Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 3387–3391
Tetrahedron Letters

# Regioselective double intramolecular bridging of *p-tert*-butylcalix[7]arene

Marco Martino, Carmine Gaeta and Placido Neri*

*Dipartimento di Chimica, Università di Salerno, Via S. Allende 43, I-84081 Baronissi, Salerno, Italy*

Received 26 January 2004; revised 19 February 2004; accepted 5 March 2004

Dedicated to Professor Adolfo Zambelli on the occasion of his 70th birthday

**Abstract**—The first examples of doubly bridged calix[7]arenes **2a**–**h** have been obtained by base-promoted O-alkylation of *p-tert*-butylcalix[7]arene **1** or 1,4-tetramethylene-bridged calix[7]arene **3a** with a variety of bis-electrophiles including $BrCH_2Cl$, oligoethylene glycol ditosylates, and 1,2-bis(bromomethyl)benzene. In the presence of $Cs_2CO_3$ as the base, in acetone, the *syn*-1,4:2,3-bis-bridged regioisomer was obtained in yields up to 76%. Assignment of bridging pattern was based on chemical shift of OH groups in conjunction with chemical correlations with known compounds. Stereochemical and conformational features were investigated with the aid of 2D and Dynamic NMR studies and MM3 calculations.

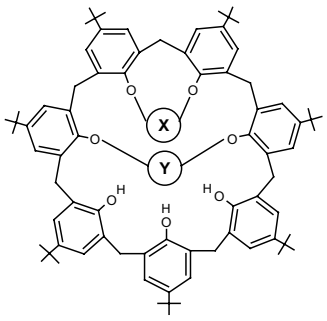

Three-dimensional preorganization of calixarene macrocycles is of particular relevance to improve both the efficiency and selectivity of their recognition abilities.[1] In this regard, the insertion of suitable scaffolding elements by intramolecular bridging is considered the most promising approach. Consequently, a very large number of intrabridged calix[*n*]arene ($n = 4$, 5, 6, 8) derivatives have been reported in the past decade.[1,2] Concerning the 'minor' odd-membered calix[7]arenes,[3] only very recently a few examples of single bridging have been reported, evidencing that the 1,4-isomer was often favored.[4] In this Letter we wish to report on the synthesis of the first examples of calix[7]arenes doubly bridged at the lower rim.

Initially we studied the intramolecular double bridging of *p-tert*-butylcalix[7]arene[5] **1** by base-promoted direct alkylation with bis-electrophiles. Thus, treatment of **1** with ethylene glycol ditosylate (Table 1, entry 1)[6] in the presence of $Cs_2CO_3$ in refluxing acetone afforded 1,4:2,3-bis(ethylene)-bridged *p-tert*-butylcalix[7]arene **2a** (1,4:2,3-calix[7]bis-crown-2) in 53% yield, after column chromatography on silica gel.[7] These conditions were extended to alkylation with di(ethylene glycol) ditosylate (Table 1, entry 2) to give 1,4:2,3-calix[7]bis-crown-3 **2b** in 76% yield. Analogously, the alkylation with 1,4-diiodobutane (Table 1, entry 3) afforded 1,4:2,3-bis-(tetramethylene)-bridged calix[7]arene **2c** in good yield (75%).

