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Synthesis and Structure of a New Type of C_2-Symmetric Chiral Crown Ether

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Abstract: A new type of chiral crown ether, (*R*,*R*)-2,12-bis(hydroxymethyl)-2,12-dimethyl-18-crown-6 possessing plural reactive functional groups, was isolated from a racemic mixture by lipase-catalyzed acetylation. The absolute configuration of the crown diol was determined based on the X-ray analysis of the complex of the derivative having plural oxyquinoline moieties with KI.

Keywords: crown ethers; enantioselection; molecular recognition; X-ray crystal structures

Although a variety of chiral macrocycles including crown ethers have been developed for discriminating the molecular chirality of organic compounds such as ammonium salts [1], there is still strong requirement for a novel type of host molecules in order to improve the enantioselectivity. In our study on a molecular design of C-pivot lariat ethers [2], we previously found that the methyl group introduced to the C-pivot carbon remarkably improves the complexation ability toward alkali metal cations. Since the methyl group is considered to work in restricting the movement of another substituent, this strategy should be also useful for chiral recognition of ammonium salts. From this point of view, *trans*-2,12-bis(bromomethyl)-2,12-dimethyl-18-crown-6 **4**, which was recently prepared as a racemic mixture by us [3], is a promising candidate for potent C_2-symmetric chiral macrocycles if the racemic mixture is optically resolved. Lipase-catalyzed acylation of alcohol or the reverse reaction is an effective method for optical resolution [4]. Accordingly, we converted **4** to the corresponding diol derivative **1** and then tried the lipase-catalyzed acetylation of **1**. We describe herein the synthesis of (*R*,*R*)-2,12-bis(hydroxymethyl)-2,12-dimethyl-18-crown-6, (*R*,*R*)-**1**, and the determination of the absolute configuration based on the X-ray analysis of the complex of the derivative having two oxyquinoline moieties with KI.

The synthetic procedure for a racemic mixture of *trans*-2,12-bis(hydroxymethyl)-2,12-dimethyl-18-crown-6 (*rac*-**1**) is shown in Scheme 1.

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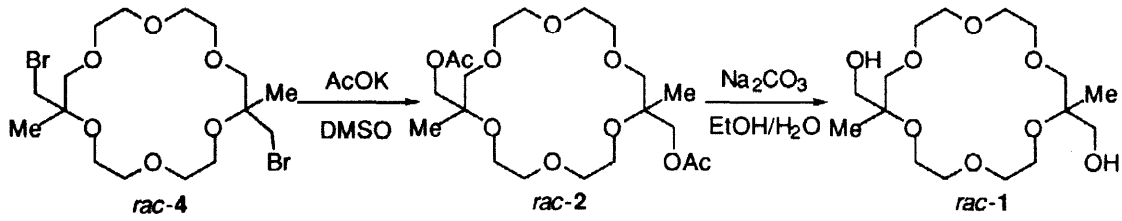
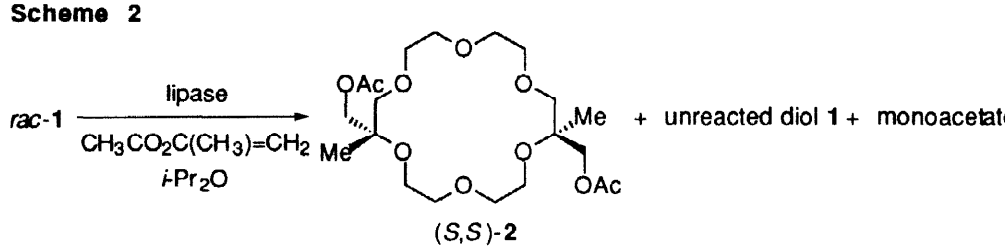
Scheme 1



rac-4 *rac*-2 *rac*-1

A racemic mixture of *trans*-2,12-bis(bromomethyl)-2,12-dimethyl-18-crown-6 (*rac*-**4**) was treated with potassium acetate in DMSO at 100 °C for 65 h to give the corresponding diacetyl derivative (*rac*-**2**). The crown diol (*rac*-**1**) was obtained by hydrolysis of *rac*-**2** in EtOH-H_2O in the presence of sodium carbonate in 65% yield from *rac*-**4**. All structures were ascertained by ^{1}H NMR and IR spectroscopy, mass spectrometry and elemental analysis [5,6].

