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Inherently Chiral Resorcin[4]arenes: A New Concept for Improving the Functionality

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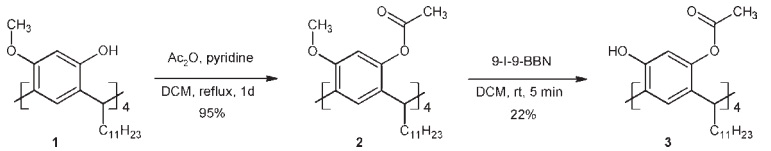
ABSTRACT



A new reactive postion at the upper rim of inherently chiral resorcin[4]arenes was introduced through cleavage of an up to now unreactive methoxy group through the demethylating reagent 9-I-9-BBN. Conservation of the inherent chirality was warranted through the use of a protecting group at the free phenol group.

Resorcin[4]arenes are easily prepared three-dimensional macrocycles that are used for various purposes in supramolecular chemistry, for example, in molecular recognition.[1] The inherently chiral resorcinarenes are a subclass of these macrocycles first described by Mocerino.[2] They can be obtained as a racemic mixture in a Lewis acid catalyzed reaction of 3-alkoxyphenols with aldehydes[2] or from the cyclization of the corresponding benzylic alcohols.[3] In addition to the central chirality at the methine carbon atom at the lower rim, there is an additional inherent chirality that originates from the topology of the nonplanar structure.

While the choice of the starting materials in the described synthesis above is rather open on the side of the aldehydes or benzylic aldehydes, the variability of the 3-alkoxyphenols is more limited. Only nine side chains have been reported so far, while 3-methoxyphenol has been most often used.[2−4] Due to the known limitations for further functionalization of 3-alkoxyphenols before the cyclization, all modifications have to be done afterward. There are two reactive positions at the upper rim of the inherently chiral resorcinarenes: the phenol group and the ortho position of the aromatic ring. For example, the phenol can be modified to a dendrimer[5] or converted with picolyl chloride.[6] The ortho position is often used in Mannich reactions in which the phenol group can be used in additional cyclizations.[4a,7] Another example is the intramolecular cross coupling to a cyclic ether.[8] In contrast, no modifications of the alkoxy group are known so far. There are two limitations involved: First the cleavage without protection of the phenol group would lead to loss of the inherent chirality. Second the dealkylating reagent must not inflict degradation to the resorcinarene scaffold plus

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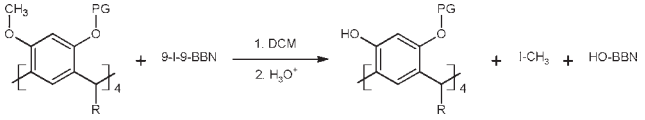
must not cleave the protected phenol group. Therefore, boron tribromide as a standard dealkylating reagent is not suitable, because it is a strong Lewis acid similar to the ones used for the synthesis of the resorcinarenes so that reopening of the macrocycle can occur. In this work, we present a route to demethylated inherently chiral resorcin[4]arenes with an acetate protected phenol group to provide a new reactive position at the upper rim.

In previous experiments with unprotected resorcinarenes, different demethylating reagents were tested upon their reactivity against the methyoxy group as well as against the resorcinarene scaffold. Lithium iodide,[9] the ionic liquid [TMAH][Al_2Cl_7][10] and lithium chloride[11] showed no cleavage properties, while 9-iodo-9-borabicyclo[3.3.1]nonane (9-I-9-BBN)[12] was successful. Additionally, no degradation of the scaffold was observed, although 9-I-9-BBN is also a Lewis acid.

Scheme 1. General Reaction of 9-I-9-BBN with Methoxy Groups (PG = Protecting Group)

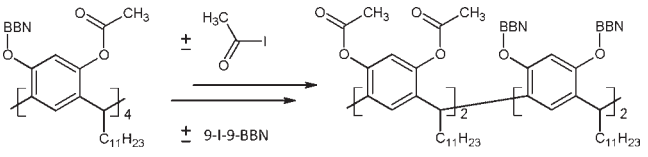


The next step was to find a protecting group for the phenol group. Esters, sulfonates and benzylic ether as protecting groups at the resorcinarene and/or at 3-methoxyphenol were examined concerning their stability against 9-I-9-BBN. The reaction processes were monitored by MALDI-ToF and GC-MS, respectively. It turned out that no protecting group was completely durable, but the acetate group showed the best results. Different reaction times, temperatures and equivalents of 9-I-9-BBN were checked for this group to yield optimized reaction conditions, namely 5 min stirring at room temperature in dichloromethane with 3 equivalents of 9-I-9-BBN per methoxy goup.

