Synthesis and Enantiomer Recognition of the 18-Crown-6 Derivative Containing Two Tert-Butyl Substituents as a Chiral Barrier

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Synopsis. The optically active 18-crown-6 derivative having two tert-butyl substituents as a chiral barrier was prepared by using (−)-(*R*)-3,3-dimethylbutane-1,2-diol as a chiral source and its chiral recognition behavior in transport of racemic guest molecules through bulk liquid membranes was investigated.

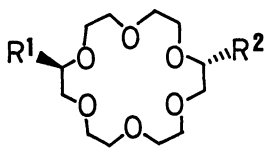
A large number of optically active crown ethers containing an alkyl group as a chiral barrier have been prepared and their chiral recognition properties have been well investigated.[1,2] But, as far as we know, there is no report on the synthesis of an optically active crown ether having a tert-butyl group as a chiral barrier. Recently, Bradshaw, Izatt, and coworkers described that a crown compound containing a tert-butyl group is predicted to yield high enantiomer recognition on the basis of calculation using empirical energy functions.[3] In this paper, we wish to report the synthesis of the 18-crown-6 derivatives (−)-(2*R*,12*R*)-**1** and (−)-(*R*)-**2** containing a tert-butyl group as a chiral barrier and their enantiomer recognition properties in transport of racemic guest molecules through bulk liquid membranes.

Optical resolution of 3,3-dimethylbutane-1,2-diol (**6**) was accomplished via **7**, prepared by acylation of **6** with (−)-camphanic chloride, whose fractional recrystallization from ether gave the sparingly soluble ester **7**, $[\alpha]_D$ −49.0°. Hydrolysis of (−)-**7** with potassium hydroxide gave (−)-**6**, $[\alpha]_D$ −24.9°, the optical purity of which was enriched by further recrystallization from pentane. The enantiomer excess (e.e.) value of **6** was determined by HPLC analysis on its bisphenylcarbamate derivative and the absolute configuration of (−)-(*R*)-**6** has been described in the literature.[4]

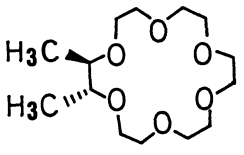
First the diol **6** was directly reacted with methoxymethyl chloride to result in the formation of a complex mixture of the methoxymethyl ethers, and then **10** needed to synthesize the diol **5** of C_2-symmetry was prepared via the monoester **8**. Acylation of (−)-**6**, $[\alpha]_D$ −27.1° (95% e.e.), with 2,2-dimethylpropanoyl chloride gave exclusively **8**, $[\alpha]_D$ −26.6°, in 89% yield, the structure of which was confirmed by oxidation with pyridinium chlorochromate giving the ketoester **11**. Treatment of (−)-**8** with methoxymethyl chloride and *N*,*N*-diisopropylethylamine gave (+)-**9**, $[\alpha]_D$ +18.8°, in 73% yield and reduction of (+)-**9** with $LiAlH_4$ gave (−)-**10**, $[\alpha]_D$ −118°, in 75% yield. When **8** was treated with dimethoxymethane under acidic conditions, intramolecular transesterification occurred to give a mixture of **9** and its structural isomer.

Condensation of (−)-**10** with diethyleneglycol bis(methanesulfonate) in the presence of NaH gave **4** and treatment with methanol and hydrochloric acid converted **4** into the C_2-diol (−)-(3*R*,13*R*)-**5**, $[\alpha]_D$ −36.3°, needed for the preparation of the 18-crown-6 derivative with C_2-symmetry.

