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Monolithiocavitands: Versatile Intermediates for New Cavitand-Based Hosts

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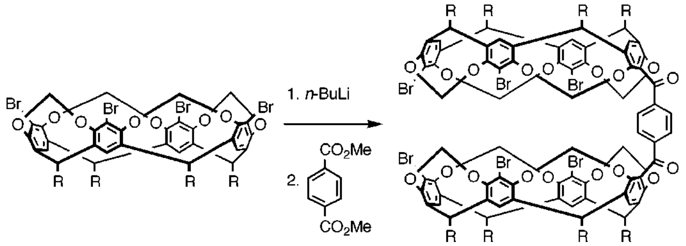
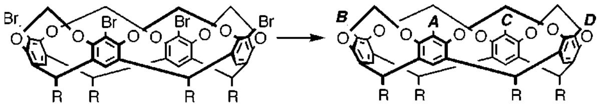
ABSTRACT



Cavitand bowls carrying two derivatizable groups at the rim have been efficiently prepared through a selective lithium/halogen exchange–electrophile quenching procedure. This methodology lends itself to the single-step preparation of the first *all carbon*-linked bis-bowl and a new class of inherently chiral cavitands.

Cavitand bowls are fascinating supramolecular building blocks.[1] The first examples of these wide (ca. 9 Å diameter), shallow (ca. 3.5−4 Å deep), rigid, curved-surface molecules were reported over 15 years ago.[2] Today, methylene-bridged resorcinarene derivatives form the basis of several classes of host compounds of significant contemporary interest, including carcerands and hemicarcerands,[3] reversible capsules,[4] holands,[5] and other covalently and coordinatively linked multibowl arrays.[6]

The ready utilization of cavitand bowls in molecular recognition studies stems from their facile conversion into compounds with binding groups at four fixed positions around the bowl rim. The full potential of the cavitand bowl platform has not been realized, however, because its synthetic manipulation has been limited, in the main, to 4-fold derivatizations, which furnish tetrafunctionalized cavitands with C_{4v} symmetry.[1] The majority of reports of unsymmetrically substituted cavitand bowls describe the isolation of small quantities of compounds from low yielding reactions that generate statistical mixtures of products.[7] We recently reported new and efficient approaches to unsymmetrical rim-brominated[8] and hydroxylated[9] cavitand bowls **2**−**5** based upon selective lithium−bromine exchange chemistry of readily accessible tetrabromide **1** (Figure 1). Herein we



1
(R = undecyl)

2 tri: ***A*** = ***B*** = ***C*** = X; ***D*** = H
3 A,C-di: ***A*** = ***C*** = X; ***B*** = ***D*** = H
4 A,B-di: ***A*** = ***B*** = X; ***C*** = ***D*** = H
5 mono: ***A*** = X; ***B*** = ***C*** = ***D*** = H

a bromo-series:[8] X = Br
b hydroxy-series:[9] X = OH

Figure 1. The parent tetrabromobowl **1** and the four possible rim substitution patterns **2**−**5** with two different groups at the rim (X and H).

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(2) Cram, D. J. *Science* **1983**, *219*, 1177−1183.

(3) (a) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967. (b) Warmuth R. *J. Inclusion Phenom. Mol. Recognit. Chem.* **2000**, *37*, 1−38.

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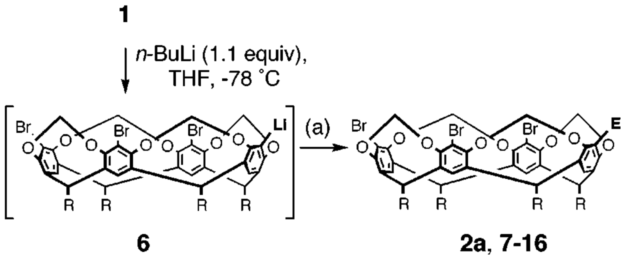
disclose our preliminary findings on the rich chemistry of monolithiocavitands.

Table 1. Conversion of Tetrabromocavitand **1** into New Monosubstituted Bowls **7**



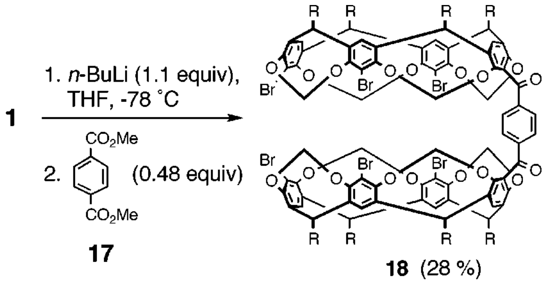
entry	electrophilic reagent (a)[a]	E	product	yield[b]
1[c]	MeOH	−H	**2a**	81%
2	B(OMe)$_3$	−OH	**7**	68%
3	I$_2$	−I	**8**	71%
4	ClSiMe$_3$	−SiMe$_3$	**9**	22%
5	MeSSMe	−SMe	**10**	80%
6	S$_8$	−SH	**11**	37%
7	MeI	−Me	**12**	57%
8	Me$_2$NCHO	−CHO	**13**	57%
9	ClCO$_2$Me	−CO$_2$Me	**14**	72%
10[d]	ClCOMe	−COMe	**15**	29%
11	ClCOPh	−COPh	**16**	42%

[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. [c] From ref 9. [d] Tribromomonoprotiobowl **2a** (32%) was also isolated.

