



# Improved stereospecific synthesis of the *trans*-isomers of dicyclohexano-18-crown-6 and the solid-state structure of the *trans-syn-trans*-isomer

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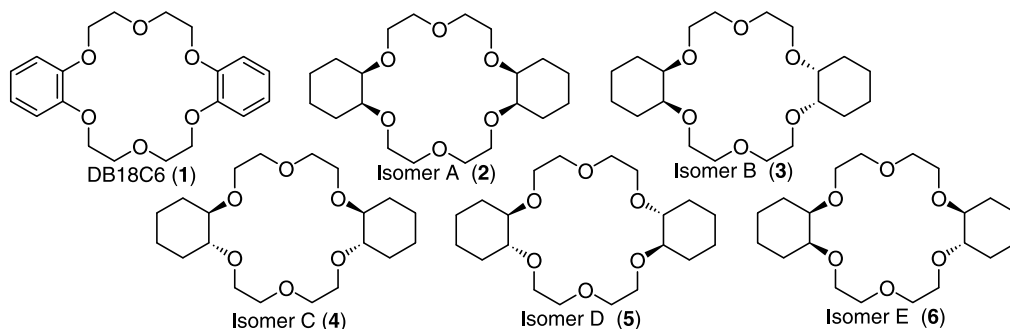
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**Abstract**—The two *trans* stereoisomers of dicyclohexano-18-crown-6 are synthesized by a two-step method from cyclohexene oxide and the solid-state structure of the *trans-syn-trans* isomer is determined. © 2002 Elsevier Science Ltd. All rights reserved.

Crown ether compounds have been widely used for complexation and separation of metal ions, phase transfer catalysis, host-guest chemistry and supramolecular chemistry.<sup>1,2</sup> Dibenzo-18-crown-6 (DB18C6, **1**) and dicyclohexano-18-crown-6 (DC18C6) are well-known crown ether compounds, which were reported in Pedersen's first crown ether synthesis paper.<sup>3</sup> The latter can exist as five different stereoisomers based on the fusion of the cyclohexane rings (*cis* or *trans*) and the relationship of the two cyclohexane units (*syn* or *anti*). Since *cis-syn-cis*-Isomer A, **2**) and *cis-anti-cis*-DC18C6 (Isomer B, **3**) are easily obtained by the catalytic hydrogenation of **1**<sup>3,4</sup> and are commercially available, the complexation and separation behavior of these two isomers have been well established,<sup>1a-c</sup> as have their solid-state<sup>5</sup> and solution<sup>6</sup> structures. However, systematic studies with all of the five isomers including *trans-syn-trans*-, *trans-anti-trans*- and *cis-trans*-DC18C6 (Isomers C, D, and E, **4–6**, respectively) have been rarely reported.<sup>7</sup> In large part, this is

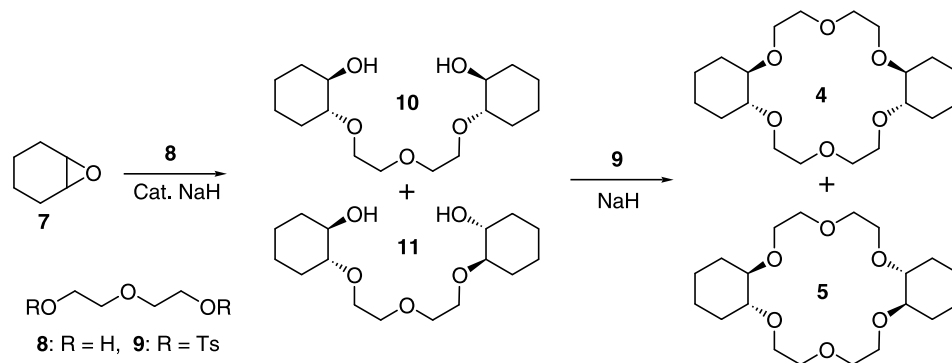
due to the difficulty of synthesis and purification, especially for Isomer D.

