

Resorcinarenes as Templates: A General Strategy for the Synthesis of Large Macrocycles

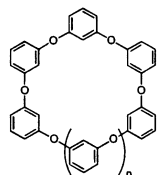
Xuehe Li, Thomas G. Upton, Corinne L. D. Gibb, and Bruce C. Gibb*

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

Received October 28, 2002; E-mail: bgibb@uno.edu

The use of templation to affect the formation of one product, from a reaction milieu that could potentially form many, is an increasingly important aspect of supramolecular chemistry.¹ The synthesis of crown ethers² is just one example of an important class of compounds whose availability predominantly relies on (metal ion) templation.³ However, for the synthesis of crown ethers possessing more than approximately 24 atoms in their macrocyclic chain, metal ion templation is less useful. As a result, large crown ethers are usually synthesized in a stepwise manner. Although fine-tuning can give reasonable overall yields for these approaches,⁴ by and large the combination of a stepwise process, the slow rate of the final cyclization step, as well as general purification difficulties, usually results in poor yields.⁵ Here we demonstrate that resorcinarenes, macrocycles that are themselves no strangers to supramolecular chemistry,⁶ can be used as covalent templates to engender the efficient synthesis of large crown ethers. The approach is a general one and should be applicable to the formation of other families of macrocycles.

Large, fully aromatic crown ethers are rare. The only two examples that have been reported^{5b} are hexabenzocrown-6 **1** and heptabenzocrown-7 **2**. Both were formed in low yield (<0.1%) using multiple Ullmann ether reactions. Initial studies into the metal binding properties of these derivatives were negative;^{5b} however, the limited amount of material precluded a thorough examination of their properties.

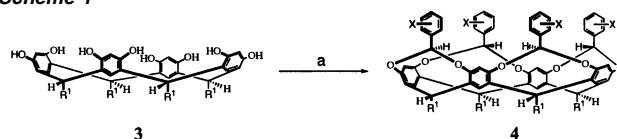


1 ($n = 1$) **2** ($n = 2$)

An alternative route to the synthesis of these types of compounds begins with resorcinarenes such as **3**.⁷ The stereoselective bridging of these compounds with benzal bromides yields a family of deep-cavity cavitands of general structure **4** (Scheme 1).⁸ The overall result of this process is to position the four new aromatic rings at set distances from each other. In other words, they are preorganized in a positional sense. This organization is apparent when the "upper" rings of **5** are linked in eight-fold Ullmann ether reactions involving resorcinol, 2-Me-resorcinol, or 5-Me-resorcinol (Scheme 2); the respective products, **6a–c**, are formed in 80–88% yield.^{9,10} This is a general process which can be expanded to include the synthesis of cavitands **6d**, **7**, and **8**. Thus, by treating **5** with 3,5-dihydroxybenzyl alcohol, hydroquinone, or 2,7-dihydroxy naphthalene, these cavitands can be isolated in 60, 45, and 70% yields, respectively.¹¹

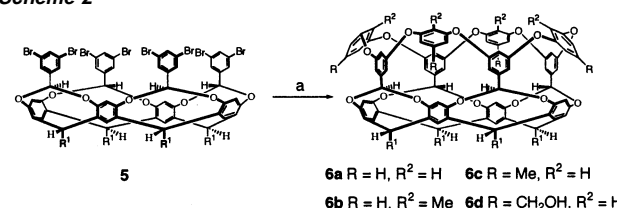
Removal of the resorcinarene template was initially attempted with dilute, aqueous HCl in THF. Only starting material was recovered. Indeed, only starting material was recovered after **6a**

Scheme 1^a



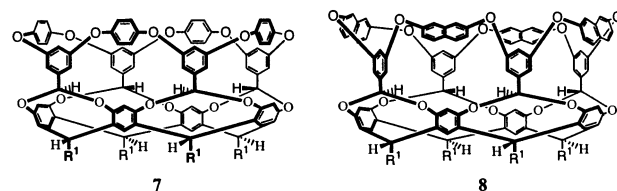
^a Key: (a) 4.4 equiv of the benzal bromide, excess K_2CO_3 , or DBU, DMA 60 °C, 3 d.

