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An updated synthesis of *octa*-acid

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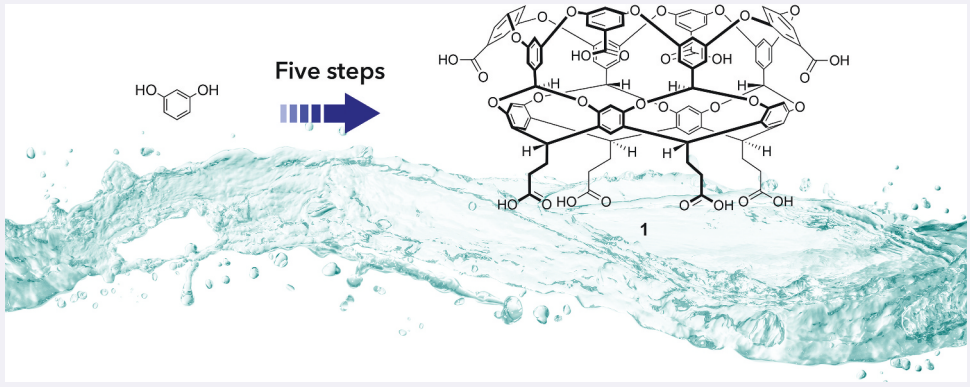
ABSTRACT

Octa-acid **1** is a water-soluble cavitand that has been used to investigate hydrophobic solvation and Hofmeister effects, control photophysical and physicochemical properties, modulate the reactivity of encapsulated guests, and as a tool to engender novel separation protocols. The synthesis of **1** has largely centered around its formation from **2**, a host that is itself most readily synthesized on the multi-gram-scale in crude form (>75% purity). In this *Methods Article* we reveal improvements in the synthesis of **2**, as well as a new synthetic strategy that efficiently converts crude **2** into pure **1**. This provides access to **1** in only a five-step linear sequence, shortening the total reaction time from previous methods, improving the purity, and increasing the final yield of **1**. We therefore anticipate that the described protocols will be of interest to researchers seeking to utilize *octa*-acid in their studies.



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Octa-acid **1** (Figure 1), a water-soluble deep-cavity cavitand first reported by our group in 2004, was the first of its kind to self-assemble in water through the hydrophobic effect into well-defined nano-capsules [1,2]. This bowl-shaped amphiphile is composed of a concave hydrophobic pocket, a wide hydrophobic rim, and a convex outer surface coated with eight water-solubilising carboxylic acid/carboxylate groups. These 'coating groups' ensure excellent solubility above pH = 8. Since it was first reported, cavitand **1** has been of utility to a number of groups for probing hydrophobic solvation [3–6], Hofmeister effects [7–10], controlling photophysical and physicochemical properties of encapsulated guests [11–14], bringing precise control to photochemical reactions [15–21], and engendering novel separation protocols [22–24].

Arguably the most important deep-cavity cavitand for the synthesis of **1**[2] and other water-soluble hosts [25] is octol **2** (Scheme 1). Crude octol is formed in three linear steps in an overall yield of ~25%. Thus, it is synthesised by first carrying out an acid catalysed Friedel-Crafts acylation of resorcinol with 2,3-dihydrofuran. This provides resorcin[4]arene **3** in 83% yield and on the tens-of-gram scale. This resorcin[4]arene is then bridged with 3,5-dibromo benzal bromide (itself made in 97% yield by treating the corresponding aldehyde with BBr_3) to give the *octa*-bromide **4** in 40%. Ullmann ether 'weaving' with 3,5-dihydroxybenzyl alcohol provides octol **2** on the multi-gram scale in 68% crude 'yield' at ~70% purity, i.e. in ~47% yield. Since the previous reported synthesis of **1**, we have made modifications to these steps, including considerable changes to the Ullmann ether 'weaving' step in response to the loss of commercial availability of CuO nano-particles of suitable size [26]. We present these updates in the attendant Supporting Information.

