Pergamon

Tetrahedron Letters 43 (2002) 5805–5808

TETRAHEDRON LETTERS

Synthesis of chiral *trans-anti-trans*-isomers of dicyclohexano-18-crown-6 via an enzymatic reaction and the solid-state structure of one enantiomer

Kazuhiro Yamato,[a] Richard A. Bartsch,[a,*] Grant A. Broker,[b] Robin D. Rogers[b] and Mark L. Dietz[c]

[a]*Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, TX 79409-1061, USA*
[b]*Department of Chemistry, The University of Alabama, Tuscaloosa, AL 35487-0336, USA*
[c]*Chemistry Division, Argonne National Laboratory, Argonne, IL 60439-4831, USA*

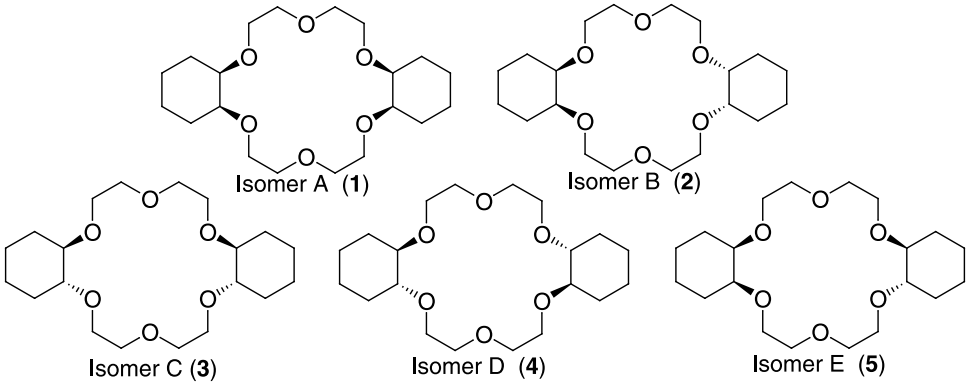
Received 6 May 2002; revised 15 June 2002; accepted 18 June 2002

Abstract—Chiral *trans-anti-trans*-dicyclohexano-18-crown-6 isomers are synthesized via a lipase-catalyzed reaction. The solid-state structure of the (*S*)-enantiomer is determined and compared with those reported for 18-crown-6 and *trans-syn-trans*-dicyclohexano-18-crown-6. © 2002 Elsevier Science Ltd. All rights reserved.

Since Pedersen's first synthesis paper,[1] crown ether compounds have been widely used for the complexation and separation of metal ions, host–guest chemistry and phase-transfer catalysis.[2,3] From such research, it is well-understood that the complexation properties of crown ethers are controlled by several structural factors, such as the ring size, number of donor atoms and stereochemistry. Dicyclohexano-18-crown-6 (DC18C6) is a well-known crown ether that can exist as five stereoisomers based on the fusion of the cyclohexane rings (*cis* or *trans*) and the relationships of the two cyclohexane ring (*syn* or *anti*). In addition, the *trans-anti-trans*- and *cis-trans*-DC18C6 (isomers D and E, respectively) can each exist as a pair of enantiomers. Since *cis-syn-cis*- and *cis-anti-cis*-DC18C6 (isomers A and B, respectively) are easily obtained by hydrogenation of dibenzo-18-crown-6 and separation of the isomers,[1,4] their complexation and separation behaviors are well established. However, systematic studies of all five isomers have been rarely reported.[5] In large part, this is due to the difficulty of synthesis and purification, especially for isomer D.

