Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 8, pp. 1873-1876, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(95)00240-5

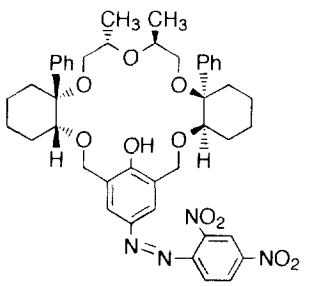
Preparation and Enantiomer Recognition of Chiral Azophenolic Crown Ethers Having three Chiral Barriers on each of the Homotopic Faces

Koichiro Naemura,* Masaki Asada, Keiji Hirose, and Yoshito Tobe

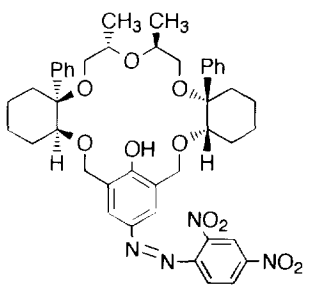
Department of Chemistry, Faculty of Engineering Science,
Osaka University, Toyonaka, Osaka 560, Japan

Abstract. Homochiral azophenolic crown ethers **1** and **2** having three chiral barriers, that is, the phenyl group, the methyl group, and the cyclohexane moiety on each of the homotopic faces have been prepared. The enantiomer recognition toward chiral 2-aminoethanol derivatives has been examined.

Various kinds of chiral crown ethers exhibiting characteristic enantiomer recognition for chiral guests have been prepared.[1] Although a crown ether having three chiral barriers which are arranged trigonally around the 18-crown-6 framework creating well-defined large, medium, and small cavities is generally expected to show high chiral recognition for a guest having the three ligands attached to the chiral center, as far as we know, almost all of stereogenic crown ethers previously prepared contain one, or at the most two, chiral subunits and only a few papers have described the preparation of chiral crown ethers constructed using three chiral subunits.[2] Our interest in the enantiomer recognition behaviour of crown ethers[3] led us to prepare chiral crown ethers having three chiral barriers. Herein we report the preparation of homochiral azophenolic crown ethers **1** and **2** which possess three chiral barriers, that is, the phenyl and the methyl substituents and the cyclohexane moiety on each of the homotopic faces. Their chiral recognition for chiral 2-aminoethanol derivatives is also examined.



