Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 53–56

TETRAHEDRON LETTERS

# Diester intrabridging of *p-tert*-butylcalix[8]arene and unexpected formation of the monospirodienone derivative

Grazia M. L. Consoli,[a] Corrada Geraci,[a,*] Francesca Cunsolo[a] and Placido Neri[b,*]

[a]*Istituto di Chimica Biomolecolare, Sezione di Catania, CNR, Via del Santuario 110, I-95028 Valverde (CT), Italy*
[b]*Dipartimento di Chimica, Università di Salerno, Via S. Allende 43, I-84081 Baronissi (SA), Italy*

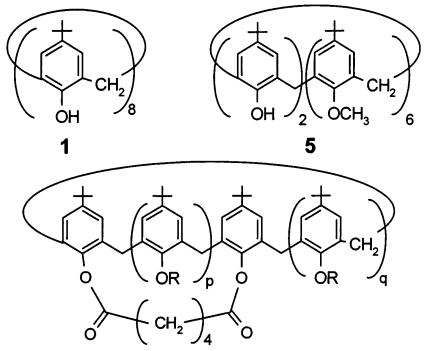
Received 24 October 2002; accepted 6 November 2002

**Abstract**—Reaction of *p-tert*-butylcalix[8]arene **1** with adipoyl chloride in the presence of NaH as the base yielded singly and doubly intrabridged esters **2–4** and **6**. Surprisingly, calix[8]arene monospirodienone derivative **7** was also isolated, which was originated by $O_2$ oxidation. The conditions of this oxidation were optimized leading to a novel synthetic approach to calixarene monospirodienones based on the $O_2$/NaH/acyl-chloride oxidizing system. Xantheno calix[8]arenes **8–8a** were obtained by rearrangement of **7**. 

Intrabridging at the lower rim of calixarenes is particularly easy because of the spatial proximity of their OH groups and, consequently, a wide variety of derivatives based on robust ether bridges have been reported.[1] The use of ester bridges is surely less diffuse, but several examples of diester-bridged calix[4–6]arenes have been reported.[2] As regards calix[8]arene, only a couple of examples are known, based on phosphate[3] or carbonate[4] bridges.

Considering the different behavior of calix[8]arenes with respect to the smaller homologues, it can be expected that study on their intramolecular acylation may lead to interesting regiochemical and conformational results. In addition, the easily hydrolyzable acyloxy functions can be considered useful protective groups for calixarene hydroxyls, thus making diester-bridged derivatives potentially useful intermediates for further synthetic elaboration. These considerations prompted us to investigate the direct intramolecular *O*-acylation of *p-tert*-butylcalix[8]arene (**1**) and here we wish to report the first intrabridged carboxylic diesters **2–4** and **6**. In addition, a new synthetic approach for the preparation of calix[8]arene monospirodienone **7** was unexpectedly found and then optimized.

On the basis of preliminary tests with various linear diacyl chlorides under different conditions, we selected adipoyl chloride as the most promising acylating agent for *p-tert*-butylcalix[8]arene. When **1** was treated with adipoyl chloride and NaH (1:3:8) in dry DMF at 80°C, in addition to the desired intrabridged derivatives **2–4**, **6** (5, 4, 10, and 7% yield, respectively) and unreacted **1** (40%), the monospirodienone derivative **7** (5% yield) was also isolated.




**2** p = 0 R = H
**3** p = 1 R = H
**4** p = 2 R = H
**4a** p = 2 R = $CH_3$

p + q = 6

The obtained compounds were characterized by elemental analysis, FAB(+) MS measurements, NMR spectroscopy and chemical transformation. $^1$H NMR spectra of **2–4** showed broad signals at room temperature and heating was generally required for their analysis.

*Keywords*: calixarenes; calix[8]arenes; intrabridged esters; oxidation; monospirodienone.

* Corresponding authors.

