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Bile Acid-Based Cage Compounds with Lipophilic Outer Shells and Inner Cavities

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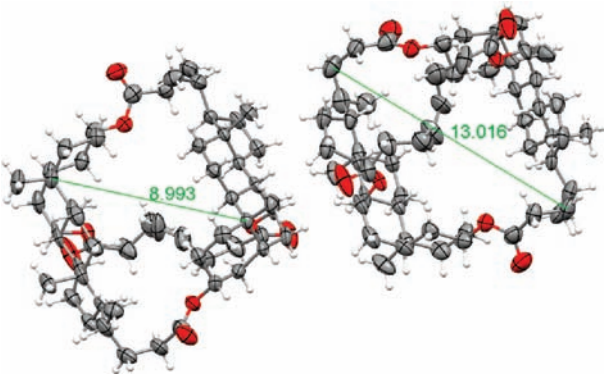
ABSTRACT



The uniquely functionalized steroid-based cyclodimers 4, *cis*-5, and *trans*-5 have been synthesized and fully characterized.The cyclodimer 5, with a *cis*–*trans* ratio of 3:1, is obtained by coupling the terminal alkenes of two 4-pentenoate groups on a cyclodimer 4 via Grubbs' intramolecular ring-closing metathesis. The crystal structure shows *cis*-5 to be a cagelike cyclic oligomer bridged by the flexible oct-4-enedioate link.

Endowed with uniquely arched surfaces, membrane permeability, and biodegradability,[1] bile acid derivatives are key building blocks for biocompatible nanoporous materials with diverse applications such as drug delivery systems,[2] a colon cancer cell growth inhibitor,[3] and a receptor for anion recognition.[4] Bile acid-based macrocycles have also been employed to probe host–guest interactions.[5] To date, very few functionalized macrocycles with bile acid backbones have been reported because of the rigidity and the topology of the bile acids, which tend to form linear oligomers and polymers.[6] Our previous efforts

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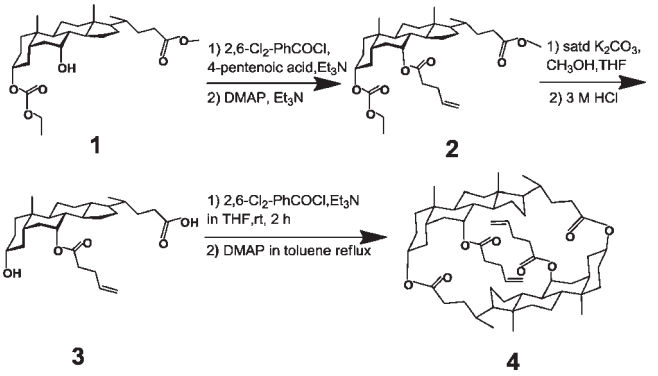
have focused on the synthesis and structural study of various functionalized linear oligomers, cyclic trimers, and tetramers of bile acids.[7] In this study, we report the first synthesis and characterization of the smallest cyclomer of chenodeoxycholic acid (CDCA) that, in addition, contains an unusual, inwardly directed side chain (**4**) and the subsequent closure of this macrocycle by fusion of the terminal vinyl groups on its two side chains by means of Grubbs' olefin metathesis.

Scheme 1. Synthesis of Cyclodimer **4**



The synthesis of CDCA cyclodimer **4** is straightforward and shown in Scheme 1. The 4-pentenoate group was introduced at the 7α position of compound **1** under Yamaguchi reaction conditions in high yield (95%) to give triester **2**. Monoester **3** was obtained by the selective removal of the 3α-ethoxycarbonyloxy and 24-ester methyl groups of **2** under mild basic conditions.[8] Cyclodimer **4** was obtained in 80% yield by condensation of two molecules of **3**. Large prisms of cyclodimer **4** were obtained by slow evaporation of a chloroform−acetone solution and proved to be suitable for X-ray analysis.

The molecular structure and crystal packing of **4** is illustrated in Figure 1. One of the 4-pentenoate side chains was inwardly directed to the upper rim of the bowl-shaped cyclodimer (Figure 1a,b). Very few macrocycles with inward-pointing side chains have been reported,[9] and compound **4** is the first cyclic steroid to have such a structure. The solvent site in this structure displays compositional disorder, with chloroform and acetone sharing the site, and the overall electron density measured by the diffraction experiment is the sum of both. In many

