Synthesis of Hydroxyl-Footed Cavitands

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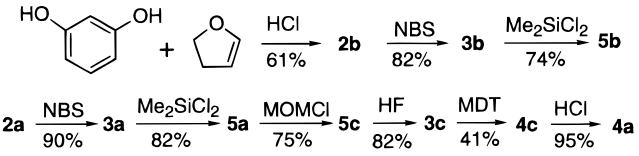
Received September 6, 1995

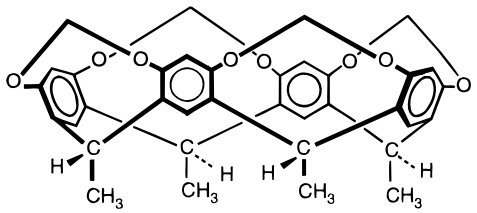
Introduction

Methylene-bridged resorcin[4]arene cavitands such as **1**[1] have been used for a variety of purposes because of their rigidity, enforced cavities, and synthetic viability. For example, these cavitands have served as precursors to carceplexes,[2] as binders of neutral guest molecules,[3] and as agents to form monolayers.[4] The interest in resorcinarene-based cavitands is still on the rise[5] as new uses in materials science and biological chemistry arise. Thus, the incorporation of new functionalities into the pendant groups of these compounds would expand their versatility toward future applications. For example, use of the pendant groups to covalently link cavitands (remote from the enforced cavity) to each other,[6] to solid supports, or to other species could lead to new materials, while short water-solubilizing pendant groups could pave the way toward biological applications such as drug delivery. One problem is that functionalities in the pendant groups often interfere with the bridging reaction that incorporates the rigidity into the molecule and enforces the cavity. To be synthetically useful, the ideal pendant group should contain a functionality that (1) can be converted into a nucleophile or an electrophile and (2) can be incorporated close to the bowl. We report here the synthesis of several short-chained hydroxyl-footed cavitands (i.e., methylene-bridged) and include a discussion of the key bridging reaction. We also present an alternative, milder route to the preparation of bridged cavitands, which may be particularly useful when the pendant groups contain even more sensitive funtionalities.

Scheme 1. Synthesis of Silicon-Bridged Cavitands 5a and 5b. Synthesis of Methylene-Bridged Cavitand 4a via a Silicon Bridge Protection/Deprotection Route[a]



[a] MDT, methylene ditosylate.



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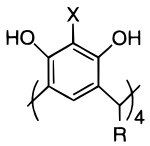
Results

Butanol-footed dodecol **2a** has been prepared by Cram in 80% yield.[7] We prepared propanol-footed dodecol **2b** in a similar manner in 61% yield (Scheme 1) so that we can eventually probe the effect of chain length in the applications mentioned above.[8] Compounds **2a** and **2b** were brominated using *N*-bromosuccinimide to give bromo dodecols **3a** (90% yield) and **3b** (82% yield), respectively (Scheme 1).



2a: R = $(CH_2)_4OH$, X = H
2b: R = $(CH_2)_3OH$, X = H
2d: R = CH_2CH_2Ph, X = H

3a: R = $(CH_2)_4OH$, X = Br
3b: R = $(CH_2)_3OH$, X = Br
3c: R = $(CH_2)_4OCH_2OCH_3$, X = Br
3d: R = CH_2CH_2Ph, X = Br

Methylene bridges were incorporated into dodecol **3a** to form the rigid cavitand **4a** both via direct bridging (Scheme 2) and via a protection/deprotection route (Scheme 1). As this bridging is often the most difficult step in the formation of resorcinarene cavitands, we

(1) (a) Moran, J. R.; Karbach, S.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 5826−5828. (b) Cram, D. J.; Karbach, S.; Kim, H. E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229−2237. For a review of unbridged resorcinarenes, see: Schneider, H.-J.; Schneider, U. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1994**, *19*, 67−83.

(2) (a) Sherman, J. C. *Tetrahedron* **1995**, *51*, 3395−3422. (b) Timmerman, P.; Nierop, K. G. A.; Brinks, E. A.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Chem. Eur.* **1995**, *1*, 132−143. (c) Helgeson, R. C.; Knobler, C. B.; Cram. D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 307−308. (d) Kurdistani, S. K.; Robbins, T. A.; Cram. D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1259−1260.

(3) (a) Tucker, J. A.; Knobler, C. B.; Trueblood, K. N.; Cram, D. J. *J. Am. Chem. Soc.* **1989**, *111*, 3688−3699. (b) Timmerman, P.; Brinks, E. A.; Verboom, W.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1995**, 417−418.

(4) (a) van Velzen, E. U. T.; Engbersen, J. F. J; de Lange, P. J.; Mahy, J. W. G.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 6853−6862. (b) Schierbaum, K. D.; Weiss, T.; van Velzen, E. U. T.; Engbersen, J. F. J; Reinhoudt, D. N.; Göpel, W. *Science* **1994**, *265*, 1413−1415. For formation of monolayers using unbridged resorinarenes, see: (c) Kurihara, K.; Ohto, K.; Tanaka, Y.; Aoyama, Y.; Kunitake, T. *J. Am. Chem. Soc.* **1991**, *113*, 444−450. (d) Adams, H.; Davis, F.; Stirling, C. J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 2527−2529. (e) Weib, T.; Schierbaum, K. D.; van Velzen, U. T.; Reinhoudt, D. N.; Göpel, W. *Sensors Actuat. B* **1995**, *26*−27, 203−207.