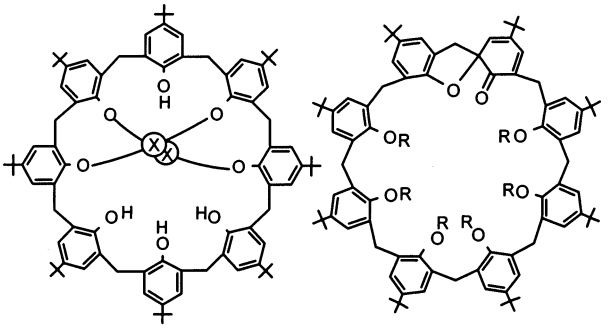
0040-4039/03/$ - see front matter 
PII: S0040-4039(02)02485-1

The structure of the 1,3-adipoyl-bridged isomer was assigned to **3** on the basis of its two-fold symmetry bisecting opposite aromatic rings (Ar–Ar symmetry), evidenced by $^1$H NMR ($CDCl_3$, 325 K) spectral data (five singlets for *tert*-butyl protons in 1:1:2:2:2 ratio and four singlets of equal intensity for $ArCH_2Ar$ groups).[5]

In a similar way, it was evidenced that **4** possesses a $CH_2$–$CH_2$ symmetry (a two-fold symmetry bisecting opposite $ArCH_2Ar$ groups), compatible with both 1,2- and 1,4-intrabridging.[5] The latter was assigned by chemical correlation. In fact, exhaustive methylation of **4** (MeI, $Cs_2CO_3$, in dry DMF) afforded hexamethoxy derivative **4a** (76% yield), quantitatively saponified to the known 1,4-dihydroxy-hexamethoxy-*p*-*tert*-butylcalix[8]arene.[6] Consequently, the 1,2-intrabridged structure was assigned to compound **2** by exclusion.

The presence of broad signals for $ArCH_2Ar$ groups in the room temperature $^1$H NMR spectra of **2**–**4** indicated a higher conformational mobility with respect to the parent calix[8]arene **1**, due to the shorter extension of the stabilizing 'circular' hydrogen bond. In accordance, its complete suppression, by methylation of OH groups, resulted in increased mobility as exemplified by **4a**, which shows sharp singlets for $ArCH_2Ar$ groups at room temperature.[5]

Interestingly, interconversion between **3** and **4** was often observed in the course of their purification, probably catalyzed by acidic or basic impurities. Further experiments demonstrated the reversibility of this transesterification. $^1$H NMR peak area measurements of equilibrium mixture of **3** and **4** showed a ratio 15:85, indicating **4** as the more stable regioisomer ($\Delta G = 4.3$ kJ/mol). In accordance with other examples of group migration observed in calix[4]arene ester derivatives,[7] the rearrangement process appears to be of intramolecular nature, as indicated by the absence of differently substituted products.



**6** X = $C(CH_2)_4C$ (O, O)

**7** R = H

**7a** R = $CH_3$

The presence of two ester bridges in compound **6** was deduced from FAB-MS, while its Ar–Ar symmetry was indicated by the typical pattern of five *t*-Bu $^1$H NMR signals (2:2:2:1:1). This symmetry is compatible with the 1,5:2,4-, 1,3:2,6-, 1,2:4,5-, or 1,4:2,5-bridging pattern. Analogously to doubly-bridged ether derivatives,[8] further acylation of 1,4-mono-bridged derivative **4** gave compound **6**, thus allowing an unequivocal structural assignment (experimental details will be reported elsewhere).

The yellow color of compound **7** was indicative of an altered calixarene structure. Moreover a signal pattern revealing $C_1$-symmetry and the absence of adipoyl resonances in its $^1$H NMR spectrum were reminiscent of the calixarene monospirodienone derivatives previously reported by Biali et al.[9] The FAB(+) MS spectrum confirmed this assumption, showing a molecular peak at 1294 $m/z$ besides a peak at 1296 $m/z$ due to parent calix[8]arene **1**. The spirodienone structure was conclusively assigned to **7**[10] on the basis of two characteristic $^{13}$C NMR resonances at 87.0 and 204.2 ppm relative to the spiro and carbonyl carbons, respectively.[11] Typical $^1$H NMR signals at $\delta$ 6.35 and 6.55 were confidently assigned to vinylic protons of the monospirodienonic moiety. In accordance with the asymmetry generated by the single spiro stereocenter eight *t*-Bu signals ($\delta$ 1.10, 1.19, 1.23, 1.24, 1.26, 1.28, 1.29, 1.31) and six OH singlets ($\delta$ 8.52, 9.40, 9.62, 9.76, 9.88, 10.04) were also seen.[10] Moreover, the diastereotopic methylene protons appeared as four doublets and broad signals, resolved at 325 K into a total of 16 partially overlapped doublets.

