Lower rim mono-functionalization of resorcinarenes†

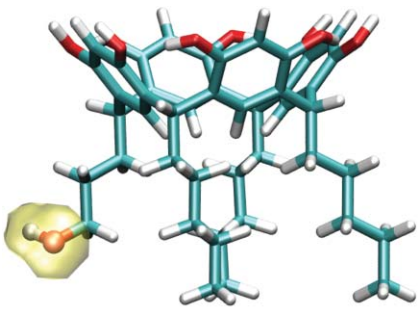
Frank Hauke, Andrew J. Myles and Julius Rebek, Jr.*

Received (in Columbia, MO, USA) 29th April 2005, Accepted 20th June 2005
First published as an Advance Article on the web 25th July 2005
DOI: 10.1039/b506048f

A versatile, scaleable, one step synthesis of a lower rim mono-functionalized resorcinarene is described.

Resorcinarenes are cyclic tetramers conveniently synthesized by condensing resorcinol with appropriate aldehydes.[1] Not only have they been shown to form hexameric capsules[2] around cations and organic molecules, their bowl shape has been used as a scaffold for building cavitands,[3] carcerands,[4] velcrands,[5] and hydrogen bonded capsules.[6]

The cavity forming functionality of resorcinarenes resides on the upper rim phenols. The lower rim can be used to append functionality for controlling the solubility[7] or manipulating their attachment to surfaces.[8] Mono-functionalization of this lower rim is desirable to expand the scope of resorcinarene based cavitands and capsules, but few examples have been reported describing the synthesis of mono-functionalized resorcinarenes.[9] All are lengthy, require difficult HPLC or reverse phase separations, and/or provide specific functionality rather than one that can be generalized. Here we report a general one step synthesis for the preparation of gram quantities of mono-functionalized resorcinarene **1**.



1

Our strategy involves condensing a 3 : 1 mixture of hexanal and 2,3-dihydrofuran with resorcinol (all commercially available), resulting in a mixture of resorcinarenes containing 0–2 hydroxy groups appended to the lower rim (Scheme 1). The hydroxy functionality was chosen to effect a significant change in interaction with silica, allowing purification by flash chromatography on silica gel. The C_v symmetric mono-hydroxy footed resorcinarene is readily isolated in 25% yield as a slightly yellow solid.

The Skaggs Institute for Chemical Biology and the Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, USA. E-mail: jrebek@scripps.edu; Fax: 858-784-2876

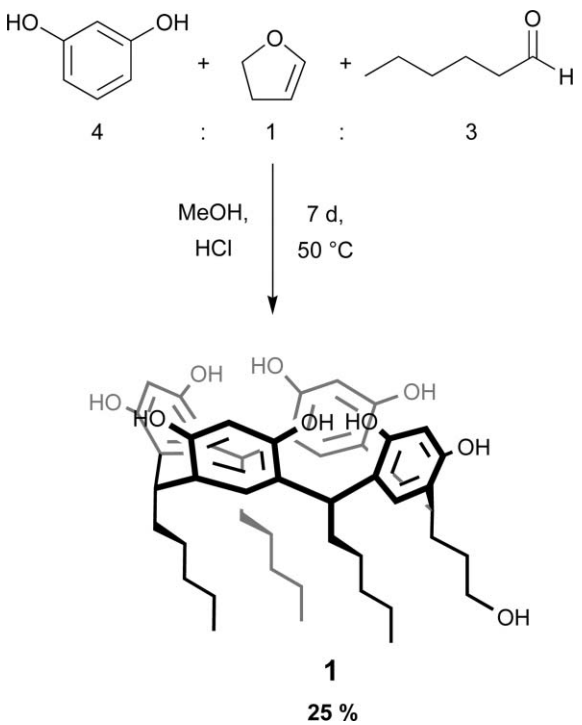
† Electronic supplementary information (ESI) available: Full experimental details for compounds **1**, **2**, **3** and **4** are included in the supplementary information. See http://dx.doi.org/10.1039/b506048f

Along with the usual resorcinarene peaks, ^{1}H-NMR showed a doublet of triplets at 3.6 ppm corresponding to the methylene protons next to the hydroxyl oxygen atom (Fig. 1). This peak integrates to two compared to the four methine bridge head protons, proving the mono-hydroxy footed resorcinarene is formed.

The ^{13}C-NMR resonance of the carbon adjacent to the oxygen atom can be detected at 61.8 ppm. ^{1}H-NMR, ^{13}C-NMR, gDQCOSY and gHMQC together with HRMS characterization confirm the structure of mono-hydroxy footed resorcinarene **1**.