(5) For uses of resorcinarene-based cavitands that contain non-methylene bridges, see: (a) Lippmann, T.; Wilde, H.; Dalcanale, E.; Mavilla, L.; Mann, G.; Heyer, U.; Spera, S. *J. Org. Chem.* **1995**, *60*, 235−242. (b) Vincenti, M.; Dalcanale, E. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1069−1076. (c) Xu, W.; Vittal, J. J.; Puddephatt, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 6456−6457. (d) Vincenti, M.; Pelizzetti, E.; Dalcanale, E.; Soncini, P. *Pure Appl. Chem.* **1993**, *65*, 1507−1512. (e) Sonicini, P.; Bonsignore, S.; Dalcanale, E.; Ugozzoli, F. *J. Org. Chem.* **1992**, *57*, 4608−4612. (f) Dalcanale, E.; Costantini, G.; Soncini, P. *J. Inclusion Phenom. Mol. Recognit. Chem.* **1992**, *13*, 87−92. (g) Xu, W.; Vittal, J. J.; Puddephatt, R. J. *J. Am. Chem. Soc.* **1995**, *117*, 8362−8371.

(6) For linkage of cavitands to each other via their rims, see ref 2 and (a) Cram, D. J.; Tunstad, L. M.; Knobler, C. B. *J. Org. Chem.* **1992**, *57*, 528−535. (b) von dem Bussche-Hünnefeld, C.; Bühring, D.; Knobler, C. B.; Cram, D. J. *J. Chem. Soc., Chem. Commun.* **1995**, 1085−1086.

(7) Compound **2a** has been reported previously, but was not fully characterized, see: 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*, 1305−1312.

(8) For the incorporation of alcohols of different chain length into the lower rim of calixarenes, see: Moran, J. K.; Georgiev, E. M.; Yordanov, A. T.; Mague, J. T.; Roundhill, D. M. *J. Org. Chem.* **1994**, *59*, 5990−5998.

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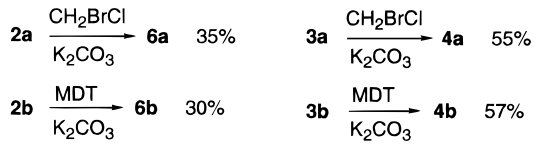
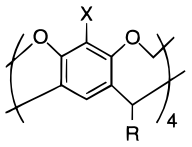
Scheme 2. Synthesis of Cavitands 4a, 4b, 6a, and 6b via Direct Methylene Bridging[a]



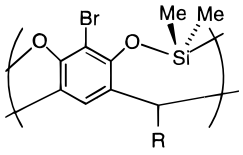
[a] MDT, methylene ditosylate.

explored a variety of conditions for direct bridging of various dodecols, including **3a**, as detailed in the Discussion section. The protection/deprotection route from dodecol **3a** toward cavitand **4a** entailed silicon bridging/protection of dodecol **3a** using Me_2SiCl_2[9] to yield silicon cavitand **5a** (82% yield), whose alcohols were protected with methoxymethyl (MOM) groups to yield the MOM-protected silicon cavitand **5c** (75% yield). The silicon bridges of **5c** were removed with HF to yield octol **3c** (82% yield), which was bridged with methylene ditosylate (MDT)[10] to yield methylene-bridged cavitand **4c** (41% yield).[11] Removal of the MOM group of **4c** with catalytic HCl in refluxing methanol/THF (1:1) gave butanol-footed cavitand **4a** (95% yield). Dodecol **3a** was also bridged directly with MDT or CH_2BrCl as were dodecols **2a**, **2b**, and **3b**, to yield hydroxyl-footed cavitands **4a** (55%), **6a** (35%), **6b** (30%), and **4b** (57%), respectively, as indicated in Table 1.



4a: R = $(CH_2)_4OH$, X = Br
4b: R = $(CH_2)_3OH$, X = Br
4c: R = $(CH_2)_4OCH_2OCH_3$, X = Br
4d: R = CH_2CH_2Ph, X = Br

6a: R = $(CH_2)_4OH$, X = H
6b: R = $(CH_2)_3OH$, X = H
6d: R = CH_2CH_2Ph, X = H



5a: R = $(CH_2)_4OH$
5b: R = $(CH_2)_3OH$
5c: R = $(CH_2)_4OCH_2OCH_3$

Discussion

The incorporation of methylene bridges into resorcinarenes is often difficult due to oligomerization, and in the case of resorcinarenes **2** and **3**, the bridging reaction is complicated by the competitive reactions caused by the pendant hydroxyl groups. In an effort to alleviate these problems, we probed the bridging reaction and hoped that some guidelines might be formulated that could be applied to derivatives that contain even more sensitive functional groups. Table 1 summarizes the conditions and yields for a variety of bridging reactions.

