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Monofunctionalised resorcinarenes

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Abstract—A convenient methodology for introducing single functional groups to the lower rim of resorcinarenes is described. The methodology allows for very convenient differential protection or derivatisation of the upper and lower rims, and a wide range of functional groups (alcohol, carboxylic acid, thiol, amine, carbamate, alkyl halide) can be incorporated as a single unit at the lower rim, opening up the way to further modification at this point and generally widening the scope for further utilising resorcinarenes. Furthermore, our approach has enabled us to link two resorcinarenes together to form novel resorcinarene dimers.
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Resorcinarenes such as **1** (Scheme 1) are cyclic tetramers readily formed by the acid-catalysed condensation of resorcinol with aldehydes.[1] The most stable crown conformer possesses a bowl-shaped molecular cavity formed by the four resorcinol units.[1,2] This has been widely exploited as a basis for making macrocyclic host molecules in a variety of supramolecular systems, as well as being the basis for their spontaneous adhesion to hydrophilic surfaces and formation of hexameric capsules.[3–6] One focus of our current work is to be able to introduce functional groups to the lower rim so that the binding properties of the cavity can be used to organise active components across a surface. As such, we desired access to a lower rim monofunctionalised resorcinarene, but very few methods for achieving this have been reported, involve lengthy synthesis and/or purification,[7] and do not furnish a range of functional groups. Here we report a simple and versatile synthetic route towards resorcinarenes with a monosubstituted lower rim bearing a range of functional groups.

The stepwise condensation of resorcinol with two different aldehydes has previously yielded a mixture of resorcinarenes but the desired all-*cis* isomer was not the major product in some cases.[8] When a terminal hydroxyl is directly incorporated using lengthy reaction times the desired isomer is the major product, but selective protection or deprotection strategies have to be used to differentiate the aryloxy groups in the bowl from the alkoxy moiety.[9] Our approach is based on the condensation of resorcinol with two structurally similar aldehydes so that the required crown conformer is obtained, and initially incorporating a very weakly nucleophilic functionality so that the bowl is very easily protected selectively. All-*cis* resorcinarenes with mixed chains in the lower rims were obtained by acid catalysed condensation of resorcinol **2** with the commercially available aldehydes, undecenal **3** and undecanal **4** (Scheme 1), overnight in a 5:1:4 ratio of **2**:**3**:**4**. Assuming a purely statistical incorporation of the differing aldehydes, a maximum proportion of 40–42% (of the overall resorcinarene yield) of the monofunctional resorcinarene is predicted for ratios of aldehydes between 1:2.1 and 1:4. The lower ratio of **3** to **4** was chosen to minimise formation of cyclic tetramers bearing more than one alkene functionalised leg. This mixture of resorcinarenes was protected as its octapivalate by treatment with pivalyl chloride, triethylamine and catalytic 4-dimethylaminopyridine. The pivalate protecting group was chosen as it leads to sharp signals in the ^{1}H NMR spectrum of the protected resorcinarenes and is considerably easier to handle (especially chromatographically) than resorcinarenes with phenolic upper rims. Analysing the mixture this way revealed the incorporation of alkene in the expected statistical proportion, so the two major products were assumed to be monoalkene **5** and tetraalkane **6**. Generally derivation at the bowl facilitates

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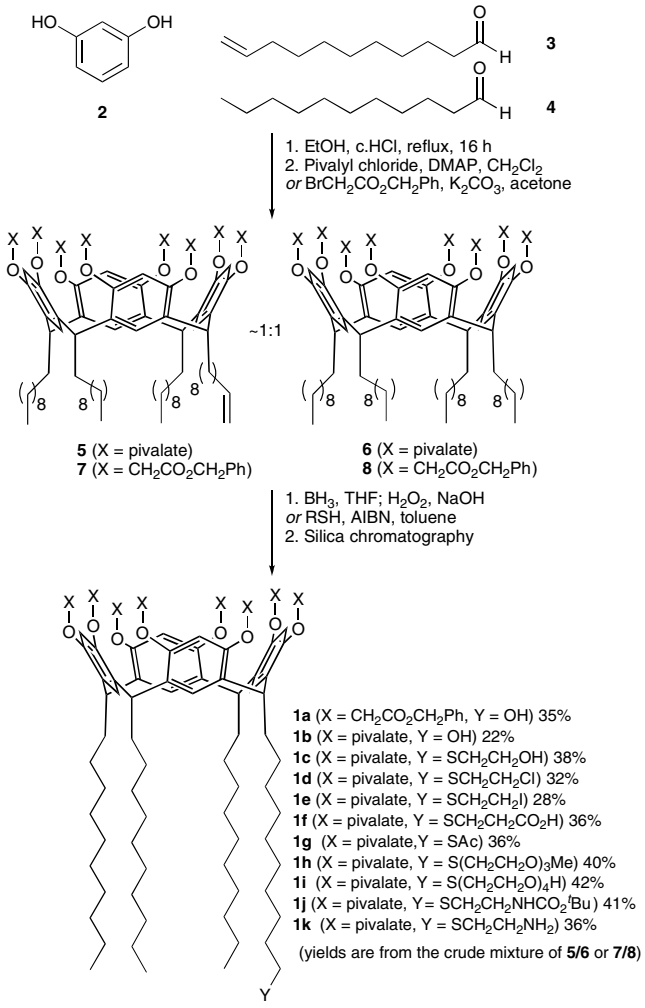


Scheme 1.

