Selective 1,2-Functionalization of Calix[4]arenes at the Lower Rim. Synthesis of a new type of bis-Calixcrown Ether

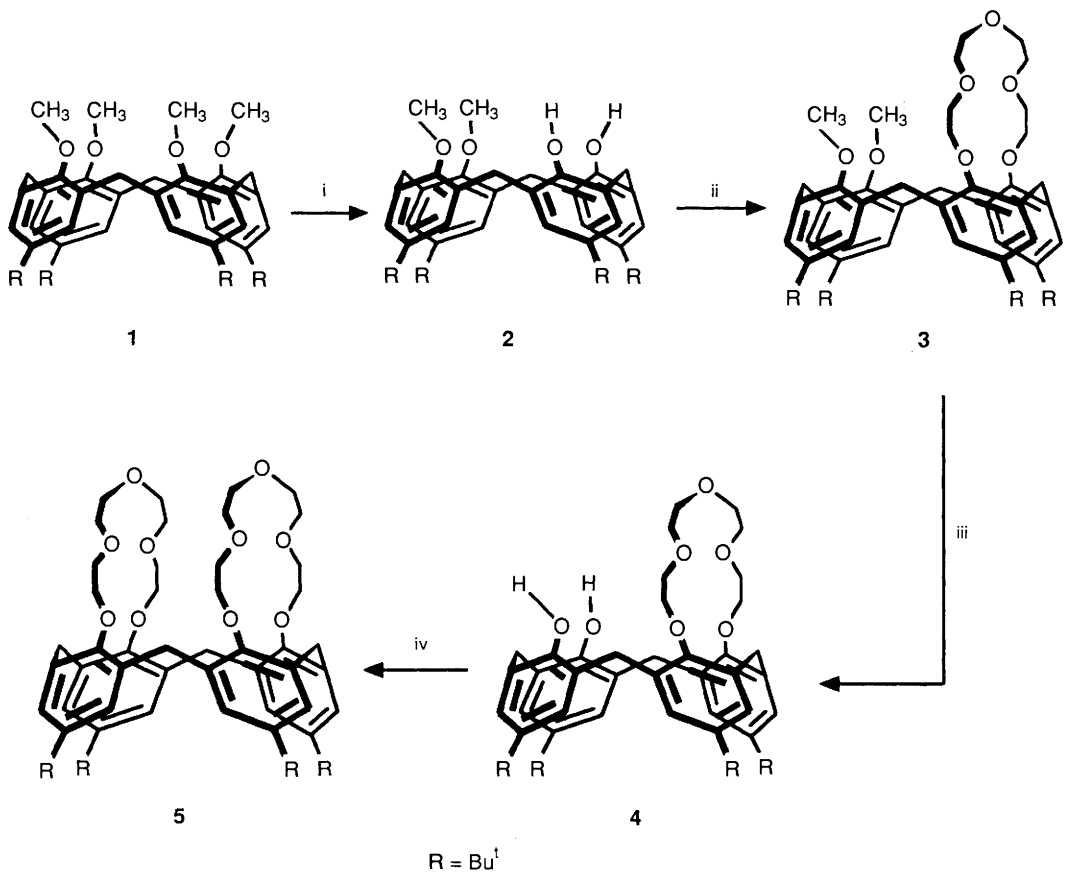
Arturo Arduini, Alessandro Casnati, Lorenzo Dodi, Andrea Pochini* and Rocco Ungaro

Istituto di Chimica Organica dell'Università Viale delle Scienze, I-43100 Parma, Italy

Proximal 1,2-bis-demethylation of tetramethoxy-*p*-t-butylcalix[4]arene **1** has been achieved for the first time by Ti(IV)-assisted reaction, which allows the synthesis of a new type of calixarene-based bis-crown ether.

The extensive study made in the last decade on the use of calixarenes[1] as ordered building blocks (or templates) for the construction of new cation receptors and carriers[2] has shown the importance of regio- and stereo-chemical factors in determining the efficiency and the selectivity of the ligands synthesized.[2,3]

These findings have stimulated the search for new regio- and stereo-selective functionalization of calix[4]arenes.



Scheme 1 *Reagents and conditions*: i, Ethanol free $CHCl_3$, 2 equiv. $TiBr_4$, room temperature, 20 min, (70%); ii, diethylene glycol di-*p*-toluenesulphonate, Bu^tOK, benzene, reflux (100%); iii, ethanol free $CHCl_3$, 2 equiv. $TiBr_4$, room temperature, 1 h (65%); iv, diethylene glycol di-*p*-toluenesulphonate, Bu^tOK, benzene reflux, 24 h (50%).

The present[4] and other authors[5] have recently reported on the selective 1,3-functionalization of these substrates both at the lower (phenolic OH groups) and upper (aromatic nuclei) rims, which has allowed the synthesis of new hosts that are potentially useful in supramolecular chemistry.

With the aim of finding new synthetically useful methodologies for the selective functionalization of calix[4]arenes we have undertaken a systematic study of the dealkylation of the easily prepared[1] calix[4]arene ethers in the presence of several ether cleavage reagents.

We have now found that when tetramethoxy-*p*-t-butylcalix-[4]arene **1** is treated with 2 equiv. of $TiBr_4$ in ethanol-free chloroform the 1,2-dimethoxy derivative **2** is obtained in good yield (Scheme 1).†

The regioselective 1,2-functionalization of calix[4]arenes at the lower rim is unusual in calixarene chemistry[1] and only one other example has been recently reported, by Pappalardo *et al.*[7] who attached picolyl groups on two adjacent OH group on the bottom rim of calix[4]arenes.