The bridging reaction entails the organization of fluxional molecules into highly rigid molecules.[1b,12] Each bridge requires the attack of a phenol (or phenoxide) on a bis-electrophile (i.e., CH_2XY), followed by attack of a second phenol (or phenoxide) on a singly-electrophilic intermediate (i.e., $ArOCH_2X$). As successive bridges form, the molecules become more rigid, which slows down subsequent bridging substantially. By examination of CPK models, the phenols appear to be highly accessible to attack on the electrophiles during the formation of the first two bridges due to the flexibility of the molecules. When there are three bridges or even two that oppose each other ("A,C"), the molecules become very rigid and the phenols lose their access to electrophilic attack. This notion is supported experimentally by the common observation of the "tris-bridged" and "A,C-bis-bridged" intermediates, which form in the presence of limited bridging reagent[1b, 12] or when the solvent is too nucleophilic and consumes the bridging reagent at the temperatures needed for final bridging.[12] The base most likely deprotonates one set of four of the eight phenols,[13] which are much more acidic than the second set, due to the formation of charged hydrogen bonds. Although this hydrogen-bonding network should rigidify the molecules, there is still enough flexibility to allow early bridges to form faster than the later bridges.

The effect of preorganization on bridging is further illustrated by the reaction of dodecols **3a** and **3b** with Me_2SiCl_2 versus trimethylsilyl chloride (TMSCl), using pyridine as the base and solvent. Use of Me_2SiCl_2 as a bridging reagent[9] gave 82 and 74% yields of silicon-bridged cavitands **5a** and **5b**, respectively. In contrast, reaction of dodecols **3a** and **3b** with TMSCl gave only mixtures with TMS groups on both the phenols and the alcohols.[14] These results may be rationalized as follows. The preorganization of the macrocycle allows the $ArO-SiMe_2Cl$ intermediates to bridge readily with the adjacent phenols (to complete the eight-membered rings), such that the relative nucleophilicity of the pendant alcohols is low. Each silicon bridge may further preorganize the macrocycle, thereby enhancing formation of the eight-membered rings, whereas the ArOTMS groups render the remaining phenols comparable in nucleophilicity (or even less so) than the pendant alcohols. The ArOTMS groups likely create steric hindrance to nucleophilic attack by the adjacent phenols and may reduce the nucleophilicity of the distal phenols by disrupting the cyclic array of charged hydrogen bonds: the cooperative formation of the charged hydrogen bonds is likely to be diminished by each ArOTMS group, whereas each $ArOSiMe_2OAr$ bridge is likely to strengthen the cyclic hydrogen-bonded network.

Several trends regarding the methylene bridging in the formation of cavitands can be observed from Table 1. The yields for the hydroxyl-footed cavitands are lower than for the phenethyl-footed cavitands,[15] and there is an optimal amount of bridging reagent for the hydroxyl-footed cavitands (data shown in Table 1 for cavitand **6b**

(9) For bridging of resorcinarenes with Me_2SiCl_2, see: Cram, D. J.; Stewart, K. D.; Goldberg, I.; Trueblood, K. N. *J. Am. Chem. Soc.* **1985**, *107*, 2574−2575.

(10) Emmons, W. D.; Ferris, A. F. *J. Am. Chem. Soc.* **1953**, *75*, 2257.

(11) The 41% yield in the methylene bridging of octol **3c** would likely increase if the MOM groups were replaced by a more robust protective group such as (methoxyethoxy)methyl.

(12) 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.

(13) (a) Schneider, H.-J.; Güttes, D.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6449−6454. (b) Sorrell, T. N.; Pigge, F. C.; White, P. S. *Inorg. Chem.* **1994**, *33*, 632−635.

(14) TMS derivatives of **3a** and **3b** were characterized by ^1H NMR.

Table 1. Conditions and Yields for Methylene-Bridging Reactions[a]