Functionalization of the lower rim hydroxyl function of **1** is difficult due to the eight phenolic hydroxyl groups on the upper rim, therefore selective protection of the upper rim is necessary to fully exploit this mono-functionalization. Benzylation of **1** using benzyl bromide, NaI and K_2CO_3 in acetone resulted in benzyl protected resorcinarene **2** in 51% yield (Scheme 2). Compound **2** was characterized by ^{1}H-NMR, ^{13}C-NMR, and HR-MS. The benzyl groups can be readily removed by hydrogenation.[7]

For functionality that may be sensitive to hydrogenation, we utilized a TBDMS protection procedure of the upper rim (Scheme 3). Global hydroxyl protection of **1** was achieved using TBDMS-Cl and imidazole in DMF to yield **3** in 50% yield.



Scheme 1 3 : 1 mixture of two different aldehydes with resorcinol leads to the formation of C_v symmetrical mono-functionalized resorcinarene **1**.

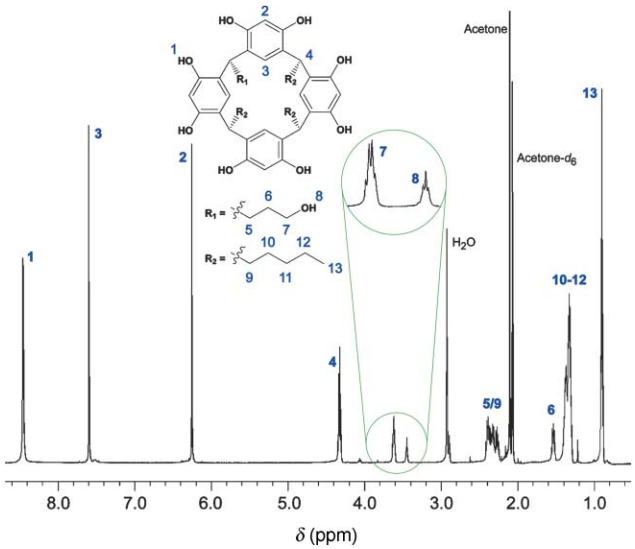
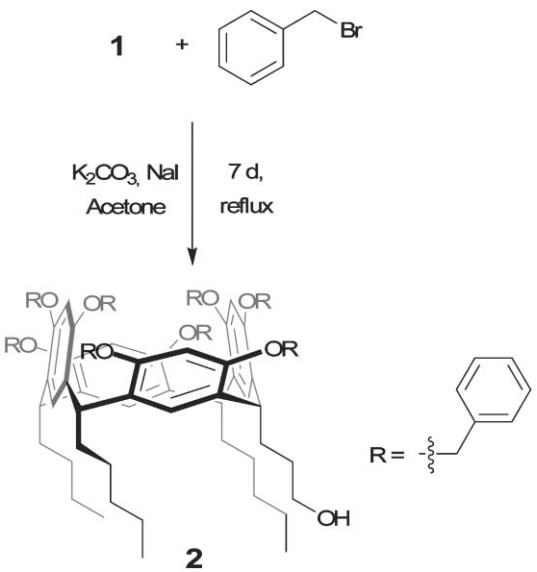


Fig. 1 ^{1}H-NMR spectrum of C_v symmetrical mono-functionalized resorcinarene **1** in acetone-d_6.

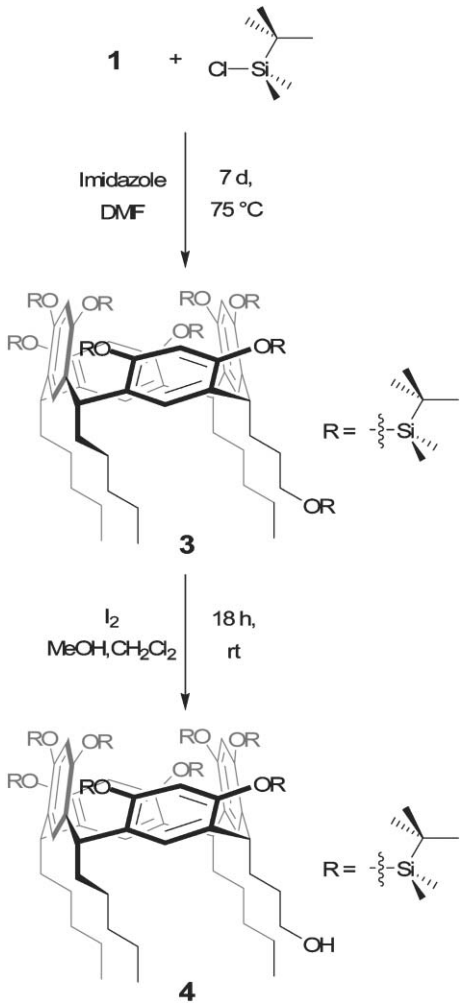


Scheme 2 Selective protection of the phenolic hydroxyl groups in **1** by benzylation.

