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Efficient *Distal*-Difunctionalization of Cavitand Bowls

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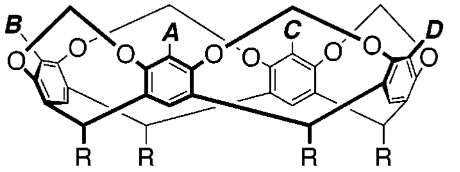
The formation of covalent bridges between the adjacent benzene rings of resorcinarenes results in the generation of cavitands.[1] Resorcinarene-derived cavitands come in a variety of subclasses, from shallow bowls to deeper vases, with the depth of the binding cavity reflecting the length of the bridging group between the resorcinol residues. Methylene-bridged resorcinarenes are used to construct several important and well-established types of host compounds, including carcerands and hemicarcerands,[2] reversible capsules,[3] and holands.[4] More recently, other classes of covalently linked cavitand hosts[5] and cavitand-based coordination cages[6] have begun to emerge.

Methylene-bridged cavitands possess four evenly spaced, sterically hindered aromatic positions at the bowl rim which can be utilized for derivatization. When two different substituents are present at the bowl rim, four compounds are possible, as shown in Figure 1.



one substituent **1** tetra: ***A*** = ***B*** = ***C*** = ***D*** = X

two substituents, X and Y
2 tri: ***A*** = ***B*** = ***C*** = X; ***D*** = Y
3 A,C-di: ***A*** = ***C*** = X; ***B*** = ***D*** = Y
4 A,B-di: ***A*** = ***B*** = X; ***C*** = ***D*** = Y
5 mono: ***A*** = X; ***B*** = ***C*** = ***D*** = Y

three substituents, X, Y and Z
6 achiral: ***A*** = ***C*** = X; ***B*** =Y; ***D*** = Z
7 chiral: ***A*** = ***B*** = X; ***C*** =Y; ***D*** = Z

Figure 1. The parent C_{4v}-symmetrical tetrasubstituted bowl **1** and the possible substitution patterns when two or three different groups are present at the bowl rim.

While the need for practical amounts of these compounds for the synthesis of new hosts is clearly evident,[7] until recently, such procedures were lacking.[8] We have focused our efforts on developing the synthetic chemistry of cavitand bowls such that the full potential of these conformationally inflexible cavity molecules might be realized.[9] Our nonstatistical reactions center upon selective lithium−bromine exchange processes of polybromocavitands. Herein we disclose our findings on a 2-fold Li/Br exchange−electrophile quench protocol, procedures which allow the first high-yield preparation of cavitands with a *distal*-difunctionalization pattern, **3**. Such a functionality pattern has been previously accessible in the cavitand series only through statistical transformations.[7,10]

A,C-Dibromo-B,D-dilithiobowl **9** was a presumed intermediate in our previously reported conversion of *undecyl*-footed tetrabromobowl into A,C-dibromo-B,D-diprotiobowl **10** (Table 1, entry 1).[9c] In this procedure, tetrabromide **8** is treated with 2.1 mol equiv of *n*-BuLi followed by methanol at low temperature. We are pleased to report that THF solutions of the corresponding *pentyl*-footed tetrabromocavitand **8**[11] also undergo selective lithium−bromine exchange reactions.[12] Moreover, THF solutions of the readily prepared pentyl-footed, A,C-dibromo-B,D-dilithiobowl **9** react with a wide variety of electrophiles (Table 1, entries 2−8) to furnish C_{2v}-

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(7) For the preparation of compounds akin to **2**−**5** via nonselective, statistical processes, see: (a) Flaunaus, M.; Herzing, M.; Kollhofer, A.; Laly, M.; Plenio, H. *Eur. J. Org. Chem.* **2001**, 1061−1068. (b) Hamada, F.; Ito, S.; Narita, M.; Nashirozawa, N. *Tetrahedron Lett.* **1999**, *40,* 1527. (c) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120,* 9818−9826. (d) Higler, I.; Boerrigter, H.; Verboom, W.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. Eur. *J. Org. Chem.* **1998**, 1857−1607. (e) Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *Liebigs Ann./Recueil* **1997**, 2247−2254. (f) van Wageningen, A. M. A.; Snip, E.; Verboom, W.; Reinhoudt, D. N.; Boerrigter, H. *Liebigs Ann./Recueil* **1997**, 2235−2245. (g) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc.* **1991**, *113,* 7717−7727; further examples are provided in ref 5.

