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PREPARATION AND CHIRAL RECOGNITION OF NEW CHIRAL 18-CROWN-6 ETHERS

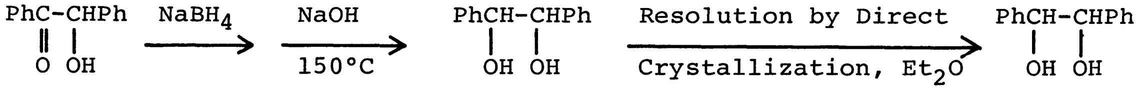
Junzo YAMASHITA*, Masaaki MINAGAWA,
Akihiro SONOBE, Shoichi OHASHI,
Misao KAWAMURA, Kunitoshi SHIMIZU, and Harukichi HASHIMOTO
Department of Applied Chemistry, Faculty of Engineering,
Tohoku University, Aramaki-Aoba, Sendai 980

Four new chiral macrocyclic polyethers of 18-crown-6 type which have phenyl, 1-naphthyl or tetramethylphenyl substituents were prepared, and their chiral recognition for 1-phenylethylamine was discussed.

Chiral macrocyclic polyethers of 22-crown-6 type derived from (R)- and (S)-binaphthols have been shown to exhibit chiral recognition in complexation equilibria towards various racemic primary alkylammonium and amino acid and ester salts.1) Although those of 18-crown-6 type have shown only the low chiral recognition,2) their ability to complex with primary alkylammonium salts has been most preferable in view of their ring sizes.3) We now report the synthesis and chiral recognition of chiral macrocyclic polyethers of 18-crown-6 type of different rigidity.4)

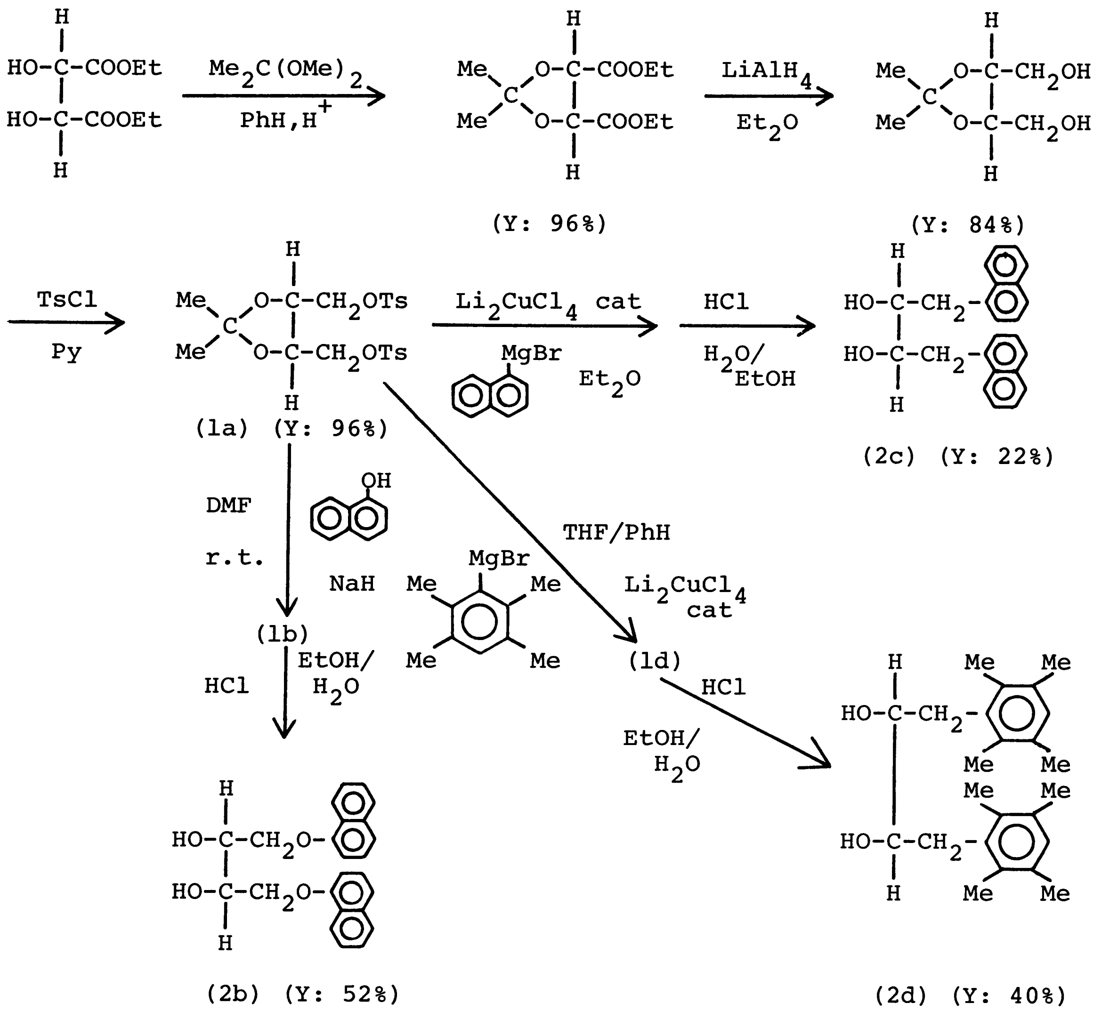
Three step reactions from ethyl-(L)-tartarate according to the known procedure5) afforded (1a) in good yield.6) The addition of (1a) to 1-naphthol and NaH in DMF at room temperature afforded (1b), which was hydrolyzed to yield (2b).7) The reaction of the Grignard reagent from 1-bromonaphthalene or 1-bromo-2,3,5,6-tetramethylbenzene in THF with (1a) catalyzed by Li_2CuCl_4 followed by hydrolysis afforded (2c)8) or (2d)9). Racemic (2a) was prepared through the reduction of benzoin with $NaBH_4$ followed by isomerization with NaOH at 150°C.10) The resolution of R- and S- (2a) were carried out by direct crystalliztion from the ether solution of the racemates according to the sign of rotation of the respective crystals dissolved in $CHCl_3$.11) Reactions of equimolar proportions of the diols (2a-d) and the bistosylate (4) with NaH in DMF at room temperature for 150-400 h gave the chiral crown ethers (3a-d)12-15) after chromatography on silica gel using $CHCl_3$, n-hexane, and n-hexane-ether(5:1-3:1) successively as eluants.

