Optimized Synthesis of Cavitand Phenol Bowls

Jacob L. Irwin and Michael S. Sherburn*

School of Chemistry, University of Sydney, Sydney, NSW 2006, Australia

E-mail: m.sherburn@chem.usyd.edu.au

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Introduction

Cavitand bowls are conformationally rigid derivatives of resorcinarenes with enforced cavities which bind complementary organic compounds.[1] Monomeric cavitand hosts continue to display unique and fascinating properties,[2] suitably functionalized cavitand derivatives self-assemble into dimeric capsules,[3] and covalently linked dimers form carceplexes and hemicarceplexes.[4] More recently, higher order multicavitand hosts have begun to emerge.[5,6] The phenol group is the most commonly incorporated functionality at the rim of the cavitand bowl since it allows simple elaboration, through ether and ester formation, into these various types of cavitand-based hosts.[1] Evidently, synthetic access to practical quantities of the four unsymmetrical phenol bowls (see Figure 1) would greatly facilitate studies into these important host compounds. The existing route to A,B-diols **4b** involves the synthesis and elaboration of triply bridged tetrabromoresorcinarenes.[7] Unfortunately, triply bridged resorcinarenes are accessible in maximum yields of ca. 50% and installation of the fourth bridge requires a separate synthetic step. Reported syntheses of the

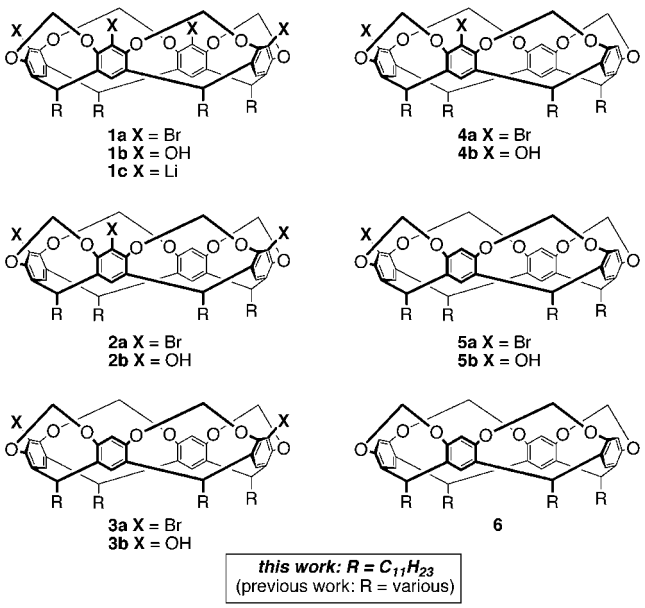

Figure 1.

remaining three unsymmetrical hydroxycavitands are very low yielding. Thus, from the parent resorcinarene (R = CH_2CH_2Ph), a three-step directed synthesis furnished a 2:1 mixture of A,C-diol **3b** and A,B-diol **4b** in 8% yield[8] and the preparation of monol **5b** was recently reported in 11% yield.[9] Herein we disclose optimized procedures for the preparation of triol **2b**, A,C-diol **3b**, A,B-diol **4b**, and monol **5b** from readily available tetrabromocavitand **1a** in 20−60% yields based upon selective lithiation methodology.[10] These functionalized cavitand derivatives serve as building blocks for the synthesis of an unprecedented array of novel host molecules.[9]

Results and Discussion

Literature procedures[6,11] for the conversion of tetrabromocavitand bowls **1a** into tetrol bowls **1b** involve lithium−bromine exchange with large excesses of *n*-BuLi (2−2.5 equiv per Br) followed by boronic ester formation with $B(OMe)_3$ (3.5−4 equiv per Br). Finally, oxidative cleavage with basic H_2O_2 gives the tetrol **1b** as the major product along with varying quantities of the triol **2b**. The triol **2b** (R = CH_2CH_2Ph), presumably formed by reaction between the tetralithiocavitand bowl intermediate **1c** and small amounts of methanol present in the trimethyl borate, was used ingeniously by Cram in the synthesis of "single portal" hemicarcerands:[12] encapsulating hosts capable of stabilizing very reactive molecules such as cyclobutadiene.[8,13]

