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A novel synthesis of parent resorc[4]arene and its partial alkyl ethers

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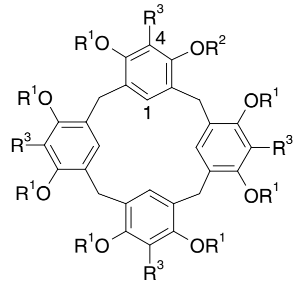
Abstract—Treatment of 2,4-diisopropoxybenzyl alcohol with chlorotrimethylsilane in acetonitrile at room temperature for 1 h afforded a novel crystalline resorc[4]arene octaisopropyl ether in 96% yield. Protecting groups were cleaved by boron trichloride in dichloromethane within 30 min and the parent resorc[4]arene was isolated by flash chromatography in 76% yield. The outcome of the deprotection step was dependent on the conditions used as it is exemplified by a preparation of resorc[4]arene heptaisopropyl ether.

The acid-catalyzed condensation reaction between resorcinol and benzaldehyde was first reported[1] by Bayer in 1872 and the correct structure of the product, resorc[4]arene, was elucidated by Erdtman only in 1968.[2] Since that time, the readily available C-alkylated calixresorcinarenes have been found to possess interesting material and complexation properties and their chemistry has been well established.[3] However, the parent resorc[4]arene **1** cannot be synthesized by this method due to the high reactivity of formaldehyde resulting in polymer formation. Thus, several alternative routes had to be developed. A treatment of 2,4-dimethoxybenzyl alcohol with trifluoroacetic acid at ambient temperature for 18 h led to resorc[4]arene octamethyl ether **2** in 95% yield.[4] Subsequent deprotection with boron tribromide followed by acetylation afforded the octaacetate **3** in 25% yield. The reaction of 2-propylresorcinol with formaldehyde diethyl acetal gave a mixture of three cyclic oligomers where resorc[4]arene **4** was a major product after 6 h.[5] More recently, octamethyl and octa-allyl ethers **2** and **5** were obtained from the cyclooligomerization of the corresponding 2,4-bis(alkoxy)benzyl alcohols in the presence of scandium trifluoromethanesulfonate.[6] The yields of **2** and **5** were 34% and 54%, respectively. Octa-allyl ether **5** was then deprotected using $PdCl_2(PPh_3)_2$ and ammonium formate and the resorc[4]arene **1** was isolated in 52% yield. The condensation of 1,3-dimethoxybenzene with paraformaldehyde in 2-ethoxyethanol was reported to produce octamethyl ether **2** as a mixture of stereoisomers, which were separated due to their different solubilities in chloroform.[7] Both isomers of **2** were prepared in 82% yield. However, the low overall yields of resorc[4]arene **1** seem to be serious drawbacks of the time consuming syntheses reported so far.



1, $R^1 = R^2 = R^3 = H$
2, $R^1 = R^2 = CH_3$, $R^3 = H$
3, $R^1 = R^2 = COCH_3$, $R^3 = H$
4, $R^1 = R^2 = H$, $R^3 = CH_2CH_2CH_3$
5, $R^1 = R^2 = CH_2CH{=}CH_2$, $R^3 = H$
6, $R^1 = R^2 = (CH_3)_2CH$, $R^3 = H$
7, $R^1 = (CH_3)_2CH$, $R^2 = R^3 = H$

Keywords: Resorc[4]arene; 2,4-Diisopropoxybenzyl alcohol; Lewis acid; Conformation; Partially alkylated resorc[4]arene.

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We describe herein an efficient and expedient synthetic route to resorc[4]arene **1** based on the observation that 2,4-diisopropoxybenzyl alcohol underwent quantitative tetramerization in the presence of chlorotrimethylsilane. The effect of a Lewis acid on the cyclooligomerization of 2,4-bis(alkoxy)benzyl alcohols[6] and 2,4-dimethoxycinnamate[8] has already been assessed but chlorotrimethylsilane seems to be the most efficient reagent with its low price making it suitable for large-scale operations.

