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Calix[4]- and Calix[5]arene-Based Multicavity Macrocycles

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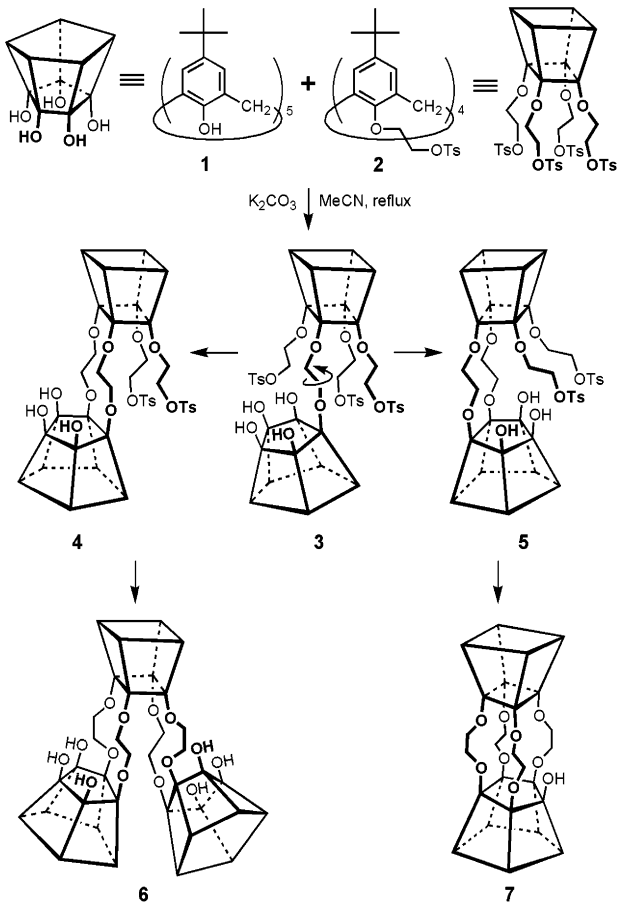
Abstract: Synthesis and single-crystal X-ray structures of mixed triple and double calixarenes **6** and **7**, obtained from the base-catalyzed condensation of calix[5]arene **1** with cone pertosylated calix[4]arene **2**, are reported. VT-NMR studies on **7** are consistent with a molecular motion arising from the *anti*−*gauche* conformational interconversion of its ethylene linkages.

The covalent assembly of two or more calixarene subunits is a useful approach to tailor multicavity supramolecular receptors displaying intriguing geometries and molecular recognition abilities, that are absent in the single-cavity molecular frameworks of their precursors.[1] During the past decade, a variety of relatively rigid double calixarenes, consisting of two calixarene subunits connected by at least two intermolecular bridges in a head-to-head, tail-to-tail, or head-to-tail arrangement, have been described. On the other hand, much less is known about more complex multicalixarenes with homo- and/or heterocavities.[2]

As part of our continuing studies on the design and synthesis of new polytopic receptor molecules based on calix[5]arenes,[3] we report here the synthesis and structural features of the first triple calixarene **6** with heterocavities, together with the full characterization of the tubular double calixarene side-product **7**.[4] Both macrocycles consist of a central calix[4]arene frame linked via four ethylene bridges to either two or one calix[5]arene subunit(s).

SCHEME 1



The condensation of *p-tert*-butylcalix[5]arene (**1**) with tetrakis[2-(tosyloxy)ethoxy]-*p-tert*-butylcalix[4]arene (**2**) (0.5 equiv) in the presence of K_2CO_3 (excess) in MeCN (reflux, 5 d) produces, after chromatographic purification, the two mixed calixarenes **6** and **7** in 65 and 7% yield, respectively (Scheme 1).

Interestingly, the formation of **6** is still favored even with a deficiency of **1**. By changing the molar ratio of **1** and **2** from 2:1 to 1:1, the reaction affords, under the same experimental conditions, an *invariant* amount (6−8%) of the side-product **7** along with **6** (30% yield) and a substantial quantity (20%) of its likely precursor **4**. These results imply that the final product composition is probably determined in the second alkylation step (18-membered ring closure leading from **3** to a mixture of the intermediate **4** and the transient diastereomeric species **5**) and is therefore sterically driven rather than controlled by a templating effect from K^+ ions. Potassium, however, seems to be the ion of choice for promoting the covalent assembly of calixarenes of different sizes, since a number of attempts to increase the yield of **7** by using bases of different nature and strength (NaH in THF or Cs_2CO_3 in MeCN) led to unidentified high molecular weight oligomers.