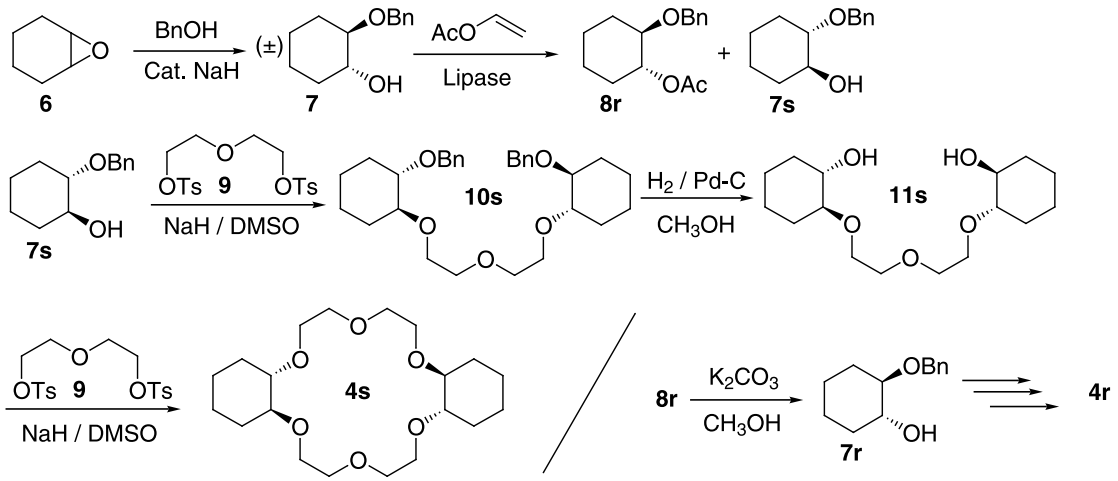
Synthesis of chiral isomer D was first reported by Hayward and co-workers.[6] Huber and Dietz also prepared chiral isomer D in their syntheses of isomers C and D.[7] In both cases, chiral *trans*-1,2-cyclohexanediol was employed as the starting material.

Recently, we reported improved stereospecific syntheses of isomers C and D.[8] Herein we describe the synthesis of isomer D as the pure enantiomers via an enzymatic



Keywords: stereospecific synthesis; chiral crown ether; enzymatic reaction; solid-state structure.
* Corresponding author. Tel.: +1-806-742-3069; fax: +1-806-742-1289; e-mail: richard.bartsch@ttu.edu

PII: S0040-4039(02)01187-5



Scheme 1. Synthesis of chiral *trans-anti-trans*-DC18C6 isomers via an enzymatic reaction.

reaction and the solid-state structure of the (*S*)-enantiomer.

The synthetic route to chiral isomer D is shown in Scheme 1. Racemic *trans*-2-benzyloxycyclohexanol[9] (**7**), which was obtained by reaction of cyclohexene oxide (**6**) and benzyl alcohol with a catalytic amount of NaH, was separated into enantiomers by lipase-catalyzed acetylation.[10,11] In the enzymatic reaction, only the (*R*)-enantiomer was acetylated. (*R*)-Acetate **8r** and (*S*)-alcohol **7s** were readily separated by column chromatography on silica gel. (*R*)-Acetate **8r** was hydrolyzed to (*R*)-alcohol **7r** by reaction with K_2CO_3 in methanol. The optical purity of each enantiomer was determined as >95% ee with a chiral NMR shift reagent. Synthesis of chiral isomer D from **7r** and **7s** followed a published procedure.[7] Coupling of 2 equiv. of chiral *trans*-2-benzyloxy-1-cyclohexanol (**7r** or **7s**) and 1 equiv. of di(ethylene glycol) ditosylate (**9**) with NaH gave the corresponding dibenzyl ether **10r** or **10s**.[12] Catalytic hydrogenolysis of the dibenzyl ether gave the chiral diol **11r** or **11s**.[13] Chiral isomer D (**4r** and **4s**) was obtained by cyclization of the diol and di(ethylene glycol) ditosylate.[14]

The crystal structure of (*S*)-isomer D (**4s**) was determined.[15] The atomic coordinates are presented in Table 1. Fig. 1 shows an ORTEP drawing[16] of **4s**. One ethylene linkage (C1–C2) was disordered. Four oxygen atoms are oriented toward one face of the crown ether cavity.