Commercially available 2,4-dihydroxybenzaldehyde was alkylated with isopropyl bromide under phase transfer catalysis (Scheme 1). 2,4-Diisopropoxybenzaldehyde was obtained in 90% yield and identified[9] from its ^{1}H NMR spectrum. Its subsequent reduction with sodium borohydride gave 2,4-diisopropoxybenzyl alcohol in 94% yield.[10] Cyclooligomerization of 2,4-diisopropoxybenzyl alcohol was carried out in several solvents (acetonitrile, *N,N′*-dimethylformamide, dichloromethane) in the presence of a mineral acid (sulfuric or hydrochloric acid), trifluoroacetic acid or a Lewis acid (boron trifluoride diethyl etherate or chlorotrimethylsilane). In all these investigations, resorc[4]arene octaisopropyl ether **6** was formed as indicated by TLC. However, the complexity of the reaction mixture was dependent on the ratio of the reagents, temperature and duration of the reaction. As the highest yield and simplest purification of resorc[4]arene **6** on a multigram scale were required, chlorotrimethylsilane and acetonitrile were then selected as the conditions of choice. Thus, the tetramerization of 2,4-diisopropoxybenzyl alcohol spontaneously afforded crystalline resorc[4]arene **6** in 96% yield[11] within 1 h at room temperature.[12] The structure of **6** was proven unequivocally by X-ray crystallography and mass spectrometry. Resorc[4]arene **6** crystallized easily yielding single crystals of good quality from acetonitrile solution.[13–15] Novel resorc[4]arene **6** occupied the *1,3-alternate* conformation in the solid state (Fig. 1). Furthermore, the structure of **6** in solution was studied by NMR spectroscopy. In accord with the previously reported octamethyl[4] and octa-allyl[6] ethers, ^{1}H and ^{13}C NMR spectra in $CDCl_3$ indicated either the *1,3-alternate* conformation or a fast equilibrium among the conformationally flexible species on the NMR time scale. Nevertheless, the NOE connectivities observed between the CH proton of the isopropyl groups and the aromatic proton H-1 suggest that the preferred conformation of **6** is more likely to be the *1,3-alternate* one. For a deeper understandings of its conformational behaviour, temperature-dependent ^{1}H NMR spectroscopy was used. There was no significant change in the ^{1}H NMR spectra within the accessible temperature range in CD_2Cl_2 (173–308 K). The protecting groups in resorc[4]arene **6** were smoothly cleaved with boron trichloride and the parent resorc[4]arene **1** was isolated by flash chromatography in 76% yield.[16] Both ^{1}H and ^{13}C NMR spectra of resorc[4]arene **1** in CD_3OD were identical with those described.[6] As observed for the protected compound **6**, the temperature-dependent ^{1}H NMR spectra of resorc[4]arene **1** did not reveal significant changes when measured in CD_3OD (193–298 K). These results suggest either a conformationally flexible structure or the *1,3-alternate* conformation. However, taking into consideration the possibility of intramolecular hydrogen bonds being able to stabilize the *cone* conformation or to generate molecular capsules,[17] further NMR investigations are in progress.

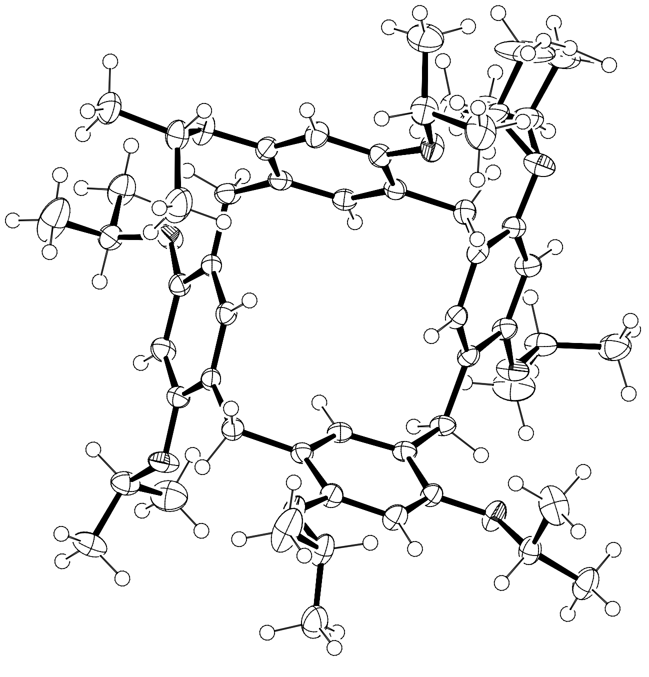
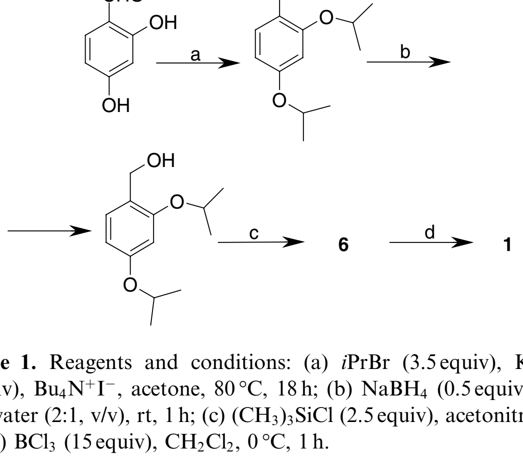