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Table 1. Preparation of Cavitand Phenols[a]

1. *n*-BuLi (1.1 equiv per Br), THF, -70 °C, 20 min
2. $B(OMe)_3$ (1.5 equiv per Br), -78 °C - RT, 1 h
3. NaOH, H_2O_2, H_2O, RT, 16 h

bromo/protio cavitand ⟶ cavitand phenol

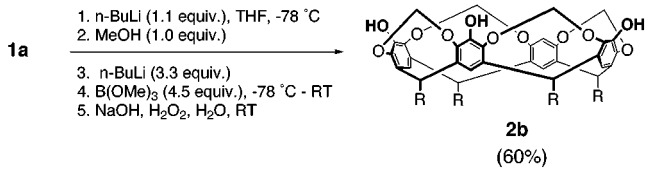
run	bromo/protio-cavitand precursor	cavitand phenol products and isolated yields (%)
1	1a	1b (73%) + 2b (15%)
2	2a	2b (70%) + 3b (10%) + 4b (5%)
3	3a	3b (67%) + 4b (7%) + 5b (16%)
4	4a	3b (15%) + 4b (54%) + 5b (22%)
5	5a	5b (73%) + 6 (25%)
6[b]	3a	3b (67%) + 5b (25%)
7[b]	4a	4b (66%) + 5b (23%)
8[c]	6	5b (17%) + 6 (80%)
9[d]	6	1b (81%) + 2b (12%)

[a] Reactions were carried out with 200 μmol of starting bromide in dry, degassed THF (10 mL) under Ar, unless otherwise stated. See Experimental Section for details. [b] 160 μmol of starting bromide in 50 mL THF. [c] Reaction carried out with 1.1 equiv *n*-BuLi at −78 °C. [d] Reaction carried out with 10 equiv *n*-BuLi at 0 °C.

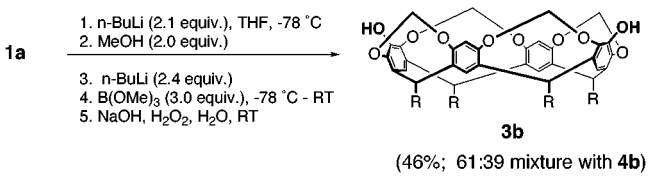
Our initial attempts to adopt these literature protocols[6,11] for the conversion of *unsymmetrical* bromides **2a**−**5a** to the corresponding phenols **2b**−**5b** resulted in the generation of complex mixtures of products. After some experimentation we found that rigorous drying of the bromocavitand precursor prior to lithiation with freshly titrated *n*-BuLi (1.1 equiv per Br) at −78 °C and addition of $B(OMe)_3$ (1.5 equiv per Br) followed by standard oxidative workup gave the corresponding cavitand phenol bowl in 67−73% isolated yield (Table 1, runs 1, 2, and 5−7). In each case, formation of the desired product is accompanied by small but significant (14−25%) amounts of the cavitand bowl having one less −OH group than expected. Even with the most careful purification and drying of solvent, starting materials, and reagent, we have been unable to avoid this product leakage.

Notably, when the dibromide reactions are carried out at 20 mM substrate concentration, while the overall yield remained high, formation of the desired diphenol was accompanied by significant amounts of the *other* regioisomeric diol (Table 1, runs 3 and 4). In line with previous observations with related compounds,[8,14] separation of these two diol regioisomers proved less than trivial, and we were eager to avoid the generation of such mixtures. In the event, clean conversion of each of the dibromocavitands **3a** and **4a** into the corresponding regioisomerically pure diphenol was accomplished by carrying out the reaction in more dilute (4 mM) solution (Table 1, runs 6 and 7). This unexpected scrambling of product regiochemistry during diol synthesis is presumably the result of equilibration between intermediate organolithium species.[15] These results prompted an investigation into the feasibility of direct lithiations of *unfunctionalized* cavitand bowls. Thus, THF solutions of tetraprotiocavitand bowl **6** were treated with different amounts of *n*-BuLi (1.1 → 10 mol equiv) at various temperatures (−78 → 0 °C) before the usual boronic ester formation and oxidation. We were surprised to find that, even upon

