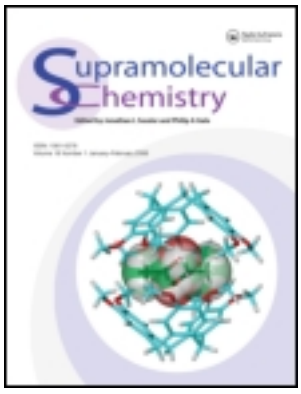

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An improved synthesis of 'octa-acid' deep-cavity cavitand

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An improved synthesis of a water-soluble deep-cavity cavitand (octa-acid, **1**) is presented. Previously (Gibb, C.L.D.; Gibb, B.C. *J. Am. Chem. Soc.* **2004**, *126*, 11408–11409), we documented access to host **1** in eight (non-linear) steps starting from resorcinol; a synthesis that required four steps involving chromatographic purification. Here, we reveal a modified synthesis of host **1**. Consisting of seven (non-linear) steps, this new synthesis involves only one chromatographic step, and avoids a minor impurity observed in the original approach. This improved synthesis is therefore useful for the laboratories that are investigating the properties of these types of host.

Keywords: host; cavitand; water-soluble; octa-acid; supramolecular chemistry

Results and discussion

Deep-cavity cavitand **1**, the so-called 'octa-acid' (Scheme 1), is a water-soluble host that is central to our studies of aqueous-based supramolecular systems (*1*). Its ease of synthesis and propensity to dimerise into supramolecular nano-capsules have proven to be of considerable interest both to our own studies (*2*, *3*) and to a number of other research groups who are independently studying it (*4–7*). The host is a bowl-shaped amphiphile composed of a concave hydrophobic pocket, a wide hydrophobic rim and a convex outer surface 'coated' with eight water-solubilising carboxylic acid groups. Because of these structural features in aqueous solution the host is essentially monomeric, but the presence of a suitable guest molecule triggers dimerisation of the host and encapsulation of the guest (or guests) (*2*, *3*, *8*). Driven by the hydrophobic effect, this assembly occurs for molecules as small as propane (*9*) and other small hydrocarbons (*10*), as large as steroids (*1*), and as polar as triethylene glycol derivatives (*11*). The significant kinetic stability of the capsule has also allowed it to demonstrate interesting function, including as a yocto-litre reaction flask for controlling the course of photochemical reactions (*12–19*), and a means to bring about the kinetic resolution of constitutional isomers (*20*).

Previously (*1*), we documented access to octa-acid **1** in eight overall steps (longest linear sequence six-steps) starting from the resorcinol condensation with dihydrofuran to give resorcinarene **2** (structure in Scheme 1). However, since this report we have noted the presence of some cavitand impurities that arise in the synthesis. Although not affecting the binding properties of the octa-acid **1**, these have caused some concern and also attenuate the overall reported yield of 9%. Furthermore, the fact that the workup of four steps required chromatography reduces the appeal of the synthesis somewhat. With these points noted, and with octa-acid **1** and related derivatives becoming increasingly utilised, we have been keen to make the synthesis of **1** more efficient. Consequently, we report here on a modified synthesis of octa-acid **1** that consists of seven total steps including a six-step linear sequence. The overall yield of this shorter process is 8%, but this value represents pure octa-acid **1**. Furthermore, in this new synthesis only one chromatographic step is required. In combination, these improvements have increased the accessibility of octa-acid and other such deep-cavity cavitands in our laboratory. We therefore believe that others who study these hosts will benefit from this modified synthesis.