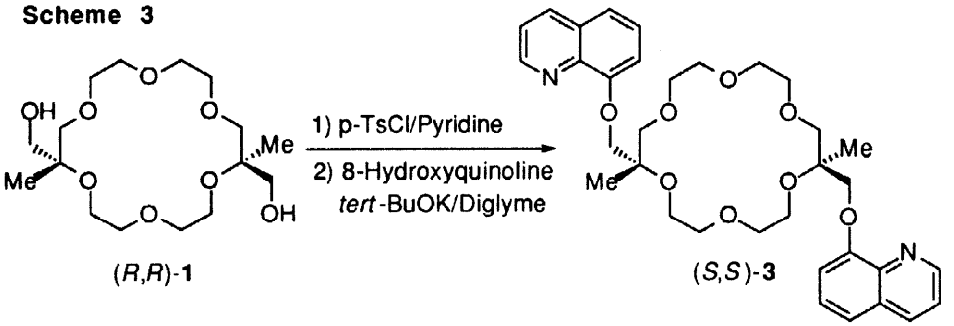
Scheme 2



(*S,S*)-**2**

In the resolution process (Scheme 2), acetylation of the diol **1** (50 mg, 0.14 mmol) with isopropenyl acetate (1 mL, 9.1 mmol) was carried out in isopropyl ether (20 mL) at 35 °C, using four kinds of commercially available lipases as the catalyst (lipase QL (0.1 g) from *Alcaligenes sp.*, lipase PS (1.0 g) from *Pseudomonas sp.*, lipase A (1.0 g) from *Aspergillus niger*, and lipase AY (1.0 g) from *Candida regosa*) [7]. The reaction was pursued by GLC and was stopped when the conversion to diacetate **2** reached 30%. The reaction times were 6 h, 60 h, and 70 h for lipase QL, lipase PS, and lipase AY, respectively. In the case of lipase A, no products were formed after 70h. Then compound **2** was isolated by centrifugal partition chromatography. The enantiomeric excess of **2** was determined by ^{1}H NMR spectroscopy, using (*R*)-(+)-α-(1-naphthyl)ethylammonium hydrochloride [8] ((*R*)-NapEt-HCl) as a shift reagent. Upon complexation with (*R*)-NapEt-HCl, the signal of the methyl protons on the C-pivot position of *rac*-**2** shifted to upfield region and split into two equal area signals due to the ring current effects of the naphthyl ring of (*R*)-NapEt-HCl [9]. Therefore, the enantiomeric excess of **2** was calculated by comparing the peak areas of the two split signals. Among four lipases examined in this study, lipase QL showed a considerably high enantiomeric excess (>98% ee for (*S,S*)-**2**) [10]. Then (*R,R*)-**1** was obtained by hydrolysis of (*S,S*)-**2**, though the absolute configuration of these compounds was unknown at this stage. For the purpose of determining the absolute configuration of the chiral **1**, **1** was converted to the corresponding derivative having two quinoline sidearms **3** according to the procedures shown in Scheme 3.

Scheme 3



The complex of **3** with KI was isolated as a pale yellow crystal from a mixture of dichloromethane and toluene. For an X-ray anomalous dispersion analysis, heavy atom (I^-) suffices to determine the absolute structure using Cu-Kα radiation. The X-ray crystal structure of the complex [11] is shown in Figure 1. The cation was captured in the three-dimensional cavity of (*S*,*S*)-**3** using the crown ring and one of the electron-donating sidearms; in other words, one sidearm was nicely coordinated to the cation and the other was free from the metal cation. To the best of our knowledge, this is the first example that the coordination of the electron-donating sidearm of the C-pivot lariat ether with the alkali metal cation was directly confirmed by X-ray crystallography [12]. The structure of **3** in the (*S*,*S*) configuration was refined to *R*w=0.047, whereas that in the (*R*,*R*) configuration was refined to *R*w=0.106. From this difference in *R*w values [13], the structure unambiguously establishes the stereochemistry of the optically pure **3** as (*S*,*S*). Therefore, the absolute configuration of chiral crown diol **1** derived from the diacetate **2** isolated in the lipase QL-catalyzed acetylation has been deduced to be (*R*,*R*). In a preliminary experiment for the chiral recognition ability of this series of crown ethers, compound **3** was ascertained to show moderate enantioselectivity for NapEt-HCl [14]. Since compound **1** possesses two reactive groups, further functionalization using the reactivity is under progress in our laboratory in pursuit of higher enantioselectivity.