entry	starting material	product	bridging reagent[b]	equiv time/temp[c]	yield (%)
1	**2a**	**6a**	BCM	4.5[d] 2 d rt, 4.5 1 d 40 °C, 4.5 3 d 65 °C	26[e]
1	**2a**	**6a**	MDT	4.5 2 d rt, 4.5 2 d 60 °C	35
3	**3a**	**4a**	BCM	4.5 d 2 d rt, 1 d rt, 4.5 1 d 40 °C, 4.5 3 d 65 °C	55[f]
4	**3a**	**4a**	MDT	4.5 2 d rt, 4.5 2 d 60 °C	40
5	**2b**	**6b**	BCM	4.5[d] 2 d rt, 1 d rt, 4.5 1 d 40 °C, 4.5 3 d 65 °C	12[e]
6	**2b**	**6b**	BCM	4.5 2 d rt, 4.5 2 d 60 °C	5
7	**2b**	**6b**	MDI	4.5 2 d rt, 4.5 2 d 60 °C	12
8	**2b**	**6b**	MDT	2.0 2 d rt, 2.5 2 d 60 °C	18
9	**2b**	**6b**	MDT	2.5 2 d rt, 2.5 2 d 60 °C	23
10	**2b**	**6b**	MDT	3.5 2 d rt, 3.5 2 d 60 °C	30
11	**2b**	**6b**	MDT	4.0 2 d rt, 4.0 2 d 60 °C	24
12	**2b**	**6b**	MDT	4.5 2 d rt, 4.5 2 d 60 °C	16
13	**2b**	**6b**	MDT	6.5 2 d rt, 5.0 2 d 60 °C	5
14	**2b**	**6b**	MDT	4.5 1 d rt, 4.5 1 d 60 °C	14
15	**2b**	**6b**	MDT	3.5 2 d rt	0
16	**3b**	**4b**	BCM	4.5[d] 2 d rt, 1 d rt, 4.5 1 d 40 °C, 4.5 3 d 65 °C	57[f]
17	**3b**	**4b**	BCM	4.5 2 d rt, 4.5 2 d 60 °C	7
18	**3b**	**4b**	MDI	4.5 2 d rt, 4.5 2 d 60 °C	13
19	**3b**	**4b**	MDT	4.5 1 d rt, 4.5 1 d 60 °C	18
20	**3b**	**4b**	MDT	4.5 2 d rt, 4.5 2 d 60 °C	30
21	**3c**	**4c**	BCM	4.5[g] 1 d rt, 1 d rt, 4.6 1 d 40 °C, 4.5 3 d 65 °C	1[e]
22	**3c**	**4c**	MDT	3.5 2 d rt, 3.5 2 d 60 °C	41
23	**2d**	**6d**	BCM	4.5[g] 1 d rt, 1 d rt, 4.5 1 d 40 °C, 4.5 3 d 65 °C	45[e]
24	**2d**	**6d**	MDT	4.5 1 d rt, 4.5 1 d 60 °C	82
25	**3d**	**4d**	BCM	4.6g 1 d rt, 1 d rt, 4.5 1 d 40 °C, 4.5 3 d 65 °C	60[e]
26	**3d**	**4d**	MDT	4.6 2 d rt, 4.6 2 d 60 °C	70
27	**3d**	**4d**	MDT	4.5 1 d rt, 4.5 1 d 60 °C	27
28	**3d**	**4d**	MDT	4.5 1 d 0 °C, 4.6 1 d 60 °C	8
29	**3d**	**4d**	MDT	4.6 1 d 60 °C, 4.6 1 d 60 °C	18

[a] All reactions were run using ca. 50 mg of starting material, K_2CO_3 as the base, and dimethylacetamide as the solvent, unless noted otherwise. [b] BCM, bromochloromethane; MDI, methylene diiodide; MDT, methylene ditosylate. [c] Number of equivalents refers to the bridging reagent. All reagents were added at once unless noted otherwise. rt, room temperature; d, days. [d] The starting material was added via syringe pump over 48 h; all other reagents were added at once. Subsequent additions of bridging reagent were all at once.[e] The reaction was run on a 0.5 g scale. [f] The reaction was run on a 10 g scale. [g] The starting material was added via syringe pump over 24 h; all other reagents were added at once. Subsequent additions of bridging reagent were all at once.

only, entries 8−13). These results indicate that the pendant alcohols can react with excess bridging reagent as expected, which diminishes the yields of cavitands. This side-reaction was further evident by an experiment in which methylene-bridged cavitand **4b** was subjected to optimal bridging conditions (3.5 equiv, 2 d at rt; 3.5 equiv, 2 d at 60 °C) using MDT as the bridging reagent. Only 49% of the cavitand was recovered, whereas under the same conditions, but omitting the MDT, 73% of **4b** was recovered. Thus, under these conditions, 24% of the hydroxyl-footed material is lost to intermolecular reaction at the pendant alcohols. Interestingly, in contrast to the methylene bridging, the silicon bridging of dodecols **3a** and **3b** proceeds very efficiently, indicating that the side reactions with the pendant hydroxyls is not a problem. This high selectivity with silicon bridging may be due to the milder conditions used for the reaction (pyridine as base and lower temperature). In fact, significantly longer reaction times were required to form TMS ethers at the pendant alcohols than for bridging the phenols with Me_2SiCl_2. Unfortunately, a stronger base (K_2CO_3) is required for the methylene bridging of the resorcinarenes, even with MDT as the bridging reagent (see below).

Other trends concerning the bridging reaction are the following. The reactivity of the bridging reagents appears to decrease in the order MDT > CH_2I_2 > CH_2BrCl (see entries 6, 7, and12 and 17, 18, and 20), which follows the order of leaving group abilities. The reaction yields are often improved by a second day at 60 °C (entries 12 and 14; 19 and 20; 26, 27, and 28), which is consistent with the later bridges being slow to form.[12] Initial reaction at 60 °C lowers the yields (entries 27, 28, and 29), perhaps due to an increase in polymerization with the less preorganized, unbridged species. Finally, the presence of a bromine in the 2-position of the resorcinols slows the bridging reaction as is evident by the extra time required to achieve a high yield when the pendant groups are phenethyl (entries 24, 26, and 27). Furthermore, when CH_2BrCl is used as the bridging reagent and the reaction is stirred at 65 °C for 3 days, the yields are higher with bromine versus hydrogen (entries 1 and 3; 5 and 16; 23 and 25); the bromine most likely hinders intermolecular bridging between the phenols. Interestingly, this differential in yields between bromine versus hydrogen in the 2-position is not observed using the bulkier MDT as the bridging reagent (entries 2 and 4; 12 and 20; 24 and 26).

