Pergamon

Tetrahedron Letters 43 (2002) 8875–8878

TETRAHEDRON LETTERS

Convenient regioselective functionalization at the upper-rim of *p-tert*-butylcalix[8]arene through a protection–deprotection procedure†

Carmine Gaeta, Luisa Gregoli, Marco Martino and Placido Neri*

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

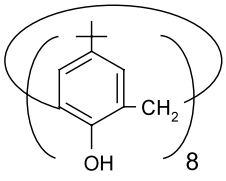
Received 2 August 2002; accepted 3 October 2002

Abstract—A viable method to obtain calix[8]arenes selectively functionalized at the upper rim of 1,5-aromatic rings is reported. The procedure relies on protected, readily accessible 1,5-xylylene-bridged derivatives, which are easily deprotected by hydrogenolysis. The method allowed the synthesis of the first examples of calix[8]arenes partially substituted with *p*-nitro, *p*-amino, quinone and hydroquinone functionalities. © 2002 Elsevier Science Ltd. All rights reserved.

In the last two decades the chemical modification of calix[*n*]arenes ($n=4$, 6, 8), has been actively investigated, enabling the synthesis of variously shaped hosts valuable in ion or molecular recognition.[1] In particular, calix[8]arenes have already shown interesting selective complexing properties toward C_{60}-fullerene,[2] cesium[3] or strontium[4] cations, and further results can be expected providing that new synthetic routes to differently functionalized calix[8]arene hosts became amenable.

Notwithstanding significant progresses made in the regioselective functionalization at the lower rim of the calix[8]arene macrocycle its selective modification at the upper rim still remains largely unexplored.[5] In fact, only two examples are known concerning: (i) the selective removal of a single *tert*-butyl group from an heptabenzoyl calix[8]arene derivative and the subsequent oxidative coupling;[6] and (ii) an acid-promoted '7+1' fragment condensation affording in 9% yield a *p-tert*-butylcalix[8]arene bearing two carboxyethyl groups at the *para* position of 1,5-aromatic rings.[7]

Current knowledge on smaller calixarenes suggests as the most convenient selective upper rim functionalization the one based on the lower reactivity of substituted versus unsubstituted phenolic rings of partially *O*-derivatized compounds.[8] Therefore, we have investigated this approach for the calix[8]arene macrocycle and we wish to report here a convenient method of regioselective functionalization at the upper rim of *p-tert*-butylcalix[8]arene **1** based on a protection–deprotection procedure.



1

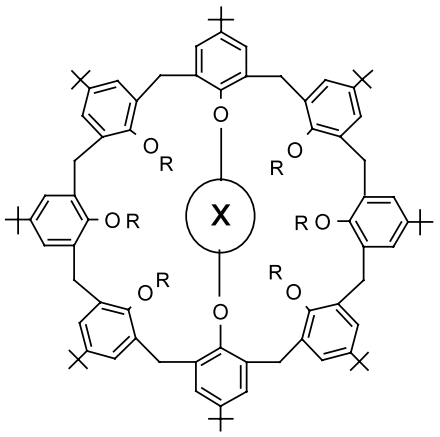
To this end, a useful protected derivative could be a xylylene-bridged calix[8]arene providing that it is readily accessible. This kind of intramolecular bridging has already been investigated by our[9] and Shinkai's[3a] groups, but the reported derivatives are of limited convenience due to the relatively modest yields coupled to the need of chromatographic separations. Therefore, we attempted to extend our recently reported efficient procedure[10] for the preparation of 1,5-crown- or 1,5-tetramethylene-bridged calix[8]arenes to xylene-based bis-electrophiles. In fact, under these conditions the 1,5-bridging with short spacers appears to be favored with respect to the longer ones.

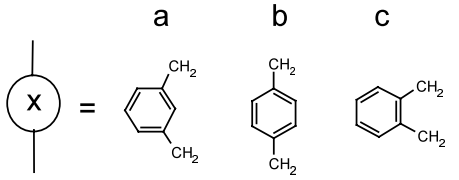
Keywords: calixarenes; calix[8]arenes; upper-rim functionalization; protection–deprotection.

* Corresponding author. Tel.: +39-089-965262; fax: +39-089-965296; e-mail: neri@unisa.it

† Dedicated to the memory of Professor Guido Sodano (Università di Salerno).