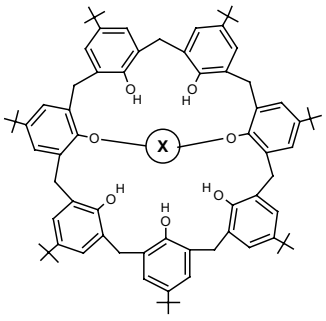
The availability of efficient synthetic procedures for the preparation of 1,4-bridged calix[7]arenes[4] induced us to explore the alkylation of a preformed singly bridged derivative to obtain doubly bridged calix[7]arenes with mixed scaffolding elements. As starting material we used 1,4-tetramethylene-bridged calix[7]arene **3a**,[7] which was obtained by treatment of **1** with 1,4-diiodobutane in the presence of KOH in refluxing THF (Table 1, entry 4), and whose structure was assigned analogously to other singly bridged calix[7]arenes.[4] Thus, the alkylation of **3a** with bromochloromethane in the presence of $Cs_2CO_3$ in refluxing acetone gave 1,4-tetramethylene-2,3-methylene-bridged calix[7]arene[7] **2d** in 55% yield (Table 1, entry 5). Under similar conditions, the alkylation of **3a** with ethylene glycol ditosylate afforded 1,4-tetramethylene-2,3-calix[7]crown-2 **2e** in 60% yield (Table 1, entry 6). Analogous treatment with di- or tri(ethylene glycol)ditosylate (Table 1, entries 7 and 8, respectively) led to the corresponding 1,4-tetramethylene-2,3-crown-3 **2f** and 1,4-tetramethylene-2,3-crown-4 **2g** derivatives in 75% and 30% yield, respectively. The procedure was also successfully extended to 1,2-bis(bromomethyl)benzene

*Keywords*: Calixarenes; Calix[7]arenes; Calixcrown; Intramolecular bridging; Doubly bridged; Lower rim.
* Corresponding author. Tel.: +39-089-965262; fax: +39-089-965296; e-mail: neri@unisa.it

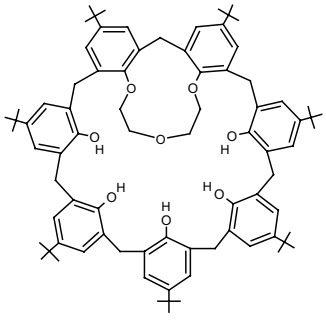
0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.03.028



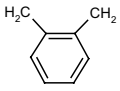
**2a-h**



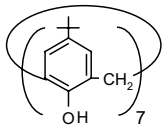
**3a-b**



**4**

| | X | Y |
|---|---|---|
| **a** | $CH_2CH_2$ | $CH_2CH_2$ |
| **b** | $CH_2CH_2OCH_2CH_2$ | $CH_2CH_2OCH_2CH_2$ |
| **c** | $CH_2CH_2CH_2CH_2$ | $CH_2CH_2CH_2CH_2$ |
| **d** | $CH_2$ | $CH_2CH_2CH_2CH_2$ |
| **e** | $CH_2CH_2$ | $CH_2CH_2CH_2CH_2$ |
| **f** | $CH_2CH_2OCH_2CH_2$ | $CH_2CH_2CH_2CH_2$ |
| **g** | $CH_2(CH_2OCH_2)_2CH_2$ | $CH_2CH_2CH_2CH_2$ |
| **h** |  | $CH_2CH_2CH_2CH_2$ |

| | X |
|---|---|
| **a** | $CH_2CH_2CH_2CH_2$ |
| **b** | $CH_2CH_2OCH_2CH_2$ |



**1**

**Table 1.** Yield of bridged calix[7]arenes in the alkylation of *p-tert*-butylcalix[7]arene (**1**), 1,4-tetramethylene-bridged calix[7]arene **3a**, 1,4-calix[7]-crown-3 **3b**, or 1,2-calix[7]crown-3 **4**, in the presence of $Cs_2CO_3$ (15 equiv) in acetone at reflux[a]

| Entry | Starting material | Alkylating agent (equiv) | Isolated compound (yield %) |
|---|---|---|---|
| 1 | **1** | $TsOCH_2CH_2OTs$ (3) | **2a** (53) |
| 2 | **1** | $TsO(CH_2CH_2O)_2$ Ts (3) | **2b** (76) |
| 3 | **1** | $CH_2CH_2CH_2CH_2$ (3) | **2c** (75) |
| 4 | **1** | $CH_2CH_2CH_2CH_2$ (1.1) | **3a** (40)[a] |
| 5 | **3a** | $BrCH_2Cl$ (1.1) | **2d** (55) |
| 6 | **3a** | $TsOCH_2CH_2OTs$ (1.1) | **2e** (60) |
| 7 | **3a** | $TsO(CH_2CH_2O)_2$ Ts (1.1) | **2f** (75) |
| 8 | **3a** | $TsO(CH_2CH_2O)_3$ Ts (1.1) | **2g** (30) |
| 9 | **3a** | 1,2-$C_6H_4(CH_2Br)_2$ (1.1) | **2h** (70) |
| 10 | **3b** | $TsO(CH_2CH_2O)_2Ts$ (1.1) | **2b** (70) |
| 11 | **4** | $TsO(CH_2CH_2O)_2Ts$ (1.1) | **2b** (60) |