Conclusions

We have prepared several hydroxyl-footed cavitands. The short three- and four-carbon chains may be useful in tail-to-tail coupling of cavitands, the incorporation of water-solubilizing groups distal to the enforced cavity of cavitands, and in the formation of monolayers where the bowls are held close to a solid surface. The factors involved in the bridging of the resorcinarenes are manifold, but conditions can be rationally adjusted to optimize the yields of the methylene-bridged cavitands. For example, MDT is more effective at methylene bridging under milder conditions. We have also developed an alternative route to methylene-bridged cavitands that

(15) Cavitand **4d** has been prepared previously in 52% yield on a 21 g scale using similar conditions to entry 25 in Table 1, see: Sherman, J. C.; Knobler, C. N.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2194−2204.

involves an unusual use of silicon bridges as protective groups. This route may be useful to incorporate methylene bridges into resorcinarenes that contain reactive funtionalities in the pendant groups.

Experimental Section

General.[16] Acetonitrile and pyridine were dried over 4 Å molecular sieves. DMF and dimethylacetamide (DMA) were stirred over BaO, then distilled *in vacuo* onto 4 Å molecular sieves, and stored under N_2. Mass spectra were obtained using a Kratos Concept IIH32 using LSIMS+ (unless noted otherwise) with thioglycerol (TG) and *m*-nitrobenzyl alcohol (NBA) as the matrices as noted. All products were dried overnight at rt at 0.1 Torr unless otherwise noted.

Dodecol 2a.[7] Resorcinol (20 g, 182 mmol) was dissolved in 150 mL of 4:1 methanol/37% HCl under N_2. 3,4-Dihydro-2H-pyran (16.6 mL, 182 mmol) was then added via syringe pump over 4 h. After an additional 4 h of stirring at rt, the mixture was heated to 50 °C. After 7 days a considerable amount of precipitate was formed and the reaction mixture was allowed to cool to rt. The solid was filtered off and then taken up in 1 L of cold distilled water and sonicated. The solid was again filtered off and dried at 0.1 Torr at rt overnight. After this period the product was taken up in dry THF. The insoluble material was filtered off and dried to give 22.8 g (65%) of the desired C_{4v} isomer **2a** as an off-white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 8.90 (s, 8 H), 7.22 (s, 4 H), 6.13 (s, 4 H), 4.29 (t, 4 H, J = 5.1 Hz), 4.18 (t, 4 H, J = 7.8 Hz), 3.30 (m, 8 H), 2.08 (m, 8 H), 1.44 (m, 8 H), 1.18 (m, 8 H); MS (NBA) *m/z* 776 (M^+, 100). Anal. Calcd for $C_{44}H_{56}O_{12}$: C, 68.02; H, 7.27. Found: C, 67.98; H, 7.27.

Dodecol 2b. Resorcinol (20 g, 182 mmol) was dissolved in 150 mL of 4:1 methanol/37% HCl under N_2. 2,3-Dihydrofuran (13.8 mL, 182 mmol) was then added via syringe pump over 4 h. After an additional 4 h of stirring at rt, the mixture was heated to 50 °C. After 7 days a considerable amount of precipitate was formed and the reaction mixture was allowed to cool to rt. The solid was filtered off and taken up in 1 L of cold distilled water and sonicated. The solid was again filtered off and dried at 0.1 Torr at rt overnight. The solid was then taken up in dry THF, and the insoluble material was filtered off and dried to give 20.0 g (61%) of the desired C_{4v} isomer **2b** as an off-white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 8.88 (s, 8 H), 7.22 (s, 4 H), 6.13 (s, 4 H), 4.29 (t, 4 H, J = 5.1 Hz), 4.18 (t, 4 H, J = 7.8 Hz), 3.40 (m, 8 H), 2.08 (m, 8 H), 1.33 (m, 8 H); MS (TG) *m/z* 720 (M^+, 60) 661 ((M − HO$(CH_2)_3)^+$, 100). Anal. Calcd for $C_{40}H_{48}O_{12}$: C, 66.65; H, 6.71. Found: C, 66.29; H, 6.66.

Dodecol 3a. Dodecol **2a** (10 g, 12.9 mmol) was added to 190 mL of 30% methanol in butanone. *N*-Bromosuccinimide (NBS, 10.3 g, 57.9 mmol) was added to this suspension, and the reaction mixture was stirred at rt in the dark for 5 h. Additional NBS (4.58 g, 25.7 mmol) was added, and the reaction mixture was stirred overnight. The reaction mixture was filtered, and the solid was washed with 100 mL of cold butanone. The solid was dried to give 12.7 g (90%) of **3a** as an off-white solid: mp 227 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.14 (s, 8 H), 7.41 (s, 4 H), 4.32 (m, 8 H), 3.34 (t, 8 H, J = 6.6 Hz), 2.21 (m, 8 H), 1.47 (m, 8 H), 1.19 (m, 8 H); MS (LSIMS-, NBA) *m/z* 1091 ((M − $H^+)^-$, 100). Anal. Calcd for $C_{44}H_{52}O_{12}Br_4$: C, 48.37; H, 4.80. Found: C, 48.36; H, 5.00.