The preparation of Isomers C and D was first reported by Stoddart and co-workers.<sup>8</sup> Both were obtained by multi-step synthesis, including the separation of diastereomers. However, the overall yields were low. These authors also described the one-pot reaction of *trans*-1,2-cyclohexanediol and di(ethylene glycol) ditosylate (**9**) to form Isomer D.<sup>8b</sup> In that case, *trans*-cyclohexano-9-crown-6 was also obtained as a by-product and was very difficult to separate from Isomer D. Hayward and co-workers reported the synthesis of an optically active form of Isomer D from chiral *trans*-1,2-cyclohexanediol.<sup>9</sup> They also attempted the same procedure with racemic *trans*-1,2-cyclohexanediol. However, only Isomer C was obtained. Very recently, Huber and Dietz published a four-step synthesis of Isomers C and D, involving mono-protected *trans*-1,2-cyclohexanediol.<sup>10</sup>



**Keywords:** stereospecific synthesis; crown ether.

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**Scheme 1.** Two-step syntheses of *trans-syn-trans*-(**4**) and *trans-anti-trans*-DC18C6 (**4**) from cyclohexene oxide (**7**).

Herein we report an improved synthesis of Isomers C and D from cyclohexene oxide requiring only two steps, along with the solid-state structure of Isomer C.

#### Improved synthesis and purification of Isomers C and D

The synthesis of Isomers C and D is summarized in Scheme 1. In the first step, di(ethylene glycol) (**8**) was reacted with two equivalents of cyclohexene oxide (**7**) and a catalytic amount of NaH by modification of a reported procedure.<sup>11,12</sup> A mixture of diols **10** and **11** was obtained in 70% yield. Without further purification, cyclization was accomplished by reaction of the diol mixture and di(ethylene glycol) ditosylate (**9**) following a literature procedure.<sup>13</sup> The crude product mixture was recrystallized from diethyl ether and the collected solid was recrystallized from methanol to give a 25% yield of pure Isomer C. The filtrate from the crystallization was evaporated in vacuo and the residue was chromatographed on alumina. The isolated impure Isomer D was found to contain ca. 5% of Isomer C by <sup>1</sup>H NMR spectroscopy. Recrystallization from hexane/diethyl ether<sup>10</sup> was ineffective in removing the contaminant. However, the use of flash column chromatography on aminopropyl silica gel or centrifugal thin layer chromatography on alumina gave pure Isomer D in 15% yield.<sup>14,15</sup> The overall yields of Isomers C and D were 18 and 10%, respectively. These compare favorably with the 20 and 15% yields, respectively, reported recently for a four-step synthesis.<sup>10</sup>

#### Crystal structure of *trans-syn-trans*-dicyclohexano-18-crown-6 (Isomer C, **4**)

Although the solid-state structure of Isomer C has been reported, neither the article nor the CCDC (Cambridge Crystallographic Data Center) listing provides the atomic coordinates.<sup>17</sup> Therefore, the crystal structure of Isomer C was determined.<sup>18</sup> The crystallographic parameters are identical with those reported earlier.<sup>17</sup> The atomic coordinates for Isomer C are presented in Table 1 and an ORTEP drawing<sup>19</sup> is shown in Fig. 1.

The solid-state structure of Isomer C is centrosymmetric. Two oxygen atoms (O3 and O3\*) that are connected to the cyclohexane rings are directed away from the crown ether cavity and two methylene groups are

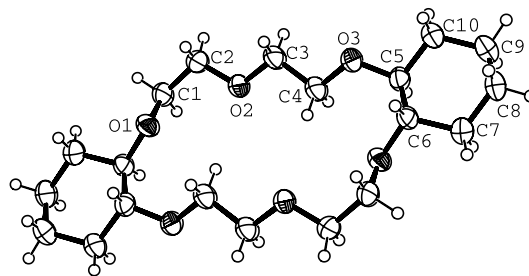
oriented into the cavity. The configuration along the OCCO bonds is  $ag^+g^-ag^-g^+$ , where  $a$  means the conformation of the two oxygens is *anti* and  $g^+$  or  $g^-$  means *gauche*.<sup>20</sup>

Fig. 2 presents a comparison of the structure of Isomer C with that reported for 18-crown-6.<sup>21</sup> As can be seen, the structures for the cyclic polyether portions of the two molecules are very similar.