Selective deprotection of the aliphatic hydroxyl group was easily accomplished using I_2–MeOH to yield mono-hydroxy TBDMS protected **4** in 69% yield (Scheme 3).[10] Compound **4** was characterized by ^{1}H-NMR, ^{13}C-NMR, and HRMS. After potential functionalization of the lower rim hydroxyl group, the TBDMS groups can be removed using I_2 or KF–HBr.[11]

With the introduction of the bulky protecting groups on the upper rim of **1** (benzyl in **2**, and TBDMS in **3** and **4**), compounds **2**, **3** and **4** should adopt the more stable "kite" conformation.[5] As one out of the four lower rim chains is different in **2**, **3** and **4**, no element of symmetry should be present, therefore all should be chiral and formed as racemic mixtures.

This phenomenon is confirmed by the ^{1}H-NMR spectra of **2**, **3** and **4**. Fig. 2 shows the ^{1}H-NMR spectrum of **4** where each of the 8 phenyl protons resonate as a singlet in the region between 6.0 and 7.2 ppm. Similar spectra for **2** and **3** were also observed. This



Scheme 3 TBDMS protection and selective deprotection sequence leading to TBDMS protected resorcinarene **4**.

together with the crystal structure of **3** (Fig. 3)‡ proves the C_1 symmetry of **2**, **3** and **4** and therefore the adoption of the C_1 "kite" conformation as opposed to the C_v "vase" conformation of **1**.

In summary, this chemistry opens up new avenues for resorcinarene research in cavitands as well as their assembly into various capsules.[12]

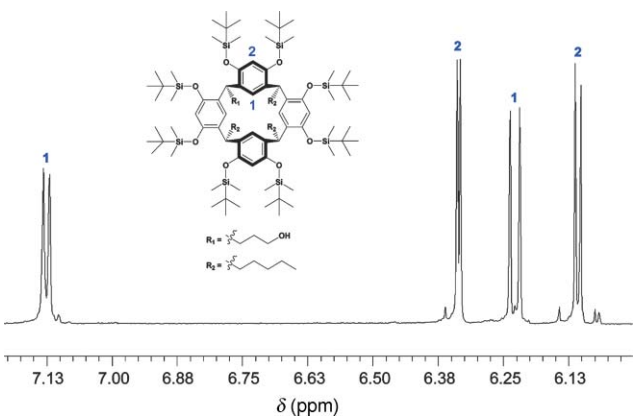


Fig. 2 ^{1}H-NMR spectrum of **4** (aromatic region shown to illustrate the C_1 symmetry—signal assignment by NOE NMR spectroscopy).

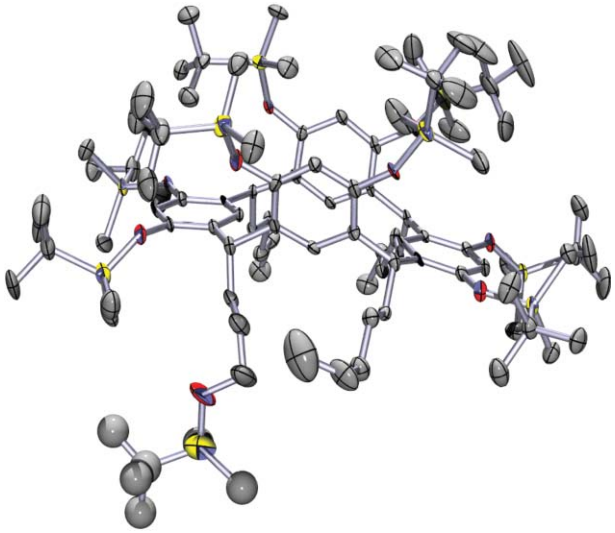


Fig. 3 Crystal structure of C_1 symmetrical **3**. Due to the bulky TBDMS groups **3** adopts the more stable "kite" conformation (hydrogen atoms omitted for clarity).‡

We would like to thank The Skaggs Institute for Chemical Biology and the National Institute of Health (GM50174) for funding. F. H. is grateful to the German Science Foundation (DFG) for funding through the "Emmy Noether-Programm". A. J. M. is grateful to the Natural Sciences and Engineering Research Council (NSERC) of Canada for a post-doctoral fellowship.