Dodecol 3b. Dodecol **2b** (10 g, 13.9 mmol) was added to 190 mL of 30% methanol in butanone. *N*-Bromosuccinimide (NBS, 11.1 g, 62.4 mmol) was added to this suspension, and the reaction mixture was stirred at rt in the dark for 5 h. Additional NBS (4.93 g, 27.7 mmol) was added, and the reaction mixture was stirred overnight. The reaction mixture was filtered, and the solid was washed with 100 mL of cold butanone. The solid was dried to give 11.8 g (82%) of **3b** as an off-white solid: mp 220 °C dec; ^{1}H NMR (DMSO-d_6) δ 9.11 (s, 8 H), 7.40 (s, 4 H), 4.34 (br, 8 H), 3.43 (t, 8 H, J = 6.5 Hz), 2.21 (m, 8 H), 1.34 (m, 8 H); MS (TG) *m/z* 1036 (M^+, 50) 977 ((M − HO$(CH_2)_3)^+$, 100). Anal. Calcd for $C_{40}H_{44}O_{12}Br_4$: C, 46.36; H, 4.28. Found: C, 46.75; H, 4.64.

Cavitand 4a. Dodecol **3a** (10.92 g, 10.0 mmol) was dissolved in 50 mL of DMA and added via syringe pump over 2 days to a stirred mixture of 350 mL of DMA, potassium carbonate (18 g, 130 mmol), and BCM (3.0 mL, 45 mmol). After stirring for another day at rt, BCM (3.0 mL, 45 mmol) was added, and the reaction mixture was stirred at 45 °C for 1 day. Additional BCM (3.0 mL, 45 mmol) was added, and the reaction mixture was stirred at 65 °C for 3 days. The reaction mixture was then cooled to rt, and the solvent was removed *in vacuo*. The solid residue was sonicated in 300 mL of water followed by slow addition of 2 M HCl until the carbonate salts were neutralized. The resulting mixture was filtered, and the solid was washed with water (3 × 50 mL), dissolved in 300 mL of THF, and dried with $MgSO_4$. The solvent was removed *in vacuo* and purified by silica gel column chromatography using 9:1 $CHCl_3$:methanol (v/v). The product was recrystallized from THF/acetonitrile to give 6.3 g of **4a** (55%) as a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.60 (s, 4 H), 5.99 (d, 4 H, J = 7.6 Hz), 4.69 (t, 4 H, J = 8.2 Hz), 4.38 (broad, 4 H), 4.30 (d, 4 H, J = 7.6 Hz), 3.40 (m, 8 H), 2.39 (m, 8 H), 1.54 (m, 8 H), 1.33 (m, 8 H); MS (LSIMS, NBA) *m/z* 1139 ((M − $H^+)^-$, 50), 1293 ((M − H^+ + NBA)$^-$, 100). Anal. Calcd for $C_{48}H_{52}O_{12}Br_4$: C, 50.55; H, 4.60. Found: C, 50.24; H, 4.58.

Cavitand 4b. Dodecol **3b** (10.36 g, 10.0 mmol) was dissolved in 50 mL of DMA and added via syringe pump over 2 days to a stirred mixture of 350 mL of DMA, potassium carbonate (18 g, 130 mmol), and BCM (3.0 mL, 45 mmol). After stirring for another day at rt, BCM (3.0 mL, 45 mmol) was added and the reaction mixture was stirred at 45 °C for 1 day. Additional BCM (3.0 mL, 45 mmol) was added, and the reaction mixture was stirred at 65 °C for 3 days. The reaction mixture was then cooled to rt, and the solvent was removed *in vacuo*. The solid residue was sonicated in 300 mL of water followed by slow addition of 2 M HCl until the carbonate salts were neutralized. The resulting mixture was filtered, and the solid was washed with water (3 × 50 mL), dissolved in 300 mL of THF, and dried with $MgSO_4$. The solvent was removed *in vacuo* and purified by silica gel column chromatography using 9:1 $CHCl_3$:methanol (v/v). The product was recrystallized from THF/acetonitrile to give 6.2 g of **4b** (57%) as a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.65 (s, 4 H), 5.99 (d, 4 H, J = 7.6 Hz), 4.69 (t, 4 H, J = 8.3 Hz), 4.50 (broad, 4 H), 4.30 (d, 4 H, J = 7.6 Hz), 3.50 (m, 8 H), 2.46 (m, 8 H), 1.44 (m, 8 H); MS (NBA) *m/z* 1085 (M^+, 100). Anal. Calcd for $C_{44}H_{44}O_{12}Br_4 \cdot H_2O$: C, 47.94; H, 4.21. Found: C, 47.95; H, 4.20.

Silicon Cavitand 5a. Dodecol **3a** (40 g, 36.6 mmol) was dissolved in 1.2 L of pyridine. To this solution was rapidly added Me_2SiCl_2 (44.4 mL, 366 mmol), and the reaction mixture was stirred for 2 h at rt. The solvent was removed *in vacuo*, giving a solid that was taken up in methanol to destroy the remaining reagent. The methanol was removed *in vacuo*, and the resulting solid was suspended in methanol, filtered, and dried to give 39.5 g of **5a** as a white solid (82% yield): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.77 (s, 4 H), 4.50 (t, 4 H, J = 8.0 Hz), 4.36 (t, 4 H, J = 5.1 Hz), 3.36 (m, 8 H), 2.35 (m, 8 H), 1.49 (m, 8 H), 1.23 (m, 8 H), 0.55 (s, 12 H), −0.62 (s, 12 H); MS (NBA) *m/z* 1316 (M^+, 100). Anal. Calcd for $C_{52}H_{68}O_{12}Br_4Si_4$: C, 47.42; H, 5.20. Found: C, 47.49; H, 5.27.