[a] In the case of entry 4 the reaction was performed in the presence of KOH (6 equiv) in THF at reflux.

as an aromatic alkylating agent, to give 1,4-tetramethylene-2,3-*o*-xylylene derivative **2h** in 70% yield (Table 1, entry 9).

Structure assignment for doubly bridged calix[7]arene derivatives **2a**–**h** was based on spectral analysis coupled to chemical correlations.[7] In particular, elemental analysis and ESI(+) MS confirmed the presence of two bridges in each of them, while assignment of the bridging pattern was based on the following arguments.

In principle, 12 regioisomers are possible for a calix[7]-arene doubly bridged with two identical elements. Among them, only three are asymmetrical (1,2:3,5, 1,2:3,6, and 1,3:2,5 isomers), whereas the remaining ones all possess a symmetry plane bisecting one aromatic ring and the opposite $ArCH_2Ar$ group (Ar–$CH_2$ symmetry), making them hardly distinguishable by simple symmetry considerations. Therefore, to this end, as for the case of selectively O-substituted[3d] and singly bridged calix[7]arenes,[4] we resorted to the classification of OH groups as 'isolated' (i), 'singly H-bonded' (s), and 'doubly H-bonded' (d), based on their $^1H$ NMR chemical shift. In particular, in addition to resonances typical of Ar–$CH_2$ symmetry, two 2:1 's,d' OH signals were usually observed for doubly bridged calix[7]arene derivatives **2a**–**c**[7] indicating the presence of three contiguous phenolic rings in their structure. This finding reduces the number of the compatible bridging patterns to three, namely 1,2:3,4, 1,4:2,3, and 1,3:2,4. The discrimination among them was obtained by chemical correlations with known singly bridged calix[7]arenes. Thus, for example, the presence of both the 1,2- and 1,4-bridge in 1,4:2,3-calix[7]bis-crown-3 **2b** was proved by its formation either

by alkylation of 1,4-calix[7]crown-3[4] **3b** and 1,2-calix[7]crown-3[4] **4** (Table 1, entries 10 and 11, respectively).

In a similar way, the 1,4:2,3 pattern of bis-hetero-bridged calix[7]arenes **2d**–**h** was unequivocally proved by the absence of 'isolated' OH signals and by their formation from the 1,4-bridged parent compound **3a**.

The presence of two bridges inhibits the conformational interconversion in calix[7]arenes **2a**–**h** as indicated by the typical AX systems for $ArCH_2Ar$ groups observed in their $^1H$ NMR spectra (Fig. 1). One exception is given by 1,4-tetramethylene-2,3-methylene-bridged calix[7]arene **2d**, which shows broad signals at 298 K indicating a slow conformational interconversion. This result is explainable by the small dimension of the 2,3-methylene bridge, which allows its passage through the annulus, notwithstanding the reduction of space caused by the 1,4-tetramethylene chain.

The relative spatial orientation of the two bridges in conformationally blocked calix[7]arenes **2a**–**h** can be inferred by the large chemical shift separations of AX systems of $ArCH_2Ar$ groups between rings at positions 2,3 ($\Delta\delta = 1.04$–$1.85$) and 1,2 or 3,4 ($\Delta\delta = 0.82$–$1.06$), which indicate a *syn* orientation of pertinent aromatic rings (Fig. 1). In the case of 1,4:2,3-calix[7]bis-crown-3 **2b** the *syn* orientation of the two bridges was also confirmed by a combined COSY/NOESY 2D NMR study, which evidenced a typical complete network of NOE interactions among the equatorial $ArCH_2Ar$ protons, their close ArH, and the pertinent *t*-Bu groups.