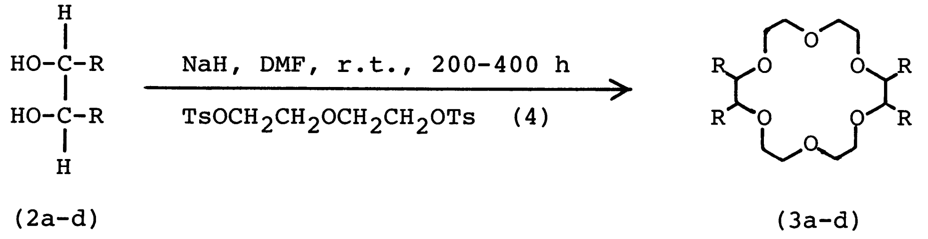
Scheme



$$\underset{\mathrm{O}\ \ \mathrm{OH}}{\mathrm{PhC\text{-}CHPh}} \xrightarrow{NaBH_4} \xrightarrow[150°C]{NaOH} \underset{\mathrm{OH}\ \ \mathrm{OH}}{\mathrm{PhCH\text{-}CHPh}} \xrightarrow[\text{Crystallization, } Et_2O]{\text{Resolution by Direct}} \underset{\mathrm{OH}\ \ \mathrm{OH}}{\mathrm{PhCH\text{-}CHPh}}$$

(2a)





(2a)	R= Phenyl:	(2R,3R,11R,12R)-2,3,11,12-Tetraphenyl-1,4,7,10,13,16-hexaoxaoctadecane
(2b)	1-Naphthoxymethyl:	(2S,3S,11S,12S)-Tetrakis(1-naphthoxymethyl)-
(2c)	1-Naphthylmethyl:	(2S,3S,11S,12S)-Tetrakis(1-naphthylmethyl)-
(2d)	2,3,5,6-Tetramethylphenyl:	(2S,3S,11S,12S)-Tetrakis(2,3,5,6-tetramethylphenyl)-

The chiral recognition was measured by distributing racemic 1-phenylethylamine salt between H_2O - $CHCl_3$ layers, the organic layer of which contained chiral crown ethers(3a-d). Thus, a solution of 5.0 ml of 0.1 M (3) in $CHCl_3$ was shaken with H_2O 5.0 ml containing racemic 1-phenylethylammonium chloride (1M) and $LiPF_6$ (1M). After the mixture was centrifuged, the 3.0 ml of $CHCl_3$ phase was carefully withdrawn using a 5 ml glass syringe.[16) The amount of extracted amine salt in $CHCl_3$ was measured by glc (Chromosorb 103 at 210°C), whose optical purity was determined by glc (SF-96 coated glass cappillary column, 20 m) after derivatization into diastereomers with N-TFA-L-alanine.[17)]