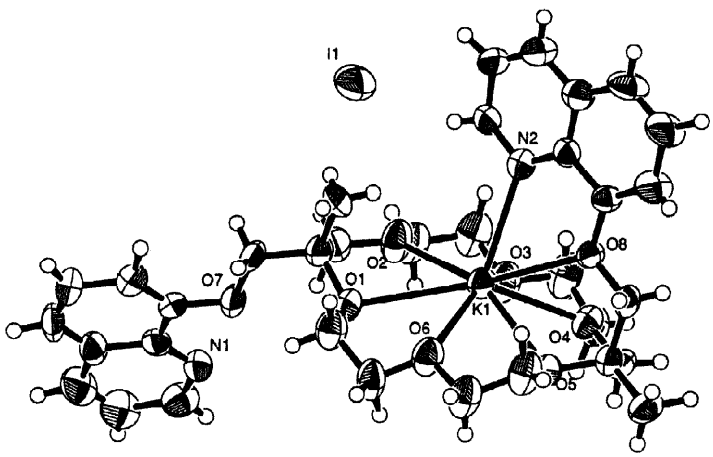


Figure 1. X-ray Crystal Structure of the Complex of (*S*,*S*)-3 with KI.

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References and Notes

[1] For example: a) Cram, D. J. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009-1020; *J. Incl. Phenom. Mol.*

Recogn. Chem. **1988**, *6*, 397-413 and references cited therein. b) Naemura, K.; Tobe, Y.; Kaneda, T. *Coord. Chem. Rev.* **1996**, *148*, 199-219 and references cited therein. c) Zhang, X. X.; Bradshaw, J. S. ; Izatt, R. M. *Chem. Rev.* **1997**, *97*, 3313-3361 and references cited therein.

[2] Nakatsuji, Y.; Nakamura, T.; Yonetani, M.; Yuya, H.; Okahara, M. *J. Am. Chem. Soc.* **1988**, *110*, 531-538.

[3] Nakatsuji, Y.; Sunagawa, T.; Masuyama, A.; Kida, T.; Ikeda, I. *J. Incl. Phenom. Mol. Recogn. Chem.* **1997**, *29*, 289-299.

[4] For example: a) Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114-120. b) Tsukube, H.; Betchaku, A.; Hiyama, Y.; Itoh, T. *J. Org. Chem.* **1994**, *59*, 7014-7018. c) Naemura, K.; Ueno, K.; Takeuchi, S.; Hirose, K.; Tobe, Y.; Kaneda, T.; Sakata, Y. *J. Chem. Soc., Perkin Trans. I*, **1996**, 383-388.

[5] *rac*-**1**: ^{1}H NMR ($CDCl_3$) δ 1.12 (s, 6H), 3.52-3.75 (m, 24H). IR (neat) 3700-3000, 2870, 1620, 1440, 1340, 1280, 1080 cm^{-1}. MS (FAB) (m/z) 353 (M^++1). Anal. Calcd for $C_{16}H_{32}O_8$: C, 54.53; H, 9.15. Found: C, 54.18; H, 9.23.

[6] *rac*-**2**: ^{1}H NMR ($CDCl_3$) δ 1.19 (s, 6H), 2.08 (s, 6H), 3.49-4.21 (m, 24H). IR (neat) 2850, 1720, 1450 1370, 1240, 1100 cm^{-1}. MS (FAB) (m/z) 437 (M^++1). Anal. Calcd for $C_{20}H_{36}O_{10}$: C, 55.03; H, 8.31. Found: C, 54.85; H, 8.42.