Dynamic NMR studies (400 MHz) on bis-bridged calix[7]arene **2b** confirmed the conformational blockage up to 355 K ($C_6D_6$) and revealed a coalescence temperature at 247 K in $CDCl_3$, below which an asymmetrical spectrum, characterized by three 1:1:1 distinct OH resonances in the 9.0–10.5 ppm range, is obtained (Fig. 1). Obviously, the spectrum at higher temperatures corresponds to an averaged symmetrical structure, which become frozen below 247 K into an asymmetrical conformer. An energy barrier of 11.2 kcal/mol was estimated for this conformational process.

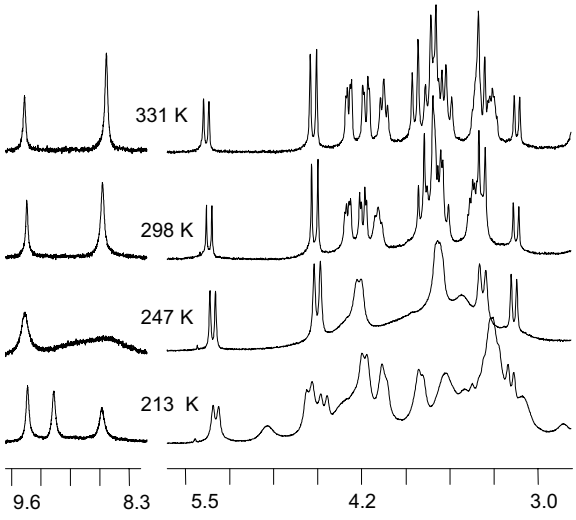



**Figure 1.** Methylene (right) and OH region (left) of the $^1H$ NMR spectrum (400 MHz, $CDCl_3$) of 1,4:2,3-calix[7]bis-crown-3 **2b** at relevant temperatures.

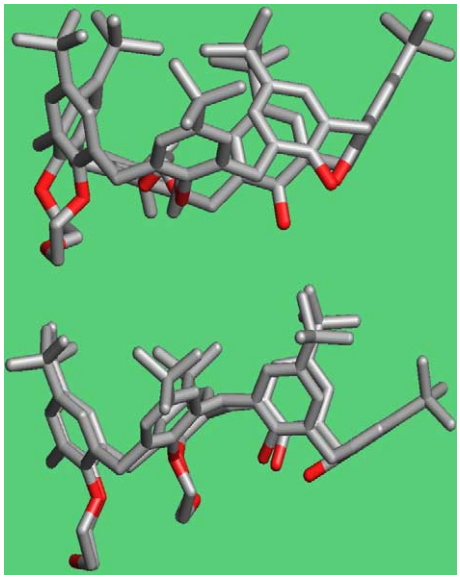


**Figure 2.** Computer models of the asymmetrical lowest MM3-energy conformation (top) and of the averaged symmetrical structure (bottom) of 1,4:2,3-calix[7]bis-crown-3 **2b**.

An insight into the conformation adopted by **2b** was obtained by a Monte Carlo conformational search using the MacroModel-7.2 program[8] (MM3, $CHCl_3$ solvent) starting from a structure built on the *double-cone pinched* conformation[9a] found in the X-ray crystal structure of *p-tert*-butylcalix[7]arene **1**.[9b] With this procedure an asymmetrical lowest energy structure was found (Fig. 2), which very likely corresponds to the frozen conformation evidenced by D-NMR studies. An independent modeling with imposed symmetry equivalences, gave an idealized symmetrical structure (Fig. 2), which can be considered as representative of the averaged conformation observed at room temperature.

In conclusion, we have described the first examples of doubly bridged, conformationally blocked calix[7]arene derivatives. Dynamic NMR studies evidenced a high level of preorganization, which preludes to their potential applications as molecular hosts in supramolecular chemistry.

## Acknowledgements

Financial support from the Italian MIUR (COFIN-2003, Supramolecular Devices Project) is gratefully acknowledged. Thanks are due to Dr. A. D'Amato (Dipartimento di Chimica, Università di Salerno) for ESI-MS measurements.