As concerns the 3D-structure of **7**, the relative arrangement of phenol hydroxyls and carbonyl group must be considered. The chemical shift of OH groups (8.52–10.04 ppm) indicated their involvement in single or double hydrogen bonds.[6,12] The downfield $^{13}$C NMR chemical shift of the carbonyl group (204.2 ppm) of **7**, compared with values found for other monospirodienone calix[*n*]arene derivatives,[9b] suggested that it is also hydrogen bonded. This was corroborated by the upfield shift at 198.8 ppm of the carbonyl observed in the hexamethoxy-monospirodienone derivative **7a**. These considerations indicate a *syn* orientation of the hydroxyls and the carbonyl group with respect to the mean macrocyclic plane in monospirodienone **7**.

Calixarene spirodienone derivatives are usually obtained by mild oxidation with trimethylphenylammonium tribromide under basic conditions.[9] Therefore, isolation of calix[8]arene monospirodienone **7** under the experimental conditions previously described was rather unexpected. We supposed that its formation could be due to the presence of air in the reaction environment. In fact, no formation of monospirodienone **7** was detected when the same reaction was carried out under nitrogen (Table 1, entry 1), while bubbling $O_2$ into the reaction mixture resulted into increased yield up to 15% (Table 1, entries 2 and 3). This yield is comparable to that obtained by Biali using trimethylphenylammonium tribromide.[11]

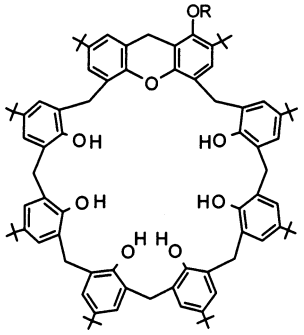
Interestingly, no monospirodienone was formed in the absence of adipoyl chloride, which seems to be necessary to start the reaction (Table 1, entry 4). Moreover, further experiments demonstrated that different mono- and diacyl chlorides could also be effective to this end (Table 1, entries 5–10). In particular, using phtaloyl and

**Table 1.** Yield of monospirodienone **7** in the oxidation of **1** in the presence of NaH (8 equiv.) in DMF

| Entry | Chloride (equiv.) | Atmosphere | Time (h) | Yield (%) |
|---|---|---|---|---|
| 1 | Adipoyl (3) | $N_2$ | 72 | – |
| 2 | Adipoyl (3) | Air | 30 | 5 |
| 3 | Adipoyl (3) | $O_2$ | 22 | 15 |
| 4 | – | $O_2$ | 72 | – |
| 5 | Glutaryl (3) | Air | 72 | 5 |
| 6 | Benzoyl (6) | $O_2$ | 22 | 15 |
| 7 | Phtaloyl (3) | Air | 72 | 8 |
| 8 | Phtaloyl (3) | $O_2$ | 22 | 20 |
| 9 | Valeryl (6) | Air | 72 | 7 |
| 10 | Valeryl (6) | $O_2$ | 22 | 26 |

valeryl chloride, an increased yield of **7** to 20 and 26% was, respectively, obtained (Table 1, entries 8 and 10). Under these conditions the procedure appears to be of good reliability constituting a valid alternative to the use of tribromide as oxidizing agent.[13]

Analogously to the oxidation reported by Biali,[9] formation of monospirodienone **7** in the presence of $O_2$/NaH/acyl-chloride probably involves an electron transfer reaction. Deprotonation of a phenol through the base and oxidation of the acyl chloride to peroxide radical[14] are key steps for the obtaining of the monospirodienone derivative. Moreover, the involvement of OH deprotonation by a strong base, such as NaH, is demonstrated by the absence of **7** when pyridine was utilized as base.