This new regioselective 1,2-demethylation method makes it possible to organize binding sites or functional groups on the lower rim of calix[4]arenes with a novel geometry, to obtain highly preorganized molecular receptors. As an attractive example we report the synthesis of a new type of bis-crown ether **5** that has the two polyether rings in close proximity on the bottom of the calix, fixed in the cone conformation. The synthesis has been accomplished in good overall yield by a sequence of dealkylation–alkylation reactions (Scheme 1).†

The intermediate calixcrown **3** has been obtained in quantitative yields through a previously reported procedure[8] and the subsequent 1,2-demethylation produces the dihydroxy-crown ether **4** in 65% yield. Finally the bis-crown ether **5** has been obtained in 50% yield using a high dilution (influction[9]) procedure. The new compound **5** is conformationally very rigid (CPK models) and highly preorganized for binding cations in a sandwich-type fashion.

The extensive studies[10] made in the past on other more flexible bis-crown ethers has shown that, in certain cases, cooperative effects render this family of ionophores more efficient and selective in cation binding than the monomeric crown ethers.

Preliminary extraction data show that compound **5** is able to bind alkali metal cations with the selectivity order $Rb^+ \approx K^+ \gg Na^+ > Cs^+$. We are currently investigating the scope of this new regioselective 1,2-dealkylation method in calixarene chemistry and synthesizing new bis-calix[4]arene crown ethers with different sizes.

This work was supported by the Italian Ministry of University, Scientific and Technological Research (M.U.R.S.T. 40%).

Received, 6th August 1990; Com. 0/03611K

† All compounds synthesized **2–5** give satisfactory elemental analyses and show molecular ion on DCI Mass Spectra. Compound **2** exists as a mixture of stereoisomers and gives a complex ^1H NMR spectrum; the X-ray crystal structure of a derivative of compound **2** confirms the 1,2-substitution.[6] ^1H NMR ($CDCl_3$, 100 MHz) of compound **5**: δ 1.17 (36H, s, CH_3), 3.12 and 3.21 (4H, d, $ArCH_2Ar$, *J* 13 Hz), 3.7–4.3 (32H, m, OCH_2CH_2O), 4.38 and 4.58 (4H, d, $ArCH_2Ar$), 6.82 (8H, s, ArH).

References

1 (*a*) C. D. Gutsche, *Calixarenes, Monograph in Supramolecular Chemistry*, vol. 1; ed. F. J. Stoddart; RSC, Cambridge, 1989; (*b*) *Calixarenes, a Versatile Class of Macrocyclic Compounds*, eds. J. Vicens and V. Böhmer, Kluwer, Dordrecht, 1990.
2 R. Ungaro and A. Pochini, *Calixarenes, a Versatile Class of Macrocyclic Compounds*, Kluwer, Dordrecht, 1990, p. 133–155.
3 P. J. Dijkstra, J. A. J. Brunink, K. E. Bugge, D. N. Reinhoudt, S. Harkema, R. Ungaro, F. Ugozzoli and E. Ghidini, *J. Am. Chem. Soc.*, 1989, **111**, 7567; E. Ghidini, F. Ugozzoli, R. Ungaro, S. Harkema, Abv. El-Fadl and D. N. Reinhoudt, *J. Am. Chem. Soc.*, in the press; S. Shinkai, T. Otsuka, K. Fujimoto and T. Matsuda, *Chem. Lett.*, 1990, 835.
4 R. Ungaro, A. Pochini and G. D. Andreeti, *J. Inclusion. Phenom.*, 1984, **2**, 199; J. D. van Loon, A. Arduini, W. Verboom, G. J. Van Hummel, S. Harkema, R. Ungaro and D. N. Reinhoudt, *Tetrahedron Lett.*, 1989, **30**, 2681; J. D. van Loon, A. Arduini, L. Coppi, W. Verboom, A. Pochini, R. Ungaro, S. Harkema and D. N. Reinhoudt, *J. Org. Chem.*, in the press.
5 E. M. Collins, M. A. McKervey and S. J. Harris, *J. Chem. Soc., Perkin Trans. 1*, 1989, 372; K. No and M. Hong, *J. Chem. Soc., Chem. Commun.*, 1990, 572.
6 L. C. Groenen, J. D. van Loon, W. Verboom, S. Harkema, A. Casnati, R. Ungaro, A. Pochini, F. Ugozzoli and D. N. Reinhoudt, *J. Am. Chem. Soc.*, submitted.
7 F. Bottino, L. Giunta and S. Pappalardo, *J. Org. Chem.*, 1989, **54**, 5407.
8 C. Alfieri, E. Dradi, A. Pochini, R. Ungaro and G. D. Andreetti, *J. Chem. Soc., Chem. Commun.*, 1983, 1075.
9 L. Mandolini, *Adv. Phys. Org. Chem.*, 1986, **22**, 1.
10 J. Smid and R. Sinta, *Top. Curr. Chem.*, 1984, **121**, 105 and references cited therein; I. Ikeda, T. Katayama, M. Okahara and T. Shono, *Tetrahedron Lett.*, 1981, 1573; T. Maeda, M. Ouchi, K. Kimura and T. Shono, *Chem. Lett.*, 1981, 1533; S. Shinkai and O. Manabe, *Top. Curr. Chem.*, 1984, **121**, 67.