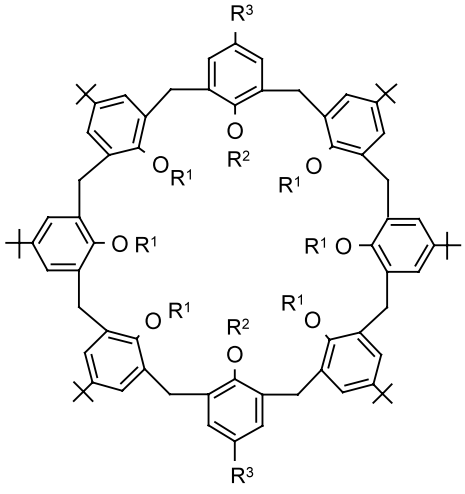
PII: S0040-4039(02)02204-9





2 R = H
3 R = *n*-Pr
4 R = Me

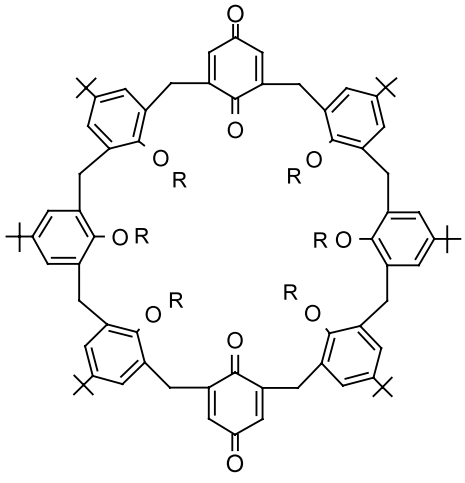
Thus, the reaction of *p*-*tert*-butylcalix[8]arene **1** with 2 equiv. of 1,3-bis(bromomethyl)benzene in DMF (at 70°C) in the presence of Cs_2CO_3 (8 equiv.) as base afforded 1,5-(*m*-xylylene)-bridged calix[8]arene **2a** in 80% yield, after the usual workup.[11,12] Interestingly, the crude product is sufficiently pure, not requiring chromatography for its use in subsequent synthetic manipulations. This successful result induced us to apply the above procedure also to the corresponding *ortho* and *para* isomeric bridges. In this way, 1,5-(*p*-xylylene)- **2b** and 1,5-(*o*-xylylene)-bridged calix[8]arene **2c**[13] were obtained in 75 and 50% yield, respectively.[12] As in the case of **2a**, the crude reaction product of **2b** was directly usable for further functionalizations.



5 R^1 = *n*-Pr; R^2 = H; R^3 = Bu*t*
6 R^1 = Me; R^2 = H; R^3 = Bu*t*
7 R^1 = *n*-Pr; R^2 = H; R^3 = NO_2
8 R^1 = Me; R^2 = H; R^3 = NO_2
9 R^1 = R^2 = *n*-Pr; R^3 = NO_2
10 R^1 = R^2 = *n*-Pr; R^3 = NH_2
13 R^1 = *n*-Pr; R^2 = H; R^3 = OH
14 R^1 = Me; R^2 = H; R^3 = OH
15 R^1 = *n*-Pr; R^2 = H; R^3 = H
16 R^1 = Me; R^2 = H; R^3 = H

Compounds **2a** and **2b** were smoothly hexapropylated by treatment with *n*-PrI in acetone to give **3a** and **3b** in 75 and 77% yield, respectively. In a similar way, the hexamethylated derivatives **4a** and **4b** were obtained in high yields (74 and 78%, respectively) by Cs_2CO_3-promoted alkylation with MeI. Removal of the xylylene bridge of **3a**–**b** and **4a**–**b** was easily accomplished by hydrogenolysis (H_2, Pd/C) to give hexapropoxy- and hexamethoxy-calix[8]arene-1,5-diol **5** and **6**, in almost quantitative yield.[12] Thus, this three-step protection–deprotection procedure afforded two 1,2,3,5,6,7-hexasubstituted calix[8]arenes having two diametrically disposed residual OH groups in an overall 60 and 54% yield. It is worthy to note that only one example of this kind of hexasubstituted derivative has been isolated in very low yield (7%) in a study on the alkylation of **1** with *p*-methylbenzyl bromide.[14]

1,5-Dihydroxycalix[8]arenes **5** and **6** represent the desired candidates for transferring the lower rim substitution pattern at the upper rim. Therefore, some typical reactions of calixarene chemistry were performed on these derivatives. Thus, treatment with HNO_3 allowed the selective *ipso*-nitration[8] at the free phenolic rings of **5** and **6** yielding 1,5-dinitrocalix[8]arenes **7** and **8**, both in 40% yield. In turn, **7** was exhaustively propylated to give **9** (70%), which was easily reduced with H_2/Raney-Ni to the corresponding 1,5-diaminocalix[8]arene **10** (60%). Undoubtedly, this latter compound is amenable to further synthetic elaboration to give compounds such as amides, ureas and peptides, particularly useful in molecular recognition or self-assembly.