We have previously established the conversion of tetrabromobowl **1** into tribromomonoprotiobowl **2a** through low-temperature treatment of **1** with *n*-BuLi (1.1 equiv) followed by methanol (Table 1, entry 1).[8] Tribromo-monolithiocavitand **6** is a necessary intermediate in this conversion. As shown in Table 1, THF solutions of this readily prepared intermediate react with a wide variety of electrophiles to furnish cavitands bearing two different derivatizable substituents at the bowl rim (entries 2–11). Simple aqueous workup[10] provides mixtures of cavitands rich in the monosubstituted product **7**–**16**.[11] The pure monosubstituted product is obtained by straightforward flash chromatographic purification, and isolated yields are typically in the 40–80% range. Boron (entry 2), halogen (entry 3), silicon (entry 4), sulfur (entries 5 and 6), alkyl carbon (entry 7), and acyl carbon (entries 8–11) electrophiles are readily incorporated, and workable (i.e., multigram) quantities of these new cavitands are easily obtained. Rigorous drying of both the tetrabromobowl precursor and the electrophile is mandatory if the formation of significant amounts of tribromomonoprotiocavitand **2a** is to be avoided.[11]

To probe the scope of this reaction we next investigated a [2 + 1] condensation of tetrabromide **1** with the symmetrical biselectrophile, 1,4-dicarbomethoxybenzene **17** (Scheme 1). In this challenging test of the robustness of the methodology, the reactants **1** and **17** contain four and two identical groups, respectively. For conversion into the desired product, cavitand **1** must react at only one of its four equivalent bromides and biselectrophile **17** must suffer nucleophilic addition by one lithiocavitand molecule per ester group. To our delight, the reaction proceeded in the required manner to afford the first *all carbon*-tethered biscavitand molecule **18** in 28% isolated yield.[12]

Scheme 1. *All Carbon*-Tethered Bis-Bowl **18** through [2 + 1] Condensation



Selective lithium–bromine exchange can also be carried out on the *unsymmetrical* bromocavitands **2a**, **3a**, and **4a**. Thus, successive treatment with *n*-BuLi (1.1 equiv), B(OMe)$_3$, and basic H$_2$O$_2$ transforms tribromomonoprotiobowl **2a**[8] in good yield into a chromatographically separable 54:46 mixture of the two regioisomeric dibromomonoprotiomonols **19** and **20** (Scheme 2). The proportion of the major product

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(4) (a) Kobayashi, K.; Shirasaka, T.; Yamaguchi, K.; Sakamoto, S.; Horn, E.; Furukawa, N. *Chem. Commun*. **2000**, 41–42. (b) Lutzen, A.; Renslo, A. R.; Schalley, C. A.; O'Leary, B. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 7455–7456. (c) Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640–1644. (d) Chapman, R. G.; Olovsson, G.; Trotter, J.; Sherman, J. C. *J. Am. Chem. Soc.* **1998**, *120*, 6252–6260.

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(7) (a) Hamada, F.; Ito, S.; Narita, M.; Nashirozawa, N. *Tetrahedron Lett*. **1999**, *40*, 1527. (b) Chapman, R. G.; Sherman, J. C. *J. Am. Chem. Soc*. **1998**, *120*, 9818–9826. (c) Higler, I.; Boerrigter, H.; Verboom, W.; Kooijman, H.; Spek, A. L.; Reinhoudt, D. N. *Eur. J. Org. Chem*. **1998**, 1597–1607. (d) Boerrigter, H.; Verboom, W.; Reinhoudt, D. N. *Liebigs Ann./Recueil*. **1997**, 2247–2254. (e) van Wageningen, A. M. A.; Snip, E.; Verboom, W.; Reinhoudt, D. N.; Boerrigter, H. *Liebigs Ann./Recueil* **1997**, 2235–2245. (f) Cram, D. J.; Tanner, M. E.; Knobler, C. B. *J. Am. Chem. Soc*. **1991**, *113*, 7717–7727. (g) Peinador, C.; Roman, E.; Abboud, K.; Kaifer, A. E. *Chem. Commun*. **1999**, 1887–1888. (h) A,B-Difunctionalized bowls have been prepared in nonstatistical yields through the ingenious (if somewhat lengthy) 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**, 155–156.

(8) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem*. **2000**, *65*, 602–605.