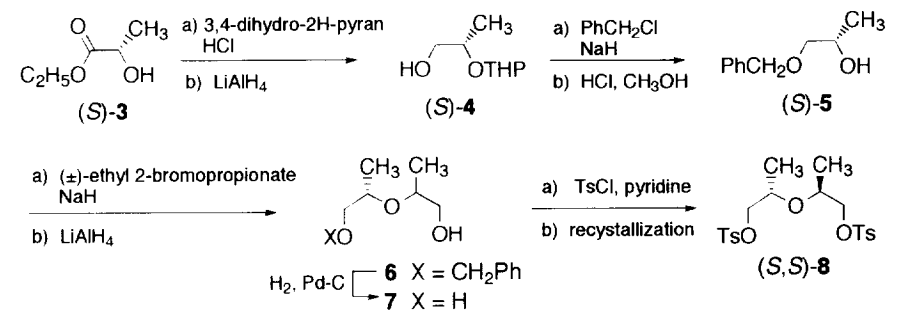
(*R*,*R*)(*S*,*S*)(*R*,*R*)-**1**



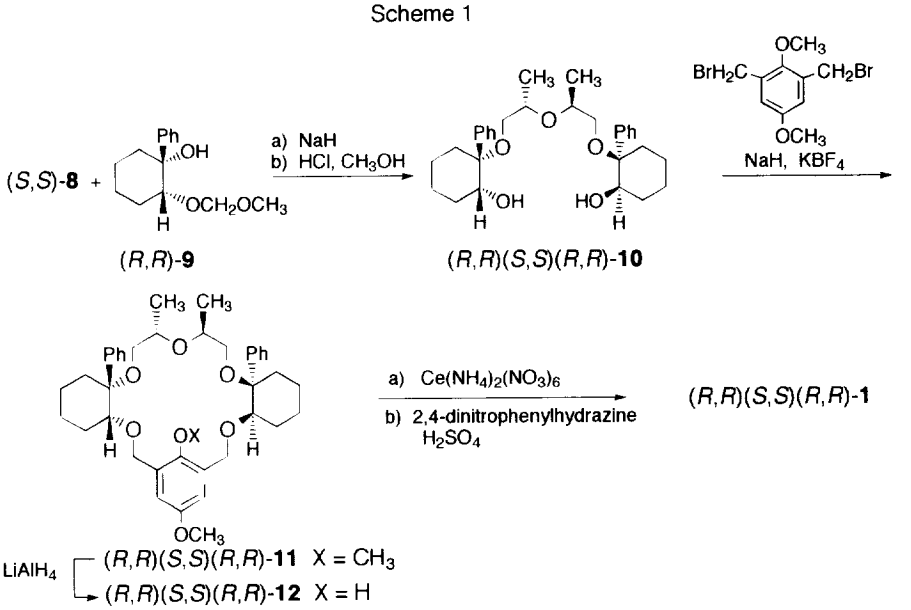
(*S*,*S*)(*S*,*S*)(*S*,*S*)-**2**

The synthesis of the chiral subunit (*S*,*S*)-**7** was carried out as shown in Scheme 1 starting from (*S*)-ethyl lectate. After protecting the hydroxyl group of (*S*)-**3**, reduction of the tetrahydropyranyl ether with $LiAlH_4$ gave (*S*)-**4** (92% yield), which was converted into (*S*)-**5** (84% yield), $[\alpha]_D^{24}$ +13.2 (c 1.0, $CHCl_3$) by treatment with benzylchloride followed by hydrolysis. Reaction of (*S*)-**5** with (±)-ethyl 2-bromopropionate in the presence of NaH followed by reduction with $LiAlH_4$ gave the mixture of (*S*,*S*)-**6** and (*S*,*R*)-**6** which was hydrogenated to give the diastereoisomeric mixture of **7** (49% yield). After ditosylation of the mixture of **7**, diastereomerically and enantiomerically pure (*S*,*S*)-**8**, $[\alpha]_D^{24}$ +3.4 (c 0.99, $CHCl_3$) was isolated by recrystallization from methanol.[4]

Condensation of (*S,S*)-**8** with 2.0 mol equiv. of (*R,R*)-**9** (>99% e.e.)[5] followed by removal of the protecting groups gave (*R,R*)(*S,S*)(*R,R*)-**10** (25% yield), $[\alpha]_D^{22}$ +7.8 (c 1.01, $CHCl_3$), which was condensed with 1,3-bis(bromomethyl)-2,5-dimethoxybenzene in the presence of NaH and KBF_4 under high dilution conditions to afford (*R,R*)(*S,S*)(*R,R*)-**11** (33% yield), $[\alpha]_D^{22}$ -172 (c 1.01, $CHCl_3$). Treatment of **11** with $LiAlH_4$ gave **12** (71% yield), which was converted into (*R,R*)(*S,S*)(*R,R*)-**1**[6] by oxidation with cerium (IV) ammonium nitrate followed by treatment with 2,4-dinitrophenylhydradine (Scheme 2). By the same sequence of reactions, (*S,S*)(*S,S*)(*S,S*)-**2** was prepared from (*S,S*)-**8** and (*S,S*)-**9** (>99% e.e.)[5] via (*S,S*)(*S,S*)(*S,S*)-**11**, $[\alpha]_D^{22}$ +111 (c 1.19, $CHCl_3$).



Scheme 1



Scheme 2

The association constants for the complexation of (*R,R*)(*S,S*)(*R,R*)-**1** and (*S,S*)(*S,S*)(*S,S*)-**2** with chiral and achiral amines in $CHCl_3$ were determined by the Benesi-Hildebrand Method[7] with the aid of the self-colour-indicating properties of the azophenolic crown ether. The *Ka*-values together with the λmax-values of complexes are given in Table 1.

On the assumption that the phenolate oxygen atom necessarily parcipitates in binding amines and the hydroxyl group of 2-aminoethanols occupies the site near the phenolate oxygen atom to make additional

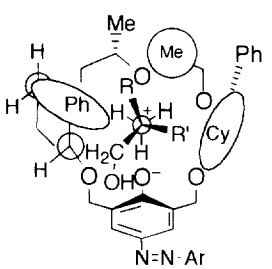
hydrogen bonding between the phenolate oxygen atom and the hydroxyl group of the amine stabilizing the complexes, the predicted geometries **13-18** of complexes are visualized by an examination of CPK molecular models of the complexes.