The ^{1}H NMR spectrum of **6** is consistent with the presence of two orthogonal planes bisecting the two pairs of opposite methylene groups of the calix[4]arene unit,

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(1) For a recent general survey on calixarenes, see: Gutsche, C. D. In *Calixarenes Revisited*; Monographs in Supramolecular Chemistry, Vol. 6; Stoddart, J. F., Ed.; RSC: Cambridge, U.K., 1998.
(2) Wang, J.; Gutsche, C. D. *J. Org. Chem.* **2002**, *67*, 4423. For a comprehensive review on double and multi-calixarenes, see: Saadioui, M.; Böhmer, V. In *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001; chapter 7, p 130.
(3) Notti, A.; Parisi, M. F.; Pappalardo, S. In *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; Kluwer: Dordrecht, The Netherlands, 2001; chapter 3, p 54.
(4) To the best of our knowledge, the only example of this family is a calix[4]/calix[8]arene derivative: Arduini, A.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1995**, 879.

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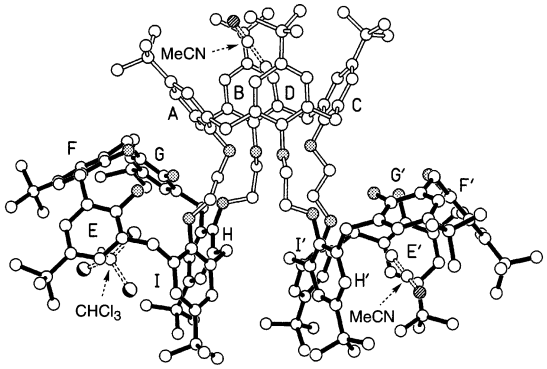

FIGURE 1. The crystal structure of **6** and the location of the bound MeCN and $CHCl_3$ guests (the MeCN molecule weakly bound to ring G has been omitted for clarity). The respective inclinations of rings E−I and E′−I′ to their reference planes are 58, 63, 32, 82, 42, and 84, 71, 36, 85, 39°.

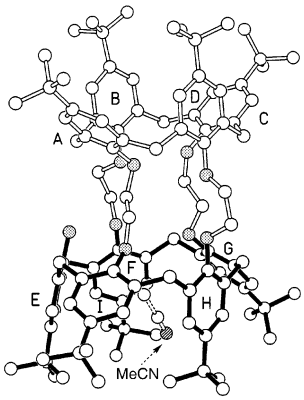

FIGURE 2. The nanotube-like geometry adopted by **7** in the solid state, and the location of the bound MeCN in the calix[5]arene cavity.

internal or external to the two newly formed 18-membered rings. The high field *t*-Bu region is characterized by a single resonance for the central calix[4]arene residue, and a set of three resonances in the ratio 2:1:2 for the two calix[5]arene moieties. The 3−5 ppm region, analyzed with the aid of a 2D-COSY spectrum, shows two AX systems (ratio 1:1) for the $ArCH_2Ar$ protons of the calix[4]arene unit and three AX systems (ratio 2:2:1) for those of the calix[5]arene units. The $\Delta\delta$ values for the geminal protons of the bridged methylenes are suggestive of a regular cone conformation for the calix[4]arene unit, and a flattened cone for the flanking calix[5]arene residues. The 1,2-interbridging of the two calix[5]arene moieties to the calix[4]arene core in **6** is corroborated by the expected resonance pattern for three contiguous OH groups (broad singlets at δ 7.76 and 8.08 ppm in C_6D_6, see Supporting Information).[5] The cone arrangement of the three cavities is further supported by the ^{13}C NMR spectrum of **6**, showing resonances for the $ArCH_2Ar$ groups in the range δ 29.0−31.2 ppm.[6]