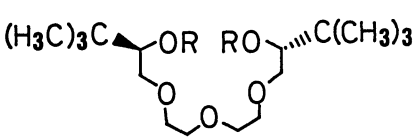
High dilution condensation of (−)-**5** with diethyleneglycol bis(methanesulfonate) in the presence of NaH and KBF_4 in tetrahydrofuran (THF) under reflux gave the C_2-crown ether (−)-(2*R*,12*R*)-**1**, $[\alpha]_D$ −7.87°,



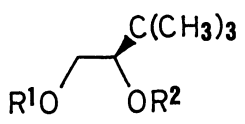
(−)-**1** $R^1=R^2=C(CH_3)_3$
(−)-**2** $R^1=C(CH_3)_3$ $R^2=H$

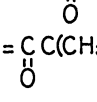


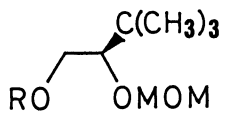
(−)-**3**



4 $R=CH_2OCH_3$ (MOM)
(−)-**5** R=H



(−)-**6** $R^1=R^2=H$
(−)-**7** $R^1=R^2=$ 
(−)-**8** $R^1=$  $C(CH_3)_3$ $R^2=H$



(+)-**9** $R=$  $C(CH_3)_3$
(−)-**10** R=H

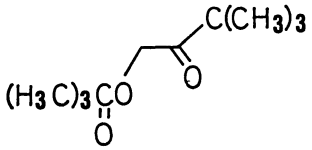


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Table 1. Differential Transport of Enantiomeric Molecules through Bulk Liquid Membranes

Host	Guest[a)]	Time	Transport	Configuration of dominant enantiomer	Optical purity
		h	%		%
(−)-**1**	a	1.8	10.1	**S**	33
(−)-**1**	b	13.5	9.9	**S**	34
(−)-**1**	c	24.0	9.9	**R**	11
(−)-**2**	a	1.6	10.0	**S**	20
(−)-**2**	b	4.5	10.0	**S**	16
(−)-**2**	c	6.5	10.2	**R**	5
(−)-**3**	a	3.5	9.8	**S**	19
(−)-**3**	b	8.5	10.1	**S**	18
(−)-**3**	c	11.5	9.9	**R**	2

a) a: (±)-1,2-diphenylethylamine hydrochloride, b: (±)-1-phenylethylamine hydrochloride, c: methyl ester of (±)-phenylglycine hydrochloride.

in 19% yield after alumina chromatography. The C_1-crown ether (−)-(*R*)-**2**, $[\alpha]_D$ −4.47°, was prepared in 17% yield by condensation of (−)-**6** with pentaethyleneglycol bis(*p*-toluenesulfonate) in the presence of NaH and KBF_4 in THF followed by chromatographic purification. In order to compare the enantiomer selectivity of **1** with that of the 18-crown-6 derivative having two methyl substituents as a chiral barrier, (−)-(2*R*,3*R*)-**2**[2] was prepared in 25% yield by condensation of (−)-(2*R*,3*R*)-butane-2,3-diol with pentaethyleneglycol bis(*p*-toluenesulfonate).

Enantiomer recognition properties of these crown ethers in transport of racemic guest molecules through bulk liquid membranes[5] were investigated and the results are summarized in Table 1. The crown ether (−)-**2** shows a higher transportability than (−)-**1**, but the enantiomer selectivity of (−)-**2** is low. The crown ether (−)-**1** exhibits a higher enantiomer selectivity towards all guest molecules examined here than (−)-**3**, and the results demonstrated evidently that a tert-butyl substituent is a more effective chiral barrier of a crown ether than a methyl substituent.

Experimental

Optical rotations were recorded with a JASCO DIP-40 automatic polarimeter. Circular dichroism data were collected with a JASCO J-500 spectropolarimeter and ultraviolet spectra were measured on a Hitachi 220A spectrometer. ^{1}H NMR spectra were obtained from a JNM-MH-100 and chemical shifts are reported in parts per million (δ) down field from tetramethylsilane. High resolution mass spectra were taken with a JEOL-DX-303 HF spectrometer.