Fig. 2 provides a comparison of the ring skeletons of (*S*)-isomer D (**4s**) with those of reported isomer C (**3**) and 18-crown-6. Previously, we noted that the ring skeletons of isomer C and 18-crown-6 are very similar.[8] However, that of isomer D is different from those of isomer C and 18-crown-6.[8,17] While 18-crown-6 and isomer C are relatively flat molecules with oxygen atoms alternating above and below a mean plane by ca. 0.3 Å, isomer D is much more distorted and unsymmetrical. A mean plane through the six oxygen atoms reveals positive deviations ranging from 0.06 to 0.37 Å for four of these atoms and negative deviations of –0.15 to –0.37 Å for the remaining two oxygens. Whereas 18-crown-6 and isomer C direct only two ethylene hydrogen atoms inward towards the cavity, six of these hydrogen atoms in isomer D are pointed inward, or directed up or down over the cavity. These differences can be explained by comparison of torsion angles (Table 2).[18] The C–O–C–C torsion angles all exhibit one *anti* and one distorted *gauche* torsion angle around each oxygen atom. The disorder around O1 and O2

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

Atom	*x*/*a*	*y*/*b*	*z*/*c*	*U*(eq)[a]
O(1)	−0.4331(5)	−0.8843(3)	0.0131(1)	0.065(1)
O(2)	−0.4258(4)	−0.6424(4)	−0.0555(2)	0.078(1)
O(3)	−0.3612(3)	−0.4797(3)	−0.1970(1)	0.052(1)
O(4)	−0.2007(3)	−0.6251(3)	−0.2887(1)	0.040(1)
O(5)	−0.2419(3)	−0.8741(3)	−0.2196(1)	0.036(1)
O(6)	−0.4242(3)	−1.0376(3)	−0.0969(1)	0.041(1)
C(1)	−0.5702(8)	−0.8105(8)	−0.0142(4)	0.040(2)
C(2)	−0.5340(1)	−0.6648(8)	−0.0092(3)	0.042(2)
C(1A)	−0.5108(1)	−0.7786(9)	0.0226(4)	0.048(2)
C(2A)	−0.5581(8)	−0.7261(8)	−0.0370(3)	0.038(2)
C(3)	−0.4617(5)	−0.5866(4)	−0.01112(2)	0.045(1)
C(4)	−0.3259(4)	−0.5463(4)	−0.01428(2)	0.038(1)
C(5)	−0.2400(4)	−0.4253(4)	−0.2299(2)	0.041(1)
C(6)	−0.2558(5)	−0.2753(5)	−0.02324(2)	0.052(1)
C(7)	−0.1325(5)	−0.2123(5)	−0.02680(2)	0.057(1)
C(8)	−0.1201(5)	−0.2719(4)	−0.03308(2)	0.054(1)
C(9)	−0.1074(4)	−0.4227(4)	−0.03284(2)	0.043(1)
C(10)	−0.2297(4)	−0.4856(3)	−0.02928(2)	0.033(1)
C(11)	−0.3227(4)	−0.7089(4)	−0.02943(2)	0.041(1)
C(12)	−0.2739(4)	−0.8483(4)	−0.02828(2)	0.038(1)
C(13)	−0.3601(4)	−0.9265(4)	−0.01871(2)	0.032(1)
C(14)	−0.3098(4)	−0.9656(4)	−0.01241(2)	0.036(1)
C(15)	−0.3935(4)	−1.0919(4)	−0.0379(2)	0.035(1)
C(16)	−0.4331(5)	−1.2378(4)	−0.0383(2)	0.047(1)
C(17)	−0.4101(6)	−1.3030(5)	0.0241(2)	0.056(1)
C(18)	−0.4883(5)	−1.2287(4)	0.0745(2)	0.047(1)
C(19)	−0.4475(4)	−1.0825(4)	0.0738(2)	0.040(1)
C(20)	−0.4754(4)	−1.0201(4)	0.0119(2)	0.038(1)

