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Hexasulfanyl analogues of cyclotriveratrylene

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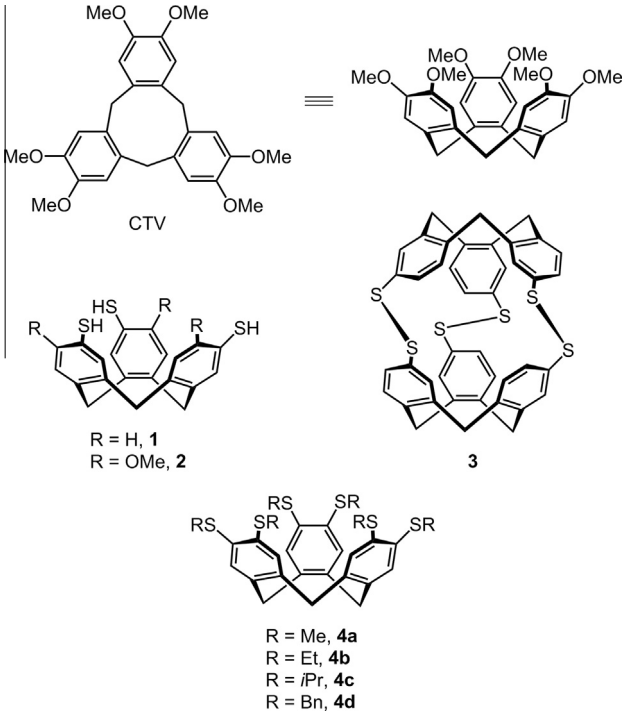
ABSTRACT

The synthesis of four 3,4-di(alkylsulfanyl)benzyl alcohol derivatives is described, in five steps from methyl 3,4-di(hydroxy)benzoate via a Newman–Kwart rearrangement. Incubation of these derivatives in formic acid affords 2,3,7,8,12,13-hexakis(alkylsulfanyl)-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene products, which are hexa-sulfanyl analogues of the well-known supramolecular cavitand host, cyclotriveratrylene (CTV). The yield of this cyclization depends strongly on the alkylsulfanyl substituents present, in the order SMe > SEt ≈ S*i*Pr ≫ SBn. A crystal structure determination of one of the cyclotrimers shows a mode of self-association that is commonly exhibited by CTV itself.

Cyclotriveratrylene (2,3,7,8,12,13-hexamethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene, CTV; Scheme 1) is a rigid bowl-shaped molecule that is an important synthon in supramolecular chemistry.[1–3] CTV itself can complex fullerenes or other globular molecular guests within its hydrophobic cavity. Moreover, other functionalities can be appended onto the CTV scaffold by derivatization of its methoxy groups, allowing organic[2–5] and metal-organic[2,6,7] cage compounds, frameworks and other supramolecular assemblies[8] based on the CTV moiety to be constructed. Recently, we[9,10] and others[11,12] have extended the chemistry of CTV by preparing thiolated analogues **1** and **2** (Scheme 1). Oxidative dimerization of **1** under high-dilution conditions affords the cryptophane-0.0.0 capsule **3**, one of the smallest organic capsules yet reported, which binds methane in solution.[9] A larger capsule molecule was similarly achieved by oxidatively coupling **1** with a trimercapto-cyclodextrin.[12] As a continuation of this work, we were keen to obtain hexa-sulfanyl analogues of CTV, bearing purely thiyl or sulfanyl substituents at the upper rim. We report here the synthesis of several new 3,4-disulfanylbenzyl alcohol derivatives, and their cyclotrimerization into 2,3,7,8,12,13-*hexakis*-(alkylsulfanyl)-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene cavitands **4a**–**4d**.

We first attempted to access hexa-sulfanyl analogues of CTV by the same method we successfully used for **1** and **2**. That is, by a



Scheme 1. Cyclotriveratrylene (CTV), and its sulfur-containing analogues referred to in this work.