Scheme 2^a



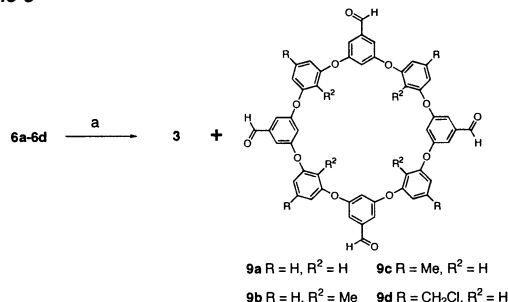
^a Key: (a) 4.4 equiv of the corresponding resorcinol, excess K_2CO_3 , CuO, pyridine, reflux, 7 d.

was dissolved in 1:1 EtOH and H_2SO_4 and the resulting solution was refluxed for 7 days. Presumably, under the reversible conditions, each acetal group that is cleaved has the chance to re-form



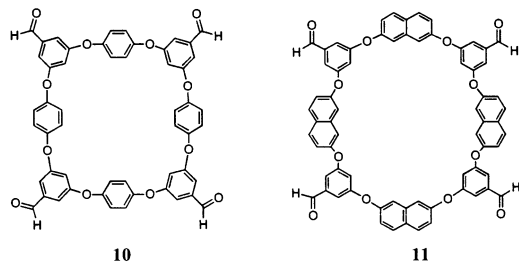
before a second acetal can be broken. Although $AlCl_3$ also proved ineffective, the stronger Lewis acid BBr_3 smoothly and rapidly furnished the removal of the template. After hydrolysis of the crude reaction mixture, the fully aromatic crown ether **9a** was isolated in 87% yield (Scheme 3).¹² This corresponds to a 50% yield starting from resorcinol **3** and the bridging material (3,5-dibromobenzal bromide). The 32-crown-8 derivative **9a** has not been previously

Scheme 3^a

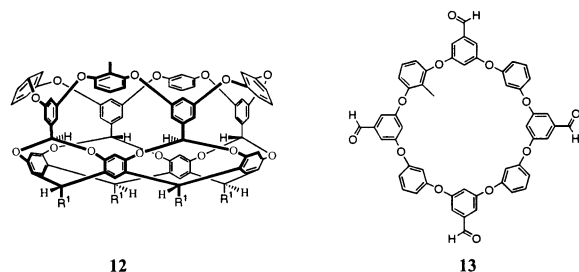


^a Key: (a) (1) For **6a–c**, 6 equiv of BBr_3 , CH_2Cl_2 , room temperature, 1 h; then CH_2Cl_2 /10% aqueous HCl, room temperature, 16 h. (2) For **6d**, 8 equiv of BCl_3 in $SOCl_2$; then 10% aqueous HCl, room temperature, 3 h.

reported. Hence, a precise measure of the efficiency of this templation protocol cannot be determined. Nevertheless, this approach is obviously a highly efficient route to previously inaccessible molecules. Exposing **6b–6c**, **7**, and **8** to conditions similar to those used in the synthesis of **9a** gave the corresponding 32-crown-8 ethers **9b** and **9c**, 36-crown-8 **10**, and 40-crown-8 **11** in 85–95% yield. This approach did not lead to the clean cleavage of the resorcinol moiety of **6d**. However, a combination of BCl_3 and SOCl_2 proved effective, producing highly functionalized **9d** in 71% yield.¹³



This strategy can be expanded to allow for the synthesis of lower symmetry crown ethers. Crown **13** is one such example. It is derived from precursor **12**, itself formed from **5** by a two-stage Ullmann ether process.¹⁴



The series of macrocycles reported here are all crown ethers. However, this approach should also be applicable to other macrocycles. Furthermore, as resorcinarenes¹⁵ and cavitands¹⁶ with up to seven resorcinol rings are now known, this methodology may be extended to the synthesis of even larger macrocycles. In theory, the only limitation to using resorcinarenes as templates is that the second bridging step, for example, **5** → **6a**, should not involve acidic or Lewis acid conditions, or else the acetal bridges will be cleaved.

In summary, we have demonstrated that resorcinarenes can be used as efficient templates for the synthesis of a variety of functionalized, aromatic crown ethers.

Acknowledgment. This work was supported by the National Science Foundation (CHE-0111133) and The Petroleum Research Fund administered by the American Chemical Society.