The overarching idea behind the synthesis was to make the isolation of each intermediate as facile as possible, and if needed, to add one chromatography step near the end of the synthesis to ensure maximum purity of the final product. The new synthetic route is shown in Scheme 1. The first step, the acid-catalysed condensation of resorcinol and dihydrofuran to give resorcinarene **2**, was originally reported to occur in 61% yield on the 20 g scale (*21*). On studying the variables in this reaction, we, however, observed that modifying the addition of dihydrofuran to the reaction solution increased the yield of **2** to 83%. The fourfold 'bridging' of **2** to form octabromide **3** (Scheme 1) requires 3,5-dibromobenzal bromide, a compound that was originally synthesised in 72% yield (two steps). More specifically, metal halogen exchange of 1,3,5-tribromobenzene *n*-BuLi and quenching the resulting lithiate with dimethylformamide gave

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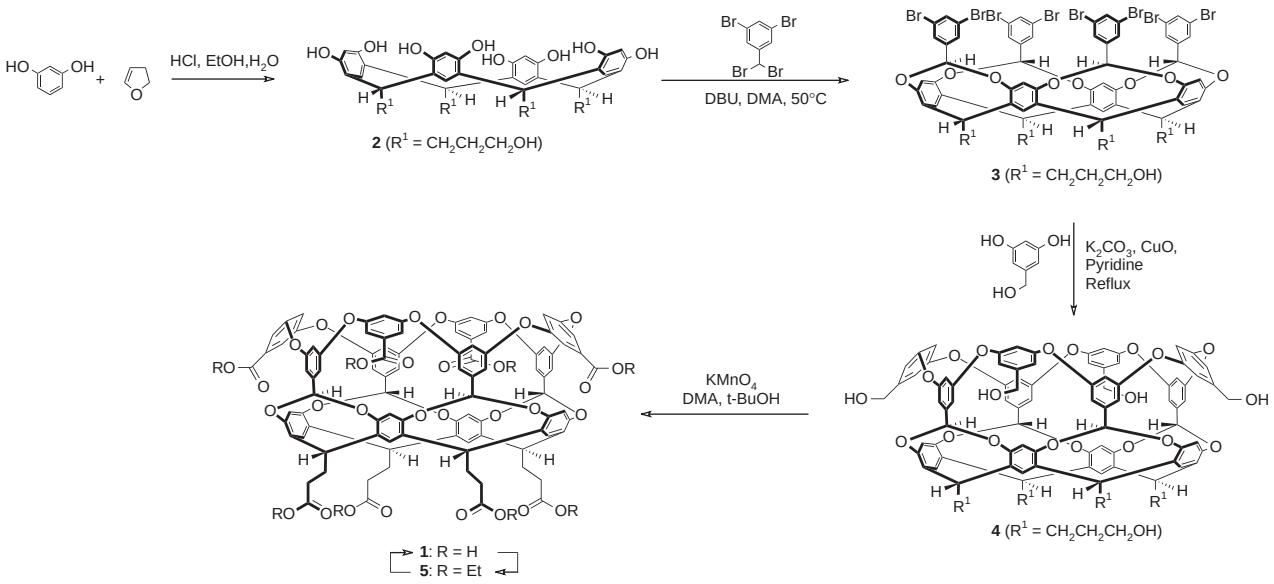


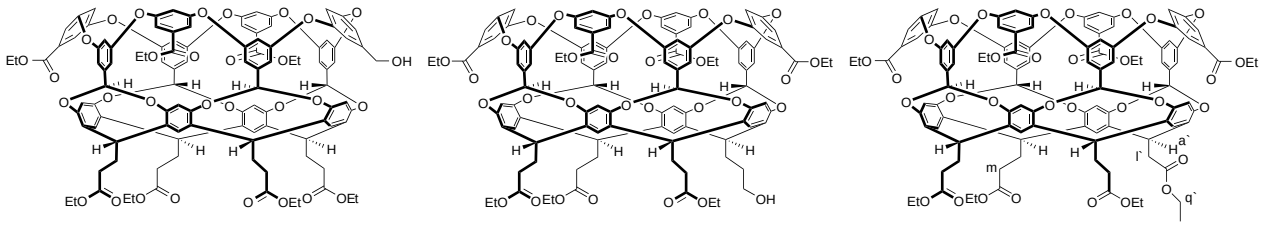
Scheme 1. Synthesis of octa-acid **1**.