**8** R = $CH_3$
**8a** R = $CH_2CH_3$

As demonstrated for other calixarene spirodienone derivatives,[9b,15] compound **7** can be considered a very useful substrate for the synthesis of a variety of interesting large-ring calixarene derivatives otherwise hardly obtainable. Thus, treatment of **7** with MeI and $Cs_2CO_3$ in acetone gave hexamethoxy-monospirodienone **7a** in quantitative yield. The appearance in its $^1$H NMR spectrum of six equally intense OMe singlets was proof of the occurred methylation.[10] Reduction of **7a** with $LiAlH_4$ in THF provided in quantitative yield the known 1,2-dihydroxy-hexamethoxycalix[8] **5**.[6]

Acid treatment of **7** with MeOH or EtOH produces its rearrangement to xantheno derivatives **8** and **8a** (both 75% yield). This high yield and the lack of ring-opening products, as observed instead for calix[5]arenes,[9b] suggest that the xanthene moiety is easily accommodated within an unstrained calix[8]arene macrocycle. The presence of broad signals for $ArCH_2Ar$ groups in the $^1$H NMR spectra of **8** and **8a** indicated their conformational mobility.[16]

In conclusion, the present work describes the first examples of singly and doubly intrabridged carboxylic ester derivatives of *p-tert*-butylcalix[8]arene. As expected, the introduction of ester intrabridging modifies the conformational features of the macrocycle, and preorganization of the calixarene skeleton is evident in the doubly-bridged derivative **6**, preluding to derivatives with improved host ability.[17] Rather serendipitously, we have also found a new approach for the preparation of calixarene monospirodienones based on the $O_2$/NaH/acyl-chloride oxidizing system, which appears a valid alternative to the tribromide/base reagent. The presence of diene, hydroxyl and carbonyl groups makes monospirodienone **7** a very attractive intermediate for the preparation of new modified calix[8]arene derivatives with novel chemical properties.

## Acknowledgements

Financial support from the Italian MIUR (Supramolecular Devices Project) is gratefully acknowledged. We thank Professor S. E. Biali for helpful discussions and Professor M. Piattelli for a critical reading of the manuscript. Thanks are also due to Mr. R. Rapisardi (I.C.T.P.-Sez. di Catania C.N.R.) for FAB MS measurements and to Dr. V. Sgarlata for collaboration during the preparation of her thesis.

## References

1. For comprehensive reviews on intrabridged calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713; (b) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998; (c) *Calixarenes 2001*; Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens J.; Eds.; Kluwer: Dordrecht, 2001.
2. (a) van Loon, J.-D.; Kraft, D.; Ankoné, M. J. K.; Verboom, W.; Harkema, S.; Vogt, W.; Böhmer, V.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5176; (b) Kanamathareddy, S.; Gutsche, C. D. *J. Am. Chem. Soc.* **1993**, *115*, 6572; (c) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 13; (d) Kraft, D.; Böhmer, V.; Vogt, W.; Ferguson, G.; Gallagher, J. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1221; (e) Ross, H.; Lüning, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2555.
3. Gloede, J.; Ozegowski, S.; Matt, D.; De Cian, A. *Tetrahedron Lett.* **2001**, *42*, 9139.
4. Sugioka, T.; Hay, A. S. J. *Polym. Sci.: Part A: Polym. Chem.* **2001**, *39*, 1149.
5. $^1$H NMR data for **2**–**4** and **4a**. Compound **2**: (250.13 MHz, $C_6D_6$, 350 K) $\delta$ 1.17, 1.23, 1.25, 1.29 (s, 18H each), 1.82, 2.49 (br s, 4H each), 3.79, 3.83, 3.85, 3.86, 3.92 (s, 4H, 4H, 4H, 2H, 2H), 7.03 (d, $J$=2.2 Hz, 4H), 7.11–7.18 (overlapped, 6H), 7.19 (d, $J$=2.5 Hz, 2H), 7.28 (d, $J$=2.5