[a] *U*(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

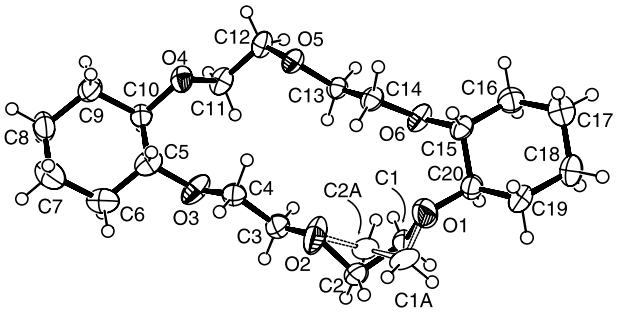


Figure 1. Solid-state structure of (*S*)-*trans*-*anti*-*trans*-DC18C6 (**4s**).

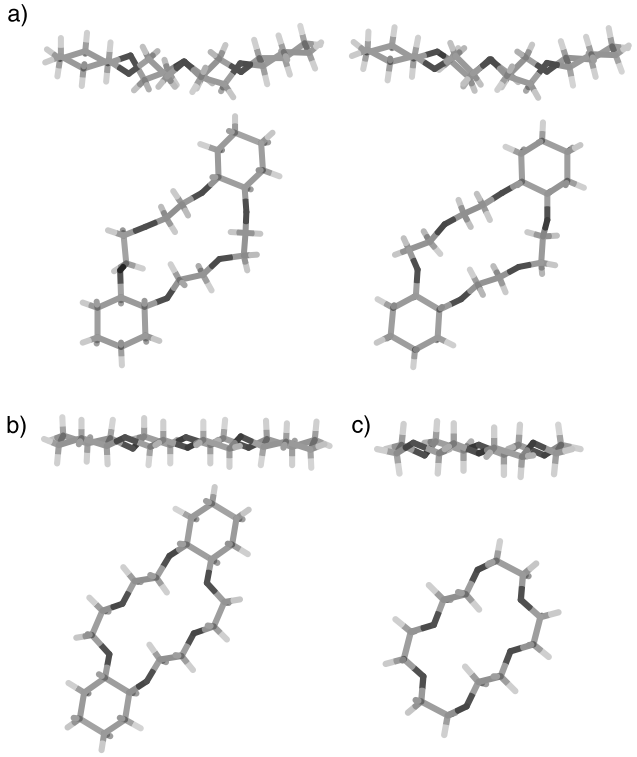


Figure 2. Stick drawings of: (a) each conformer of (*S*)-*trans*-*anti*-*trans*-DC18C6 (**4s**); (b) *trans*-*syn*-*trans*-DC18C6 (**3**); and 18-crown-6.

produces one conformation that has two *anti* C–O–C–C torsion angles around these two oxygens. isomer C has only two *gauche* C–O–C–C torsion angles, the remaining ones all being *anti*.

In summary, we have described a new synthesis of chiral *trans*-*anti*-*trans*-DC18C6 enantiomers. The solid-state structure of one enantiomer provides insight into the structural differences among the DC18C6 isomers and the effect of crown ether stereochemistry on metal ion complexation.

Acknowledgements

This work was supported by the Chemical Sciences, Geosciences, and Biosciences Division of the Office of Basic Energy Sciences, US Department of Energy through Grant No. DE-FG03-94ER14416 to R.A.B., Grant No. DE-FG02-96ER14673 to R.D.R., and Contract No. W-31-109-ENG-38 for the research conducted at ANL. Professor Purnendu K. Dasgupta is thanked for useful suggestions about the solvent circulation system. We also thank Professor Guigen Li and Dr. Sun-Hee Kim for measurement of the optical rotations. We thank NSF for Grant CHE-9808436 that was used to purchase the Varian INOVA NMR spectrometer.