Table 1. Association constants *Ka* (M^{-1}), the ratio of *Ka*-values, and absorption maxima of the crown ethers **1** and **2**-amine complexes

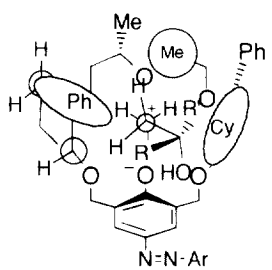
Amine	(*R,R*)(*S,S*)(*R,R*)-**1**		(*S,S*)(*S,S*)(*S,S*)-**2**	
	Ka[a] relative ratio (λmax/nm in $CHCl_3$)		*Ka* relative ratio (λmax/nm in $CHCl_3$)	
ethanolamine	73.6		34.8	
	(585)		(580)	
2-methoxyethyl amine	6.23		7.93	
	(600)		(595)	
(*S*)-2-amino-1-propanol	19.7	2.04	9.72	1.00
	(580)		(570)	
(*R*)-2-amino-1-propanol	9.65	1.00	10.1	1.03
	(582)		(565)	
(*S*)-1-amino-2-propanol	48.0	1.00	17.5	1.25
	(588)		(574)	
(*R*)-1-amino-2-propanol	59.3	1.24	14.0	1.00
	(582)		(577)	

[a] Determined by the Benesi-Hildebrand method at 25 °C in $CHCl_3$.

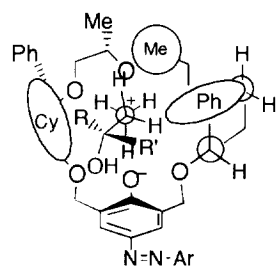
Compared with the low enantiomer selectivity (relative ratio of *Ka*-values=1.13) of the azophenolic crown ether having two chiral barriers, that is the phenyl group and the cyclohexane moiety towards 2-amino-1-propanol,[8] the methyl barrier improved the enantiomer selectivity of the (*R,R*)(*S,S*)(*R,R*)-**1**. The geometries **13** and **14** are illustrated for the (*R,R*)(*S,S*)(*R,R*)-**1**-2-amino-1-propanol complexes. The enantiomer selectivity observed is rationalized in terms of serious steric repulsion between the ligand R' of the amine and the cyclohexane barrier making the (*R,R*)(*S,S*)(*R,R*)-**1**-(*R*)-guest complex with the geometry **14** clearly less stable than the (*R,R*)(*S,S*)(*R,R*)-**1**-(*S*)-guest complex with the geometry **13**.



13 R=CH_3, R'=H
14 R=H, R'=CH_3



15 R=CH_3, R'=H
16 R=H, R'=CH_3



17 R=CH_3, R'=H
18 R=H, R'=CH_3

In the case of complexation with 1-amino-2-propanol, the $CH(CH_3)OH$ group is too bulky to occupy the site near the phenyl barrier. Thus the geometries **15** and **16** are illustrated for the complexes of (*R,R*)(*S,S*)(*R,R*)-**1** with (*R*)-amine and with (*S*)-amine, respectively, and the geometries **17** and **18** for the complexes of (*S,S*)(*S,S*)(*S,S*)-**2** with (*R*)-amine and with (*S*)-amine, respectively. The results are understandable in terms of steric repulsion between the methyl group of the guest and the cyclohexane barrier making the complexes

with the geometry **16** and with the geometry **17** unfavorable.

As mentioned above, the methyl chiral barrier in (*R,R*)(*S,S*)(*R,R*)-**1** improved enantiomer selectivity towards the 2-aminoethanol derivative of a type LMSC*NH_2, but the binding ability of the crown ethers **1** and **2** towards amines examined here were rather reduced by an increase in steric repulsions between the barriers and the guest.

References and Notes:

1. G. W. Gokel, and S. H. Korzeniowski, *Macrocyclic Polyether Syntheses*; Springer-Verlag: New York, 1982; J. F. Stoddart, Chiral Crown Ethers. *In Topics in Stereochemistry*; E. L. Eliel and S. H. Wilen, Eds.; Wiley-Interscience: New York, 1988; Vol. 17, pp 207; S. Misumi, *Top. Curr. Chem.*, **1993**, 165, 163.
2. F. de Jong, M. G. Siegel, and D. J. Cram, *J. Chem. Soc., Chem. Commun.*, **1975**, 551; D. G. Andrews, P. R. Ashton, D. A. Laidler, J. F. Stoddart, and J. B. Wolstenholme, *Tetrahedron Lett.*, **1979**, 2629.
3. K. Naemura, and R. Fukunaga, *Chem. Lett.*, **1985**, 1651; K. Naemura, R. Fukunaga, and M. Yamanaka, *J. Chem. Soc., Chem. Commun.*, **1985**, 1560; K. Naemura, M. Komatsu, K. Adachi, and H. Chikamatsu, *J. Chem. Soc., Chem. Commun.*, **1986**, 1675; K. Naemura, T. Matsumura, M. Komatsu, Y. Hirose, and H. Chikamatsu, *J. Chem. Soc., Chem. Commun.*, **1988**, 239; K. Naemura, R. Fukunaga, M. Komatsu, M. Yamanaka, and H. Chikamatsu, *Bull. Chem. Soc. Jpn.*, **1989**, 62, 83; K. Naemura, S. Takeuchi, K. Hirose, Y. Tobe, T. Kanada, and Y. Sakata, *J. Chem. Soc. Perkin Trans.* 1, **1995**, 213.
4. The synthesis of (±)-**8** has been reported in the literature; D. G. Parsons, *J. Chem. Soc. Perkin Trans.* 1, **1975**, 245.
5. All new compounds were fully characterized by IR, ^{1}H-NMR and MS or elemental analysis. **(S,S)- 8**; mp 82.0-82.5 °C; $[\alpha]_D^{24}$ +3.4 (*c* 0.99, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) 1.04 (6H, d, *J* 6.2, Me), 2.45 (6H, s, ArMe), 3.6-3.8 (2H, m, CH), 3.85 (4H, d, *J* 5.2, CH_2), 7.34 (4H, d, *J* 8.4, ArH) and 7.77 (4H, d, *J* 8.4, ArH); *m/z* (FAB$^+$) 443 (MH^+); (Found: C, 54.00; H, 5.7; S, 14.44. $C_{20}H_{26}O_7S_2$ requires C, 54.28; H, 5.92; S, 14.49%); **(R,R)(S,S)(R,R)-1**; IR(KBr): 3200, 2930, 2860, 1590, 1530, 1345, 1130, 1110, 1080, 1060 and 700 cm^{-1}; ^{1}H–NMR ($CDCl_3$): 0.95 (6H, d, *J* 6.4, Me), 1.21-2.17 (16H, m, CH_2), 2.85 (2H, dd, *J* 9.2 and 5.5, OCH_2), 3.32 (2H, dd, *J* 9.2 and 5.5, OCH_2), 3.93 (2H, d, *J* 5.0, CH), 4.06-4.13 (2H, m, OC<u>H</u>Me), 4.68 (2H, d, *J* 10.8, $ArCH_2$), 4.75 (2H, d, *J* 10.8, $ArCH_2$), 7.23-7.51 (10H, m, ArH), 7.74 (2H, s, HOArH), 7.82 (1H, d, *J* 8.9, O_2NArH), 8.47 (1H, dd, *J* 8.9, 2.5, O_2NArH), 8.74 (1H, d, *J* 2.5, O_2NArH), 9.57 (1H, s, OH); λmax ($CHCl_3$)/nm 415 (log ε 4.34); *m/z* (FAB$^+$) 795 (MH^+); **(S,S)(S,S)(S,S)-2**; ^{1}H–NMR ($CDCl_3$): 1.02 (6H, d, *J* 6.4, Me), 1.40-2.11 (16H, m, CH_2), 2.87 (2H, dd, *J* 8.5 and 6.1, OCH_2), 3.25 (2H, dd, *J* 8.5 and 6.1, OCH_2), 4.04-4.11 (4H, m, CH and OC<u>H</u>Me), 4.67 (2H, d, *J* 10.9, $ArCH_2$), 4.72 (2H, d, *J* 10.9, $ArCH_2$), 7.23-7.51 (10H, m, ArH), 7.70 (2H, s, HOArH), 7.83 (1H, d, *J* 8.9, O_2NArH), 8.47 (1H, dd, *J* 8.9, 2.3, O_2NArH), 8.74 (1H, d, *J* 2.3, O_2NArH), 10.1 (1H, s, OH); λmax ($CHCl_3$)/nm 415 (log ε 4.38); *m/z* (FAB$^+$) 795 (MH^+).
6. K. Naemura, H. Miyabe, Y. Shingai, and Y. Tobe, *J. Chem. Soc. Perkin Trans.* 1, **1993**, 1073.
7. H. A. Benesi, and J. H. Hildebrand, *J. Am. Chem. Soc.*, **1949**, 71, 742.
8. K. Naemura, K. Ueno, S. Takeuchi, Y. Tobe, T. Kaneda, and Y. Sakata, *J. Am. Chem. Soc.*, **1993**, 115, 8475.

(*Received in Japan* 20 *June* 1995)