Supporting Information Available: Detailed experimental procedures and characterization data for compounds **6d**, **7–15**, and **8** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

References

- (1) Diederich, F.; Stang, P. J., Eds. *Templated Organic Synthesis*; Wiley-VCH: Weinheim, 2000.
- (2) For recent reviews, see: (a) Bradshaw, J. S.; Izatt, R. M.; Bordunov, A. V.; Zhu, C. Y.; Hathaway, J. K. In *Comprehensive Supramolecular Chemistry*; Lehn, J.-M., Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Elsevier Science Ltd.: London, 1996; Vol 1, p 35–95. (b) Bradshaw, J. S.; Izatt, R. M. *Acc. Chem. Res.* **1997**, *30*, 338–345. (c) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529–2586.
- (3) For examples of template effects and the formation of crown ethers, see: (a) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017–7036. (b) Greene, R. N. *Tetrahedron Lett.* **1972**, 1793–1796. (c) New Mandolini, L.; Reinhoudt, D. N.; De Jong, F.; Tomassen, H. P. M. *Tetrahedron Lett.* **1979**, *22*, 2067–2070. (d) Habata, Y.; Fujishiro, F.; Akabori, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, *9*, 953–957. (e) Bowsher, B. R.; Rest, A. J. *Inorg. Chim. Acta* **1981**, *53*, L175–L176. (f) Wingfield, J. N. *Inorg. Chim. Acta* **1980**, *45*, L157–L159.
- (4) Gibson, H. G.; Bheda, M. C.; Engen, P.; Shen, Y. X.; Sze, J.; Zhang, H.; Gibson, M. D.; Delaviz, Y.; Lee, S.-H.; Liu, S.; Wang, L.; Nagvekar, D.; Rancourt, J.; Taylor, L. T. *J. Org. Chem.* **1994**, *59*, 2186–2196.
- (5) (a) Masci, B. *Tetrahedron* **1989**, *45*(7), 2201–2212. (b) Kime, D. E.; Norymberski, J. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1048–1052.
- (6) (a) Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663–2704. (b) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests*; Royal Society of Chemistry: Cambridge, 1994.
- (7) All resorcinarenes and cavitands discussed here are phenethyl footed ($\text{R}^1 = \text{CH}_2\text{CH}_2\text{Ph}$).
- (8) (a) Xi, H.; Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *Chem. Commun.* **1998**, 1743–1744. (b) Xi, H.; Gibb, C. L. D.; Gibb, B. C. *J. Org. Chem.* **1999**, *64*, 9286–9288. (c) Green, J. O.; Baird, J.-H.; Gibb, B. C. *Org. Lett.* **2000**, *2*, 3845–3848.
- (9) Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2001**, *123*, 5849–5850.
- (10) Laugherey, Z.; Gibb, C. L. D.; Gibb, B. C. *Chem.-Eur. J.*, in press.
- (11) The reaction between **5** and 3,5-dihydroxybenzyl alcohol required more concentrated conditions than those used in the synthesis of **6a–c**. As a result, the amount of polymer increased at the expense of **6d**. We have also tried bridging with 3,5-dihydroxy benzoic acid and 3,5-dihydroxy benzaldehyde. The former gave no reaction, and the latter gave a very small amount of partially bridged intermediates.
- (12) The slightly weaker Lewis acid BCl_3 gave lower yields.
- (13) Using a combination of BBr_3 and SOCl_2 resulted in the formation of an inseparable mixture of macrocycles arising from Br/Cl exchange.
- (14) Gibb, C. L. D.; Li, X.; Gibb, B. C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4857–4862.
- (15) (a) Konishi, H.; Ohata, K.; Morikawa, O.; Kobayashi, K. *Chem. Commun.* **1995**, 309–310. (b) Konishi, H.; Nakamura, T.; Ohata, K.; Morikawa, O.; Kobayashi, K. *Tetrahedron Lett.* **1996**, *37*, 7383–7386.
- (16) Naumann, C.; Romàn, E.; Peinador, C.; Ren, T.; Patrick, B. O.; Kaifer, A. E.; Sherman, J. C. *Chem.-Eur. J.* **2001**, *7*, 1637–1645.

JA029116G