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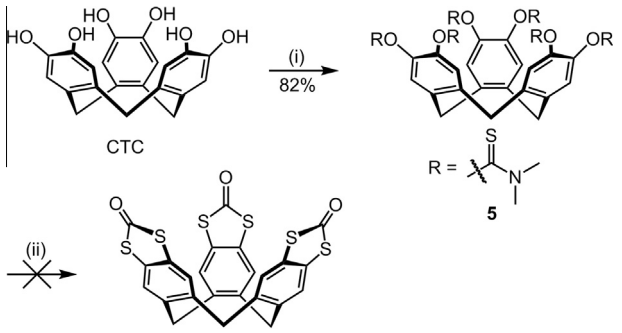
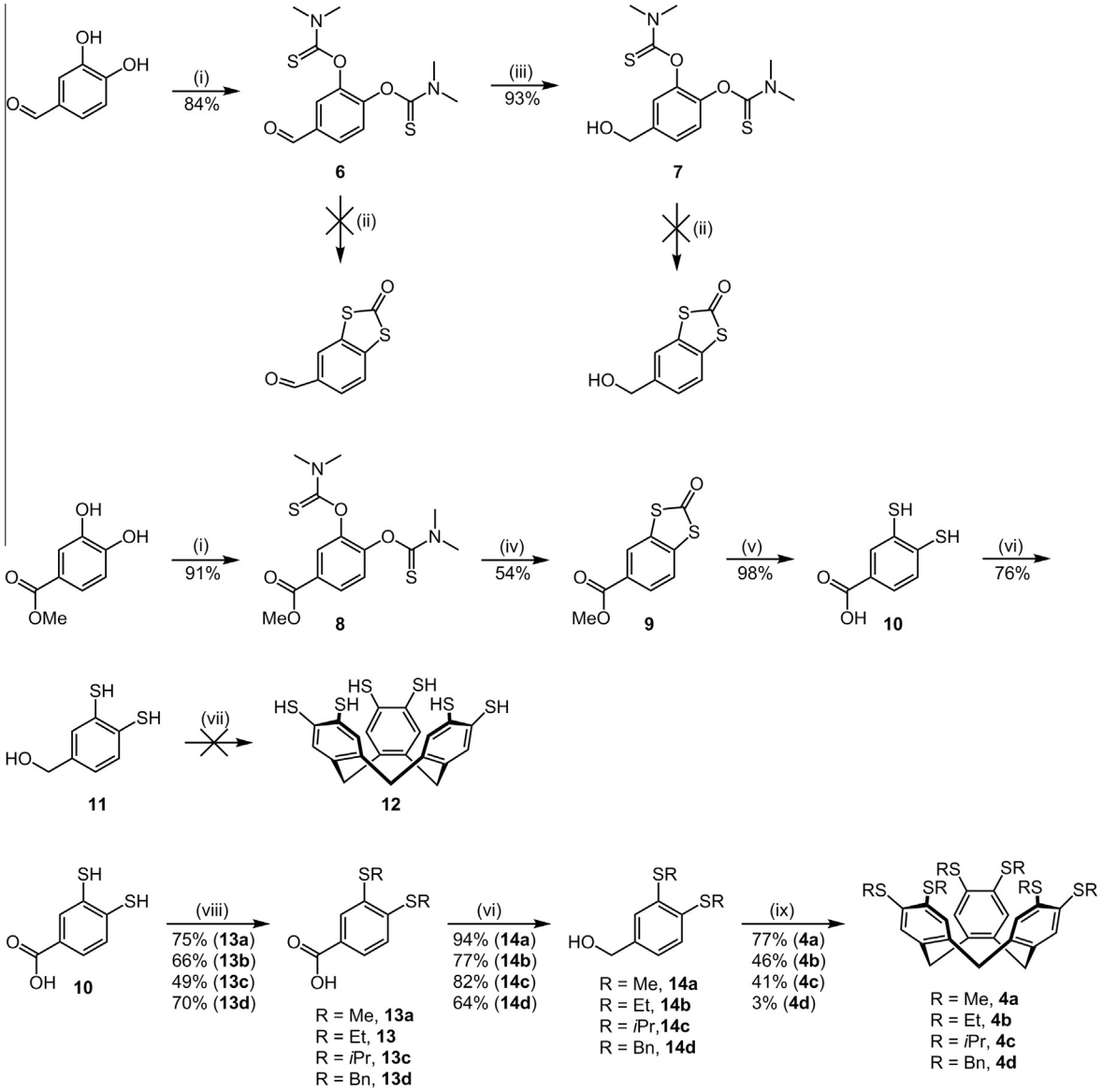


Scheme 2. Attempted Newman–Kwart rearrangement from pre-formed cyclotricatechylene. Reagents and conditions: (i) $Me_2NC(S)Cl$, Cs_2CO_3, DMF; (ii) Ph_2O, 180 °C.