3,5-dibromobenzaldehyde, and subsequent bromination with BBr_3 gave the corresponding benzal bromide (*1*, *22*). Recently, however, we identified a commercial source of 3,5-dibromobenzaldehyde (Beta Pharma Inc., Branford, CT, USA) that eliminated the synthesis and the (chromatographic) purification of this material. In addition, we devised a modification to the workup of the bromination step that avoided the chromatographic purification of the benzal bromide but still allowed it to be isolated in 92% yield after crystallisation. These modifications provided rapid access to the benzal bromide in the tens of grams scale.

We did not identify an improved synthesis of octabromide **3** (45% yield), but we did determine an efficient means to isolate this highly insoluble compound. Previously, crude **3** was directly treated with benzyl bromide/NaH to generate the soluble tetra-benzyl ether that was isolated using chromatography. The protecting group was subsequently removed at a later stage in the synthesis. Wishing to improve on this procedure, we determined a workup that took advantage of the insolubility of **3** so that the pure product could be obtained from a slow precipitation process. This avoided the benzylation step and its attendant chromatographic purification, but without prior benzylation the workup of the subsequent eightfold 'weaving' reaction to make octol **4** presented a new problem: how to handle the very insoluble **4** to attain a sufficiently pure product for the synthesis of octa-acid **1**. After considerable investigation, we ultimately identified a workup procedure that allowed the isolation of **4** in 75–80% purity. NMR (in DMSO-d_6) suggested that the impurities at this stage were not deep-cavity cavitands but intermediates in the 'weaving' process and/or incorrectly 'woven' products and could be readily removed at the end of the synthesis. Hence, this 75–80% pure **4** was considered satisfactory for the next step in the synthesis. That noted, **4** is itself a potentially useful intermediate for the synthesis of different cavitands, so we determined that the corresponding pure octa-acetate could be isolated in 75% yield by heating a solution of **4** in acetic anhydride, and that this could then be converted into pure **4** by treatment with aqueous dimethylacetamide and lithium hydroxide (92% yield).

Returning to the formation of **1**, potassium permanganate was directly used to oxidise the crude **4** to give octa-acid **1** of an estimated 75–80% purity. ^{1}H NMR analysis of the crude mixture revealed that it contained trace amounts of the same impurity occasionally observed in the earlier synthesis (*1*).

Octa-acid **1** is difficult to be purified on the 100–1000 mg scale, and so to obtain pure **1** we carried out an esterification/hydrolysis procedure. Upon esterification with EtOH/HCl, chromatography of the crude mixture revealed and separated three deep-cavity cavitands in an approximate 7:2:1 ratio (overall 75–80% yield), as well as the 20–25% of non-deep-cavity cavitand impurities. ^{1}H NMR analysis of the cavitands revealed two points. First, the respective products were the anticipated octa-ester **5** (Scheme 1), and the hepta-ester mono-ols **6** and **7** (Figure 1) arising from incomplete oxidation. Second, each product contained a minor cavitand impurity ($<5\%$). In an attempt to increase the yield of **5**, the reaction time and equivalents of $KMnO_4$ in the prior oxidation of **4** were increased, but these changes did not ultimately increase its yield at the expense of **6** or **7**. However, these experiments did indicate increased amounts of the minor products, and this was confirmed by oxidising crude **4**, isolating the crude octa-acid **1** and then oxidising the sample a second time. Esterification of this crude reaction mixture and



6 7 8

Figure 1. Chemical structures of esters **6**–**8**.