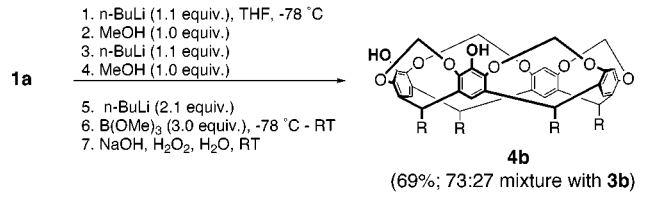
Scheme 1



Scheme 2



Scheme 3



treatment with stoichiometric amounts of *n*-BuLi at low temperatures, some lithiation of the cavitand bowl rim was occurring. Indeed, monol **5b** could be prepared in 17% yield in this way, with excellent mass balance after recovery of unreacted starting material (Table 1, run 8). With 10 mol equiv of *n*-BuLi at 0 °C, an excellent yield of tetrol **1b** (81%) was obtained (Table 1, run 9).

While these results clearly represent efficient synthetic routes to the hitherto relatively inaccessible phenols **2b**, **3b**, **4b**, and **5b** from tetrabromocavitand **1a**, two discrete reactions are necessary to accomplish each transformation.[16] Since both reactions involve organolithium intermediates, the development of "one-pot" procedures seemed a reasonable proposition for achieving yet higher synthetic efficiency. Operationally, the most straightforward one-pot approach would involve successive additions of two electrophiles to tetralithiocavitand **1c** followed by an oxidative work up. All attempts to obtain selectivity in reactions such as these have thus far been unsuccessful, with complex mixtures of products being isolated. In light of this apparent lack of selectivity in the reaction of the tetralithiocavitand **1c** with electrophiles, we explored an alternative approach which instead relies upon selective lithium−bromine exchange chemistry. Thus, transformation of a THF solution of tetrabromide **1a** to the tribromide **2a**[10] followed by a sequential, in situ Ar−Br to Ar−OH conversion resulted in isolation of the triol **2b** in 60% yield (Scheme 1). In a similar way, A,C-diol **3b** (Scheme 2) and A,B-diol **4b** (Scheme 3) were prepared in 46 and 33% isolated yields, respectively, from tetrabromide **1a**. In the latter case, two successive monolithiation-protiolyses were carried out to secure the optimimum quantity of A,B-dibromide **4a** in the reaction mixture prior to boronic ester formation. Due to difficulties encountered in separating the two regioisomeric diphenols (vide supra), the somewhat cleaner, two-step synthesis is the preferred method for the preparation of these compounds. The most effective synthesis of monol **5b** from tetrabro-

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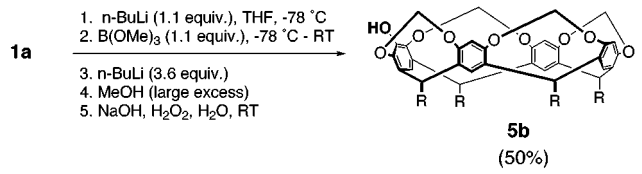
(15) A significant amount of precipitation occurs in the reaction between *n*-BuLi and **3a**/**4a** at [substrate] = 20 mM at −78 °C. Equilibration could be facilitated under these conditions by the forced close proximity of the lithiocavitands.

(16) *ie.* **1a** → unsymmetrical bromocavitand → unsymmetrical cavitand phenol.

Scheme 4



mide **1a** involved a one-pot transformation, with boronic ester formation being carried out prior to reduction (Scheme 4). Respectable yields of monol **5b** (50%) were thereby obtained, allowing synthetically useful quantities of compounds of this type to be prepared for the first time.