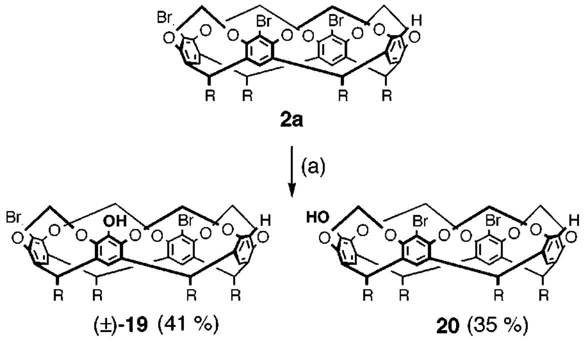
(9) Irwin, J. L.; Sherburn, M. S. *J. Org. Chem*. **2000**, *65*, 5846–5848.

(10) See the Supporting Information for full details.

(11) The monosubstituted product comprises ca. 80% of the product mixture.

(12) Yield optimization and guest binding studies with **18** are under way.

Scheme 2. Monolithiation−Boronation of Tribromomonoprotiobowl **2a**[a]

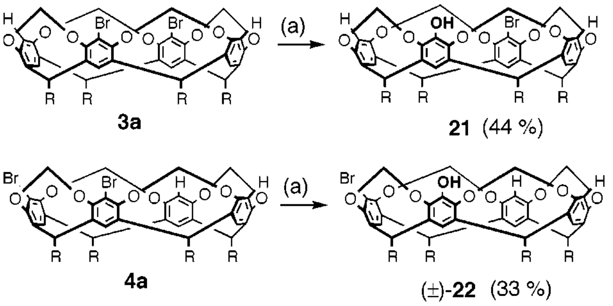


[a] (a) 1. *n*-BuLi (1.1 equiv.), THF, −78 °C; 2. $B(OMe)_3$ (1.5 equiv.), −78 °C − RT; 3. NaOH, H_2O_2, H_2O, RT.

19 is slightly less than would be expected from a nonselective lithium−bromine exchange process. The reason for this nonstatistical outcome is, at this stage, unclear.[13]

In an analogous fashion, the two regioisomeric dibromodiprotiobowls **3a**[8] and **4a**[8] afford the corresponding diprotiomonobromomonols **21** and **22** in reasonable yields (Scheme 3), but only when the reaction is conducted at low (4 mM) substrate concentration. At higher concentrations, precipitation of organolithium species is witnessed, an event accompanied by the generation of complex mixtures of products. Bromophenols **19** and **22** are the first of a new class of *inherently chiral* cavitands.[14−16] Resolution of these racemates would furnish enantiomerically pure bowls with asymmetric binding and catalysis possibilities.[17]

Scheme 3. Monolithiation-Boronation of Dibromodiprotiobowls **3a** and **4a**[a]



[a] (a) (1) *n*-BuLi (1.1 equiv), THF, −78 °C; (2) $B(OMe)_3$ (1.5 equiv), −78 °C to rt; (3) NaOH, H_2O_2, H_2O, rt.

In summary, selective lithium−bromine exchange of bromides **1**, **2a**, **3a**, and **4a** affords monolithiocavitand intermediates that react with a wide range of electrophiles to furnish several new cavitand bowl varieties. Cavitands with orthogonal functionality at the rim, chiral bowls, and the first *all carbon*-tethered bis-bowls are accessible in practical quantities from reactions with nonstatistical product distributions. The compounds described herein serve as starting points for the elaboration of new hosts with useful supramolecular functions.

Acknowledgment. We thank Dr. Kelvin Picker for assistance with HPLC separations and the Australian Research Council for funding.

Supporting Information Available: Experimental procedures, characterization data and ^1H and ^{13}C NMR spectra of all new compounds (**7−16**, **18−22**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) We noted a similar result in the preparation of **4a**; see ref 8.

(14) For examples of inherently chiral cavitands resulting from unsymmetrical bridging arrangements, see: (a) Cram, D. J.; Tunsted, L. M.; Knobler, C. B. *J. Org. Chem.* **1992**, *57*, 528−535. (b) Soncini, P.; Bonsignore, S.; Dalcanale, E.; Ugozzoli, F. *J. Org. Chem.* **1992**, *57*, 4608−4612. We thank a referee for drawing our attention to these papers.

(15) For chiral cavitands formed by appending stereogenic moieties to the bowl, see: Mezo, A. R.; Sherman, J. C. *J. Am. Chem. Soc.* **1999**, *121*, 8983−8994.

(16) For cycloenantioisomerism in self-folding, deep cavity cavitands, see: Lucking, U.; Tucci, F. C.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2000**, *122*, 8880−8889 and references therein.

(17) Attempted separation of the enantiomers of **22** on chiral HPLC columns have thus far proved unsuccessful. Efforts are ongoing in this regard.