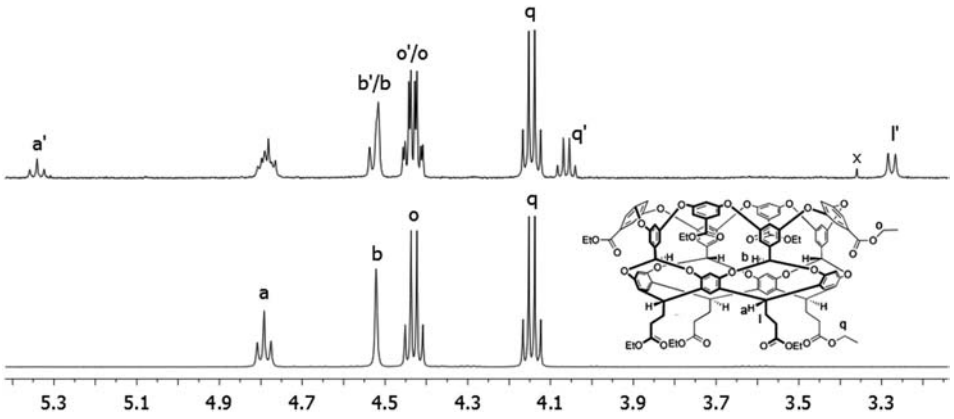


Figure 2. Partial ^{1}H NMR spectra of pure octa-ester **5** (lower spectrum) and minor product of 80–90% purity (upper spectrum). *x* indicates unknown trace impurity.

chromatographic and NMR analyses revealed that the sample consisted mostly of **5** and its attendant impurity, and very little of **6** and **7**. In this sample, it was not possible to completely resolve cavitand **5** from its respective minor product by column chromatography. However, partial separation was achieved to yield pure **5** (in overall 54% yield from **4**) and the minor product in *ca*. 80–90% purity. A combination of MS and NMR identified the minor product. Figure 2 shows a portion of its ^{1}H NMR spectrum along with that of pure octa-ester **5**. The NMR of the former contains signals essentially identical to **5** but also characteristic shifted signals for methine signal a (a′ at 5.35 ppm), methylene signal q (q′ at 4.05 ppm) and methylene signal l (not shown is l′ at 3.25 ppm).

These observed signals could be explained by a shortening of one or more of the pendant groups of the cavitand, and MALDI-MS has proven this to be the case. Thus, the MS spectrum of 80–90% pure sample (Figure 3) showed a small peak for **5** (2061.9, $[M + Ag]^+$), a major peak corresponding to a cavitand missing one methylene group (2047.9, $[M + Ag]^+$), as well as three other peaks of decreasing intensity that differ by 14 Daltons (2033.9, 2019.9 and 2003.9).[1] Thus, the major impurity of octa-ester **5** is octa-ester **8** (Figure 1), but also formed are cavitands in which two, three and four pendant groups have been shortened. Considering the amount of **6**, **7** and the truncated versions of **5**–**7** which are formed in the oxidation of **4**, we were interested in examining alternatives to the oxidation conditions. However, of the many variations we considered none proved as effective as the $KMnO_4$/DMA/*t*-BuOH combination that had been previously identified. Regardless, the final step in the synthesis of **1**, i.e. the hydrolysis of pure octa-ester **5**, occurred without incident (91% yield).

We believe that in larger-scale syntheses of octa-acid using the original procedure, both hepta-acid mono-ols and the pendant group shortened derivatives are present

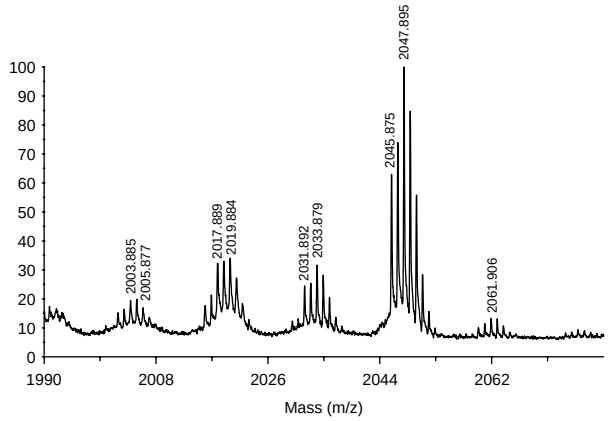


Figure 3. MALDI-TOF-MS of enriched pendant-shortened cavitands (matrix: $AgNO_3$ + TFA).