Since these NMR data could not rule out an alternate diastereomeric form of **6** of the same symmetry, having six facing OH groups, a single-crystal X-ray analysis of **6** was undertaken. Crystals of the triple calixarene **6** were obtained by slow evaporation of a $CHCl_3$/MeCN solution. In the solid state the molecule is seen (Figure 1) to have approximate C_2 symmetry about an axis passing through the center of the calix[4]arene cavity. The calix[4]arene component of **6** is quite regular and approaches C_{4v} symmetry. The four linking methylene carbon atoms are coplanar to within 0.03 Å, and the phenyl rings A−D are inclined by 52, 74, 58, and 73°, respectively, to this plane. This moiety is linked to two calix[5]arene units by four ethylene bridges, which adopt cyclically alternating anti and gauche conformations. By contrast, the two calix[5]-arene subunits are less symmetric (approximating C_s). Their five linking methylene carbon atoms are coplanar to only 0.50 and 0.64 Å, respectively, for the two units, and the phenyl rings are inclined by between 32 and 85° to these "reference" planes. Notably, in both calix[5]arene units, two of the phenyl rings (G, I and G′, I′) are appreciably less steeply inclined than the rest. The reference planes of the two calix[5]arene ring systems subtend an angle of 116° and are inclined by 43 and 22° to the calix[4]arene plane. They are also oriented so as to produce a propeller-like arrangement with respect to the molecular C_2 axis. All three calixarene rings have solvent molecules bound within their cavities. The calix-[4]- and both of the calix[5]arene rings have CH···π-bound MeCN molecules with H···π of 2.63, 2.92, and 2.66 Å to rings D, G, and E′ respectively. The calix[5]arene unit comprising rings E to I also hosts a second guest, namely a $CHCl_3$ molecule, which is both deeply embedded and attached by a very short CH···π interaction to ring E (H···π 2.47 Å, CH···π 160°). Both calix[5]arene rings have peripheral patterns of intramolecular OH···O hydrogen bonds.

Because of the current interest in tubular receptors (e.g. nanotubes[7] and (thia)calix[4]tubes[8]) as potential artificial channels for the transport of ions and molecules, X-ray studies were also extended to the mixed calix[4]-[5]tube[9] **7**. Crystals of **7** suitable for X-ray analysis were obtained by slow evaporation of a CH_2Cl_2/MeCN solution. The X-ray structure shows the molecule to have an extended nanotube-like geometry (Figure 2) with an overall molecular length of ca. 2 nm. Here the calix[4]-arene unit has molecular C_{2v} symmetry, and the aryl rings A, B, C, and D are inclined by 43, 84, 39, and 85° respectively to the plane of the four methylene linkages (which are coplanar within 0.08 Å). In common with **6** the four ethylene chains connecting the two calixarene subunits of **7** have alternating gauche and anti geometries. The calix[5]arene residue is less symmetric (approximating C_s) having a conformation very similar to those seen in **6**. The five-membered ring formed by linking the bridging methylene carbon atoms has an envelope-like conformation and the aromatic rings, E−I,

(5) Kraft, D.; Arnecke, R.; Böhmer, V.; Vogt, W. *Tetrahedron* **1993**, *49*, 6019. Caccamese, S.; Notti, A.; Pappalardo, S.; Parisi, M. F.; Principato, G. *J. Inclusion Phenom. Mol. Recogn.* **2000**, *36*, 67.

(6) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372. Stewart, D. R.; Krawiec, M.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 586.

(7) Ikeda, A.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1994**, 2375. Pérez-Adelmar, J.-A.; Abraham, H.; Sánchez, C.; Rissanen, K.; Prados, P.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1009.

(8) (a) Schmitt, P.; Beer, P. D.; Drew, M. G. B.; Sheen, P. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1839. (b) Matthews, S. E.; Felix, V.; Drew, M. G. B.; Beer, P. D. *New J. Chem.* **2001**, *25*, 1355.

(9) The term "calixtube" has been introduced by Beer et al.[8a]

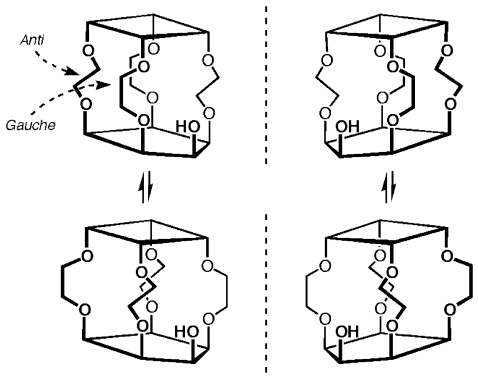

FIGURE 3. Schematic representation of the anti−gauche conformational interconversion of the ethylene chains in calix[4][5]tube **7**.

are tilted by 78, 65, 43, 86, and 40°, respectively, to the best plane through these five carbon atoms. Within the cavity of the calix[5]arene is located an acetonitrile molecule of crystallization, which although not totally ordered, is probably held in position by a combination of weak CH···π and CH···O interactions. The cavity of the calix[4]arene is empty.