Table 2. Comparison of torsion angles (°) for three crown ethers

Torsion angle	18-Crown-6	Isomer C	Isomer D
O(1)–C(1)–C(2)–O(2)	65.1	69.4	72.2
O(1)–C(1A)–C(2A)–O(2)			−84.2
C(1)–C(2)–O(2)–C(3)	−175.2	−177.4	100.3
C(1A)–C(2A)–O(2)–C(3)			−179.0
C(2)–O(2)–C(3)–C(4)	−172.4	175.6	166.6
C(2A)–O(2)–C(3)–C(4)			−159.6
O(2)–C(3)–C(4)–O(3)	−173.7	−174.5	−175.2
C(3)–C(4)–O(3)–C(5)	−169.2	−165.4	175.2
C(4)–O(3)–C(5)–C(10)	−80.3	−77.0	119.2
O(3)–C(5)–C(10)–O(4)	74.7	68.8	−64.3
C(5)–C(10)–O(4)–C(11)	−154.9	−158.8	98.0
C(10)–O(4)–C(11)–C(12)	165.6	165.6	−174.5
O(4)–C(11)–C(12)–O(5)	−65.1[a]	−69.4[a]	72.8
C(11)–C(12)–O(5)–C(13)	175.2	177.4	93.2
C(12)–O(5)–C(13)–C(14)	172.4	−175.6	173.0
O(5)–C(13)–C(14)–O(6)	173.7	174.5	−170.3
C(13)–C(14)–O(6)–C(15)	169.2	165.4	175.8
C(14)–O(6)–C(15)–C(20)	80.3	77.0	109.2
O(6)–C(15)–C(20)–O(1)	−74.7	−68.8	−61.4
C(15)–C(20)–O(1)–C(1)	154.9	158.8	108.0
C(15)–C(20)–O(1)–C(1A)			142.0
C(20)–O(1)–C(1)–C(2)	−165.6	−165.6	175.8
C(20)–O(1)–C(1A)–C(2A)			−93.6

[a] The remaining torsion angles in the list are generated by a crystallographic center of symmetry.

References

1. Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495–2496, 7017–7036.
2. For recent reviews on crown ether and related systems, see: (a) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1991**, *91*, 1721–2085; (b) Izatt, R. M.; Bradshaw, J. S.; Pawlak, K.; Bruening, R. L.; Tarbet, B. J. *Chem. Rev.* **1992**, *92*, 1261–1354; (c) Izatt, R. M.; Pawlak, K.; Bradshaw, J. S.; Bruening, R. L. *Chem. Rev.* **1995**, *95*, 2529–2586; (d) Gokel, G. W. *Crown Ether and Cryptands*; Royal Society of Chemistry: Cambridge, 1991; (e) Zhang, X. X.; Bradshaw, J. S.; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313–3361; (f) Balzani, V.; Credi, A.; Raymo, F. M.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 3349–3391.
3. Starks, C. M.; Liotta, C. *Phase-Transfer Catalysis Principles and Techniques*; Academic Press: New York, 1978; Chapter 3, pp. 57–90.
4. Izatt, R. M.; Haymore, B. L.; Bradshaw, J. S. *Inorg. Chem.* **1975**, *14*, 3132–3133.