The reaction of 9-I-9-BBN, similar to that of 9-Br-9-BBN,[13] with the methoxy or, as an unwanted side reaction, the protecting group yields an organic iodide and a borinic ester of the phenol group which in a second step can be cleaved under acidic conditions. The volatility of the leaving organic iodide is very important for the success of the reaction. While methyl iodide is leaving the reaction mixture quite easily, the particular protecting group iodides can remain in solution. We found in the 9-I-9-BBN reaction with benzoyl protected resorcinarene, that the backward reaction with benzoyl iodide and phenol groups also occurred, resulting in a distribution of one- to 4-fold, but also five- and 6-fold benzoylated resorcinarene observed by MALDI-ToF. This unwanted reaction will be relevant as an ulterior motive below.

Inherently chiral resorcin[4]arene **1** was synthesized according to literature procedures.[2] The 4-fold acetylated inherently chiral resorcinarene **2** was synthesized with acetic anhydride and pyridine by analogy to the preparation of the 8-fold acetylated classic resorcinarene.[14] Resorcinarene **2** was stirred in dichloromethane under Schlenk conditions while a solution of 9-I-9-BBN in hexane was rapidly added through a syringe. After 5 min the reaction was stopped by injecting diluted hydrochloric acid. After washing with water the organic layer was concentrated and dried in vacuum. The residue was filtered through a pad of silica gel eluting with ethyl acetate. The following HPLC was done with chloroform/methanol (98:2). A compound with a matching mass for the resorcinarene **3** was obtained as a colorless solid in a yield of 22%. ^{1}H NMR-spectroscopy indicated a symmetrical structure. As shown in the reaction of benzoyl protected resorcinarene, it could be possible that a backward reaction with acetate iodide lead to an exchange of the acetate groups (Scheme 2).

Scheme 2. Hypothetical Reaction to a C_{2v}-Symmetrical Acetylated Resorcinarene



Various other products are possible, but only a symmetrical resorcinarene can fit to the found ^{1}H NMR-spectra. The formation of C_{2v}-symmetrical resorcinarenes with acid chlorides is known from literature.[15]

At normal temperatures resorcinarenes can switch between the so-called crown- and boat-conformation (Figure 1).[16] At lower temperature the exchange is prevented to yield the favorable boat-conformation. Because of steric effects, the aromatic rings with the acetate groups of the C_{2v}-symmetrical resorcinarene will lay in the plane, which is defined by the four methine carbon atoms. So this compound will then show only one signal for the acetate protons, while a C_4-symmetrical resorcinarene will show two signals.

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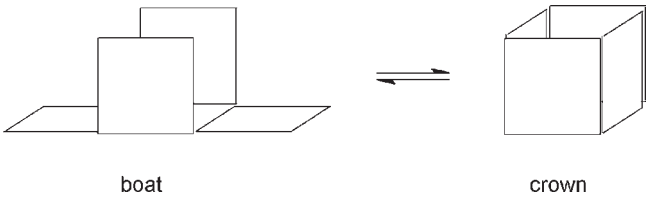

Figure 1. Schematic presentation of the boat- and crown-conformation of resorcinarenes.

^{1}H NMR-spectra of the obtained compound were measured at different temperatures to distinguish between the C_4-symmetrical inherently chiral resorcinarene **3** and the C_{2v}-symmetrical isomer. As shown in Figure 2, there are two signals for the acetate groups around 2 ppm at 273 K. Line broadening is due to increasing viscosity of the solvent chloroform-d. Another solvent with lower freezing point was not practical because of the poor solubility of resorcinarene **3** in that solvents. Finally, the two signals highlight the conservation of the C_4-symmetry and the presence of resorcinarene **3**.

In summary, we have pointed out a synthetic pathway to an inherently chiral resorcinarene with a new reactive position next to the phenol group and the ortho position at the upper rim. This novel site provides an interesting approach for further synthesis. The molecular recognition of chiral guest can now be increased by introduction of better coordinating groups than methoxy groups.

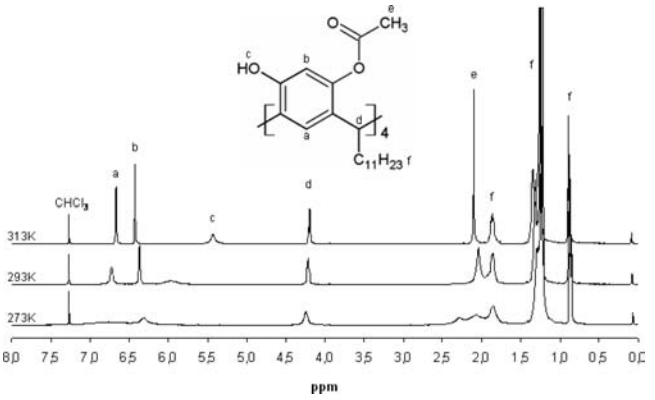

Figure 2. Temperature-dependent ^{1}H NMR-spectra of resorcinarene **3**.

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Supporting Information Available. Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.