## References and notes


1. For general reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713; (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713; (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; (d) *Calixarenes, 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Dordrecht: Kluwer, 2001.
2. For very recent, selected examples, see: Calix[4]arenes: Haverlock, T. J.; Mirzadeh, S.; Moyer, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1126; Calix[5]arenes: De Salvo, G.; Gattuso, G.; Notti, A.; Parisi, M. F.; Pappalardo, S. *J. Org. Chem.* **2002**, *67*, 684; Calix[6]arenes: Chen, Y.; Gong, S. *J. Incl. Phenom. Macrocycl. Chem.* **2003**, *45*, 165; Calix[8]arenes: Consoli, G. M. L.; Geraci, C.; Cunsolo, F.; Neri, P. *Tetrahedron. Lett.* **2003**, *44*, 53.
3. For a review on the chemistry of calix[7]arenes, see: (a) Martino M., Neri P. *Mini-Rev. Org. Chem.*, **2004**, *1*, in press; For some recent papers, see: (b) Atwood, J. L.; Hardie, M. J.; Raston, C. L.; Sandoval, C. A. *Org. Lett.* **1999**, *1*, 1523; (c) Ludwig, R.; Lentz, D.; Nguyen, T. K. D. *Radiochim. Acta* **2000**, *88*, 335; (d) Martino, M.; Gregoli, L.; Gaeta, C.; Neri, P. *Org. Lett.* **2002**, *4*, 1531; (e) Fleming, S.; Gutsche, C. D.; Harrowfield, J. M.; Ogden, M. I.; Skelton, B. W.; Stewart, D. F.; White, A. H. *Dalton Trans.* **2003**, 3319.
4. Martino, M.; Gaeta, C.; Gregoli, L.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 9521.
5. Compound **1** was prepared according to the acid-catalyzed one-pot procedure described in Stewart, D. R.; Gutsche, C. D. *J. Am. Chem. Soc.* **1999**, *121*, 4136; For additional synthetic procedures, see: Nakamoto, Y.; Ishida, S.-I. *Makromol. Chem., Rapid Commun.* **1982**, *3*, 705; Vocanson, F.; Lamartine, R.; Lanteri, P.; Longeray, R.; Gauvrit, J. Y. *New J. Chem.* **1995**, *19*, 825.
6. **Typical procedure for the preparation of doubly bridged calix[7]arenes 2a–h.** A suspension of *p*-tert-butylcalix[7]arene (**1**) or 1,4-tetramethylene-bridged calix[7]arene **3a** (0.176 mmol) and $Cs_2CO_3$ (2.64 mmol) in $Me_2CO$ (20 mL) was stirred for 2 h under reflux. Then a solution of the alkylating agent (1.1 or 3 equiv, see Table 1) in $Me_2CO$ (5 mL) was slowly added. The mixture was stirred for 48 h under reflux, dried under vacuum, and partitioned between $CH_2Cl_2$ (3×20 mL) and 0.1 M HCl (20 mL). The total organic phase was washed with $H_2O$ (3×20 mL) and dried. The crude product was subjected to column chromatography (CC) on silica gel to give the isolated compounds (Table 1 and Ref. 7).