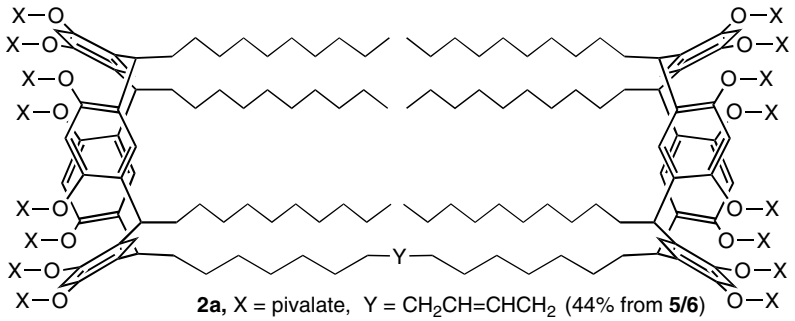
chromatographic separations and reaction with benzyl bromoactetate is equally facile (giving **7** and **8**).

For both rim derivatives, the alkene was readily converted to an alcohol by hydroboration/oxidation. The polarity change that this introduces allows the simple separation of the monofunctional resorcinarene from the major side product (the all alkyl resorcinarene is formed in comparable yields), which has a far higher R_f value. Thus, we obtained pure monofunctional resorcinarenes **1a** (35% from the mixture of **7** and **8**) and **1b** (22% from the mixture of **5** and **6**) which can be selectively functionalised at either the rim or the bowl with ease.

A hydroxyl could also be introduced by radical addition of 2-mercaptoethanol to the alkene of the octapivalate protected mixture to give the monoalcohol resorcinarene **1c**. Again, the addition of the polar end group allowed **1c** (R_f 0.4; eluant 3:1 petroleum ether 40–60/ethyl acetate) to be easily separated from tetraalkane **6** (R_f 0.9) in 38% yield. The terminal hydroxyl was readily converted to chloride using TsCl and pyridine to give **1d** (85%); treatment of **1d** with NaI in acetone provided iodide **1e** (86%).

The radical addition methodology presented the additional advantage that the terminal functional group can be easily varied, and we were able to repeat the thiol radical addition reaction with a range of thiols possessing different terminal functional groups. Thus, the radical addition of both 3-mercaptopropionic acid and thioacetic acid gave the corresponding monofunctionalised resorcinarenes **1f** and **1g** in yields of 36%. Addition of 1-mercapto-3,6,9-trioxadecane to the octapivalate protected mixture gave the monomethyl(triethyleneglycol)ether resorcinarene **1h** in moderate yield (40%). Likewise, the monotetra(ethyleneglycol) resorcinarene **1i** was prepared in 42% yield from 11-mercapto-3,6,9-trioxaundecan-1-ol. Using the protected amine 2-mercaptoethylamine gave **1j** (41%), which could be readily deprotected to give **1k** (87%). These monofunctionalised resorcinarenes **1a**–**k** are attractive intermediates as they allow direct access to resorcinarenes substituted on the lower rim with alcohol, halide, thiol, carboxylate or amine functionality.

Finally, we noted that the presence of a single alkene functionality allowed the opportunity to link two resorcinarene units together through metathesis. If there are two or more alkenes per resorcinarene, polymerisation and intramolecular cyclisation would compete with the simple coupling reaction. Using the first generation Grubbs' catalyst, resorcinarene dimer **2a** was successfully formed (44%) from the mixture of **5** and **6** as a mixture of alkene isomers. The alkene functionality could be removed using hydrogenation catalysed by $Pd(OH)_2$ to leave only a simple alkyl link between the units (**2b**,



94%), or else hydroborated and oxidised (**2c**, 69%) to furnish an attachment point midway between the two covalently linked bowls. We note that this strategy could be adapted, through the introduction of different protecting groups after the initial condensation step, to yield resorcinarene dimers with differential protection on each rim.

In conclusion, we have developed a simple and effective method for the introduction of monofunctionality at the lower rim of resorcinarenes that provides a lower rim attachment site for additional functionality. We are currently exploring some of these and will report them in due course.

Acknowledgement

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Supplementary data

Full experimental details for compounds **1a**–**k** and **2a**–**c** are available as Supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.12.110.

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