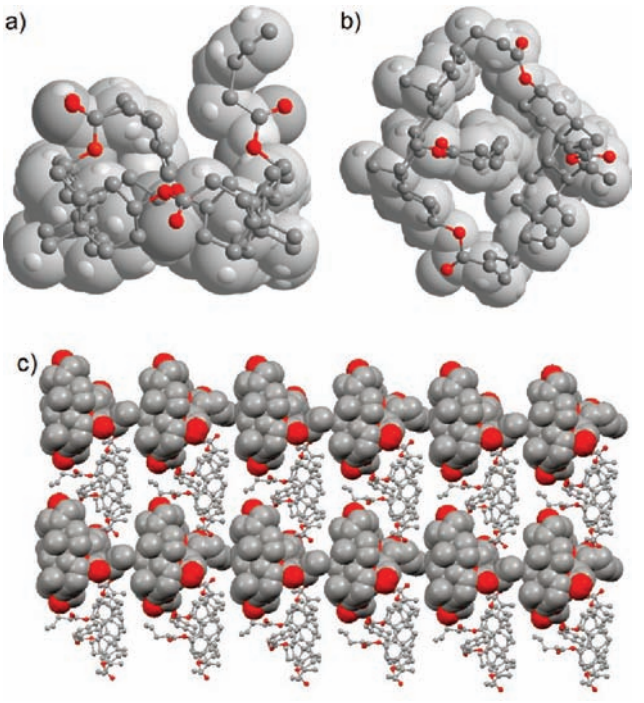
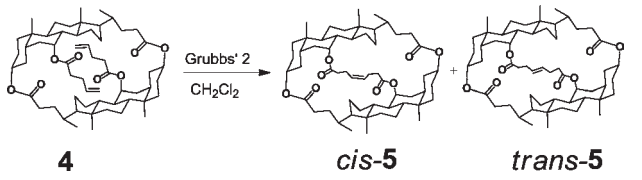


Figure 1. X-ray structure of cyclodimer **4**. (a) Side view of the molecular structure showing one of the pentenoates folded into the cavity and the other excluded. (b) Top view of the molecular structure. (c) Extended packing of cyclodimer **4** along the crystallographic *b* axis. Hydrogen atoms and included solvent molecules have been omitted for clarity.

respects, the inwardly directed side chain is just a proxy for more solvent that would otherwise occupy the macrocycle's cavity in the crystal. The molecules of **4** are assembled head to tail in a supermolecular nanotubular motif along the *c* axis (Figure 1c). The voids between adjacent nanotubes in the same layer are filled by another layer of an identical nanotube network and therefore stabilize the crystal pattern. The adjacent nanotube motif layers are oriented in opposite directions and are mutually interpenetrating and interlocked to form a 2-fold three-dimensional network.

The *cis*/*trans* mixture of the bridged macrocycle **5** was generated by treatment of cyclodimer **4** with the second-generation Grubbs' catalyst in refluxing CH_2Cl_2 as shown in Scheme 2. After passing through a flash column, the crude product, a mixture of *cis* and *trans* isomers in 90%

Scheme 2. Synthesis of Bridged Cyclodimers



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total yield, was obtained. A 3:1 ratio of the *cis* and *trans* isomers was determined by integration of the two triplets at δ 5.61 and δ 5.55 in its ^{1}H NMR spectrum (Figure 2b). The *cis* and *trans* isomers were then separated on a second column. Both isomers were obtained in pure form and were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS (see the Supporting Information). Large prisms of *cis*-**5** were obtained by slow evaporation of a CH_2Cl_2–acetone solution and proved suitable for X-ray analysis. In addition, the trace presence of an intermolecular metathesis product (a bis-cyclodimer) was evident in the HRFAB mass spectrum. The precise mass observed was 1771.2489, in excellent agreement with that calculated for the bis-cyclodimer, 1771.2514 ($C_{112}H_{170}O_{16}$).

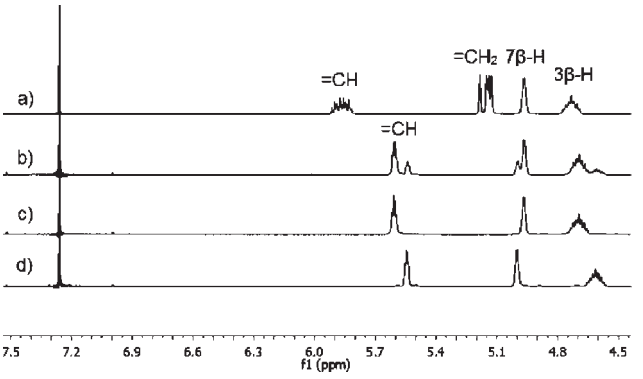

Figure 2. (a) Partial ^{1}H NMR spectrum of cyclodimer **4**. (b) Partial ^{1}H NMR spectrum of the 3:1 mixture of *cis*-**5** to *trans*-**5**. (c) Partial ^{1}H NMR spectrum of *cis*-**5**. (d) Partial ^{1}H NMR spectrum of *trans*-**5**.