Silicon Cavitand 5b. Dodecol **3b** (500 mg, 0.48 mmol) was dissolved in 20 mL of pyridine. To this solution was rapidly added Me_2SiCl_2 (0.66 mL, 5.4 mmol), and the reaction mixture was stirred for 2 h at rt. The solvent was removed *in vacuo*, giving a solid that was taken up in methanol to destroy the remaining reagent. The methanol was removed *in vacuo*, and the resulting solid was suspended in methanol, filtered, and dried to give 450 mg of **5b** as a white solid (74% yield): mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.80 (s, 4 H), 4.50 (t, 4 H, J = 8.0 Hz), 4.41 (t, 4 H), 3.45 (t, 8 H, J = 6.4 Hz), 2.39 (m, 8 H), 1.37 (m, 8 H), 0.55 (s, 12 H), −0.61 (s, 12 H); MS (NBA) *m/z* 1260 (M^+, 100). Anal. Calcd for $C_{48}H_{60}O_{12}Br_4Si_4$: C, 45.72; H, 4.80. Found: C, 45.46; H, 4.91.

Silicon Cavitand 5c. Silicon cavitand **5a** (10 g, 7.60 mmol) was suspended in 150 mL of DMF. While vigorous stirring was maintained, diisopropylethylamine (20 mL, 115 mmol) and MOM-Cl (5.8 mL, 76 mmol) were added. Within 1 h full dissolution had occurred, and the reaction was stirred overnight

(16) For further general experimental details, see: Fraser, J. R.; Borecka, B.; Trotter, J.; Sherman, J. C. *J. Org. Chem.* **1995**, *60*, 1207−1213.

at rt. The solvent was removed *in vacuo*, and the crude product was taken up in ethyl acetate. The organic layer was washed with dilute HCl, then saturated potassium carbonate, and finally distilled water. The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give a solid that was recrystallized from acetone and dried to give 8.5 g (75%) of **5c** as a white solid: mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 7.20 (s, 4 H), 4.64 (t, 4 H, J = 8.1 Hz), 4.57 (s, 8 H), 3.84 (t, 8 H, J = 6.5 Hz), 3.32, (s, 12 H), 2.20 (m, 8 H), 1.66 (m, 8 H), 1.34 (m, 8 H), 0.60 (s, 12 H), −0.53 (s, 12 H); MS (NBA) m/z 1492 (M^+, 100). Anal. Calcd for $C_{60}H_{84}O_{16}Br_4Si_4$: C, 48.26; H, 5.67. Found: C, 48.10; H, 5.65.

Octol 3c. Silicon cavitand **5c** (5 g, 3.35 mmol) was dissolved in 180 mL of DMF in a polypropylene flask. To this stirring solution was added HF (1.39 mL of a 48% solution, 33.4 mmol). The reaction mixture was stirred overnight at rt, the solvent was removed *in vacuo* (T < 40 °C), and the crude product was taken up in ethyl acetate. The organic layer was washed three times with distilled water before being dried ($MgSO_4$). The solvent was removed *in vacuo*, giving a solid that was recrystallized from acetone and dried at 0.1 Torr at 77 °C for 24 h to give 3.5 g (82%) of **3c** as a white solid: mp 230 °C dec; ^{1}H NMR (acetone-d_6) δ 8.25 (s, 8 H), 7.62 (s, 4 H), 4.52 (s, 4 H), 4.47 (t, 4 H, J = 7.8 Hz), 3.45 (t, 8 H, J = 6.5 Hz), 3.25 (s, 12 H), 2.34 (m, 8 H), 1.62 (m, 8 H), 1.36 (m, 8 H); MS (TG) m/z 1286 ((M + H_2O)$^+$, 100) 1268 (M^+, 65) 1206 ((M − MOMOH)$^+$, 60). Anal. Calcd for $C_{52}H_{68}O_{16}Br_4$: C, 49.23; H, 5.40. Found: C, 49.00; H, 5.40.

Cavitand 4c. Octol **3c** (500 mg, 0.394 mmol), potassium carbonate (900 mg, 6.5 mmol), and MDT (505 mg, 1.42 mmol) were added, with stirring, to 15 mL of DMA. The reaction mixture was stirred for 2 days before additional MDT (505 mg, 1.42 mmol) was added, and the temperature was increased to 70 °C. After 2 days, the solvent was removed *in vacuo*, and the residue was taken up in THF and filtered. The filtrate was evaporated *in vacuo*, and the residue was purified by silica gel colunm chromatography (3:1 THF:hexanes) and dried at 0.1 Torr at 77 °C for 24 h to give 210 mg (41%) of **4c** as a white solid: mp 193 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.01 (s, 4 H) 5.94 (d, 4 H, J = 7.3 Hz), 4.87 (t, 4 H, J = 8.1 Hz), 4.60 (s, 8 H), 4.37 (d, 4 H, J = 7.3 Hz), 3.52 (t, 8 H, J = 6.5 Hz), 3.33 (s, 12 H), 2.23 (m, 8 H), 1.71 (m, 8 H), 1.44 (m, 8 H); MS (NBA) m/z 1316 (M^+, 100). Anal. Calcd for $C_{56}H_{68}O_{16}Br_4$: C, 51.08; H, 5.21. Found: C, 51.07; H, 5.19.