Notes and references

‡ Crystal data for resorcinarene **3**: $C_{100}H_{186}O_9Si_9$, M_r = 1785.31, triclinic, $P\bar{1}$, a = 13.414(3), b = 18.126(4), c = 24.712(5) Å, α = 73.28(3), β = 87.08(3), γ = 79.42(3)°. V = 5657(2) Å^3, Z = 2, μ = 0.212 mm^{-1}, $2\theta_{max}$ = 50.00, λ(Mo Kα) = 0.71073 Å, T = 188(2) K, 18626 total reflections, R_1 = 0.1267 and wR_2 = 0.3318 for 9314 reflections ($I > 2\sigma(I)$). CCDC 271454. See http://dx.doi.org/10.1039/b506048f for crystallographic data in CIF or other electronic format.

1 (*a*) A. G. S. Hogberg, *J. Am. Chem. Soc.*, 1980, **102**, 6046; (*b*) A. G. S. Hogberg, *J. Org. Chem.*, 1980, **45**, 4498; (*c*) P. Timmerman, W. Verboom and D. N. Reinhoudt, *Tetrahedron*, 1996, **52**, 2663.
2 (*a*) L. R. MacGillivray and J. L. Atwood, *Nature*, 1997, **389**, 469; (*b*) A. Shivanyuk and J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA*, 2001, **98**, 7762; (*c*) A. Shivanyuk and J. Rebek, Jr., *Chem. Commun.*, 2001, 2424; (*d*) L. Avram and Y. Cohen, *J. Am. Chem. Soc.*, 2002, **124**, 15148.
3 (*a*) Z. R. Laughrey, C. L. D. Gibb, T. Senechal and B. C. Gibb, *Chem. Eur. J.*, 2003, **9**, 130; (*b*) D. J. Cram and J. M. Cram, *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, 1994.
4 A. Jasat and J. C. Sherman, *Chem. Rev.*, 1999, **99**, 931.
5 D. J. Cram, H. J. Choi, J. A. Bryant and C. B. Knobler, *J. Am. Chem. Soc.*, 1992, **114**, 7748.
6 (*a*) T. Heinz, D. M. Rudkevich and J. Rebek, Jr., *Nature*, 1998, **394**, 764; (*b*) F. Hof, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *Angew. Chem., Int. Ed.*, 2002, **41**, 1488.
7 T. Haino, D. M. Rudkevich, A. Shivanyuk, K. Rissanen and J. Rebek, Jr., *Chem. Eur. J.*, 2000, **6**, 3797.
8 (*a*) B.-H. Huisman, D. M. Rudkevich, F. C. J. M. van Veggel and D. N. Reinhoudt, *J. Am. Chem. Soc.*, 1996, **118**, 3523; (*b*) Y. Yamakoshi, R. R. Schlittler, J. K. Gimzewski and F. Diederich, *J. Mater. Chem.*, 2001, **11**, 2895; (*c*) A. Rafai Far, Y. L. Cho, A. Rang, D. M. Rudkevich and J. Rebek, Jr., *Tetrahedron*, 2002, **58**, 741.
9 (*a*) K. Paek, *Bull. Korean Chem. Soc.*, 1994, **15**, 706; (*b*) Y. Hayashi, T. Maruyama, T. Yachi, K. Kudo and K. Ichimura, *J. Chem. Soc., Perkin Trans. 2*, 1998, **4**, 981; (*c*) S. Saito, D. M. Rudkevich and J. Rebek, Jr., *Org. Lett.*, 1999, **1**, 1241; (*d*) H. Ihm, J.-S. Ahn, M. S. Lah, Y. H. Ko and K. Paek, *Org. Lett.*, 2004, **6**, 3893.
10 B. H. Lipshutz and J. Keith, *Tetrahedron Lett.*, 1998, **39**, 2495.
11 A. K. Sinhababu, M. Kawase and R. T. Borchardt, *Synthesis*, 1988, 710.
12 See for example: R. K. Castellano, S. L. Craig, C. Nuckolls and J. Rebek, Jr., *J. Am. Chem. Soc.*, 2000, **122**, 7876.

