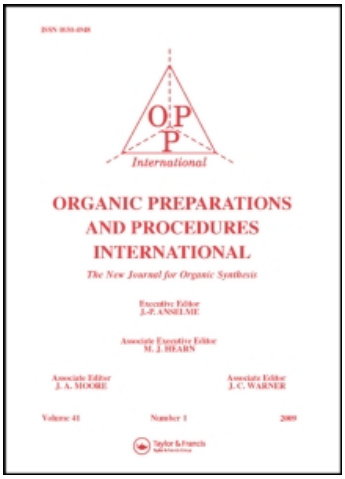

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IMPROVED SYNTHESIS AND PURIFICATION OF CAVITANDS

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IMPROVED SYNTHESIS AND PURIFICATION OF CAVITANDS

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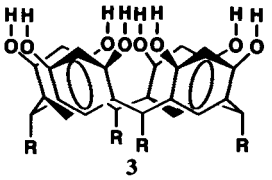
The acid-catalyzed condensation of resorcinol and aldehydes produces resorcinarenes such as **3**. Resorcinarenes are known to possess hydrophilic (upper rim) and hydrophobic (lower rim) regions and a cavity, which can accommodate small organic molecules.[1] Cavitands of the general structure **4** are synthesized from resorcinarenes *via* bridging reactions of the hydroxyl groups.[1,2] The bridges serve to impart conformational rigidity to the existing aryl skeleton and help form the bowl-shaped cavitand.[3,4] Resorcinarenes and cavitands have found applications as surfactants, as liquid crystals, and in the complexation of metals, ammonium compounds, alcohols, diols, sugars, amino acids and carboxylic acids.[5]



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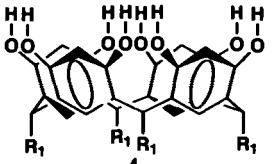

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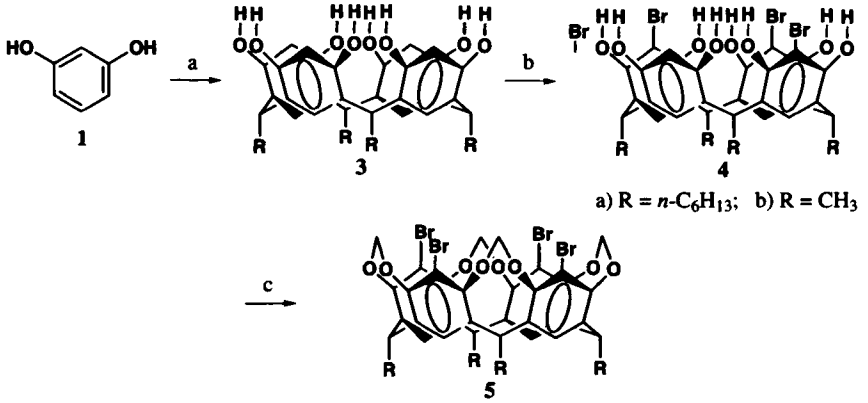
R = $(CH_2)n$
n = 1,2,3

The synthesis of cavitands **5a** and **5b** *(Scheme 1)* began with the acid-catalyzed condensation of resorcinol (**1**) and heptaldehyde (**2a**) or acetaldehyde (**2b**) in 95% ($EtOH/H_2O$) under reflux, to afford resorcinarenes **3a** and **3b** in 96% and 87% yields, respectively. Subsequent aromatic bromination using *N*-bromosuccinimide in 2-butanone gave tetrabromides **4a** and **4b** in 75% and 71% yields, respectively. Addition of stoichiometric excess of Cs_2CO_3 with bromochloromethane, as the bridging reagent, in DMF (in a 1:1 ratio) gave the bromo-substituted cavitands **5a** and **5b** in 68% and 65% yield, respectively.