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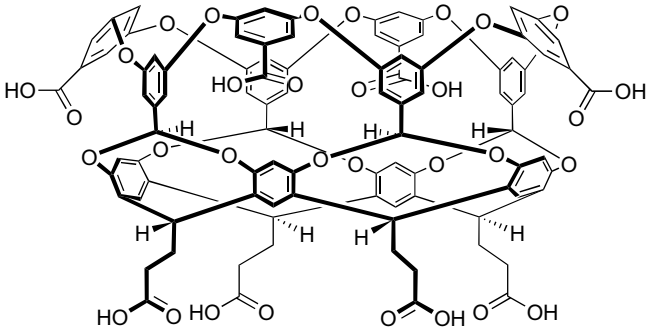
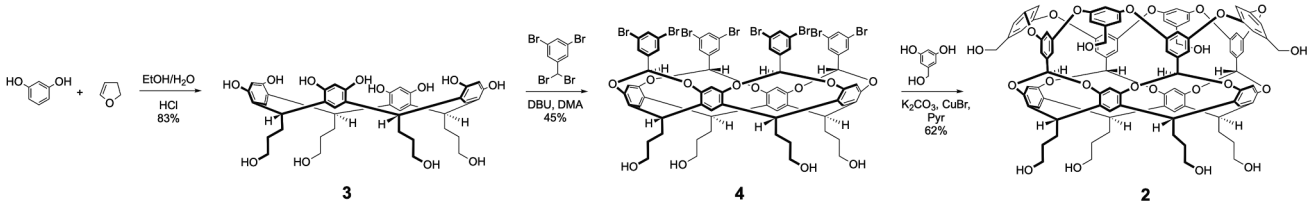


Figure 1. *octa*-acid **1**.

Neither the resorcin[4]arene nor the cavitands shown in Scheme 1 is amenable to chromatographic or crystallisation protocols. Consequently, the over-arching problem with the synthesis of **1** has largely been how to convert the readily available, gram quantities of crude octol **2**, into pure *octa*-acid **1**. As a solution to this problem, the first reported synthesis of *octa*-acid **1** employed *tetra*-benzylation of **4** with BnBr (combined 40% yield for bridging to form **4**, and subsequent benzyl protection). Protected **4** could then be purified by column chromatography. Subsequent Ullmann ether weaving gave, after a second chromatographic purification, the pendent group benzyl-protected derivative of **2** in 40% yield. Quantitative debenzylation (H_2 and Pd/C) gave pure **2**, and oxidation ($KMnO_4$) gave **1** in 92% yield. Unfortunately, as evidenced by ^{1}H NMR signal broadening, the *octa*-acid obtained from this procedure is now estimated to have been typically 90–95% pure (Table 1).

This synthesis was improved upon in 2011 (Table 1) [1]. The primary strategic change was to remove the protection and deprotection steps used to form pure **2**, and forego obtaining the clean cavitand. Rather, crude **2** was taken forward to generate crude *octa*-acid **1**, which was purified by esterification, column chromatography of the *octa*-ester, and then hydrolysis. This had the advantage of removing a single chromatographic purification and providing *octa*-acid **1** in higher purity. In this *Methods Article,* we detail a shorter and faster synthesis of *octa*-acid **1**, involving only four linear steps from resorcin[4]arene **3**. Furthermore, the total reaction time for these steps has been more than halved compared to the 2011 strategy. Nevertheless, the overall yield for 98% + pure **1** has been doubled.

As mentioned, the over-arching problem here is how to convert gram quantities of crude octol **2** into pure *octa*-acid **1**. The 2011 synthesis solved this by forming an *octa*-ester of **1**, which could be subjected to chromatographic purification before being hydrolysed back to the target [1]. As an alternative to this, we sought a reaction that could convert crude **2** into a direct precursor of **1**, which was itself amenable to chromatography. As shown in Scheme 2, we identified the Parikh-Doering oxidation as a suitable strategy [27]. Thus, a combination of anhydrous DMSO, triethylamine, and sulphur trioxide pyridine complex was found to oxidise crude octol **2** smoothly and rapidly into crude *octa*-aldehyde **5** [28]. This readily soluble mixture could then be chromatographically purified to yield pure *octa*-aldehyde **5** in 40% yield (full characterisation of this novel host is provided in the Supporting Information). We also converted pure **2** (obtained by acetylation (Ac_2O), chromatography, and hydrolysis (LiOH/DMA)) to pure **5** in 66% yield [29]. Like many deep-cavity cavitands, pure **5** was found to have limited solubility. It was found to be insoluble in many common solvents, be of limited solubility in halogenated solvents, but be soluble in polar aprotic solvents such as DMSO.