in small quantities. Spectroscopically, the former are very hard to be identified, while the latter were collectively evident by small signals analogous to those as shown in Figure 2. However, the presence of trace quantities of these compounds is unlikely to significantly affect the observed binding and assembly properties of octa-acid **1**. Likewise, their similar molecular masses to **1** mean that it is unlikely that they significantly affect stoichiometry calculations for binding studies. Regardless, having as the penultimate step in the synthesis a workup that requires chromatography does allow these impurities to be removed and hence gives essentially pure octa-acid **1** in an overall 8% yield.

In summary, we have devised a slightly shorter, but considerably more efficient synthesis of cavitand **1** that allows for the removal of trace quantities of cavitand side-products. In addition, we have devised a route to the isolation of pure **4**; a cavitand that is an important intermediate in the synthesis of many cavitands with alternative outer coats that can bestow water solubility. We will report on these in due course, but the more efficient synthesis of **1**, a procedure that allows the ready isolation of gram quantities of the host, should be of utility to those interested in the fascinating binding and assembly properties of octa-acid.

Experimental

General

3,5-Dibromobenzaldehyde and 3,5-dihydroxybenzyl alcohol were purchased from Beta Pharma Inc.; other reagents were purchased from Sigma-Aldrich, St Louis, MO, USA and were used without purification. DMA was dried over 4 Å molecular sieves and degassed before use; other solvents were used directly without additional purification. All reactions were performed under N_2. NMR spectra were recorded on a Varian Inova 500 MHz spectrometer. Chemical shifts are reported relative to $CDCl_3$ (7.26 ppm) or $(CD_3)_2SO$ (2.50 ppm). MALDI-MS spectra were collected using a Bruker-Daltonics MALDI-TOF Autoflex III mass spectrometer. Elemental analysis was performed by Atlantic Microlab Inc., Norcross, GA, USA.

Dodecanol 2

The synthesis of this compound has been previously reported (see Ref. (*21*)) but we now use a slightly modified procedure. Typically, 20 g (182 mmol, 1 equiv.) of resorcinol was dissolved in 120 ml of methanol and 30 ml of 37% HCl under N_2 and the solution was cooled to 0°C. To this stirring solution, 13.8 ml (182 mmol, 1 equiv.) of 2,3-dihydrofuran was then added via syringe over a 10-min period. The stirring reaction was maintained at 0°C for 30 min. The mixture was subsequently heated to 50°C for 5 days. During this time, a considerable amount of precipitate was formed. After this time, the reaction mixture was allowed to cool to RT, the solid was filtered off and taken up in 0.5 l of distilled water and sonicated. The solid was again filtered off, washed again with distilled water and dried at RT then at 120°C (27.10 g, yield: 83%).

3,5-Dibromobenzal bromide

To a dry one litre round-bottomed flask containing 500 ml of dichloromethane 60 g (227.4 mmol, 1.0 equiv.) of 3,5-dibromobenzaldehyde was added. To this stirring solution 23.8 ml (251.8 mmol, 1.1 equiv.) of BBr_3 was added. The mixture was stirred at RT for 24 h (precipitate observed). Subsequently, 250 ml of water was added slowly to quench excess BBr_3 and dissolve the water-soluble boronic acid side-product (Caution: quenching liberates HBr gas). The water and organic layers were separated, and the organic phase was washed twice with water (2×300 ml) before Na_2SO_4 and active charcoal were added to the organic layer to dry and decolourise the solution. The solvent was removed under reduced pressure, and the solid was dried for 30 min under high vacuum. Crystallisation from hexane afforded the benzal bromide as colourless crystals (85.4 g, yield: 92%).

