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‘Cloverleaf’ crown ether resorcin[4]arenes

Yanwei Cai, Peter P. Castro, Linda M. Gutierrez-Tunstad *

Department of Chemistry and Biochemistry, California State University Los Angeles, 5151 State University, Drive Los Angeles, CA 90032, USA

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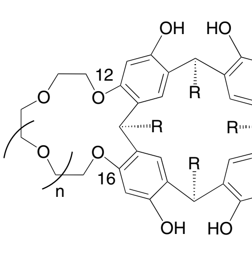
Abstract

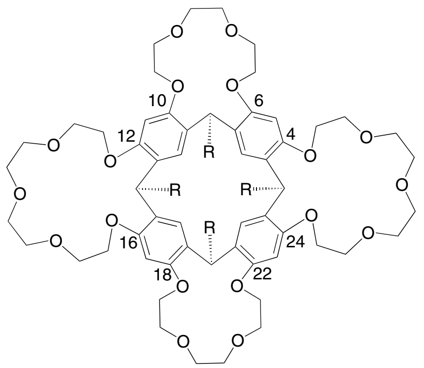
Crown ether resorcin[4]arenes **1a**, **1b**, and **2b** with a novel connectivity have been prepared from diquinoxaline cavitands in yields of 68%, 73%, and 25%, respectively. The reaction involves bridging the contiguous oxygen atom pairs with tri-, tetra- or pentaethylene glycol ditosylates.

The introduction of crown ethers by Charles Pedersen in the mid 1960s heralded the birth of Host–Guest chemistry.[1] Researchers have reported thousands of crown ethers and their substituted analogs capable of complexing cations such as lithium, sodium, potassium, and cesium as well as ammonium ions.[1,2] Crown ethers have been attached to various positions on porphyrins,[3] cyclodextrins,[4] calixarenes,[5] and resorcin[4]arenes.[6] Di- and polytopic crown receptors have been inspired by natural systems.[7] Compounds containing multiple crown ethers are of interest in the study of allosteric effects and multiple ion binding interactions.[6,7]

We describe here the synthesis of novel crown ether resorcin[4]arenes **1a**, **1b**, and **2b**, having one or two distal pairs of crown ethers annulated directly to the macrocycle via the peripheral resorcyl oxygen atoms, Figure 1. We use



1a n = 1
1b n = 2



2b

Fig. 1. ‘*Cloverleaf*’ resorcin[4]arene crown ethers, R = Pentyl.

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[*] Corresponding author. Tel.: +1 323 343 2307.
E-mail address: ltunsta@calstatela.edu (L. M. Gutierrez-Tunstad).

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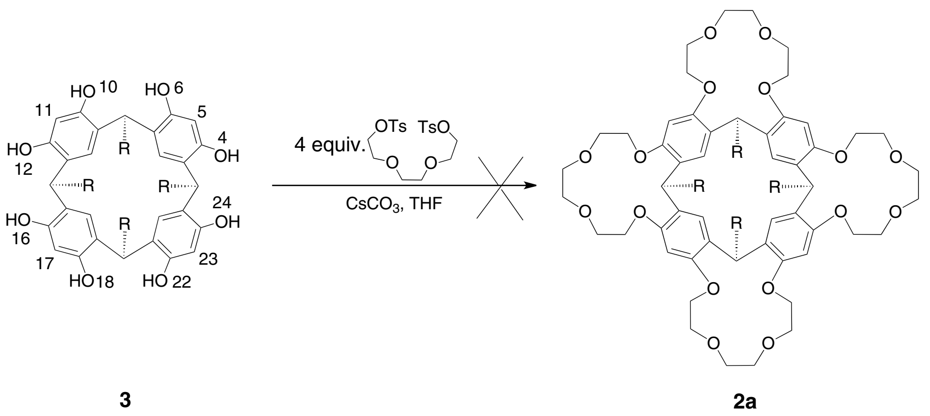


Scheme 1. Direct reaction of resorcin[4]arene (R = Pentyl) with triethylene glycol ditosylate.

the term '*Cloverleaf*' crown ethers because their CPK models resemble two- or four-leaf clovers. The two pairs of crowns need not be of the same size.

Direct synthesis of tetracrown cavitand **2a** was attempted by reacting resorcin[4]arene **3** with 4 equiv of triethylene glycol ditosylate under Williamson ether synthesis conditions for 48 h, Scheme 1.