The calix[4][5]tube **7** is less rigid than the previously reported centrosymmetric calix[4]tube.[8a] Dynamic NMR studies in the temperature range 233 to 393 K have shown that the ethylene bridges of **7** undergo an anti−gauche conformational interconversion (Figure 3), arising from a screwing/unscrewing motion along the axis passing through the center of the two cavities,[10] which is fast on the NMR time-scale at high temperatures and slow at low temperatures (Figure 4). At temperatures lower than 293 K ($CDCl_3$) only the C_1 conformation is present (nine well resolved singlets of equal intensity for the *t*-Bu groups, Figure 4a), while at 393 K in $C_2D_2Cl_4$ an averaged C_s symmetry (five resonance pattern for the *t*-Bu groups, Figure 4d) is observed through the fast exchange between the two enantiomeric structures shown in Figure 3.

We believe that compounds **6** and **7**, either as such or after derivatization of the residual hydroxy group(s), may act as potential hetero(poly)topic host molecules for a variety of guest species and/or as ion channels. In view of the well-known inclusion properties of single-cavity calix[5]arenes,[3,11] **6** and **7** are currently being tested as multisite hollow molecular modules. These species are of interest in supramolecular chemistry because of their potential for forming noncovalent assemblies by iterative inclusion processes with appropriate ditopic connectors.[12]

Experimental Section[13]

Condensation of 1 and 2. A warm solution of pertosylate **2** (0.72 g, 0.5 mmol) in MeCN (75 mL) was added dropwise, over 2 h, to a stirred suspension of **1** (0.81 g, 1 mmol) and K_2CO_3 (2.07 g, 15 mmol) in MeCN (100 mL). The reaction mixture was allowed to reflux for 5 d. The solvent was evaporated in vacuo,

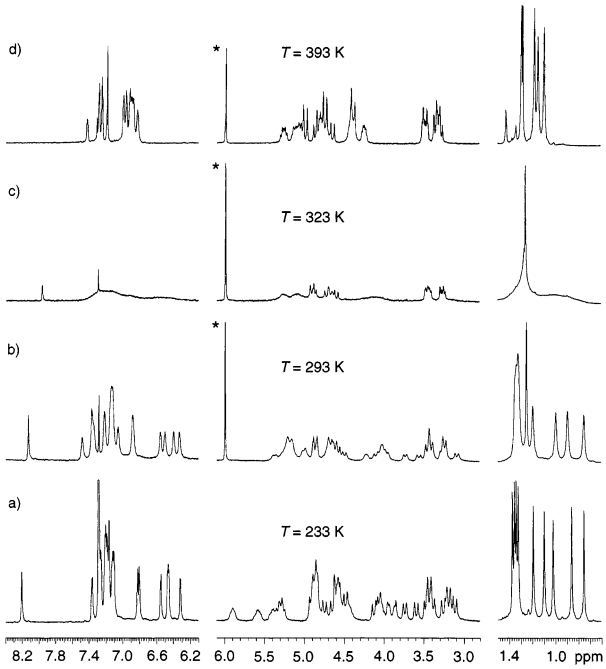

FIGURE 4. VT-NMR spectra (300 MHz) of calix[4][5]tube **7**. Trace (a) in $CDCl_3$ and traces (b−d) in $C_2D_2Cl_4$. Asterisk indicates residual solvent.

and the residue was partitioned between 1 N HCl and CH_2Cl_2 (3 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to give a solid. TLC analysis (petroleum ether−CH_2Cl_2 80/20, three consecutive elutions) showed the presence of three components, which were separated by column chromatography (CC) on silica gel. The column was eluted with a CH_2Cl_2 gradient (20 to 35%) in petroleum ether to give unreacted **1** (15%), followed by **7** (7%) and **6** (65%). Compounds **6** and **7** were further purified by recrystallization from acetonitrile−chloroform. When equimolar amounts of **1** and **2** were condensed under the experimental conditions described above, the reaction gave after CC **7** (6−8%), **6** (30%), and **4** (20%) in that order.