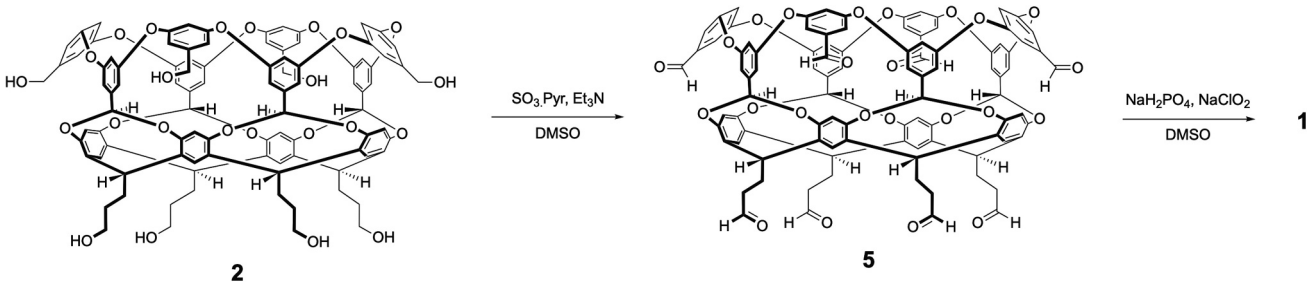


Scheme 1. Column-free synthesis of octol **2**.

Table 1. Summary of *octa*-acid syntheses.

Year	Total steps	Rct. time (d)	No. columns	Yield of *octa*-acid 1 from resorcin[4]arene 3
2004	5	14	2	12%[a]
2011	5	31	1	4%[b]
2023	4	9	1	8%[c]

[a]Purity of **1** was 90–95%.
[b]Yield for 98%+ pure **1**. For 95%+ purity the yield was 8%.
[c]Purity of **1** 98%+.



Scheme 2. New late-stage steps for the synthesis of *octa*-acid **1**.

We note in passing the importance of aldehydes in organic transformations and the potential for **5** to therefore act as a key precursor for other targets. However, for the task at hand, we sought a clean oxidation procedure that would convert **5** into pure *octa*-acid **1**. The cleanness and efficiency of the Pinnick oxidation made it a prime candidate, and ultimately, we found that the combination of DMSO, water, NaH_2PO_4 and $NaClO_2$, identified by Dalcanale and Montanari [30], worked best. Thus, by this approach *octa*-aldehyde **5** could be converted to *octa*-acid **1** in an excellent 83% yield. As was necessary, the workup for this reaction was straightforward: removal of the solvent, suspension in aqueous HCl, and then washing the product with acetone and drying gave the pure product.

Overall, as Table 1 reveals, this new synthesis of *octa*-acid **1** doubles the yield of high-purity host. Not only is the total reaction time of the new synthesis considerably shorter, and avoids the use of environmentally costly MnO_4^-, but all steps are amenable to scale-up, such that batches of *octa*-acid **1** can be synthesised on triple the scale as previously, i.e. >1 g scale.

In summary, in this *Methods Article,* we demonstrate a new, efficient synthesis of high-purity *octa*-acid **1**. This has been made possible by a new two-step conversion of crude **2** to pure **1**, combined with changes to the reaction conditions and work-up protocols for the formation of crude **2**. A such, we believe the described work will be of interest to those studying water-soluble hosts and encapsulation phenomena.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Supporting information

Supporting Information available: Updated synthesis of octol **2**, the Parikh-Doering oxidation of **2** into **5**, characterisation of host **5**, and Pinnick oxidation procedure to convert **5** to *octa*-acid **1**.

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