Found 679.2529.

Isomer 1b′: Yield (27 mg, 93%). ^{1}H NMR (600 MHz, Acetone-d_6) δ: 0.91 (m, 15H), 1.30 (m, 40H), 1.47 (m, 10H), 1.83 (m, 10H), 3.70 (s, 10H), 3.86 (s, 10H), 6.91 (m, 10H). ^{13}C NMR (150 MHz, Acetone-d_6) δ: 14.1, 14.2, 23.1, 26.7, 26.8, 31.4, 32.4, 32.4, 68.8, 69.3, 113.9, 114.9, 118.8, 126.6, 126.9, 129.7, 146.9, 147.8, 150.2, 150.7. HRMS (ESI/QTOF) *m/z*: $[M]^+$ Calcd for $C_{75}H_{109}O_{10}$ 1169.8021; Found 1169.8063.

Isomer 4b′: Yield (24 mg, 83%) ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.88 (m, 15H), 1.33 (m, 40H), 1.47 (m,10H), 1.74 (m, 10H), 3.52 (m, 10H), 3.91 (m, 6H), 4.13 (m, 4H), 6.62 (s, 5H), 6.79 (s, 5H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 10.8, 13.8, 13.9, 22.2, 22.4, 23.3, 25.9, 28.4, 28.9, 29.3, 29.6, 29.8,32.0, 33.2, 38.1, 67.4, 67.5, 113.5, 114.6, 115.2, 117.6, 126.0, 127.8, 128.7, 131.6, 131.7, 138.8, 147.2, 148.2, 167.0. HRMS (ESI/QTOF) *m/z*: $[M]^+$ Calcd for $C_{75}H_{109}O_{10}$ 1169.8021; Found 1169.8075.

Preparation of single crystals for X-ray diffraction

Single crystals of the synthesized pillar[5]arenes and their inclusion complexes were grown using either the slow solvent evaporation method or by the diffusion method using dichloromethane and *n*-hexane. The data were collected on an R-AXIS RAPID diffractometer (Rigaku, Japan) at −123 °C using the Crystal Clear software package (Rigaku, Japan). All structures were solved and refined using the Bruker SHELXTL Software Package (structure solution program: SHELXS-97; refinement program: SHELXL-97). The crystallographic data for all structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publications (CCDC 1552627-1552637). Copies of the data can be obtained, free of charge, upon submission of application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supporting Information. Crystallographic information (CIF), HPLC traces, ^{1}H and ^{13}C NMR spectra for new compounds. This material is available free of charge at http://pubs.acs.org.

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