Optical Resolution of 3,3-Dimethylbutane-1,2-diol (6). To a solution of (±)-**6** (8.35 g, 70.8 mmol) in pyridine (120 mL) was added (−)-camphanic chloride (30.7 g, 0.142 mmol) with ice cooling and then the mixture was stirred for 12 h at room temperature. The reaction mixture was poured into ice water and a solid was collected to give **7** (32.5 g). Fractional recrystallization of **7** from ether (four times) yielded (−)-**7** (22.4 g), $[\alpha]_D^{22}$ −49.0° (*c* 1.06, $CHCl_3$). To a solution of KOH (22.0 g) in aqueous methanol (450 mL) was added (−)-**7** (20.0 g) and the mixture was gently refluxed for 9 h. After methanol was removed in vacuo, the residue was diluted with water and extracted with ether. Removal of the solvent gave (−)-**6** (4.90 g), $[\alpha]_D^{22}$ −24.9° (*c* 0.720, $CHCl_3$), which was recrystallized from pentane to give (−)-**6** (3.24 g), $[\alpha]_D^{24}$ −27.1° (*c* 0.850, $CHCl_3$); mp 36—38 °C.

A mixture of (−)-**6**, $[\alpha]_D$ −27.1°, (35 mg, 0.30 mmol) and phenyl isocyanate (180 mg, 1.51 mmol) was stirred for 24 h at room temperature and a preparative TLC of the product gave the bis(phenylcarbamate) derivative (69 mg, 65% yield), whose e.e. value was determined to be 95% by HPLC analysis. HPLC analysis was carried out on Simadzu LC-6A using a chiral column; Opti-Pak KC (Waters).

(−)-(*R*)-2-Hydroxy-3,3-dimethylbutyl 2,2-Dimethylpropanoate (8). To a chilled solution of (−)-**6**, $[\alpha]_D$ −27.1°, (4.70 g, 39.8 mmol) in pyridine (50 mL) was added 2,2-dimethylpropanoyl chloride (4.80 g, 39.8 mmol) with ice cooling, After stirring for 12 h at room temperature, the reaction mixture was poured into ice water and a deposited solid was collected. The solid was distilled to give (−)-**8** (7.17 g, 89% yield), bp 114—116 °C (15 mmHg (1 mmHg=133.32 Pa)); $[\alpha]_D^{23}$ −26.6° (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.98 (9H, s), 1.23 (9H, s), 2.23 (1H, s), 3.50 (1H, dd, *J*=2.9, 8.6 Hz), 4.00 (1H, dd, *J*=8.6, 11.5 Hz), 4.27 (1H, dd, *J*=2.9, 11.5 Hz). Found: C, 65.17; H, 10.84%. Calcd for $C_{11}H_{22}O_3$: C, 65.13; H, 10.96%.

3,3-Dimethyl-2-oxobutyl 2,2-Dimethylpropanoate (11). A solution of (±)-**8** (1.00 g, 4.94 mmol) in dichloromethane (10 mL) was added to a suspension of pyridinium chlorochromate (2.15 g, 10.0 mmol) in dichloromethane (12 mL) and the mixture was stirred for 12 h at room temperature. The organic solution was separated by decantation and chromatographed on Florisil. Fractions eluted with hexane-ether gave **11** (850 mg, 86% yield) as a white solid, mp 49—50.5 °C; ^{1}H NMR ($CDCl_3$) δ=1.20 (9H, s), 1.29 (9H, s), 4.88 (2H, s); IR (KBr) 1740, 1720 cm^{-1}. Found: C, 65.83; H, 9.99%. Calcd for $C_{11}H_{20}O_3$ C, 65.97; H, 10.07%.