Hz, 2H), 7.44 (d, $J=2.2$ Hz, 2H). Compound **3**: (250.13 MHz, $CDCl_3$, 325 K) $\delta$ 1.09, 1.21, 1.24, 1.28, 1.30 (s, 9H, 9H, 18H, 18H, 18H), 2.28 (br s, 4H), 3.76, 3.82, (s, 4H each), 3.87, 3.92 (br s, 4H each), 6.45 (s, 2H), 7.04 (d, $J=2.2$ Hz, 4H), 7.09 (s, 2H), 7.15 (d, $J=2.5$ Hz, 2H), 7.18 (d, $J=2.2$ Hz, 2H), 7.22 (d, $J=2.0$ Hz, 2H), 7.23 (d, $J=2.2$ Hz, 2H), 8.26 (br s, 2H); 8.55 (br s, 1H). Compound **4**: (250.13 MHz, $C_6D_6$, 350 K) $\delta$ 1.15, 1.23, 1.29, 1.32 (s, 18H each), 1.68, 2.45 (br s, 4H each), 3.80, (s, 6H), 3.85 (s, 8H), 3.92 (s, 2H), 6.93 (d, $J=2.2$ Hz, 2H), 7.11 (d, $J=2.5$ Hz, 2H), 7.13–7.19 (overlapped, 6H); 7.23 (s, 2H), 7.26 (br s, 4H). Compound **4a**: (250.13 MHz, $CDCl_3$, 298 K) $\delta$ 0.90 (br s, 4H), 1.06, 1.12, 1.13, 1.32 (s, 18H each), 1.75 (br s, 4H), 3.27, 3.39 (s, 6H each), 3.72 (s, 4H), 3.75 (s, 6H), 3.91, 3.95, 3.96, 4.00 (s, 4H, 4H, 2H, 2H), 6.60 (d, $J=2.5$ Hz, 2H), 6.82 (d, $J=2.3$ Hz, 2H), 6.91 (d, $J=2.5$ Hz, 2H), 7.00 (br s, 4H), 7.11 (d, $J=2.5$ Hz, 2H), 7.16 (d, $J=2.3$ Hz, 2H), 7.23 (d, $J=2.5$ Hz, 2H).

6. Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *J. Org. Chem.* **1998**, *63*, 6852.
7. (a) Hesek, D.; Inoue, Y.; Drew, M. G. B.; Beer, P. D.; Hembury, G. A.; Aoki, F. *Org. Lett.* **2000**, *2*, 2237; (b) Tairov, M. A.; Vysotsky, M. O.; Kalchenko, O. I.; Pirozhenko, V. V.; Kalchenko, V. I. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1405 and references cited therein.
8. (a) Geraci, C.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 7627; (b) Caccamese, S.; Principato, G.; Geraci, C.; Neri, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1169.
9. (a) Aleksiuk, O.; Grynszpan, F.; Biali, S. E. *J. Chem. Soc., Chem. Commun.* **1993**, 11; (b) Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Am. Chem. Soc.* **1995**, *117*, 9645. For a review on spirodienone calixarenes, see: Aleksiuk, O.; Grynszpan, F.; Litwak, M. A.; Biali, S. E. *New J. Chem.* **1996**, *20*, 473 and Ref. 1c: Biali, S. E. Chapter 14, pp. 266–279.
10. Compound **7** was already mentioned by Biali (see: Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *Pure Appl. Chem.* **1996**, *68*, 1249), but no spectral data have yet been reported. $^1$H NMR data for **7** and **7a**. Compound **7** (250.13 MHz, $CDCl_3$, 295 K) $\delta$: 1.10, 1.19, 1.23, 1.24, 1.26, 1.28, 1.29, 1.31 (s, 9H each), 3.19–3.39 (AB, $J=15.9$ Hz, 2H), 3.48 (br s, 1H), 3.58–4.43 (AX, $J=16.3$ Hz, 2H), 3.60–4.30 (overlapped, 11H), 6.35 (d, $J=2.3$ Hz, 1H), 6.55 (br s, 1H), 6.95 (br s, 1H), 7.00 (d, $J=2.2$ Hz, 1H), 7.08 (d, $J=2.2$ Hz, 1H), 7.11–7.17 (overlapped, 6H), 7.18 (d, $J=2.7$ Hz, 1H), 7.20 (d, $J=2.7$ Hz, 1H), 7.21–7.29 (overlapped, 3H), 8.52, 9.40, 9.62, 9.76, 9.88, 10.04 (br s, 1H each). Compound **7a**: $^1$H NMR (400.13 MHz, $CDCl_3$, 295 K) $\delta$ 0.97, 1.01, 1.08, 1.09, 1.10, 1.13, 1.17, 1.19 (s, 9H each), 3.12 (d, $J=15.6$ Hz, 1H), 3.29 (s, 3H), 3.33 (s, 3H), 3.38 (s, 3H), 3.41 (br s, 1H), 3.45 (s, 3H), 3.46 (s, 3H), 3.49 (s, 3H), 3.55 (d, $J=16.2$ Hz, 1H), 3.75 (d, $J=16.4$ Hz, 1H), 3.84 (d, $J=15.9$ Hz, 1H), 3.93 (d, $J=15.4$ Hz, 1H), 3.97 (d, $J=14.7$ Hz, 2H), 4.02 (br s, 4H), 4.06 (d, $J=15.6$ Hz, 2H), 4.10 (d, $J=15.1$ Hz, 2H), 6.11, 6.75, 6.77, 6.89, 6.90 (br s, 1H each), 6.92–7.19 (overlapped, 11H).
11. Additional useful information at this regard were kindly provided by Professor S. E. Biali (personal communication).
12. For a discussion on the OH chemical shift in other calix[8]arene derivatives, see: (a) Neri, P.; Battocolo, E.; Cunsolo, F.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1994**, *59*, 3880; (b) Geraci, C.; Piattelli, M.; Chessari, G.; Neri, P. *J. Org. Chem.* **2000**, *65*, 5143.
13. It was recently shown that a mixture of $I_2$/KOH/PEG can also be used as the oxidation reagent (Wang, W.-G.; Zhang, W.-C.; Huang, Z.-T. *J. Chem. Res. (S)* **1998**, 462).
14. It is known that $RC(O)O_2^{\bullet}$ is among the most strongly oxidizing peroxyl radicals (von Sonntag, C.; Schuchamann, H.-P. In *Peroxyl Radicals*; Alfassi, Z., Ed.; Wiley: New York, 1997; Chapter 8, pp. 173–234).
15. (a) Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 5482; (b) Agbaria, K.; Wöhnert, J.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 7059; (c) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495; (d) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136.
16. $^1$H NMR data for **8** and **8a**. Compound **8**: (400.13 MHz, $CDCl_3$, 295 K) $\delta$ 1.01, 1.05, 1.20 (s, 9H each), 1.25 (s, 27H), 1.26 (s, 9H) 1.31 (s, 9H), 3.70–3.90 (overlapped, 8H), 3.84 (s, 3H), 3.92 (br s, 2H), 3.96 (s, 2H), 4.01 (br s, 4H), 6.49, 6.55, 6.89, 6.92, 7.09 (br s, 1H each), 7.13, 7.15 (br s, 4H each), 7.18 (d, $J=2.0$ Hz, 1H), 7.20 (d, $J=2.0$ Hz, 1H), 8.47 (br s, 1H), 8.53 (br s, 1H), 9.82 (s, 1H), 9.87 (s, 1H), 9.94 (br s, 2H). Compound **8a**: (400.13 MHz, $CDCl_3$, 295 K) $\delta$ 0.98 (s, 9H), 1.03 (s, 9H), 1.22 (s, 9H), 1.24 (s, 9H), 1.25 (s, 9H), 1.26 (s, 9H), 1.27 (s, 9H), 1.30 (s, 9H), 1.52 (t, 3H), 3.75–3.90 (overlapped, 8H), 3.91 (s, 2H), 3.93 (br s, 2H), 3.94 (s, 2H), 4.02 (br s, 4H), 6.42 (br s, 1H), 6.50 (br s, 1H), 6.91 (br s, 1H), 6.96 (s, 1H), 7.08 (bs, 1H), 7.09 (d, $J=2.3$ Hz, 1H), 7.117 (d, $J=2.6$ Hz, 1H), 7.124 (d, $J=2.6$ Hz, 2H), 7.14 (d, $J=2.3$ Hz, 2H), 7.15 (d, $J=2.3$ Hz, 2H), 7.18 (d, $J=2.6$ Hz, 1H), 7.20 (d, $J=2.3$ Hz, 1H), 8.42 (bs, 4H), 9.93 (br s, 2H).
17. For examples of conformationally blocked bridged calix[8]arenes, see: (a) Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917; (b) Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2002**, *4*, 2649.