Octa bromide 3

To a dry one litre flask containing 500 ml of degassed DMA 10.0 g (13.87 mmol, 1.0 equiv.) of dodecanol **2** and 27.2 g (66.71 mmol, 4.8 equiv.) of 3,5-dibromobenzal bromide were added. After adding 16.6 ml (111.0 mmol, 8.0 equiv.) of diazabicyclo[5.4.0]undec-7-ene (DBU), the stirred reaction mixture was heated to 50°C for 2 days. The DMA was subsequently removed under reduced pressure, and the residue was dried overnight under high vacuum. A total of 500 ml of $CHCl_3$ was then added to dissolve the crude mixture, and the solution was washed with water (3×300 ml). Particulate matter in the aqueous phase was discarded. The organic layer was dried quickly with anhydrous Na_2SO_4 (<5 min) and filtered. A prolonged drying process resulted in the precipitation of the product. The volume of solution was reduced under reduced pressure to *ca.* 150 ml and refrigerated (5°C) for 12 h. The pure product, having precipitated from the solution, was filtered, washed with $CHCl_3$ and dried at 120°C (10.7 g, yield: 45%). Mp >250°C. ^{1}H NMR (500 MHz, DMSO) δ 7.93 (s, 8H), 7.72 (s, 4H), 7.12 (s, 4H), 5.50 (s, 4H), 4.71 (t, $J = 10.0$, 4H), 4.49 (t, $J = 6.2$, 4H), 3.53 (q, $J = 8.3$, 8H), 2.49–2.45 (m, 8H), 1.57–1.43 (m, 8H). MS (MALDI): Calcd. 1813 $[M + Ag]^+$, Found: 1813 $[M + Ag]^+$. Anal. Calcd. for $C_{68}H_{56}Br_8O_{12}$: C, 47.92; H, 3.31 Found: C, 47.58; H, 3.35.

Crude octol 4

For 10 min, N_2 gas was bubbled through a stirring suspension of 6.84 g (4.0 mmol, 1.0 equiv.) of octa-bromide

3, 3.36 g (24.0 mmol, 6.0 equiv.) of 3,5-dihydroxybenzyl alcohol and 6.62 g (48.0 mmol, 12 equiv.) of K_2CO_3 in 300 ml of pyridine. After this time, 3.80 g (48.0 mmol, 12 equiv.) of CuO nano-powder was added, and the mixture was heated to a vigorous reflux by sand bath (a normal reflux was not sufficient to bring about reaction) for 3 weeks. After the solvent was removed by reduced pressure, the crude material was dried on a high vacuum line for 1 h (excessive drying and/or exposing the mixture to air for extended periods led to greatly reduced yields). Subsequently, 250 ml of THF was added, and the reaction mixture was sonicated for 30 min. The mixture was then filtered through THF-wet Celite, and the solvent of the filtrate was evaporated under reduced pressure to give a brown crude solid. This material was dried at RT overnight under high vacuum. To the dried solid 50 ml of $CHCl_3$ was added, and the suspension was sonicated for 20 min. The solid obtained after filtration (the filtrate should be green) was suspended once again in $CHCl_3$, sonicated for 20 min and dried under vacuum for overnight at 120°C to give ~3.9 g crude octol 4 as an off-white powder (yield by weight: 65%, *ca*. 75% purity by NMR, therefore, 45% estimated yield).