(+)-(*R*)-2-Methoxymethoxy-3,3-dimethylbutyl 2,2-Dimethylpropanoate (9). To a chilled solution of (−)-**8** (7.16 g, 35.4 mmol) and *N*,*N*-diisopropylethylamine (7.20 g, 55.7 mmol) in dichloromethane (200 mL) was added methoxymethyl chloride (4.48 g, 55.7 mmol) with ice cooling. After stirring for 20 h under rexflux, the reaction mixture was washed with water, dried ($MgSO_4$) and concentrated in vacuo. Ether (50 mL) was added to the residue and a deposited solid was removed by filtration. The filtrate was chromatographed on silica gel and fractions eluted with hexane-benzene gave an oily product, which was distilled to give (+)-**9** (6.31 g, 73% yield), bp 110—110.5 °C (8 mmHg); $[\alpha]_D^{22}$ +18.8° (*c* 2.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ=0.98 (9H, s), 1.20 (9H, s), 3.36 (1H, dd, *J*=3.3, 6.7 Hz), 3.40 (3H, s), 3.98 (1H, dd, *J*=6.7, 11 9 Hz), 4.35 (1H, dd, *J*=3.3, 11.9 Hz), 4.63 (1H, d, *J*=6.5 Hz), 4.82 (1H, d, *J*=6.5 Hz). Found: C, 63.27; H, 10.54%. Calcd for $C_{13}H_{26}O_4$: C, 63.38; H, 10.64%.

Reaction of (±)-8 with Dimethoxymethane and Phospho-

rus Pentaoxide. To a solution of (±)-**8** (1.04 g, 5.14 mmol) and dimethoxymethane (30 mL) in dry chloroform (30 mL) was slowly added phosphorus pentaoxide (9.00 g, 63.4 mmol), and then the mixture was stirred for 1 h at room temperature. The organic solution was separated by decantation and poured into aqueous solution of sodium carbonate and ice. The organic layer was separated, washed with water, dried (Na_2SO_4), and concentrated in vacuo to give a 77 : 23 mixture (1.15 g) of **9** and its isomer (by GLC analysis).

(−)-(*R*)-2-Methoxymethoxy-3,3-dimethyl-1-butanol (10). A solution of (+)-**9** (6.31 g, 25.6 mmol) in dry ether (150 mL) was added to a suspension of $LiAlH_4$ (740 mg, 19.5 mmol) in dry ether (150 mL) and the mixture was refluxed for 8 h. After addition of aqueous solution of ammonium chloride to the chilled reaction mixture, a solid was removed by filtration and the filtrate was dried ($MgSO_4$). After removal of the solvent, the residue was distilled to give (−)-**10** (3.10 g, 75% yield), bp 88.0—88.5 °C (14 mmHg); $[\alpha]_D^{22}$ −118° (*c* 0.720, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.92 (9H, s), 3.10 (1H, dd, *J*=2.3, 7.7 Hz), 3.44 (3H, s), 3.20—3.90 (3H, m), 4.60 (1H, d, *J*=6.5 Hz), 477 (1H, d, *J*=6.5 Hz). Found: C, 59.10; H, 11.10%. Calcd for $C_8H_{18}O_3$: C, 59.23; H, 11.18%.

(−)-(3*R*,13*R*)-2,2,4,4-Tetramethyl-5,8,11-trioxapentadecane-3,13-diol (5). A solution of (−)-**10** (3.10 g, 19.1 mmol) in dry THF (90 mL) was added to a suspension of NaH (530 mg, 22.1 mmol) in dry THF (80 mL) and the mixture was refluxed for 2 h. To the mixture was added a solution of diethyleneglycol bis(methanesulfonate) (2.28 g, 8.70 mmol) in dry THF (80 mL). After the mixture was stirred for 64 h under reflux, a solid was removed by filtration and the filtrate was concentrated in vacuo. The residue was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$) and concentrated in vacuo to give an oily product (3.78 g), which was chromatographed on alumina. Fractions eluted with hexane-benzene gave **4** (1.55 g) as an oil, which was stirred with methanol (20 mL) and four drops of hydrochloric acid at room temperature for 20 h. After the solvent was removed in vacuo, the residue was chromatographed on alumina. Fractions eluted with ether gave (−)-**5** (1.41 g, 24% yield) as an oil, $[\alpha]_D^{25}$ −36.3° (*c* 2.22, $CHCl_3$), which was used in the next reaction without further purification.