7. Satisfactory microanalytical and spectral data were obtained for all new compounds. $^1H$ and $^{13}C$ NMR spectra were acquired at 400 and 100 MHz, respectively, in $CDCl_3$, $CDCl_2CDCl_2$, $CD_3CO$, or $C_6D_6$. ESI(+) MS measurements were performed using a mixture of $H_2O$/$CH_3CN$ (1:1) and 5% HCOOH as solvent.
   Compound **2a**: CC (cyclohexane/EtOAc, 8:2 v/v); ESI(+) MS *m/z* 1189 ($MH^+$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 1.22, 1.29, [s, $C(CH_3)_3$, 45H, 18H], 3.48 (d, $ArCH_2Ar$, $J = 14.3$ Hz, 1H), 3.70–3.76 (overlapped, $ArCH_2Ar$, 4H), 3.79 (bs, $OCH_2$, 4H), 3.86 (bs, $ArCH_2Ar$, 2H), 3.90 (bs, $ArCH_2Ar$, 2H), 4.19 (bs, $OCH_2$, 4H), 4.31 (bs, $ArCH_2Ar$, 4H), 4.80 (d, $ArCH_2Ar$, $J = 14.3$ Hz, 1H), 6.98 (bs, ArH, 2H), 7.02 (bs, ArH, 2H), 7.05 (bs, ArH, 2H), 7.10 (bs, ArH, 4H), 7.16 (bs, ArH, 4H), 8.40, 9.01 (bs, OH, 2H, 1H).
   Compound **2b**: CC (cyclohexane/EtOAc, 8:2 v/v); ESI(+) MS *m/z* 1277 ($MH^+$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 1.11, 1.23, 1.30, 1.35 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 2.89 (bs, $CH_2O$, 2H), 3.39 (d, $ArCH_2Ar$, $J = 13.5$ Hz, 1H), 3.55 (d, $ArCH_2Ar$, $J = 15.7$ Hz, 2H), 3.66 (overlapped, $OCH_2$, 2H), 3.84 (d, $ArCH_2Ar$, $J = 12.4$ Hz, 2H), 3.92 (d, $ArCH_2Ar$, $J = 14.5$ Hz, 2H), 3.90 (overlapped, $OCH_2$, 8H), 3.97 (d, $ArCH_2Ar$, $J = 14.5$ Hz, 2H), 4.24 (b t, $OCH_2$, 2H), 4.29 (d, $ArCH_2Ar$, $J = 12.4$ Hz, 2H), 4.42 (overlapped, $OCH_2$, 2H), 4.58 (d, $ArCH_2Ar$, $J = 15.7$ Hz, 2H), 5.24 (d, $ArCH_2Ar$, $J = 13.5$ Hz, 1H), 6.76 (d, ArH, $J = 1.2$ Hz, 2H), 7.06 (d, ArH, $J = 1.9$ Hz, 2H), 7.10 (d, ArH, $J = 1.9$ Hz, 2H), 7.17, 7.23 (bs, ArH, 2H, 2H), 7.26 (d, ArH, $J = 1.9$ Hz, 2H), 7.32 (d, ArH, $J = 1.9$ Hz, 2H), 8.50, 9.36 (bs, OH, 2H, 1H).
   Compound **2c**: CC (cyclohexane/EtOAc, 9:1 v/v); ESI(+) MS *m/z* 1245 ($MH^+$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 1.13, 1.24, 1.30, 1.33 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 2.08, 2.27 (bs, $CH_2$, 4H, 4H), 3.12 (bs, $OCH_2$, 4H), 3.33 (d, $ArCH_2Ar$, $J = 12.9$ Hz, 1H), 3.62 (d, $ArCH_2Ar$, $J = 15.8$ Hz, 2H), 3.78 (bs, $ArCH_2Ar$, 4H), 3.95, 3.99 (bs, $OCH_2$, 2H, 2H), 4.47 (bs, $ArCH_2Ar$, 4H), 4.58 (d, $ArCH_2Ar$, $J = 15.8$ Hz, 2H), 4.93 (d, $ArCH_2Ar$, $J = 12.9$ Hz, 1H), 6.81 (bs, ArH, 2H), 7.07 (bs, ArH, 2H), 7.11 (bs, ArH, 2H), 7.13 (bs, ArH, 2H), 7.16 (bs, ArH, 2H), 7.19 (s, ArH, 2H), 7.23 (bs, ArH, 2H), 8.35 (bs, OH, 3H).