Newman–Kwart rearrangement[13] from the tris-catechol *cyclo*-tricatechylene (2,3,7,8,12,13-hexahydroxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononene, CTC; Scheme 2), which is readily prepared by exhaustive demethylation of CTV with BBr_3.[14] The *hexakis*-*N*,*N*-dimethylthiocarbamoyl Newman–Kwart precursor **5** was obtained in good yield by treatment of CTC with $Me_2NC(S)Cl$ in the presence of excess Cs_2CO_3. However, heating **5** in diphenyl ether led to its decomposition above 180 °C, with no rearrangement product being observed. This is an insufficiently high temperature for a Newman–Kwart rearrangement to proceed in this system. For comparison, the corresponding rearrangement reactions in the syntheses of **1** and **2** from preformed CTV-type precursors proceed at 255 °C and 305 °C, respectively.[9] Palladium catalysis can reduce the temperature required for the Newman–Kwart rearrangement.[15] That was not attempted in this study, however, because that protocol did not give useful yields in the synthesis of **1** and **2**.[9]

CTV is prepared by the acid-catalysed trimerization of 3,4-dimethoxybenzyl alcohol.[1] We therefore pursued (previously unknown) 3,4-disulfanylbenzyl alcohol derivatives, that could be similarly cyclotrimerized to form **4a**–**4d**. Since 3,4-di(hydroxy)-benzyl derivatives are readily available, a Newman–Kwart route to these products was also employed (Scheme 3).



Scheme 3. Synthesis of 3,4-di(alkylsulfanyl)benzyl alcohol derivatives, and their conversion into the desired cyclic trimer cavitand compounds **4a**–**4d**. Reagents and conditions: (i) $Me_2NC(S)Cl$, DABCO, DMF; (ii) Ph_2O, 160–280 °C; (iii) $NaBH_4$, THF; (iv) Ph_2O, 240 °C, 1 h; (v) NaOH (aq), 70 °C, 6 h then 1 M HCl; (vi) $LiAlH_4$, THF, 0 °C → rt, 18 h; (vii) HCO_2H, 70 °C or $Sc(CF_3SO_3)_3$, MeCN, 60 °C; (viii) NaOH, MeOH then RBr or RI, acetone, reflux, 4 h; (ix) HCO_2H, 70 °C, 48 h.

Attempted Newman–Kwart rearrangements employing 3,4-di(*N*,*N*-dimethylthiocarbamoyloxy)benzaldehyde (**6**) or 3,4-di(*N*,*N*-dimethylthiocarbamoyloxy)benzyl alcohol (**7**) were also unsuccessful, with decomposition being observed near 160 °C before a sufficiently high temperature could be reached (see above).[15] However, methyl 3,4-di(*N*,*N*-dimethylthiocarbamoyl-oxy)benzoate (**8**) is more thermally robust, affording the dithione **9** in moderate yield after heating at 240 °C in Ph_2O. Heating **9** with aqueous NaOH leads to simultaneous removal of the thione protecting group and hydrolysis of the ester function, affording 3,4-dimercaptobenzoic acid (**10**) almost quantitatively.[16] Reduction of **10** with $LiAlH_4$ afforded 3,4-dimercaptobenzyl alcohol (**11**) in good yield. Alternatively, alkylation of **10** with the appropriate alkyl bromide or alkyl iodide in the presence of NaOH gave the 3,4-di(alkylsulfanyl)benzoic acid derivatives **13a**–**13d**, which were then reduced to the equivalent benzyl alcohols **14a**–**14d** with $LiAlH_4$. Although **13a**–**13d** all contained 15–20% of mono-alkylated impurities, this did not interfere with their use in the reduction step and **14a**–**14d** were subsequently purified by chromatography. Attempts to shorten this reaction sequence, by reducing **9** to the corresponding alcohol with $NaBH_4$ or $LiAlH_4$, led to preferential removal of the thione moiety with little reduction of the ester group being observed.