[7] Lipase QL (Meito Sangyo Co.), lipase PS (Amano Pharmaceutical Co.), lipase A (Amano Pharmaceutical Co.), and lipase AY (Amano Pharmaceutical Co.) were used as received without further purification.

[8] (*R*)-NapEt-HCl was prepared by treating the (*R*)-(+)-α-(1-naphthyl)ethylamine in C_2H_5OH with diluted aqueous hydrochloric acid. After evaporation under reduced pressure, the salt was crystallized from a CH_3CN/CH_3OH mixture. The salt was a white solid.

[9] The racemic mixture of **1**: ^{1}H NMR($CDCl_3$) δ 1.05 (s, 3H, *R*,*R*-form), 1.01 (s, 3H, *S*,*S*-form), 3.52-3.75 (m, 24H).

[10] Both lipase PS and lipase AY disappointedly gave 75% ee and their catalytic activities were much inferior to that of lipase QL.

[11] (*S*,*S*)-**3**: $[\alpha]_D^{30}$=-8.9 (c 0.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 1.46 (s, 6H), 3.63-3.88 (m, 20H), 4.15 (d, 2H, *J*=9.5 Hz), 4.36 (d, 2H, *J*=9.5 Hz), 7.18 (d, 2H, *J*=7.4 Hz), 7.38-7.47 (m, 6H), 8.12 (d, 2H, *J*=8.0 Hz), 8.92 (d, 2H, *J*=4.0 Hz). MS (FAB) (m/z) 607 (M^++1). Anal. Calcd for $C_{34}H_{42}O_8N_2 \cdot KI$: C, 52.85; H, 5.48; N, 3.63. Found: C, 52.76; H, 5.52; N, 3.77.
Crystal data: $C_{34}H_{42}O_8N_2KI$, *M*=772.72, *T*=296(1) K, Crystal dimensions=0.13x0.04x0.01 mm, Monoclinic, Space group $P2_1$, *a*=9.975(2) Å, *b*=13.779(2) Å, *c*=12.870(2) Å, β=97.46(1)°, *V*=1754.0(5) Å^3, *Z*=2, *F*(000)=792, μ(Cu-Kα)=86.63 cm^{-1}, D_{calc} 1.463 g/cm^3. The final *R* and *Rw* were 0.060 and 0.047 for 4576 observed reflections ($I>1.00\sigma(I)$), *GOF*=1.82. All measurements were made on a Rigaku AFC5R diffractometer with ß-filtered Cu-Kα radiation and a rotating anode generator. The structure was solved by direct methods [15] (SIR92), expanded using Fourier techniques [16], and refined by full-matrix least-squares techniques using the teXsan Structure analysis Software of Molecular Structure Corporation.

[12] Inoue, Y.; Gokel, G. W. Cation Binding by Macrocycles; Marcel Dekker, Inc.: New York, 1990.

[13] a) Hamilton, W. C. *Acta Cryst.* **1965**, *18*, 502. b) Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881. For the anomalous dispersion analysis, models corresponding to the two enantiomeric isomers were refined separately. The (*S*,*S*) isomer gave an *Rw* value of 0.047, whereas the inverted (*R*,*R*) isomer could be refined under same conditions only to *Rw*=0.106. This significant difference in *R*-values proves the absolute configuration of lariat ether **3** to be (*S*,*S*).

[14] Chiral recognition ability of (*S*,*S*)-**3** for NapEt-HCl was evaluated using the ^{1}H NMR titration method in a $CDCl_3/CD_3OD$ (9/1) solvent mixture [1c]. The degree of chiral recognition, Δ(log *K*), was 0.41 (log *K*=2.68 for the (*S*)-enantiomer and log *K*=2.27 for the (*R*)-form, respectively).

[15] SIR92: Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, M.; Giacovazzo, C.; Guagliardi, A.; Polidori, G. *J. Appl. Cryst.* **1994**, *27*, 435.

[16] DIRDIF94: Beurskens, P. T.; Admiraal, G.; Beurskens, G.; Bosman, W. P.; de Gelder, R.; Israel, R.; Smits, J. M. M. The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen, The Netherlands, 1994.