(8) A,B-difunctionalized bowls (**4**, Figure 1) have been prepared in nonstatistical yields through the ingenious derivatization of triply bridged resorcinarenes: Timmerman, P.; Boerrigter, H.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19,* 167−191. Sorrell, T. N.; Richards, J. L. *Synlett* **1992**, 155.

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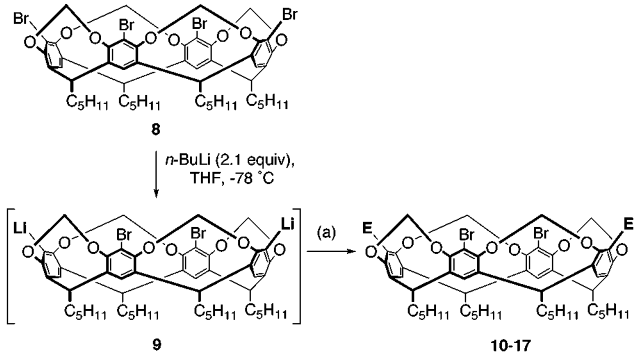
(10) The selective *distal*-difuctionalization of *resorcinarenes* via tetraester derivatives is known: Shivanyuk, A.; Paulus, E. F.; Boehmer, V.; Vogt, W. *J. Org. Chem.* **1998**, *63,* 6448−6449. Shivanyuk, A.; Schmidt, C.; Boehmer, V.; Paulus, E. F.; Lukin, O.; Vogt, W. *J. Am. Chem. Soc.* **1998**, *120,* 4319−4326.

10.1021/jo015988+ CCC: $20.00

Table 1. Conversion of Tetrabromobowl 1 into New A,C-Dibromo-B,D-disubstituted-bowls 10−17



entry	electrophilic reagent (a)[a]	E	product	yield, %[b]
1[c]	MeOH	H	**10**[c]	46
2	MeOH	H	**11**	65[d]
3	$B(OMe)_3$	OH	**12**	58
4	I_2	I	**13**	63[e]
5	MeI	Me	**14**	63
6	Me_2NCHO	CHO	**15**	71
7	$ClCO_2Me$	CO_2Me	**16**	68
8	ClCOPh	COPh	**17**	30[f]
9[g]	$B(OMe)_3$	OH	**18**	68

[a] Quantities of electrophilic reagent employed, reaction times, and workup procedures vary. See the Supporting Information for full details. [b] Unoptimized yield of isolated material for reactions carried out on 1 mmol scale. [c] Result for undecyl-footed bowl, from ref 9c. [d] Triprotio-monobromobowl (13%) was also isolated. [e] A,C-dibromo-monoiodo-monoprotiobowl (20%) was also isolated. [f] Tribromo-monobenzoylbowl (12%) was also isolated. [g] The dibromodimethylbowl (product of entry 5) was employed as precursor.

symmetrical cavitands bearing two different derivatizable substituents at diametrically opposed positions about the bowl rim (cf. **3**, Figure 1). Simple aqueous workup[13] provides mixtures of cavitands rich in the A,C-disubstituted cavitand, from which the pure product is obtained by flash chromatography in isolated yields that are typically in the 60−70% range. Electrophiles of different types are readily incorporated and workable (i.e., multigram) quantities of these new cavitands are easily obtained. The strong A,C-selectivity of this process is highlighted by the fact that the A,B-disubstituted product would be dominant in a *statistical* disubstitution reaction.