11 R = *n*-Pr
12 R = Me

Quinone group represents another useful functionality introducible in **5** or **6**, that is unprecedented in calix[8]arene chemistry to date.[5] Direct selective transformation of *p*-*tert*-butylphenol rings to quinone has been accomplished with Tl(III) based oxidants on the smaller calixarenes.[8] Therefore, we subjected 1,5-dihydroxycalix[8]arenes **5** and **6** to treatment with $Tl(OCOCF_3)_3$ in the presence of trifluoroacetic acid (TFA) to give 1,5-calix[8]diquinones **11** and **12** in 25–28% yield. Reduction of quinone functions of both compounds with $NaBH_4$ yielded 1,5-calix[8]dihydroquinones **13** and **14** in quantitative yield.

An additional route to the upper rim functionalization could involve the selective de-*tert*-butylation as the primary step. Consequently, we investigated the selective *trans*-butylation of 1,5-dihydroxycalix[8]arenes **5** and **6** using $AlCl_3$ in the presence of toluene or phenol as acceptor. Unfortunately, under a large variety of conditions only modest amounts (10–14%) of the 1,5-de-*tert*-butylated calix[8]arenes **15** and **16** could be isolated from reaction mixtures containing products of further de-alkylation and/or unreacted starting material.

Compounds **2**–**16** were fully characterized by elemental analysis and spectral data. Molecular masses were confirmed by FAB(+) mass spectrometry, while ^1H and ^{13}C NMR data were fully consistent with the synthetic transformation.[12] In particular, the presence of two orthogonal symmetry elements was always readily evident from the ^1H NMR spectra acquired at room temperature (some representative examples are shown in Fig. 1). In fact, compounds **2**–**16** are all conformationally mobile, and give rise to singlets for the two groups of symmetry related $ArCH_2Ar$ groups. Only in the case of hexapropylated 1,5-(xylylene)-bridged calix[8]arenes **2** significantly broadened signals were observed indicating a slightly reduced conformational mobility. This is in accordance with recent results from our group indicating that groups bulkier than *n*-hexyl or benzyl are required to curtail conformational inversion in a similar 1,5-tetramethylene-bridged calix[8]-arene.[15]

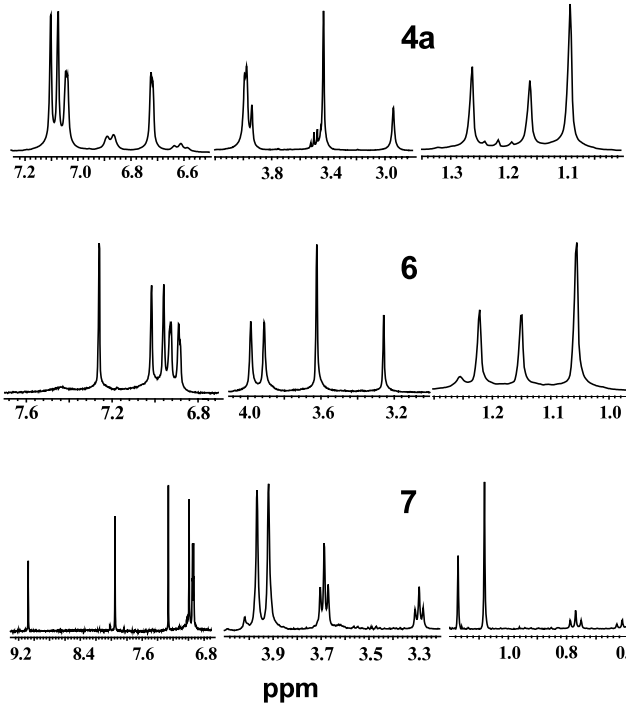


Figure 1. Significant portions of the ^1H NMR spectra (400 MHz, $CDCl_3$, 298 K) of compounds **4a**, **6**, and **7** (different scales are used).

In conclusion, the present paper reports on a convenient method to obtain calix[8]arenes selectively functionalized at the upper rim of 1,5-aromatic rings. The procedure relies on protected, readily accessible 1,5-xylylene-bridged derivatives, which can be easily deprotected by hydrogenolysis. The resulting products are susceptible of selective functionalization at the opposite aromatic rings of calix[8]arene macrocycle. This procedure has thus enabled the synthesis of the first examples of calix[8]arenes partially substituted with *p*-nitro, *p*-amino, quinone and hydroquinone functionalities. These results can be considered as a groundwork for an expansion of the potentialities of calix[8]arene macrocycle in host–guest and supramolecular chemistry.