The bridging reaction to form the cavitand is known to be a low yield step;[1-3] moreover, the sparing solubility of these macrocycles in organic solvents requires large quantities of solvent to purify the product *via* column chromatography.[3] We have developed a new approach to the cavity closing reaction and its purification, that involves a significant modification of previously



a) **2a**, **2b**, RCHO, 95% $EtOH/H_2O$, HCl, reflux; b) NBS, 2-butanone, r.t.; c) Cs_2CO_3, 1:1 DMF/ CH_2BrCl

Scheme 1

reported reaction conditions. The experimental procedure for cavitand formation[1-6] employs a DMF solvent system containing 0.03 M of the tetrabromoresorcinarene precursor in DMF to which only a small amount (1 mL) of CH_2BrCl is added. These reports suggest one gram of the tetrabromoresorcinarene in 40 mL of DMF (a 0.03 M solution). We have found that yields can be improved considerably by increasing the concentration of the tetrabromoresorcinarene to 0.04 M in a solvent system consisting of 1:1 mol ratio of DMF:CH_2BrCl. Thus a typical procedure requires one gram of the tetrabromoresorcinarene in 30 mL of 1:1 DMF/CH_2BrCl.

We next sought to enhance the purification procedure. Literature methods involve purification of the cavitand *via* column chromatography using silica gel with mixtures of solvents such as methylene chloride, chloroform, ethyl acetate, hexanes, etc. as eluents.[1-4] Column chromatography purification of 20 g of crude product requires as much as 8 L of solvent and takes many hours to complete. We attribute this phenomenon to the poor solubility of the compounds in the silica gel/solvent system. As an alternative, we investigated the use of Soxhlet extraction to circumvent these problems The procedure reported here is specifically suited for a

larger scale synthesis, *e.g.* 20 g of crude product, **5a** or **5b** can be purified by Soxhlet extraction using an average of only 700 mL of 7:1-hexane:ethyl acetate mixture, producing cavitands **5a** and **5b**. Cram *et al.* have reported a maximum yield of 50% for the cavitand reaction after purification *via* column chromatography.[1-4] Our yields for the same reactions are on the order of 67%.

EXPERIMENTAL SECTION

Commercially available reagents were purchased from Acros Chemical Co. or Aldrich Chemical Co. and were used without further purification. Cs_2CO_3 was dried by heating to 250°C for 24 h and then cooled to ambient temperature in a vacuum desiccator. N-bromosuccinimide (NBS) was recrystallized from boiling water: 1 g NBS/100 mL water. DMF was stored over molecular sieves (3Å) for 24 hours and degassed prior to use. Thin layer Chromatography was performed using Whatman silica gel (60Å) with fluorescent indicator on 250-micrometer thickness glass backed, with hexanes/ethyl acetate as the mobile phase. NMR spectra were recorded on a Bruker 250 MHz, spectrometer in $CDCl_3$ or DMSO containing 0.03% TMS. Chemical shifts are listed in δ downfield relative to TMS. Coupling constants are given in Hz. Mass spectrometric analysis was performed on a Bruker Autoflex MALDI-TOF MS with DHB as the matrix. HRESIMS data were obtained using either PEG (polyethylene glycol) or the PPG (polypropylene glycol) as internal standard. Data were obtained on JEOL Model JMS-T100LC (The AccuTOF) by spraying in MeOH. Elemental analysis was performed on a Perkin-Elmer 240 element analyzer, Galbraith Laboratories (Knoxville, TN).

Resorcinarene (3a).- A solution of resorcinol (**1**, 20 g, 0.181 mol) in 120 mL of 95% ethanol/water, and (36 mL, 37% aqueous HCl) was cooled in an ice bath and 25.3 mL (0.181 mol) of heptaldehyde (**2a**) was added dropwise over a period of 1 h. The mixture was allowed to warm slowly to 25°C and then maintained at 80°C for 12 h. The yellow needles that separated were collected and washed with cold 1:1 ethanol-water until the material was pale yellow, and the washes were neutral to pH paper. Drying under vacuum at 100°C for 16 h afforded 35.9 g (96%) of **3a**, mp. 310-315°C. The crude obtained was used in the next step without further purification. ^{1}H NMR (250 MHz, DMSO): δ 0.829 (t, 12 H, CH_3), 1.21 (m, 32 H, $CH_2CH_2CH_2CH_2$), 2.07 (m, 8 H, CH_2 α to methine), 4.23 (t, 4 H, methine, J = 7.3 Hz), 6.13 (s, 4 H, ArH), 7.12 (s, 4 H, ArH), 8.85 (s, 8 H, Ar-OH); MALDI-TOF *m/z*: 847 ($M+Na^+$). HRESIMS *m/z*: 847.5547 $[M+Na]^+$ (Calcd for $C_{52}H_{72}O_8Na$: 847.5558).