(−)-(2*R*,12*R*)-2,12-Bis(1,1-dimethylethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (1). A solution of (−)-**5** (470 mg, 1.54 mmol) and diethylenglycol bis(methanesulfonate) (410 mg, 1.56 mmol) in dry THF (80 mL) was slowly added to a suspension of NaH (96 mg, 4.0 mmol) and KBF_4 (220 mg, 1.75 mmol) in dry THF (80 mL) under reflux over a 10 h period. After stirring for an additional 56 h under reflux, a solid was removed by filtration and the filtrate was concentrated in vacuo. The residue was extracted with chloroform and the extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give an oily product (680 mg). The product was chromatographed on alumina and fractions eluted with hexane-benzene furnished (−)-**1** (110 mg, 19% yield) as an oil, $[\alpha]_D^{23}$ −7.87° (*c* 0.850, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.90 (18H, s), 3.09 (2H, dd, *J*=2.4, 8.1 Hz), 3.42 (2H, dd, *J*=8.1, 10.0 Hz), 3.5—4.1 (18H, m); HRMS Found: *m/z* 376.2825. Calcd for $C_{20}H_{40}O_6$: *m/z* 376.2823.

(−)-(2*R*)-2-(1,1-Dimethylethyl)-1,4,7,10,13,16-hexaoxacyclooctadecane (2). A solution of (−)-**6** (800 mg, 6.78 mmol) and pentaethyleneglycol bis(*p*-toluenesulfonate) (3.71 g, 6.78 mmol) in dry THF (100 mL) was slowly added to a suspension of NaH (358 mg, 14.9 mmol) and KBF_4 (940 mg, 7.50 mmol) in dry THF (100 mL) under reflux over a 10 h period and the mixture was refluxed for an additional 34 h. After the same workup described above, the crude product (2.85 g) was chromatographed on alumina. Fractions eluted with hexane-benzene furnished (−)-**2** (370 mg, 17% yield) as an oil, $[\alpha]_D^{25}$ −4.47° (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$) δ=0.90 (9H, s), 3.10 (1H, dd, *J*=2.8, 7.7 Hz), 3.3—4.1 (22H, m); HRMS Found: *m/z* 320.2191. Calcd for $C_{16}H_{34}O_6$: *m/z* 320.2199.

(−)-(2*R*,3*R*)-2,3-Dimethyl-1,4,7,10,13,16-hexaoxacyclooctane (3). By using the similar procedure described for the preparation of (−)-**2**, (−)-**3** (193 mg, 22% yield), $[\alpha]_D^{22}$ −7.36° (*c* 1.13, $CHCl_3$), was prepared from (−)-(2*R*,3*R*)-butane-2,3-diol (270 mg, 3.00 mmol), pentaethyleneglycol bis(*p*-toluenesulfonate) (1.80 g, 3.30 mmol), and NaH (180 mg, 7.50 mmol) in dry THF. Found: C, 57.30; H, 9.61%. Calcd for $C_{14}H_{28}O_{46}$: C, 57.51; H, 9.65%.

Enantiomer Differential Transport. Enantiomer differential transport was carried out in an apparatus which consisted of an outer cylindrical glass vessel (24.5 mm inner diameter) and a central glass tube (15.5 mm inner diameter). The chloroform solution of an optically active crown ether (0.005 M (1 M=1 mol dm^{-3})) separated the inner aqueous phase (0.01 M HCl) and the outer aqueous phase (0.08 M HCl) containing $LiPF_6$ (0.2 M) and the racemic guest molecule (0.04 M). The organic layer was stirred at a constant speed (60 rpm) at 20±2 °C. Transport was monitored by ultraviolet spectrum and e.e. value of the guest molecule transported was monitored by circular dichroism.

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