Analysis of the crude reaction mixture by mass spectrometry revealed no masses consistent with the mono-di-, tri-, or tetracrown compounds. Only oligomeric material appeared to be present.

These are the first examples of resorcin[4]arenes bearing crown ethers which span contiguous oxygen atoms on adjacent aryl rings, for example, positions 6 and 10 or 12 and 16 (see compound **3** for numbering sequence). Earlier reported crown ether resorcin[4]arene compounds have the crowns extended from one or more of positions 5, 11, 17, and/or 23 or from the 'R' groups.[6a,c,d] Other examples have the crown ether spanning two aryl positions (5 and 11 or 5 and 17)[6e] or are attached on alternating oxygen atoms (4, 22 and 10, 16).[6b]

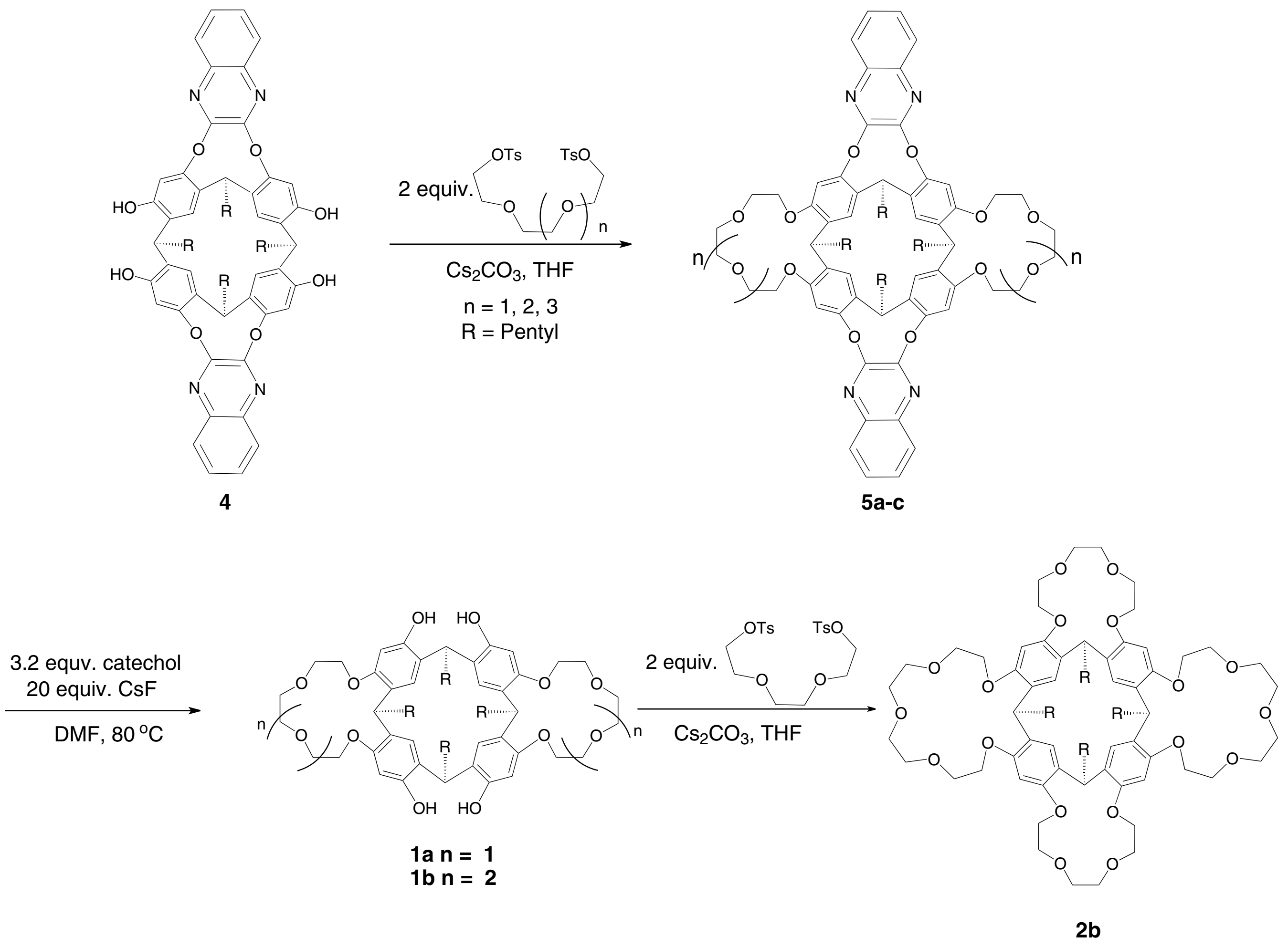
Resorcin[4]arene **3** is a versatile scaffold in supramolecular chemistry. Its well-defined bowl shape and eight phenolic groups around the rim of the bowl allow it to be bridged to form cavitands of different depths.[8] Cavitands bearing four identical bridges are usually obtained in excellent yields.[8a] However, the similar reactivity of the eight resorcyl oxygen atoms of **3** makes it challenging to prepare di- and tribridged analogs. Attempts by Cram and later by Diederich to make di- and tribridged cavitands by limiting the amount of bridging material (bromochloromethane or 2,3-dichloroquinoxaline) afforded low to moderate yields of their desired materials in addition to trace amounts of tetra-bridged material and oligomers.[9,10] In addition, the dibridged material consists of isomers, AB- and AC-, further reducing the yields.[10b] Masking some phenolic oxygens in **3** with acyl[11a,c] or tosyl[11b] groups results in protection that occurs at positions 4, 6, 16, and 18. This precludes the preparation of crown resorcin[4]-arenes of types **1** or **2**.