5. (a) Dietz, M. L.; Bond, A. H.; Hay, B. P.; Chiarizia, R.; Huber, V. J.; Herlinger, A. W. *Chem. Commun.* **1999**, 1177–1178; (b) Bond, A. H.; Chiarizia, R.; Huber, V. J.; Dietz, M. L.; Herlinger, A. W.; Hay, B. P. *Anal. Chem.* **1999**, *71*, 2757–2765.
6. Hayward, R. C.; Overton, C. H.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2413–2415.
7. Huber, V. J.; Dietz, M. L. *Tetrahedron Lett.* **2001**, *42*, 2945–2948.
8. Yamato, K.; Bartsch, R. A.; Dietz, M. L.; Rogers, R. D. *Tetrahedron Lett.* **2002**, *43*, 2153–2156.
9. Posner, G. H.; Rogers, D. Z. *J. Am. Chem. Soc.* **1977**, *99*, 8208–8214.
10. Optical resolution of **7** was accomplished by adapting a literature procedure.[11] Racemic **7** (1.24 g, 6.0 mmol) and vinyl acetate (1.53 g, 18 mmol) were dissolved in 8 mL of *tert*-butyl methyl ether. The solution was circulated through a glass column filled with lipase (Amano Lipase PS-D1 (immobilized on diatomite) purchased from Aldrich, 1 g) with a peristaltic pump for 24 h. The solution was evaporated in vacuo and the residue was purified by column chromatography (SiO_2:hexane–ethyl acetate (20:1→4:1)) to yield **7s** (35%) and **8r** (35%). **8r** was dissolved in 10 mL of methanol and K_2CO_3 was added. The mixture was stirred overnight and filtered The filtrate was evaporated in vacuo to give **7r** quantitatively.
11. Laumen, K.; Seemayer, R.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1990**, 49–51.
12. Compound **10s** was synthesized by a literature method.[7] A solution of **7s** (2.40 g, 11.6 mmol) in DMSO (15 mL) was added to a suspension of 60% NaH (1.00 g, 25 mmol) in DMSO (100 mL). After 0.5 h, **9** (2.41 g, 5.8 mmol) was added and the reaction mixture was stirred at room temperature. After stirring overnight, a second portion of **9** (1.20 g, 2.9 mmol) was added. The mixture was stirred for 10 h at room temperature. Water was added and the mixture was extracted three times with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (Al_2O_3, hexane:ethyl acetate (45:1→20:1)). Yield 40%.
13. To a methanol solution of **10s**, 10% Pd–C and a few drops of acetic acid were added. The mixture was shaken for 12 h under H_2 (70 psi). The catalyst was removed by filtration through Celite and the filtrate was evaporated in vacuo to give **11s** quantitatively that was used without further purification.
14. A solution of **11s** (700 mg, 2.5 mmol) in DMSO (10 mL) was added to a suspension of 60% NaH (0.30 g, 7.5 mmol) in DMSO (100 mL). After 0.5 h, **9** (1.03 g, 2.5 mmol) was added and the reaction mixture was stirred for 40 h at room temperature. Brine was added and the mixture was extracted three times with Et_2O. The combined extracts were washed with brine, dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (Al_2O_3, hexane:ethyl acetate (10:1→4:1)). Yield 38%, mp 68–70°C (lit.[6] mp 71–74°C). $[\alpha]_D^{25}=+43.0$ ($c=0.230$, EtOH) (lit.[6] $[\alpha]_D^{20}=+39.2$ ($c=1$, EtOH)).
15. A colorless single crystal (0.25×0.11×0.03 mm) was obtained by recrystallization from heptane. Diffraction data were collected with a Siemens CCD area detector-equipped diffractometer with MoKα ($\lambda=0.071073$ Å) radiation at −100°C using a stream of nitrogen gas. The crystal structure was solved by direct methods using the SHELXTL software package. All non-hydrogen atoms were anisotropically refined and hydrogen atoms were calculated ($d_{C-H}=0.97$ Å) and fixed with the thermal parameters based upon the carbon atom to which they are bonded. Crystal data for **4s**: formula $C_{20}H_{36}O_6$, $Fw=372.49$, orthorhombic, space group $P2_12_12_1$ (#19), $a=9.333(6)$, $b=10.160(7)$, $c=21.955$ (14) Å, $V=2082(2)$ Å^3, $Z=4$, $D_{calcd}=1.188$ g cm^{-3}, $R_1=0.0736$, $wR_2=0.1989$ ($I>2\sigma(I)$). One ethylene group was observed to be disordered and refined in two alternate orientations with 50% occupancy each. Though it appears that O(2) may also be fractionally disordered, this disorder could not be resolved. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 184304. A copy of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
16. Ortep 3 for Windows: Farrugia, J. L. *J. Appl. Cryst.* **1997**, *30*, 565.
17. Dunitz, J. D.; Seiler, P. *Acta Crystallogr., Sect. B* **1974**, *30*, 2739–2741. CCDC reference code: HOXOCD.
18. (a) Coxon, A. C.; Laidler, D. A.; Pettman, R. B.; Stoddart, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 8260–8262; (b) Dale, J. *Isr. J. Chem.* **1980**, *20*, 3–11.