Figure 1. X-ray crystal structure of resorcinarene **6**.



Scheme 1. Reagents and conditions: (a) *i*PrBr (3.5 equiv), K_2CO_3 (2 equiv), $Bu_4N^+I^-$, acetone, 80 °C, 18 h; (b) $NaBH_4$ (0.5 equiv), ethanol/water (2:1, v/v), rt, 1 h; (c) $(CH_3)_3SiCl$ (2.5 equiv), acetonitrile, rt, 1 h; (d) BCl_3 (15 equiv), CH_2Cl_2, 0 °C, 1 h.

During deprotection of resorc[4]arene **6** we found that the isopropyl groups could be removed stepwise and the ratio of partially alkylated derivatives of resorc[4]arene **1** depended on the conditions used. Thus, treatment of resorc[4]arene **6** with boron trichloride (4 equiv) at 0 °C for 30 min gave a complex mixture from which resorc[4]arene heptaisopropyl ether **7** was isolated in 18% yield and its identity was confirmed by MS and NMR studies.[18]

Partially O-alkylated *C*-alkyl resorcinarenes were prepared in good yields by a Lewis acid catalyzed reaction of 3-methoxyphenol with octanal[19] or 3-cyclopentyloxyphenol with 1,1-dimethoxyhexane.[20] In both cases, the reaction proceeded with remarkable regioselectivity and the corresponding C_4-symmetric resorc[4]arene tetraalkyl ether was isolated. Several monoalkyl ethers of calix[4]arene, obtained either via selective dealkylation[21] or partial alkylation,[22] have also been reported. In contrast, partially alkylated derivatives of resorc[4]arene **1** have not yet been described. Although selective deprotection of octaisopropyl ether **6** gave a mixture of at least six partially alkylated products, we were able to separate five of them by flash chromatography on silica gel. The identification of a number and the position of isopropyl groups employing NMR experiments forms a part of our ongoing work in this area.

In conclusion, we have established that cyclooligomerization of 2,4-diisopropoxybenzyl alcohol in the presence of chlorotrimethylsilane followed by deprotection represents a simple and effective route to the parent resorc[4]arene which was isolated in 73% overall yield. Furthermore, it is expected that partial deprotection of resorc[4]arene octaisopropyl ether **6** could offer a way in which resorc[4]arene can be functionalized selectively. Thus tailoring of different types of selectively functionalized resorc[4]arenes enables the synthesis of new types of receptors with enhanced selectivity and geometrical stability. Our initial study shows its feasibility and demonstrates this very promising approach.