   Compound **2d**: CC (cyclohexane/EtOAc, 8:2 v/v); ESI(+) MS *m/z* 1203 ($MH^+$); $^1H$ NMR ($CDCl_2CDCl_2$, 373 K): $\delta$ 1.26, 1.30, 1.36, 1.39 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 1.42 (bs, $CH_2$, 4H), 3.49 (m, $OCH_2$, 4H), 3.84, 3.95, 4.05, 4.12 (bs, $ArCH_2Ar$, 4H, 4H, 4H, 2H), 5.76 (bs, $OCH_2O$, 2H), 6.55 (bs, ArH, 2H), 7.13 (d, ArH, $J = 1.9$ Hz, 2H), 7.17 (d, ArH, $J = 1.9$ Hz, 2H), 7.18 (d, ArH, $J = 2.4$ Hz, 2H), 7.20 (d, ArH, $J = 2.4$ Hz, 2H), 7.32 (s, ArH, 2H), 7.35 (d, ArH, $J = 1.5$ Hz, 2H), 8.22, 8.66 (bs, OH, 2H, 1H).
   Compound **2e**: CC (cyclohexane/EtOAc, 85:15 v/v); ESI(+) MS *m/z* 1217 ($MH^+$); $^1H$ NMR ($CDCl_3$, 298 K): $\delta$ 1.17, 1.22, 1.30, 1.34 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 1.43 (bs, $CH_2$, 4H), 3.33 (bs, $OCH_2$, 2H), 3.43 (d, $ArCH_2Ar$, $J = 13.6$ Hz, 1H), 3.63 (d, $ArCH_2Ar$, $J = 13.9$ Hz, 4H), 3.72 (d, $ArCH_2Ar$, $J = 14.1$ Hz, 2H), 3.78 (bs, $OCH_2$, 2H), 3.90 (d, $ArCH_2Ar$, $J = 14.1$ Hz, 2H), 4.24 (d, $ArCH_2Ar$, $J = 14.2$ Hz, 2H), 4.21 (s, $OCH_2$, 4H), 4.45 (d, $ArCH_2Ar$, $J = 13.6$ Hz, 2H), 4.86 (d, $ArCH_2Ar$, $J = 13.6$ Hz, 1H), 6.92 (bs, ArH, 2H), 7.07 (bs, ArH, 2H), 7.08 (bs, ArH, 2H), 7.10 (bs, ArH, 2H), 7.15 (s, ArH, 2H), 7.26 (bs, ArH, 2H), 7.28 (bs, ArH, 2H), 8.53, 8.68 (bs, OH, 2H, 1H).
   Compound **2f**: CC (cyclohexane/EtOAc, 8:2 v/v); ESI(+) MS *m/z* 1261 ($MH^+$); $^1H$ NMR ($CDCl_3$, 323 K): $\delta$ 1.13, 1.25, 1.28, 1.31 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 1.49 (bs, $CH_2$, 4H), 3.06 (bs, $OCH_2$, 2H), 3.38 (d, $ArCH_2Ar$, $J = 12.4$ Hz, 1H), 3.58 (d, $ArCH_2Ar$, $J = 16.1$ Hz, 2H), 3.64 (bs, $OCH_2$, 2H), 3.69 (d, $ArCH_2Ar$, $J = 13.8$ Hz, 2H), 3.76 (d, $ArCH_2Ar$, $J = 13.8$ Hz, 2H), 3.82–3.85 (overlapped, $ArCH_2Ar$, 4H), 3.97 (t, $OCH_2$, $J = 9.2$ Hz, 2H), 4.04 (t, $OCH_2$, $J = 9.2$ Hz, 2H), 4.26 (bd, $OCH_2$, $J = 11.7$ Hz, 2H), 4.36 (bd, $OCH_2$, $J = 9.5$ Hz, 2H), 4.68 (d, $ArCH_2Ar$, $J = 16.1$ Hz, 2H), 5.20 (d, $ArCH_2Ar$, $J = 12.4$ Hz, 1H), 6.75 (bs, ArH, 2H), 7.08 (bs, ArH, 2H), 7.10 (bs, ArH, 2H), 7.14 (s, ArH, 2H), 7.20 (bs, ArH, 4H), 7.31 (bs, ArH, 2H), 8.16, 8.24 (bs, OH, 2H, 1H).
   Compound **2g**: CC (cyclohexane/EtOAc, 8:2 v/v); ESI(+) MS *m/z* 1305 ($MH^+$); $^1H$ NMR ($CDCl_3$, 328 K): $\delta$ 1.15, 1.26, 1.28, 1.30 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 1.51 (bs, $CH_2$, 4H), 3.14 (bs, $OCH_2$, 2H), 3.42 (d, $ArCH_2Ar$, $J = 13.0$ Hz, 1H), 3.57 (d, $ArCH_2Ar$, $J = 16.8$ Hz, 2H), 3.62 (bs, $OCH_2$, 2H), 3.69–3.73 (overlapped, $ArCH_2Ar$, 4H), 3.81–3.85 (overlapped, $ArCH_2Ar$ and $OCH_2$ 8H), 4.00 (overlapped, $OCH_2$, 2H), 4.10–4.15 (overlapped, $OCH_2$, 4H), 4.65 (d, $ArCH_2Ar$, $J = 16.8$ Hz, 2H), 5.00