7: decomposes at 280 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 27 °C) δ 0.79, 0.89, 1.01, 1.15 (br s, ratio 1:1:1:1, *t*-Bu, 36 H), 1.21 (s, *t*-Bu, 9 H), 1.33−1.37 (overlapping br s, *t*-Bu, 36 H), 3.1−3.6 (equatorial ArCH_2Ar, 9 H), 3.71 (br d, 1 H), 3.95−4.18 (br m, 5 H), 4.56−4.84 (m, 10 H), 4.88−5.04 (br m, 4 H), 5.24−5.36 (br m, 3 H), 5.52, 5.62 (br s, 1 H each), 6.37, 6.50, 6.58, 6.84, 6.88 (br s, ratio 1:2:1:1:1, Ar, 6 H), 7.07−7.36 (m, 12 H), 7.91 (s, OH, 1 H) ppm; ^{13}C NMR δ 28.6, 29.0, 29.7, 30.9, 32.0, 32.2, 32.6 (t, ArCH_2Ar), 31.2, 31.5, 31.7 (q, *t*-Bu), 33.6, 33.9, 34.1 (s, *t*-Bu), 71.2, 72.3, 72.8, 75.4, 75.9 (t, OCH_2), 124.4, 125.2, 125.9, 126.3, 126.8 (d, Ar), 127.4, 128.1, 130.7, 131.2, 131.4, 132.0 (×4), 132.4,

(10) A similar torsional motion has very recently been observed for a thiacalix[4]tube.[8b]

(11) Garozzo, D.; Kohnke, F. H.; Gattuso, G.; Malvagna, P.; Notti, A.; Occhipinti, S.; Pappalardo, S.; Parisi M. F.; Pisagatti, I. *Tetrahedron Lett.*, in press.

(12) For a short review on the formation of molecular networks based on inclusion phenomena, see: Hosseini, M. W.; De Cian, A. *Chem. Commun*. **1998**, 727.

(13) Melting points were determined on a Kofler or electrothermal melting point apparatus and are uncorrected. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$, at 300 and 75 MHz respectively, using TMS as an internal standard. ^{1}H NMR peak assignments follow from 2D-COSY experiments. ^{13}C NMR spectra were acquired with the APT technique. FAB (+) mass spectra were recorded using 3-nitrobenzyl alcohol as a matrix. All chemicals were reagent grade and were used without further purification. Anhydrous solvents (MeCN, THF, and DMF) were either obtained commercially or prepared according to standard procedures. All reactions were carried out under anhydrous conditions. Compounds **1**[14] and **2**[15] were synthesized according to literature procedures.

(14) Stewart, D. R.; Gutsche, C. D. *Org. Prep. Proced. Int.* **1993**, *25*, 137.

(15) Cobben, P. L. H. M.; Egberink, R. J. M.; Bomer, J. G.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573. Arnaud-Neu, F.; Browne, J. K.; Byrne, D.; Marrs, D. J.; McKervey, M. A.; O'Hagan, P.; Schwing-Weill, M. J.; Walker, A. *Chem. Eur. J.* **1999**, *5*, 175.

132.7, 133.9, 134.5 (×2), 134.9, 135.3, 135.5, 135.7 (s, bridgehead-C), 142.0 (s, C_{sp2}−*t*-Bu, unalkylated ring), 144.1, 144.4, 144.7, 144.9, 145.2, 147.1 (s, C_{sp2}−*t*-Bu, alkylated rings), 149.1 (C_{sp2}−O, unalkylated ring), 150.1, 152.7 (×2), 153.8, 154.4, 154.8 (×2), 155.1 (C_{sp2}−O, alkylated rings) ppm; FAB (+) *m*/*z* 1695 [MCs^+], 1562.3 [M^+]. Anal. Calcd for $C_{107}H_{134}O_9$: C, 82.16; H, 8.63. Found: C, 81.93; H, 8.95.