Octa-acetate of octol 4

To 10 ml of Ac_2O 1 g (0.62 mmol) of crude octol **4** was added. The mixture was heated to 100°C (oil bath) for 16 h. The homogeneous solution was then cooled to RT, and the solvent was removed under high vacuum. The residue was dried for 2 h and purified by chromatography (0.91 g, yield: 75%). $R_f = 0.25$ ($CHCl_3$/Acetone, 15:1, v/v). Mp >250°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, $J = 2.0$, 8H), 7.14 (s, 4H), 6.98 (t, $J = 2.2$, 4H), 6.54 (t, $J = 2.0$, 4H), 6.51 (d, $J = 2.2$, 8H), 6.01 (s, 4H), 5.20 (s, 8H), 4.82 (t, $J = 8.2$, 4H), 4.53 (s, 4H), 4.16 (t, $J = 6.5$, 8H), 2.32 (q, $J = 8.0$, 8H), 2.12 (s, 12H), 2.07, (s, 12H), 1.71–1.65 (m, 8H). MS (MALDI): Calcd. 2061 $[M + Ag]^+$, Found: 2061 $[M + Ag]^+$. Anal. Calcd. for $C_{112}H_{96}O_{32}$: C, 68.85; H, 4.95 Found: C, 68.18; H, 4.94.

Pure octol 4

To 910 mg (0.46 mmol, 1 equiv.) of octa-acetate **5** in 60 ml DMA 10 ml of H_2O and 625 mg (14.9 mmol, 32 equiv.) of $LiOH{\cdot}H_2O$ were added. The solution was heated to 50°C for 24 h. The solvent was removed under high vacuum, and the residue was dried at RT for 16 h. A total of 30 ml of 1 M HCl and 120 ml of H_2O were added to the resulting solid, and the mixture was sonicated for 30 min. Filtration and washing with solid with distilled water gave octol **4**, which was dried at RT for 16 h. Acetone (10 ml) was then added to this solid, and the mixture was sonicated for 2 min and allowed to stand for 2 h. Filtration and drying of the solid under high vacuum (at 120°C) afforded pure octol **4** (690 mg, yield: 92%).

Crude octa-acid 1

To a solution of 3.5 g (2.16 mmol, 1.0 equiv.) of crude octol **4** in 300 ml degassed DMA and 300 ml of *t*-BuOH 9.57 g (60.55 mmol, 28.0 equiv.) of $KMnO_4$ was added. The resulting purple solution was stirred at RT for 2 days. The reaction mixture was filtered, and the solid was washed thoroughly with 4 × 200 ml distilled water. The combined filtrate was evaporated under high vacuum and dried at RT for 16 h. A total of 20 ml of 20% HCl was then added to the solid, and the suspension was sonicated for 5 min. Following filtration, the solid was shaken with 150 ml of distilled water. Filtration and washing with water gave crude octa-acid **1**, which was dried at 120°C for overnight (~3.4 g).

Octa-ester 5 (hepta-esters 6 and 7)