The C_{2v}-symmetry of products **10**−**17** was assigned after inspection of NMR spectra. The *distal*-disubstitution pattern was later confirmed by single-crystal X-ray analysis of A,C-dibromo-B,D-diol **12** (Figure 2).[13] The crystal structure has three ethanol solvate molecules for each cavitand molecule, and one of these solvate molecules is nestled methyl-group-first into the cavitand bowl. There are two similar orientations of the bound ethanol molecule, one of which is dominant (occupancy ratio: 80:20). Interestingly, these two ethanol orientations are distinct from those recently reported for an aryl phosphate-bridged cavitand·EtOH complex,[14] and for a 1,2-crown[6]cavitand·EtOH complex.[15]

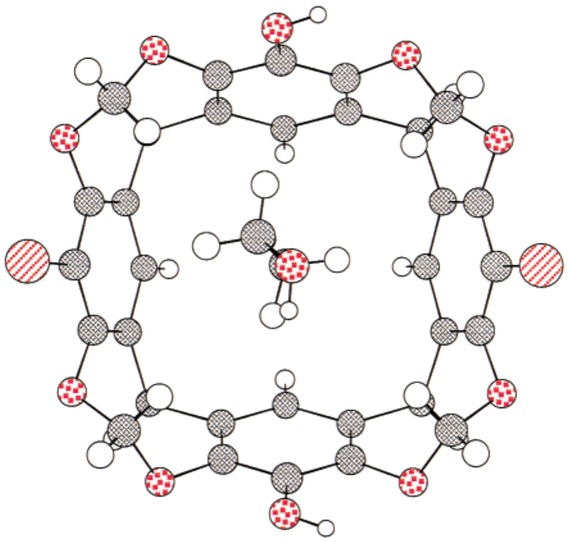
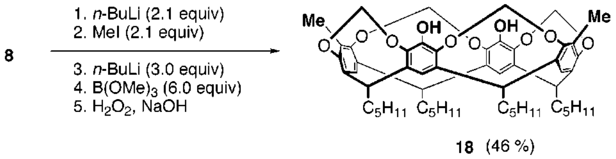


Figure 2. Chem 3D rendering of the molecular structure of the major caviplex **12**·EtOH obtained from single-crystal X-ray analysis of A,C-dibromo-B,D-diol **12** after slow crystallization from CH_2Cl_2−EtOH. Pentyl "feet" are omitted for clarity.

Scheme 1. One-Pot Conversion of Tetrabromide 8 into A,C-Dimethyl-B,D-diol 18



We were curious to learn whether the products from these difunctionalization reactions could themselves serve as precursors in further dilithiation reactions. Thus, when exposed to the standard reaction conditions for Ar−Br to Ar−OH conversion, A,C-dimethyl-B,D-dibromo bowl **14** (the product of entry 5, Table 1) was smoothly converted in 68% yield into the desired A,C-dimethyl-B,D-diol **18** (Table 1, entry 9). Moreover, this compound can be prepared directly from tetrabromobowl **1** in a one-pot conversion whose overall yield is gratifyingly close to the product of the yields of the two individual processes (Scheme 1). The order of addition of successive electrophiles is important in such one-pot conversions: when the order of addition of MeI and $B(OMe)_3$ is reversed, a very messy reaction ensues, from which the desired product **18** is isolated in only 12% yield.

All the examples described thus far involve selective functionalization stemming from nonstatistical lithium−bromine exchange processes. An alternative, potentially fruitful avenue for exploration involves restricting a

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(11) Resorcinarene formation: Aoyama, Y.; Tanaka, Y.; Sugahara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397−5404. Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305−12. Bromination: Byrant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167−2172. Acetal formation: A slightly modified procedure is provided for this last step in the Supporting Information.

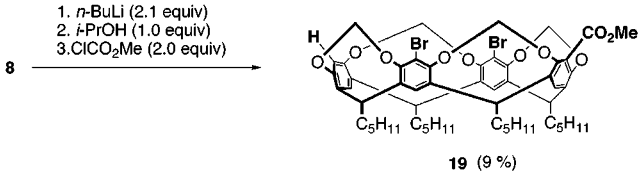
(12) Thus far, all previous reports (ref 9) were concerned with the undecyl-footed cavitand. Isolated yields for selective lithium−halogen exchange/electrophile quench reactions in the *pentyl*-footed series are invariably higher than those in the *undecyl*-footed series, cf. Table 1, entries 1 vs 2 and Barrett, E. S.; Irwin, J. L.; Sherburn, M. S. Unpublished results. The reasons behind this improvement in yield are not apparent at this stage.