The molecular structure of *cis*-**5** as revealed by X-ray crystallography is shown in Figure 3. Compound *cis*-**5** crystallized in the space group *P*1. The included solvent molecules in this structure were severely disordered and were removed by the SQUEEZE/BYPASS procedure.[10] The structure contains two independent molecules of *cis*-**5** oriented facing in opposite directions in the crystal. The two independent molecules I and II make tight interactions with themselves. For instance, the molecule I composed of subunits A and B contacts its symmetry generated self, and the other molecule composed of C and D acts the same way and forms wrinkled layers composed of only AB molecules or CD molecules. The solvent resides in the spaces between the layers. In the crystal structure, all the carbonyl O atoms have fairly tight contacts. Two types of short contacts are observed.

Short contacts between two independent molecules [d(C(25)═O(3)---H(7β)-C) = 2.529 and 2.518 Å, as shown in Figure 3c, and d(H(27)---O(4)═C(23)) = 2.513 and 2.717 Å] seem to direct the crystal packing. The flexible oct-4-enedioate side chains form an "m"-shaped linkage

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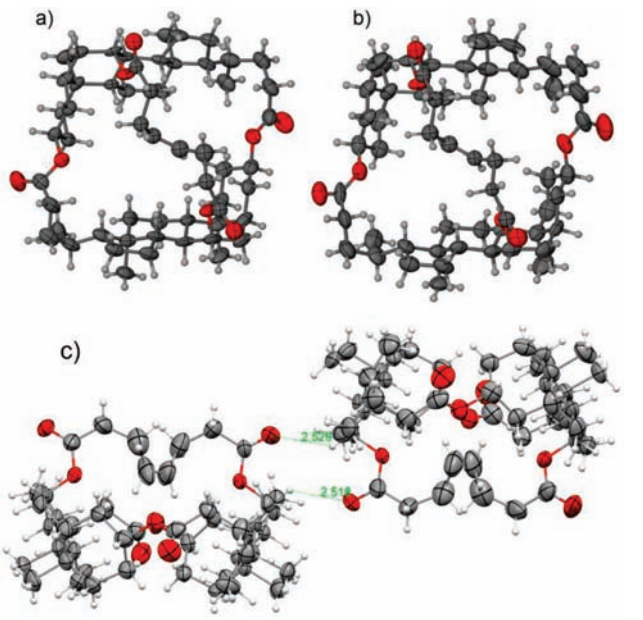

Figure 3. (a) X-ray structure of cyclodimer *cis*-**5**. a) Independent molecule I composed of subunits A and B. (b) Independent molecule II composed of subunits C and D. (c) View of the two independent molecules facing up and down in the crystal structure. The dashed line shows the tight C–H---O contacts between two independent molecules which possibly direct the packing. Thermal ellipsoids have been drawn at the 50% level.

connecting two 7α positions of the steroid skeleton. Additionally, the *cis* double bond on the oct-4-enedioate chain adopts the "in conformation" being oriented toward the ring centroid to fill the voids of the cavity. The shortest distances from the two hydrogen atoms on the *cis* double bond to hydrogen atoms on cyclodimer upper rim are 2.563 and 2.631 Å, indicating that *cis*-**5** has a sterically crowded conformation. It also suggests that the flexible oct-4-enedioate chain must be stretched away from the cavity in order to form a *trans* C═C double bond to avoid steric hindrance from the upper rim of cyclodimer ring.

A molecular structure simulation (MM2) shows that *cis* and *trans* isomers of **5** have essentially the same energy. The *cis* geometry is not thermodynamically favored; however, the bridge of *cis*-**5** in its crystal structure resembles the inwardly directed side chain of the precursor compound **4**. Furthermore, the chemical shifts observed in the ^{1}H and ^{13}C NMR spectra for *cis*-**5**, for example, the chemical shifts of 3β-H, 7β-H, and C17, are much closer to the corresponding chemical shifts of cyclodimer **4** than those of *trans*-**5**. This suggests a lower energy for the transition state when forming the *cis* conformation; therefore, *cis*-**5** is a kinetic product.

In summary, a bowl-shaped cyclodimer of CDCA with an inwardly directed side chain was synthesized, and the terminal vinyl side chains were coupled by Grubbs' catalyst to yield the first bridged cyclodimer of a steroid-based macrocycle.

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Supporting Information Available. Experimental details for the synthesis of compounds, ^{1}H and ^{13}C NMR spectra, mass spectra, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.