HCl gas was bubbled through a solution of 2.5 g of crude octa-acid **1** in 150 ml of ethanol for ~2 min. To this suspension 100 ml of $CHCl_3$ was added, and the solution was heated up to reflux for 4 days. The solvent was then removed, and 10 ml of ethanol was added to the residue, the resulting suspension was shaken and then filtered. The resulting off-white solid was dried at 120°C for 16 h. Chromatography of the crude product afforded three main products: octa-ester **5** (1.26 g), hepta-ester-rim-OH **6** (0.38 g) and hepta-ester-feet-OH **7** (0.17 g). Octa-ester **5**: $R_f = 0.33$ ($CHCl_3$/Acetone, 40:1, v/v). Mp >250°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, $J = 2.2$, 8H), 7.19 (s, 4H), 7.02 (t, $J = 2.1$, 4H), 6.78 (t, $J = 2.2$, 4H), 6.52–6.50 (m, 8H), 5.97 (s, 4H), 4.79 (t, $J = 8.3$, 4H), 4.52 (s, 4H), 4.43 (q, $J = 7.1$, 8H), 4.14 (q, $J = 7.1$, 8H), 2.58 (q, $J = 7.7$, 8H), 2.31 (t, $J = 7.4$, 8H), 1.44 (t, $J = 7.1$, 12H), 1.26 (t, $J = 7.1$, 12H). MS (MALDI): Calcd. 2061 $[M + Ag]^+$, Found: 2061 $[M + Ag]^+$. Anal. Calcd. for $C_{112}H_{96}O_{32}$: C, 68.85; H, 4.95 Found: C, 69.09; H, 4.90. Hepta-ester-rim-OH **6**: $R_f = 0.37$ ($CHCl_3$/Acetone, 15:1, v/v). Mp >250°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89–7.87 (m, 6H), 7.23 (d, $J = 1.9$, 2H), 7.19 (s, 4H), 7.01 (m, 4H), 6.78 (m, 3H), 6.54 (m, 1H), 6.51 (m, 8H), 6.01 (s, 1H), 5.98 (d, $J = 2.4$, 3H), 4.84 (s, 2H), 4.80 (m, 4H), 4.53 (s, 4H), 4.43 (q, $J = 7.1$, 6H), 4.15 (qd, $J = 7.1$, 1.1, 8H), 2.59 (q, $J = 7.5$, 8H), 2.32 (t, $J = 7.0$, 8H), 1.44 (t, $J = 7.1$, 9H), 1.26 (td, $J = 7.1$, 1.2, 12H). MS (MALDI): Calcd. 2019 $[M + Ag]^+$, Found: 2019 $[M + Ag]^+$. Anal. Calcd. for $C_{110}H_{94}O_{31}$: C, 69.10; H, 4.96 Found: C, 68.21; H, 5.05. Hepta-ester-feet-OH **7**: $R_f = 0.24$ ($CHCl_3$/Acetone, 15:1, v/v). Mp >250°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.86 (m, 8H), 7.24 (s, 2H), 7.17 (s, 2H), 7.02 (m, 4H), 6.78 (m, 4H), 6.54–6.50 (m, 8H), 5.97 (s, 4H), 4.82–4.74 (m, 4H), 4.54 (s, 1H), 4.52 (s, 3H), 4.43

(qd, $J = 7.1$, 2.2, 8H), 4.18–4.10 (m, 6H), 3.75 (q, $J = 5.9$, 2H), 2.72–2.46 (m, 6H), 2.46–2.24 (m, 8H), 1.59–1.51 (m, 2H), 1.44 (td, $J = 7.1$, 1.5, 12H), 1.26 (m, 9H). MS (MALDI): Calcd. 2019 $[M + Ag]^+$, Found: 2019 $[M + Ag]^+$. Anal. Calcd. for $C_{110}H_{94}O_{31}$: C, 69.10; H, 4.96 Found: C, 68.44; H, 4.96.

Pure octa-acid 1

To 430 mg (0.22 mmol, 1 equiv.) of octa-ester **5** in 43 ml DMA 2.65 ml of 2.0 M (5.3 mmol, 24 equiv.) aqueous LiOH was added. The solution was heated to 50°C, and small amounts of distilled water were added until the precipitate was fully dissolved. The resulting clear solution was stirred at 50°C for 24 h. After this time, the solution was filtered, the solvent was removed under high vacuum and the residue was dried for 2 h. Subsequently, 5 ml of 20% HCl was added to the solid, and the suspension was sonicated for 1 min before a further 40 ml of water was added and the suspension was shaken. Filtration and washing with water gave octa-acid **1**, which was dried at RT for 3 h. Acetone (5 ml) was then added to the solid, the mixture was sonicated for 2 min and then left to stand for 2 h. Filtration and drying at 120°C for 48 h under high vacuum afforded pure octa-acid **1** (370 mg, yield: 91%).

Acknowledgements

BCG, SL and CLDG acknowledge the financial support of the National Institutes of Health (GM074031). SWI acknowledges a fellowship from the Louisiana Board of Regents Graduate Fellows Program.

Note

1. These masses correspond to the largest signal in each envelope and to the theoretical isotope distribution for each cavitand, with the exception of the weakest signal at 2003.9. In this case, noise contributes to the mis-shaping of the isotope distribution envelop relative to the theoretical.

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