In summary, practical procedures have been developed for the preparation of the four partially rim-hydroxylated cavitand bowls **2b**, **3b**, **4b**, and **5b**, building blocks for a diverse range of novel hosts. Along the way, conditions have been developed for carrying out clean lithium−bromine exchange reactions of *all* possible rim-brominated cavitand bowls. An enormous variety of new cavitand derivatives are now accessible by trapping these different lithiocavitand intermediates with electrophiles other than $B(OMe)_3$. In addition, the first *direct* lithiations of tetraprotiobowls have been carried out. Finally, protocols for multiple in situ lithiation−electrophile-quenching sequences have been delineated: procedures that permit the efficient one-pot conversion of tetrabromocavitand bowls into selectively functionalized derivatives in a controlled manner.

Experimental Section[17]

Standard Procedure. To a one-necked 25-mL round-bottomed flask fitted with a septum and stir bar containing the bromocavitand precursor (0.200 mmol) was added dry, freshly distilled THF (2.0 mL). The resulting solution was evaporated to dryness and then heated at 80 °C at 1.0 mmHg for 1 h. The vacuum was replaced with Ar, and the procedure was repeated two more times. The required amount of *n*-butyllithium (freshly titrated solution in hexanes) was added rapidly to a solution of dried bromocavitand (0.200 mmol) in THF maintained at −78 °C (bath temperature). After 20 min, trimethyl borate was introduced at −78 °C, the cooling bath was removed, and the resulting mixture was warmed to 25 °C and stirred at this temperature for 1 h. The solution was cooled to −78 °C, and the reaction was quenched with a 1:1 mixture of 30% aqueous H_2O_2 and 3.0 M aqueous NaOH and then stirred at 25 °C for 18 h. After cautious addition of 10% aqueous sodium metabisulfite solution, the product cavitand phenols were extracted into EtOAc. The aqueous phase was further extracted with EtOAc, the combined organic phases were washed with 10% aqueous sodium hydrogencarbonate solution, water, and saturated brine and dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo. Pure cavitand phenol bowls were obtained by chromatography on SiO_2.

***C*-Undecylcavitandtetrol 1b from *C*-Undecyltetrabromocavitand 1a (Table 1, Entry 1).** Following the standard procedure, dry *C*-undecyltetrabromocavitand **1a** (294 mg, 0.200 mmol) in THF (10 mL) was treated with *n*-butyllithium (0.820 mmol) followed by trimethyl borate (1.21 mmol). Chromatography (15 g of SiO_2, 3:1 hexane:EtOAc) gave tetrol **1b** (177 mg, 73%) and triol **2b** (35 mg, 15%) as colorless powders.

***C*-Undecylcavitandtetrol 1b from *C*-Undecyltetraprotiocavitand 6 (Table 1, Entry 9).** Dry *C*-undecyltetraprotiocavitand **6** (231 mg, 0.200 mmol) in THF (10 mL) was treated with *n*-butyllithium (2.00 mmol) at 0 °C followed by trimethyl borate (2.20 mmol) at 0 °C. Standard workup and chromatography (15 g of SiO_2, 3:1 hexane:EtOAc) gave tetrol **1b** (197 mg, 81%) and triol **2b** (28 mg, 12%) as colorless powders.

***C*-Undecylcavitandtriol 2b from *C*-Undecyltribromocavitand 2a (Table 1, Entry 2).** Following the standard procedure, dry *C*-undecyltribromocavitand **2a** (278 mg, 0.200 mmol) in THF (10 mL) was treated with *n*-butyllithium (0.660 mmol) followed by trimethyl borate (0.901 mmol). Chromatography (15 g of SiO_2, 1:1 → 1:2 hexane:EtOAc) gave the triol **2b** (167 mg, 70%) as a colorless powder.