Cyclotrimerization of **14a**–**14d** to the desired 2,3,7,8,12,13-hexakis(alkylsulfanyl)-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*]cyclononenes **4a**–**4d** was achieved by heating in formic acid (Scheme 3).[17] The yields of the reaction depended significantly on the alkylsulfanyl substituents present, in the order **4a** (R = Me) > **4b** (R = Et) ≈ **4c** (R = *i*Pr) ≫ **4d** (R = Bn). The trace yield of **4d** is consistent with the mechanism of the reaction, which couples the benzyl alcohol monomers by a sequence of electrophilic aromatic substitution steps. These will be disfavored by the more inductively withdrawing sulfanyl substituents on the benzyl alcohol precursors. Formation of the macrocyclic products was confirmed by the ^{1}H NMR signature of their chemically equivalent CH_2 groups, which are diastereotopic in the rigid bowl-shaped conformation adopted by the molecules. These groups are observed as two geminally coupled doublets near 3.7 and 4.7 ppm, assignable to the H_{exo} and H_{endo} environments, respectively. Attempted cyclotrimerization of dithiol **11** to the hexa-mercapto derivative **12**, in formic acid[17] or in MeCN with a $Sc(CF_3SO_3)_3$ catalyst,[18] did not go to completion and gave a mixture of bis-(di{alkylsulfanyl}phenyl)methane-containing species by mass spectrometry.

The identity of **4c** was confirmed by a crystal structure determination, which showed it to adopt the expected bowl-shaped conformation (Fig. 1). While four of the six *Si*Pr substituents are approximately coplanar with their bound phenylene group, the other two project into the molecular bowl. Molecular models imply that this should reflect steric congestion between *iso*-propyl groups around the rim of the molecule. Interconversion between the *Si*Pr group conformations in **4c** is slow in solution by ^{1}H NMR spectroscopy, since the *i*Pr methyl groups are observed as at least three overlapping doublets whose integrals sum to the expected 36H (see the Supplementary information). There is no comparable splitting of the substituent resonances in the ^{1}H NMR spectra of the other cyclotrimers with smaller, less hindered sulfanyl groups.

Molecules of **4c** associate into centrosymmetric dimers in the crystal, by inclusion of one 'out-of-plane' *iso*-propyl group from each molecule into the hydrophobic cavity of its neighbour (Fig. 2). This 'handshake' dimerization is common in crystalline CTV derivatives, which associate by intermolecular inclusion of their methyl groups.[19] The observation of the same motif in **4c**,

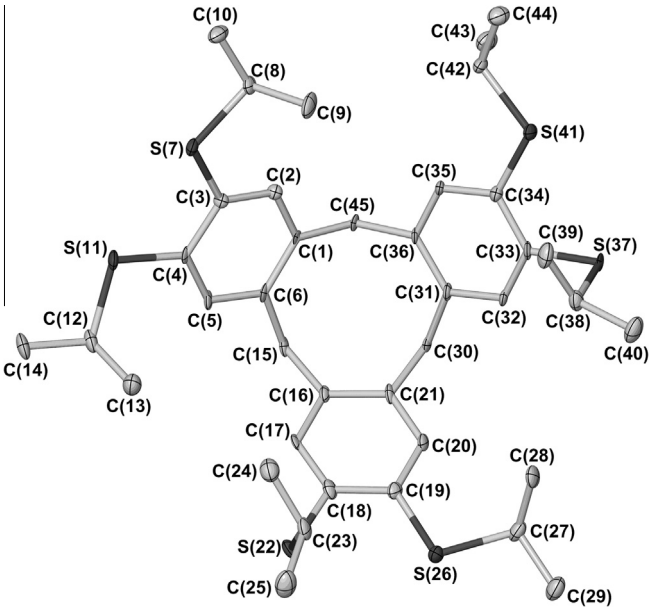


Figure 1. View of the molecule of **4c** in its crystal structure, showing the atom numbering scheme employed. Displacement ellipsoids are at the 50% probability level, and H atoms have been omitted.