Table Chiral recognition of enantiomers of 1-phenylethylamine salt in $CHCl_3$

Crown ether	Extracted Amine in $CHCl_3$/ (3) in $CHCl_3$ (mol/mol)	% ee
(3a)	0.90	8(R)
(3b)	0.78	0
(3c)	0.51	14(R)
(3d)	0.56	14(R)

Crown ether (3a), (3c), and (3d) except (3b) recognize the chirality of the amine salt. A rather rigid conformation is assumed for (3a) as the phenyl groups are directly attached to the crown framework. The substituents of (3c) and (3d) are large, but their conformations are not so rigid because they are connected to the crown ring through the flexible CH_2 group. 1-Naphthyl groups of (3b), which are connected to the crown ring through the more flexible CH_2O group, are not large enough to recognize the chirality.

Work is in progress to prepare other chiral 18-crown-6 type ethers with larger and rigid substituents.

References

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6) (1a): mp 91.3-92.1°C; $[\alpha]_D^{24}$ -12.3°(c=5.0, $CHCl_3$).
7) (2b): mp 158.3-159.4°C; $[\alpha]_D^{23}$ -17.3°(c=3.24, THF); NMR($(CD_3)_2SO$) δ=3.95-4.43(6H, m), 5.20-5.26(2H, b), 6.70-8.32(14H, m).
8) (2c): mp 139.2-141.4°C; $[\alpha]_D^{23}$ +29°(c=0.98, $CHCl_3$); NMR($CDCl_3$) δ=2.07(2H, b), 3.29(4H, d), 3.91(2H, m), 7.03-7.90(14H, m).
9) (2d): mp 152.0-153.0°C; $[\alpha]_D^{23}$ -2.4°(c=0.82, $CHCl_3$); NMR($CDCl_3$) δ=2.10(24H, s), 2.92(4H, d), 3.59(2H,m), 6.70(2H, s).
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11) J. Read, I. G. M. Campbell, and T. V. Barker, J. Chem. Soc., 1930, 2305; G. Berti and F. Bottari, J. Org. Chem., 25, 1286(1960); R-(2a): mp 148.0-149.0°C, $[\alpha]_D^{22}$ +94.8°(c=1.0, EtOH).

12) (3a): Yield 65%; mp 109.5-110.5°C; $[\alpha]^{20}_{436}$ +25.0°(c=2.0, $CHCl_3$); NMR($CDCl_3$) δ=3.45-3.95(16H, m, CH_2), 4.43(4H, s, CH), 6.75-7.15(20H, m, ArH); EA Found: C, 75.75; H, 7.16; M^+ 568. Calcd for $C_{36}H_{40}O_6$: C, 76.03; H, 7.09; M 568.

13) (3b) Yield 32%; mp 153.8-155.7°C; $[\alpha]^{22}_{D}$ -25.9°(c=4.95, $CHCl_3$); NMR($CDCl_3$) δ= 3.4-4.0(16H, m, OCH_2CH_2O), 4.1-4.6(12H, m, $OCHCH_2O$), 6.6-8.3(28H, m, ArH); EA Found: C, 75.12; H, 6.44; M^+ 888.3872. Calcd for $C_{56}H_{56}O_{10}$: C, 75.65; H, 6.35; M 888.3872.

14) (3c): Yield 30%; mp 97.0-98.0°C; $[\alpha]^{23}_{D}$ -107°(c=0.74, $CHCl_3$); NMR($CDCl_3$) δ= 2.33-3.40(28H, m, CH, CH_2), 7.06-7.98(28H, m, ArH); EA Found: C, 81.83; H, 6.92; MH^+ 825. Calcd for $C_{56}H_{56}O_6$: C, 81.55; H, 6.80; M 824.

15) (3d): Yield 28%; mp 88.7- 90.6°C; $[\alpha]^{22}_{D}$ -42.3°(c=1.24, $CHCl_3$); NMR($CDCl_3$) δ=2.17(48H, s, $ArCH_3$), 2.76-3.28(24H, m, CH_2), 3.57(4H, m, CH), 6.74(4H, s, ArH); EA Found: C, 78.73; H, 9.84; M^+ 848. Calcd for $C_{56}H_{80}O_6$: C, 79.25; H, 9.43; M 848.

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