Acknowledgements

Financial support from the Italian MURST (Supramolecular Devices Project) is gratefully acknowledged. Thanks are due to Mr. R. Rapisardi (I.C.T.P., Sez. di Catania, C.N.R.) for FAB MS measurements.

References

1. For general reviews on 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) Atwood, J. L.; Koutsantonis, G. A.; Raston, C. L. *Nature* **1994**, *368*, 229; (b) Suzuki, T.; Nakashima, K.; Shinkai, S. *Chem. Lett.* **1994**, 699; (c) See Ref. 1c: Zhong, Z.-L.; Ikeda, A.; Shinkai, S.; Chapter 26, pp. 476–495.
3. (a) Ikeda, A.; Akao, K.; Harada, T.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 1621; (b) Ikeda, A.; Suzuki, Y.; Akao, K.; Shinkai, S. *Chem. Lett.* **1996**, 963; (c) Geraci, C.; Chessari, G.; Piattelli, M.; Neri, P. *Chem. Commun.* **1997**, 921.
4. Casnati, A.; Barboso, S.; Rouquette, H.; Schwing-Weill, M.-J.; Arnaud-Neu, F.; Dozol, J.-F.; Ungaro, R. *J. Am. Chem. Soc.* **2001**, *123*, 12182.
5. See Ref. 1c, Chapter 5, pp. 89–109.
6. Bottino, A.; Cunsolo, F.; Piattelli, M.; Garozzo, D.; Neri, P. *J. Org. Chem.* **1999**, *64*, 8018.
7. Tsue, H.; Ohmori, M.; Hirao, K. *J. Org. Chem.* **1998**, *63*, 4866. For a study on the formation of the numerous by-products of this reaction, see: Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071. Tsue, H.; Enyo, K.; Hirao, K. *Helv. Chim. Acta* **2001**, *84*, 849.