***C*-Undecylcavitandtriol 2b from *C*-Undecyltetrabromocavitand 1a (Scheme 1).** *n*-Butyllithium (137 μL of a 1.61 M solution in hexanes, 0.220 mmol) was added rapidly to a solution of dry *C*-undecyltetrabromocavitand **1a** (294 mg, 0.200 mmol) in THF (10 mL) with the temperature maintained at −78 °C (bath temperature). After 20 min, methanol (81 μL of a 10% v/v solution in THF, 0.20 mmol) was introduced at −78 °C, and the resulting mixture was stirred at −78 °C for an additional 20 min. Still at −78 °C, more *n*-butyllithium (410 μL of a 1.61 M solution in hexanes, 0.660 mmol) was added rapidly, and after 20 min trimethyl borate (101 μL, 0.900 mmol) was added. The resulting mixture was warmed to 25 °C, and stirred at this temperature for 1 h, and then cooled to −78 °C. The reaction was quenched with a 1:1 mixture of 30% aqueous H_2O_2 and 3.0 M aqueous NaOH and stirred at 25 °C for 18 h. Standard workup gave a colorless solid (263 mg) which was absorbed onto silica gel and chromatographed (15 g of SiO_2, 1:1 → 1:2 hexane/EtOAc) yielding triol **2b** (144 mg, 60%) as a colorless powder.

***C*-Undecylcavitand-A,C-diol 3b from *C*-Undecyl-A,C-dibromocavitand 3a (Table 1, Entry 6).** Dry *C*-undecyl-A,C-dibromocavitand **3a** (210 mg, 0.160 mmol) in THF (50 mL) was treated with *n*-butyllithium (0.352 mmol) at −70 °C. After 30 s, trimethyl borate (56 μL, 0.480 mmol) was introduced, the cooling bath was removed, and the resulting mixture was warmed to 25 °C and stirred at this temperature for 1 h. Standard workup and chromatography (15 g of SiO_2, 4:1 → 1:1 → 1:4 hexane/EtOAc) gave A,C-diol **3b** (126 mg, 67%) as a colorless powder.

***C*-Undecylcavitand-A,B-diol 4b from *C*-Undecyl-A,B-dibromocavitand 4a (Table 1, Entry 7).** Dry *C*-undecyl-A,B-dibromocavitand **4a** (210 mg, 0.160 mmol) gave A,B-diol **4b** (125 mg, 66%) as a colorless powder in a procedure identical to that for the preparation of A,C-diol **3b**.

***C*-Undecylcavitandmonol 5b from *C*-Undecylmonobromocavitand 5a (Table 1, Entry 5).** Following the standard procedure, dry *C*-undecylmonobromocavitand **5a** (247 mg, 0.200 mmol) in THF (10 mL) was treated with *n*-butyllithium (0.220 mmol) followed by trimethyl borate (0.30 mmol). Chromatography (15 g of SiO_2, 7:3 hexane/EtOAc) gave the monol **5b** (172 mg, 73%) as a colorless powder.

***C*-Undecylcavitandmonol 5b from *C*-Undecyltetrabromocavitand 1a (Scheme 4).** *n*-Butyllithium (137 μL of a 1.61 M solution in hexanes, 0.220 mmol) was added rapidly to a solution of dry *C*-undecyltetrabromocavitand **1a** (294 mg, 0.200 mmol) in THF (10 mL) with the temperature maintained at −78 °C (bath temperature). After 20 min, trimethyl borate (25 μL, 0.22 mmol) was added, and the reaction mixture was warmed to 25 °C and stirred at this temperature for 1 h. After cooling to −78 °C, additional *n*-butyllithium (447 μL of a 1.61 M solution in hexanes, 0.720 mmol) was added rapidly, and after 20 min the reaction was quenched by the addition of methanol (1.0 mL, 25 mmol). While at −78 °C, a 1:1 mixture of 30% aqueous H_2O_2 and 3.0 M aqueous NaOH was introduced, the cooling bath was removed, and the reaction mixture was stirred at 25 °C for 18 h. Standard workup gave a colorless solid (254 mg) which was absorbed onto silica and chromatographed (15 g of SiO_2, 7:3 hexane/EtOAc) yielding monol **5b** as a colorless powder (118 mg, 50%).

Acknowledgment. The authors thank Dr Ian Luck for assistance with NMR experiments and The Australian Research Council for funding.

Supporting Information Available: General experimental procedures, product characterization data and ^1H and ^{13}C NMR spectra of **1b**, **2b**, **3b**, **4b**, and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

(17) For general details see Supporting Information.

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