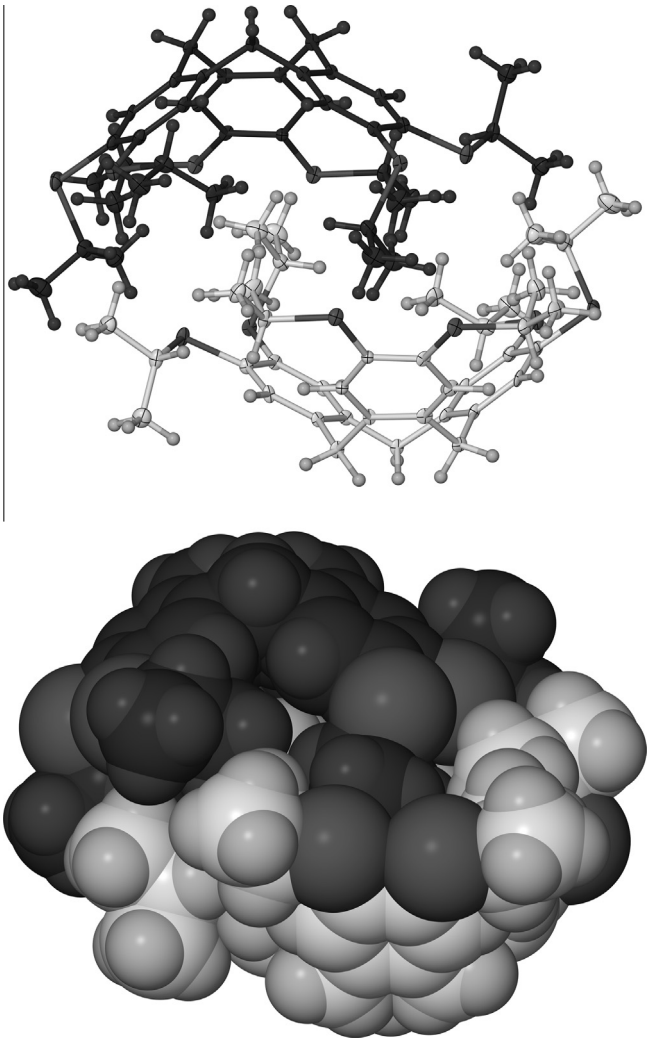


Figure 2. Top: the 'handshake' dimerization of **4c** in the crystal. The C and H atoms in the two molecules have pale and dark colouration. Bottom: the same view as a space-filling plot.

despite the increased bulk of the included *iso*-propyl groups, indicates that the host:guest chemistry of **4a**–**4d** should be comparable to CTV derivatives.

In conclusion, we have reported here a general synthesis of 3,4-di(alkylsulfanyl)benzyl alcohols, employing a Newman–Kwart rearrangement procedure. These can be converted into cyclic, bowl-shaped molecules that are hexa-sulfanyl analogues of the well-known supramolecular cavitand CTV. Preliminary attempts to obtain the hexa-mercapto derivative **12** by a Pummerer rearrangement from **4a**,[11] and by deprotection of **4b** with Na/HMPA,[20] have been unsuccessful. While the benzyl groups in **4d** should be easier to remove, the low yield of that compound precludes its use as a precursor to **12**. Nonetheless, as well as being of interest in their own right, **4a**–**4d** could also be used as components in metal/organic supramolecular assemblies, through chelation of transition ions by their 1,2-di(alkylsulfanyl) moieties.[21] Our synthetic route to **4a**–**4d** could also be adapted to yield larger hexasulfanyl assemblies or cage compounds based on thioether linkers. Current work is aimed at investigating these possibilities.

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Supplementary data

Synthetic procedures and characterization, and experimental data for the crystal structure determination. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.025. Crystallographic data (excluding structure factors) for the structure of **4c** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 979574. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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