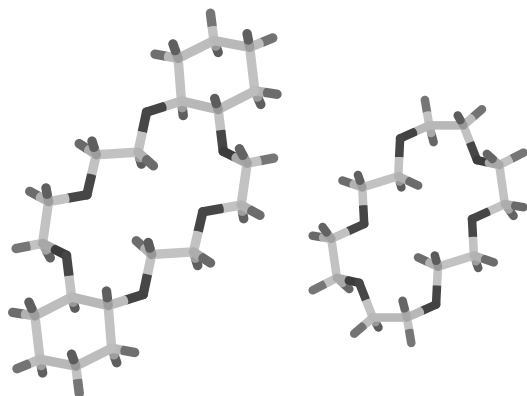
**Table 1.** Atomic coordinates and equivalent isotropic displacement parameters for *trans-syn-trans*-DC18C6 (**4**)

| Atom | $x/a$     | $y/b$     | $z/c$     | $U(\text{eq})^a$ |
|------|-----------|-----------|-----------|------------------|
| O1   | 0.1421(2) | 0.4112(2) | 0.7698(2) | 0.0469(4)        |
| O2   | 0.4100(2) | 0.6856(2) | 0.6073(2) | 0.0530(5)        |
| O3   | 0.8614(2) | 0.7819(2) | 0.4370(2) | 0.0497(4)        |
| C1   | 0.1304(3) | 0.5999(3) | 0.7548(3) | 0.0512(6)        |
| C2   | 0.3145(3) | 0.6714(4) | 0.7454(3) | 0.0556(7)        |
| C3   | 0.5890(3) | 0.7447(3) | 0.5901(3) | 0.0484(6)        |
| C4   | 0.6783(3) | 0.7394(4) | 0.4451(3) | 0.0514(6)        |
| C5   | 0.9656(3) | 0.8289(3) | 0.2946(2) | 0.0430(5)        |
| C6   | 1.0170(3) | 0.6611(3) | 0.2563(2) | 0.0416(5)        |
| C7   | 1.1564(3) | 0.7090(4) | 0.1197(3) | 0.0555(7)        |
| C8   | 1.3195(3) | 0.8063(4) | 0.1346(3) | 0.0682(8)        |
| C9   | 1.2645(3) | 0.9793(4) | 0.1650(3) | 0.0638(8)        |
| C10  | 1.1301(3) | 0.9279(4) | 0.3052(3) | 0.0532(6)        |

<sup>a</sup>  $U(\text{eq})$  is defined as one third of the trace of the orthogonalized  $U_{ij}$  tensor.



**Figure 1.** Solid-state structure of *trans-syn-trans*-DC18C6 (**4**).<sup>19</sup>



**Figure 2.** Stick drawings for *trans-syn-trans*-DC18C6 (**4**) (left) and 18-crown-6 (right).<sup>21</sup>

In summary, we have described an efficient two-step synthesis of the two *trans*-isomers of DC18C6. This method can provide multi-gram amounts of both isomers, which will enable more systematic studies about the effect of crown ether stereochemistry to be conducted. The complexation and extraction properties of these isomers are, in fact, currently under investigation in this laboratory.