(13) See the Supporting Information for full details.

(14) Pinalli, R.; Nachtigall, F. F.; Ugozzoli, F.; Dalcanale, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 2377−2380. The difference in binding between **12** and Dalcanale's sensor molecules is hardly surprising in light of the much stronger two point hydrogen bonding/C−H···π interaction capability of the latter host.

(15) Higler, I.; Boerrigter, H.; Verboom, W.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 1597−1607. Reinhoudt's caviplex resembles the minor ethanol orientation of **12**·EtOH more closely than the major orientation.

Scheme 2. Attempted Selective Monoprotonation−Monoacylation of Dilithiodibromobowl 9

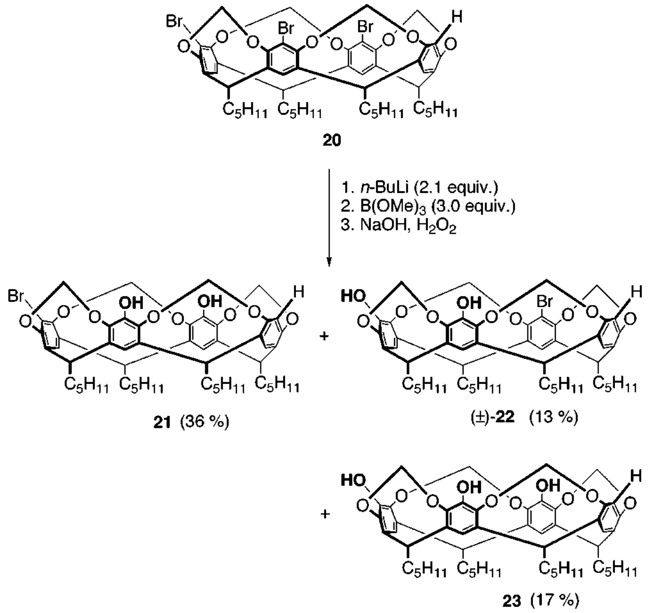


dilithiocavitand to a single chemoselective reaction to furnish a monolithio-monosubstituted cavitand product. Such a process would allow, through the successive introduction of two electrophilic reagents, the convenient incorporation of two dissimilar groups at the rim of the bowl. All our efforts to accomplish such a transformation in a synthetically useful fashion thus far have been in vain: complex mixtures and low yields of the targeted compound invariably result (Scheme 2).

When the dilithiation−boronation−oxidative hydrolysis procedure was carried out upon tribromo-monoprotiobowl **20**[16] (Scheme 3), a mixture of three compounds was produced in a combined yield that was comparable to reactions on tetrabromide **8** (Table 1). This reaction furnishes almost three times as much A,C-diol **21** as A,B-diol **22**, indicating once again a clear preference for the A,C-substitution pattern. A purely statistical process would have resulted in twice as much A,B-diol **22** as A,C-diol **21**. Thus, the one-step, *distal*-disubstitution reaction of cavitands is not limited to symmetrical tetrabromides such as **8**.

In summary, high-yielding one-step procedures for the simultaneous introduction of two groups at diametrically opposed positions of cavitand bowls have been developed. Bowls with XYXY- and X_2YZ-rim substitution types are accessible using this chemistry. Moreover, the experimental protocols described herein are operationally simple and synthetically useful quantities (i.e., multigram amounts) of these new bowls are readily obtained.

Scheme 3. Dilithiation−Boronation of Tribromo-monoprotio-bowl 20



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Supporting Information Available: Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of all new compounds, and X-ray analysis details for **12·EtOH**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] Prepared in 78% yield in an analogous manner to the undecyl-footed tribromo-monoprotiobowl.[9c]