Cavitand 6a. Dodecol **2a** (50 mg, 0.064 mmol), potassium carbonate (90 mg, 0.65 mmol), and MDT (103 mg, 0.29 mmol) were added to 2 mL of DMA, and the solution was stirred at rt for 2 days. Additional MDT (103 mg, 0.29 mmol) was added, and the reaction mixture was stirred at 60 °C for 2 days. The solvent was removed *in vacuo*, and the ensuing solid was sonicated in 50 mL of water for 10 min followed by slow addition of 2 M HCl until the carbonate salts were neutralized. The resulting mixture was filtered, and the solid was washed with water (3 × 15 mL), dissolved in 50 mL of THF, and dried with $MgSO_4$. The solvent was removed *in vacuo*, and solid was purified by silica gel column chromatography using 9:1 $CHCl_3$:methanol (v/v) to give 19 mg (35%) of **6a** as a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.57 (s, 4 H), 6.50 (s, 4 H), 5.70 (d, 4 H, J = 7.8 Hz), 4.56 (t, 4 H, J = 8.1 Hz), 4.38 (d, 4 H, J = 7.6 Hz), 4.36 (t, 4 H, J = 5.0 Hz), 3.40 (m, 8 H), 2.36 (m, 8 H), 1.54 (m, 8 H), 1.32 (m, 8 H); MS (TG) m/z 825 (M^+, 100). Anal. Calcd for $C_{48}H_{56}O_{12}\cdot{}^1/_2H_2O$: C, 69.13; H, 6.89. Found: C, 69.13; H, 7.04.

Cavitand 6b. Dodecol **2b** (46 mg, 0.064 mmol), potassium carbonate (90 mg, 0.65 mmol), and MDT (80 mg, 0.22 mmol) were added to 2 mL of DMA, and the solution was stirred at rt for 2 days. Additional MDT (80 mg, 0.22 mmol) was added, and the reaction mixture was stirred at 60 °C for 2 days. The solvent was removed *in vacuo* and the ensuing solid was sonicated in 50 mL of water for 10 min followed by slow addition of 2 M HCl until the carbonate salts were neutralized. The resulting mixture was filtered, and the solid was washed with water (3 × 15 mL), dissolved in 50 mL of THF, and dried with $MgSO_4$. The solvent was removed *in vacuo*, and the solid was purified by silica gel column chromatography using 9:1 $CHCl_3$:methanol (v/v) to give 15 mg (30%) of **6b** as a white solid: mp >250 °C; ^{1}H NMR (DMSO-d_6) δ 7.60 (s, 4 H), 6.49 (s, 4 H), 5.70 (d, 4 H, J = 7.6 Hz), 4.55 (t, 4 H, J = 8.1 Hz), 4.43 (t, 4 H, J = 5.0 Hz), 4.34 (d, 4 H, J = 7.6 Hz), 3.50 (m, 8 H), 2.40 (m, 8 H), 1.45 (m, 8 H); MS (TG) m/z 769 (M^+, 100). Anal. Calcd for $C_{44}H_{48}O_{12}$: C, 68.74; H, 6.29. Found: C, 68.82; H, 6.45.

Cavitand 6d. Octol **2d**[17] (50 mg, 0.055 mmol) was dissolved in 1 mL of DMA and added via syringe pump over 4 h to a mixture of potassium carbonate (90 mg, 0.65 mmol) and MDT (89 mg, 0.25 mmol) in 2.5 mL of DMA. The reaction mixture was stirred for 1 day at rt, before MDT (89 mg, 0.25 mmol) was added, and the reaction mixture was stirred at 60 °C for 1 day. The reaction mixture was then cooled to rt, and the solvent was removed *in vacuo*. The solid residue was stirred in water and extracted with $CHCl_3$. The solvent was removed *in vacuo* and purified by silica gel column chromatography (3:1 $CHCl_3$:hexanes) to give 43 mg (82%) of **6d** as a white solid: mp >250 °C; ^{1}H NMR ($CDCl_3$) δ 7.23−7.12 (m, 24 H), 6.52 (s, 4 H), 5.75 (d, 4 H, J = 7.1 Hz), 4.82 (t, 4 H, J = 7.9 Hz), 4.45 (d, 4 H, J = 7.1 Hz), 2.65 (m, 8 H), 2.51 (m, 8 H); MS (TG) m/z 953 (M^+, 100). Anal. Calcd for $C_{48}H_{56}O_{12}\cdot{}^1/_2H_2O$: C, 79.89; H, 5.97. Found: C, 79.95; H, 5.95.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support. R.G.C. thanks NSERC for a graduate fellowship. Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

JO951633C

(17) For the preparation of octol **2d**, see ref 7.