(d, $ArCH_2Ar$, $J = 13.0$ Hz, 1H), 6.86 (bs, ArH, 2H), 7.11 (bs, ArH, 4H), 7.15 (s, ArH, 2H), 7.16 (bs, ArH, 2H), 7.19 (bs, ArH, 2H), 7.20 (bs, ArH, 2H), 8.11, 8.19 (bs, OH, 2H, 1H).

Compound **2h**: CC (cyclohexane/EtOAc, 9:1 v/v); ESI(+) MS $m/z$ 1293 ($MH^+$); $^1H$ NMR ($CDCl_3$, 303 K): $\delta$ 1.13, 1.25, 1.31, 1.37 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 1.49 (bs, $CH_2$, 4H), 3.12 (d, $ArCH_2Ar$, $J = 13.1$ Hz, 1H), 3.25 (bs, $OCH_2$, 2H), 3.70 (bs, $OCH_2$, 2H), 3.79 (bs, $ArCH_2Ar$, 8H), 3.83 (d, $ArCH_2Ar$, $J = 16.1$ Hz, 2H), 4.20 (d, $ArCH_2Ar$, $J = 13.1$ Hz, 1H), 4.63 (d, $ArCH_2Ar$, $J = 16.1$ Hz, 2H), 5.21 (d, $OCH_2Ar$, $J = 11.7$ Hz, 2H), 5.71 (d, $OCH_2Ar$, $J = 11.7$ Hz, 2H), 6.84 (bs, ArH, 2H), 6.92 (bs, ArH, 2H), 6.99 (bs, ArH, 2H), 7.08 (bs, ArH, 2H), 7.14 (bs, ArH, 2H), 7.16 (bs, ArH, 2H), 7.28 (bs, ArH, 2H), 7.34–7.38 (overlapped, ArH, 4H), 8.27 (bs, OH, 2H), 8.33 (bs, OH, 1H).

Compound **3a** was obtained as described above for **2a–c** using KOH (1.06 mmol) as the base and THF (20 mL) as the solvent (Table 1, entry 4): CC (cyclohexane/EtOAc, 9:1 v/v); ESI(+) MS $m/z$ 1191 ($MH^+$); $^1H$ NMR (acetone-$d_6$, 298 K): $\delta$ 0.98, 1.09, 1.17, 1.27 [s, $C(CH_3)_3$, 18H, 18H, 9H, 18H], 2.73 (bs, $CH_2$, 4H), 3.26 (bs, $OCH_2$, 4H), 3.72, 3.83, 3.91, 3.98 (bs, $ArCH_2Ar$, 4H, 4H, 2H, 4H), 6.55 (d, ArH, $J = 2.1$ Hz, 2H), 7.00 (d, ArH, $J = 2.1$ Hz, 2H), 7.11(d, ArH, $J = 2.3$ Hz, 2H), 7.20, 7.26 (m, ArH, 4H, 4H), 8.33, 8.40, 8.47 (bs, OH, 2H, 1H, 2H).

8. Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.
9. (a) Harada, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1995**, 2231; (b) Andreetti, G. D.; Ugozzoli, F.; Nakamoto, Y.; Ishida, S.-I. *J. Incl. Phenom. Mol. Recognit. Chem.* **1991**, *10*, 241.