8. (a) van Loon, J. D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639; (b) de Mendoza, J.; Carramolino, M.; Cuevas, F.; Nieto, P. M.; Prados, P.; Reinhoudt, D. N.; Verboom, W.; Ungaro, R.; Casnati, A. *Synthesis* **1994**, *00*, 47.
9. (a) Cunsolo, F.; Piattelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917; (b) Cunsolo, F.; Consoli, G. M. L.; Piattelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 715.
10. (a) Geraci, C.; Piattelli, M.; Chessari, G.; Neri, P. *J. Org. Chem.* **2000**, *65*, 5143; (b) Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Neri, P. *Org. Lett.* **2001**, *3*, 1605.
11. **Synthesis of 1,5-xylylene-bridged calix[8]arenes 2a–c**: To a solution of **1** (0.5 g, 0.385 mmol) in DMF (75 ml) was added Cs_2CO_3 (1.0 g, 3.08 mmol) under stirring. The mixture was kept under stirring at 70°C for 2 h and then a solution of 1,2-, 1,3-, or 1,4-bis(bromomethyl)benzene (0.75, 0.75, and 0.77 mmol, respectively) in DMF (4 ml) was added dropwise. The reaction was stirred at 70°C for 24–36 h. After concentration under vacuum, the residue was triturated with 1N HCl (100 ml), collected by filtration, washed with MeOH and dried. Analytically pure samples were obtained by crystallization or by chromatography on silica gel.
12. Satisfactory microanalytical and spectral data were obtained for all new compounds. ^{1}H NMR data of some representative compounds are reported in the following. Compound **2a**: ^{1}H NMR (250 MHz, $CDCl_2CDCl_2$, 393 K), δ 1.10, 1.13, 1.16 [s, $(CH_3)_3$, 18H, 36H, 18H], 3.62, 3.92 (s, $ArCH_2Ar$, 8H, 8H), 5.34 (s, OCH_2, 4H), 7.00–7.12 (overlapped, ArH, 18H), 7.40 (s, ArH, 2H), 8.05 (bs, OH, 4H), 8.47 (bs, OH, 2H). Compound **3a**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 0.63, 0.85 (bt, $OCH_2CH_2CH_3$, 6H, 12H), 1.01, 1.22, 1.24 [s, $(CH_3)_3$, 18H, 18H, 36H], 1.83 (m, $OCH_2CH_2CH_3$, 12H), 3.53 (bt, $OCH_2CH_2CH_3$, 12H), 3.98 (bs, $ArCH_2Ar$ and OCH_2, 20H), 6.63, 6.96, 7.10, 7.14 (s, ArH, 4H, 4H, 6H, 6H). Compound **4a**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 1.09, 1.16, 1.26 [s, $(CH_3)_3$, 36H, 18H, 18H], 2.94, 3.43, (s, OCH_3, 6H, 12H), 3.94, (s, OCH_2, 4H), 3.98, 3.99 (s, $ArCH_2Ar$, 8H, 8H), 6.72, 7.04 (d, $J=2.0$ Hz, ArH, 4H, 4H), 7.07, 7.10 (s, ArH, 6H, 6H). Compound **4b**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 0.58, 1.16, 1.38 [s, $(CH_3)_3$, 18H, 36H, 18H], 3.65, 3.83 (s, OCH_3, 12H, 6H), 3.41, 4.04 (bs, $ArCH_2Ar$, 8H, 8H), 4.08 (s, OCH_2, 4H), 5.94, 6.73 (s, ArH, 4H, 4H), 6.88, 7.22 (d, $J=2.1$ Hz, ArH, 4H, 4H), 7.26 (s, ArH, 4H). Compound **5**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 0.39 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 6H), 0.86 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 12H), 1.00, 1.17, 1.22 [s, $(CH_3)_3$, 36H, 18H, 18H], 1.73 (m, $OCH_2CH_2CH_3$, 12H) 3.11 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 4H), 3.73 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 8H), 3.92, 3.97 (s, $ArCH_2Ar$, 8H, 8H), 6.82, 6.89 (s, ArH, 4H, 4H), 6.96, 7.00 (bs, ArH, 4H, 4H), 7.48 (s, OH, 2H). Compound **6**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 1.05, 1.15, 1.22 [s, $(CH_3)_3$, 36H, 18H, 18H], 3.26, 3.62, (s, OCH_3, 6H, 12H), 3.91, 3.98 (s, $ArCH_2Ar$, 8H, 8H), 6.88 (d, $J=2.1$ Hz, ArH, 4H), 6.93 (d, $J=2.1$ Hz, ArH, 4H), 6.95 (s, ArH, 4H), 7.01 (s, ArH, 4H), 7.42 (s, OH, 2H). Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 0.61, 0.77 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 6H, 12H), 1.08, 1.17, [s, $(CH_3)_3$, 36H, 18H], 1.41, 1.65 (m, $OCH_2CH_2CH_3$, 4H, 8H) 3.29, 3.69 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 4H, 8H), 3.92, 3.97 (s, $ArCH_2Ar$, 8H, 8H), 6.93, 6.94, 6.99, 7.95 (s, ArH, 4H, 4H, 4H, 4H), 9.07 (s, OH, 2H). Compound **11**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 0.75, 0.85 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 6H, 12H), 1.09, 1.20, [s, $(CH_3)_3$, 36H, 18H], 1.56 (m, $OCH_2CH_2CH_3$, 12H), 3.46, 3.53 (t, $J=7.2$ Hz, $OCH_2CH_2CH_3$, 4H, 8H), 3.73, 3.99 (s, $ArCH_2Ar$, 8H, 8H), 5.96, (s, Quin-H, 4H), 6.83 (s, ArH, 4H), 6.99, 7.06 (bd, $J=2.4$ Hz, ArH, 4H, 4H). Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$, 298 K), δ 1.08, 1.20 [s, $(CH_3)_3$, 18H, 36H], 3.46, 3.48 (s, OCH_3, 6H, 12H), 3.75, 4.00 (s, $ArCH_2Ar$, 8H, 8H), 5.96 (s, Quin-H, 4H), 6.83 (s, ArH, 4H), 6.99, 7.05 (d, $J=2.0$ Hz, ArH, 4H, 4H). Compound **14**: ^{1}H NMR [400 MHz, $(CD_3)_2CO$, 298 K], δ 1.11, 1.18 [s, $(CH_3)_3$, 36H, 18H], 3.32, 3.61 (s, OCH_3, 6H, 12H), 3.88, 4.00 (s, $ArCH_2Ar$, 8H, 8H), 6.48, 7.05 (s, ArH, 4H, 4H), 6.97, 7.08 (d, $J=2.4$ Hz, 4H, 4H), 7.24, 7.40 (s, OH, 2H, 2H).
13. Compound **2c** was previously obtained in 13% yield by Shinkai and co-workers, by direct alkylation of **1** in the presence of NaH (see Ref. 3a).
14. Neri, P.; Geraci, C.; Piattelli, M. *J. Org. Chem.* **1995**, *60*, 4126.
15. Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2002**, *4*, 2649.