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- Under nitrogen, 95% NaH (0.50 g, 20 mmol, 10 mol%) was added to di(ethylene glycol) (**7**) (10.70 g, 100 mmol) and the reaction mixture was heated at 80°C until a solution was obtained. The temperature was raised to 130°C and cyclohexene oxide (19.60 g, 200 mmol) was added dropwise. The mixture was stirred for 3 h at 130°C and cooled to room temperature. After CH<sub>2</sub>Cl<sub>2</sub> (100 ml) was added, the solution was washed with brine, dried over MgSO<sub>4</sub> and evaporated in vacuo. Yield 21.2 g (70%). The <sup>1</sup>H NMR and IR spectral data are consistent with reported values.<sup>8</sup>
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- Synthesis of **4** and **5** was accomplished following a literature procedure.<sup>10</sup> Under nitrogen, a DMSO solution of **10** and **11** (15.20 g, 50 mmol) was added to a DMSO suspension of 60% NaH (6.00 g, 150 mmol). After 0.5 h, **8** (20.50 g, 50 mmol) was added. The reaction mixture was stirred for 40 h at room temperature. Brine was added and the mixture was extracted three times with diethyl ether. The combined extracts were washed with brine, dried over MgSO<sub>4</sub> and evaporated in vacuo. Recrystallization from diethyl ether gave **4**, which was purified by recrystallization from methanol. Compound **4**: Yield 25%, mp 118–120°C (lit.<sup>8b</sup> mp 120–121°C). <sup>1</sup>H NMR (500 MHz) δ (CDCl<sub>3</sub>) 1.13–1.24 (m, 8H), 1.65–1.67 (m, 4H), 1.98–2.03 (m, 4H), 3.17–3.22 (m, 4H), 3.62–3.75 (m, 12H), 3.79–3.84 (m, 4H). <sup>13</sup>C NMR (126 MHz) δ (CDCl<sub>3</sub>) 24.06, 30.66, 69.02, 70.64, 82.24. The filtrate was evaporated in vacuo. The residue was purified by column chromatography (Al<sub>2</sub>O<sub>3</sub>, hexane:AcOEt (10:1→4:1) and further purified by the procedures described below.<sup>14,15</sup> Compound **5**: Yield 15%, mp 70–73°C (lit.<sup>8b</sup> mp 76–77°C). <sup>1</sup>H NMR (500 MHz), δ (CDCl<sub>3</sub>) 1.14–1.25 (m,

- 8H), 1.65–1.67 (m, 4H), 2.00–2.02 (m, 4H), 3.13–3.18 (m, 4H), 3.64–3.74 (m, 12H), 3.88–3.93 (m, 4H).  $^{13}\text{C}$  NMR (126 MHz)  $\delta$  ( $\text{CDCl}_3$ ) 24.18, 30.91, 69.92, 70.89, 82.73.
- Compound **5** was purified by flash column chromatography on aminopropyl silica gel (Bakerbond Amino ( $\text{NH}_2$ ) 40  $\mu\text{m}$  average particle diameter) with acetonitrile as eluent.
  - Centrifugal TLC:<sup>16</sup> The TLC plate (Alumina: EM Science 60 PF<sub>254</sub>) for the purification was prepared according to a literature procedure.<sup>16</sup> Compound **5** was purified by centrifugal chromatography on a Chromatoron (Harrison Research Corporation) with chloroform as eluent.
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  - A colorless parallelepiped single crystal (0.50×0.25×0.14 mm) was obtained by recrystallization from diethyl ether. Diffraction data were collected on an Enraf Nonius CAD-4 diffractometer with graphite monochromated  $\text{MoK}\alpha$  radiation. Crystal data for **4**: formula  $\text{C}_{20}\text{H}_{36}\text{O}_6$ ,  $F_w = 372.49$ , triclinic, space group  $P-1$  (#2),  $a = 7.499(2)$ ,  $b = 7.756(2)$ ,  $c = 9.674(3)$  Å,  $\alpha = 67.54(3)$ ,  $\beta = 83.26(2)$ ,  $\gamma = 87.52(2)^\circ$ ,  $V = 516.4(2)$  Å<sup>3</sup>,  $Z = 1$ ,  $D_{\text{calcd}} = 1.198$  g cm<sup>-3</sup>,  $R_1 = 0.0423$ ,  $wR_2 = 0.1043$  ( $I > 2\sigma(I)$ ). A CIF file with data for **4** has been deposited. CCDC reference code: 176278.
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