We have reported a methodology whereby two quinoxaline moieties can be extracted from tetraquinoxaline cavitand to yield AC-diquinoxaline cavitand **4** in excellent yields.[12] By using the quinoxaline excision methodology as a way to 'deprotect' the necessary positions of tetraquinoxaline cavitand, we have introduced crown ethers of various ring sizes on the periphery of resorcin[4]arene attached via adjacent, convergent oxygen atoms. The synthesis of di- and tetracrown cavitands **1a**, **1b**, and **2b** is shown in Scheme 2.

Diquinoxaline dicrown cavitands **5a–c** were prepared under high dilution conditions in THF by reacting AC- diquinoxaline tetrol **4** with 2 equiv of tri-, tetra-, or pentaethylene glycol ditosylates using Cs_2CO_3 as base. Separation by flash chromatography to remove oligomers afforded **5a**, **5b**, or **5c** in yields ranging from 13% to 35% depending on the crown size, see Table 1. We observed that larger rings provided lower yields. Repeating the quinoxaline excision reaction on **5a** or **5b** afforded di-crown cavitands **1a** or **1b**, respectively, in yields of 68–73%. Bridging of the vicinal oxygen pairs of **1b** with triethylene glycol ditosylate using Cs_2CO_3/THF afforded tetracrown cavitand **2b** in a 25% yield. Further elaboration of **1a** was not attempted at this time.

The structure of **2b** was confirmed by MALDI-TOF mass spectra, ^1H and ^{13}C NMR. Mass spectra showed a molecular ion peak for tetracrown **2b** at 1314.399 ($M+H^+$). The ^1H NMR spectrum of **2b** in acetone-d_6 at 298 K showed two broad singlets at 6.85 and 6.49 ppm in a 1:1 ratio for the aromatic bowl protons, two triplets at 4.86 and 4.69 ppm for the methine protons, an envelope of signals between 4.03 and 3.66 ppm for the crown protons and two broad singlets and a triplet at 1.85, 1.32, and 0.87 ppm, respectively, for the pentyl chain. The highly symmetrical structure of **2b** simplified the ^{13}C NMR. In particular the seven singlets at 71.14, 70.74, 70.33, 69.92, 69.67, 68.74, and 68.47 ppm were indicative of the crown ether carbons.

In conclusion, we have presented a method for the synthesis of new and novel resorcin[4]arenes having multiple



Scheme 2. Synthesis of 'four-leaf clover' crown-resorcin[4]arene **2b**.

Table 1
Isolated yields of resorcin[4]arene crown ethers

Compound	No. of oxygens	Yield (%) **5**	Yield (%) **1**	Yield (%) **2**
a	4	35	68	—
b	5	23	73	25
c	6	13	—	—

annulated crown ethers. These compounds extend the existing crown ether resorcin[4]arene family. We are conducting studies on crowns **1**, **2**, and **5** to determine their extent of binding and selectivity properties.

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Supplementary data

Experimental procedures and spectral data are provided for compounds **1a**–**b**, **5a**–**c**, and **2b**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.01.092.

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