Anal. Calcd for $C_{52}H_{72}O_8$: C, 75.68; H, 8.80; O, 15.52. Found: C, 75.53; H, 8.89; O, 15.58.

Tetrabromoresorcinarene (4a).- To a stirred solution of resorcinarene (**3a**, 30 g, 0.036 mol) in 180 mL of 2-butanone was added 38.5 g (0.216 mol) of *N*-bromosuccinimide in portions. After 5 min, the product began to precipitate. The mixture was stirred for an additional 3 h, and the product was collected and washed with cold 2-butanone, dried *in vacuo* at 100°C for 12 h to afford 30.9 g (75%) of **4a** as a white solid, mp. 240-243°C. The crude product was used in the next step without further purification. ^{1}H NMR (250 MHz, DMSO): δ 0.818 (t, 12 H, CH_3), 1.28 (m, 32 H, $CH_2CH_2CH_2CH_2$), 2.13 (m, 8 H, CH_2 α to methine), 4.34 (t, 4 H, methine, J = 7.1 Hz),

7.31 (s, 4 H, ArH), 9.06 (s, 8 H, Ar-OH); MALDI-TOF *m/z*: 1163 (M+Na$^+$). HRESIMS *m/z*: 1163.8692 [M+Na]$^+$ (Calcd for $C_{52}H_{68}Br_4NaO_8$: 1163.8693).

Anal. Calcd for $C_{52}H_{68}Br_4O_8$: C, 54.73; H, 6.01; O, 11.22. Found: C, 54.85; H, 5.90; O, 11.34.

Tetrabromocavitand (5a).- Tetrabromoresorcinarene (**4a**, 20 g, 23 mmol) was dissolved in a vigorously stirred mixture of 300 mL of DMF and 300 mL of bromochloromethane. Then Cs_2CO_3 (120 g, 0.37 mol), was added slowly the mixture was stirred at 80°C for 48 h. The insoluble inorganic salts were then filtered off and the solvent was removed *in vacuo* to give a dark powdery residue, which was extracted using a Soxhlet extractor for 6 hours with a 9:1-hexane:ethyl acetate mixture to yield 14.2 g (68%) of pure tetrabromocavitand **5a** as off-white needles, mp. 200-205°C. ^{1}H NMR (250 MHz, $CDCl_3$): δ 0.92 (t, 12 H, CH_3), 1.39 (m, 32 H, $CH_2CH_2CH_2CH_2$), 2.24 (m, 8 H, CH_2 α to methine), 4.4 (d, 4 H, inner OCH_2, J = 7.31 Hz), 4.88 (t, 4 H, methine, J = 7.8 Hz), 5.97 (d, 4 H, outer OCH_2, J = 7.31 Hz), 7.03 (s, 4 H, ArH), 9.06 (s, 8 H, Ar-OH); MALDI-TOF *m/z*: 1207 (M+Na$^+$). HRESIMS *m/z*: 1207.4334 [M+Na]$^+$ (Calcd for $C_{56}H_{68}Br_4NaO_8$: 1207.4311).

Anal. Calcd for $C_{56}H_{68}Br_4O_8$: C, 56.56; H, 5.77; O, 10.77. Found: C, 56.82; H, 5.84; O, 10.61.

Cavitand **5b** was synthesized *via* the procedure described, and NMR spectral data were in agreement with literature reports.[3] mp **3b**: 300-302°C, mp **4b**: 230-232°C mp **5b** 399-401°C.

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