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10. Selected analytical data for 2,4-diisopropoxybenzyl alcohol: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, 1H, H_{arom}, $J = 8.0$ Hz), 6.45 (s, 1H, H_{arom}), 6.41 (d, 1H, H_{arom}, $J = 8.0$ Hz), 4.58 (s, 2H, CH_2), 4.55–4.50 (m, 2H, CH, $J = 6.1$ Hz), 2.50 (s, 1H, OH), 1.35 (d, 6H, CH_3, $J = 6.1$ Hz), 1.32 (d, 6H, CH_3, $J = 6.1$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 156.8, 129.5, 122.5, 106.0, 102.3, 70.1, 69.9, 61.9, 22.0, 21.9.
11. Selected analytical data for **6**: mp 169–170 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.43 (s, 4H, H-4), 6.34 (s, 4H, H-1), 4.35 (sept, 8H, $J = 6.0$ Hz, $CH(CH_3)_2$), 3.71 (s, 8H, CH_2), 1.26 (d, 48 H, $J = 6.0$ Hz, $CH(CH_3)_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 154.28 (C-3), 131.41 (C-1), 123.65 (C-2), 103.00 (C-4), 71.24 ($CH(CH_3)_2$), 27.99 (CH_2), 22.33 ($CH(CH_3)_2$). Anal. calcd for $C_{52}H_{72}O_8$ (825.14): C, 75.69; H, 8.80; Found: C, 75.36; H, 8.72.
12. Optimized procedure: 2,4-Diisopropoxybenzyl alcohol (13.3 g, 59 mmol) was dissolved in CH_3CN (29 mL) and chlorotrimethylsilane (20 mL, 158 mmol) was added in one portion. The mixture turned violet immediately and was allowed to stand at room temperature for 1 h. Crystals of resorc[4]arene **6** were filtered off, washed with CH_3CN and dried under vacuum (11.7 g, 96%).
13. $C_{52}H_{72}O_8$, MW 825.136, monoclinic system, space group P121/n1, $a = 15.0660(2)$, $b = 22.6530(4)$, $c = 15.8310(2)$ Å, $\beta = 113.57(4)$, $V = 4952.2(1)$ Å^3, $Z = 4$, $D_c = 1.1067\ \mathrm{g\,cm^{-3}}$, $\mu(\mathrm{MoK}\alpha) = 0.729\ \mathrm{cm^{-1}}$, crystal dimensions of $0.4 \times 0.5 \times 0.6$ mm. Data were measured at 150 K on a KappaCCD diffractometer with graphite monochromated MoKα radiation ($\lambda = 0.710730$ Å). The structure was solved by direct methods[14] and anisotropically refined by full matrix least-squares on F values[15] to final $R = 0.045$, $R_w = 0.054$ and $S = 1.112$ with 568 parameters using 7775 independent reflections ($\theta_{range} = 1.73$–27.5). Hydrogen atoms were located from the expected geometry and were not refined. Crystallographic data were deposited in CSD under CCDC registration number 217280.
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16. Selected analytical data for **1**: ^{1}H NMR (500 MHz, CD_3OD) δ 6.87 (s, 4H, H-1), 6.26 (s, 4H, H-4), 3.63 (s, 8H, CH_2). ^{13}C NMR (125.8 MHz, CD_3OD) δ 153.80 (C-2), 132.69 (C-1), 121.85 (C-2), 104.02 (C-4), 29.99 (CH_2). HRMS (ESI) for $C_{28}H_{23}O_8$ $(M-1)^-$: Calcd 487.1390; Found. 487.1755.
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18. Selected analytical data for **7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (br s, 1H, OH), 6.70 (s, 1H, arom), 6.68 (s, 2H, arom), 6.51 (s, 1H, arom), 6.49 (s, 2H, arom), 6.46 (s, 1H, arom), 6.39 (s, 1H, arom), 4.62 (sept, 1H, $J = 6.0$ Hz, $CH(CH_3)_2$), 4.50–4.30 (m, 6H, $J = 6.0$ Hz, $CH(CH_3)_2$), 3.76 (s, 2H, CH_2), 3.75 (s, 4H, $2\times CH_2$), 3.62 (s, 2H, CH_2), 1.45 (d, 6 H, $J = 6.0$ Hz, $CH(CH_3)_2$), 1.36–1.30 (3×d, 18H, $J = 6.0$ Hz, $3\times CH(CH_3)_2$), 1.29–1.20 (3×d, 18H, $J = 6.0$ Hz, $3\times CH(CH_3)_2$). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 155.15, 154.56, 154.54, 154.46, 154.01, 153.90, 152.51, 151.53 (C-3 and C-5), 132.74, 131.59, 131.21, 131.11, 129.44 (C-1), 125.39, 124.37, 123.81, 123.73, 122.87, 122.50, 122.00, 118.90 (C-2 and

C-6), 103.14, 102.76, 102.35, 101, 38 (C-4), 71.64, 71.53, 71.28, 71.12, 70.89, 70.48 (CH(CH$_3$)$_2$), 29.39, 28.58, 27.20, 27.01 (CH$_2$), 22.25, 22.22, 22.20, 22.13, 22.05, 21.87 (CH(CH$_3$)$_2$). HRMS (ESI) for $C_{49}H_{65}O_8$ $(M-1)^-$: Calcd 781.4680; Found. 781.4761.

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