6: mp > 300 °C; ^{1}H NMR δ 1.09, 1.16, 1.21, 1.26 (s, ratio 4:4:2:4, *t*-Bu, 126 H), 3.04 and 4.65 (AX, J = 13.8 Hz, $ArCH_2Ar$, 4 H), 3.26 and 4.39 (AX, J = 12.5 Hz, $ArCH_2Ar$, 4 H), 3.35 and 4.26 (AX, J = 13.9 Hz, $ArCH_2Ar$, 8 H), 3.36 and 3.98 (AX, J = 14.0 Hz, $ArCH_2Ar$, 8 H), 3.46 and 5.09 (AX, J = 13.1 Hz, $ArCH_2$-Ar, 4 H), 4.27, 4.49, 4.67, 4.84 (br m, OCH_2CH_2O, 4 H each), 6.84 and 6.94, 7.05 and 7.08, 7.11 and 7.13 (3×ABq, J = 2.5 Hz, ArH, 8 H each), 7.12 (s, ArH, 4 H), 7.8−7.9 (hump, OH, 6 H) ppm; ^{13}C NMR δ 29.0, 31.0, 31.2 (t, Ar*C*H_2Ar), 31.40, 31.44, 31.55 (q, C(*C*H_3)$_3$), 33.84, 33.86, 34.1 (s, *C*(CH_3)$_3$), 73.7, 74.4 (t, OCH_2), 125.1, 125.4, 125.5, 125.6, 125.9, 126.1 (d, Ar), 126.80, 126.88, 126.95, 131.9, 132.8, 132.9, 134.6 (s, bridgehead-C), 142.5, 142.8 (s, C_{sp2}−C(CH_3)$_3$, unalkylated rings), 144.8, 146.2 (s, C_{sp2}−C(CH_3)$_3$, alkylated rings), 148.5, 149.2 (C_{sp2}−O, unalkylated rings), 152.1, 153.2 (C_{sp2}−O, alkylated rings) ppm; FAB (+) MS *m*/*z* 2373 (MH^+). Anal. Calcd for $C_{162}H_{204}O_{14}$: C, 81.91; H, 8.66. Found: C, 81.67; H, 8.81.

4: mp 195−200 °C; ^{1}H NMR δ 1.057, 1.060, 1.15, 1.24, 1.28 (s, ratio 2:2:2:1:2, *t*-Bu, 81 H), 2.42 (s, Me, 6 H), 2.91 and 3.97 (AX, J = 12.5 Hz, $ArCH_2Ar$, 2 H), 2.94 and 4.24 (AX, J = 12.7 Hz, $ArCH_2Ar$, 4 H), 3.34 and 4.93 (AX, J = 13.0 Hz, $ArCH_2Ar$, 2 H), 3.39 and 3.87 (AB, J = 14.3 Hz, $ArCH_2Ar$, 4 H), 3.52 and 4.42 (AX, J = 13.9 Hz, $ArCH_2Ar$, 4 H), 3.63 and 4.95 (AX, J = 13.8 Hz, $ArCH_2Ar$, 2 H), 3.94−4.03 (m, 4 H), 4.14−4.29 (m, 8 H), 4.59−4.66 (m, 2 H), 4.75−4.83 (m, 2 H), 6.67 and 6.73, 6.69 and 6.83, 7.07 and 7.14, 7.11 and 7.19 (4×AB, J = 2.4 Hz, ArH, 4 H each), 7.10 (s, ArH, 2 H), 7.25 and 7.58 (2d, J = 8.3 Hz, TsH, 8 H), 7.29 and 8.14 (br s, ratio 2:1, OH) ppm; ^{13}C NMR δ 21.7 (q, Me), 30.5, 30.8, 31.2, 31.8 (t, Ar*C*H_2Ar), 31.32, 31.35, 31.40, 31.5, 31.6 (q, *t*-Bu), 33.8, 33.9, 34.2 (s, *t*-Bu), 68.9, 71.5, 73.2 (t, OCH_2), 124.7, 125.1, 125.3, 125.6, 125.68, 125.73, 126.2 (d, Ar), 126.8, 127.0 127.4 (s, bridgehead-C, unalkylated rings), 127.9, 129.8 (d, Ts), 132.3, 132.8, 132.9, 133.1, 133.2, 133.7, 134.4 (s, bridgehead-C, unalkylated rings and Ts), 142.7, 142.8 (s, C_{sp2}−*t*-Bu, unalkylated rings), 144.7, 144.9, 145.1 (s, C_{sp2}−*t*-Bu, alkylated rings), 146.8 (s, Ts), 148.8, 149.3 (C_{sp2}−O, unalkylated rings), 151.7, 152.2, 153.0 (C_{sp2}−O, alkylated rings) ppm; FAB (+) MS *m*/*z* 1907 [MH^+]. Anal. Calcd for $C_{121}H_{150}O_{15}S_2$: C, 76.15; H, 7.92. Found: C, 75.86; H, 8.20.

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Supporting Information Available: ^{1}H NMR spectra of **6** (in C_6D_6) and **7** (at different temperatures), and crystallographic data for compounds **6** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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