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Chiral recognition of secondary amines by using chiral crown ether and podand†

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Abstract—Chiral crown ether (*S*,*S*)-**3** having a pseudo-24-crown-8 ring and chiral podand (*R*,*R*)-**4** were prepared and both exhibited good chiral recognition ability toward secondary amines, *N*-α-dimethylbenzylamine (**15**) and propranolol (**16**). © 2002 Published by Elsevier Science Ltd.

A number of chiral amines are known to possess potent biological activities and many of them are employed as important pharmaceuticals and their intermediates. Since each enantiomer of these amines has, in principle, different activities, it is an important issue to develop convenient methods for optical resolution and determination of optical purity. Despite the abundance of reports on chiral recognition of primary amines,[1] to the best of our knowledge, there are only two reports on chiral recognition of secondary amines.[2] Namely, Fuji et al. reported that binaphthyl derivatives bound valine derivatives with high enantiomer selectivity.[3] Recently, Steffeck et al. achieved enantiomeric separation of racemic secondary amines with a liquid chromatography stationary phase based on a chiral 18-crown-6.[4] On the other hand, we reported that the optically active pseudo-18-crown-6 ethers like (*S*,*S*)-**1** exhibited high enantiomer selectivity toward primary amines.[5] Accordingly, we planned to prepare artificial receptors having the same structural features as those of (*S*,*S*)-**1** for the enantiomer discrimination of secondary amines. The salient features of (*S*,*S*)-**1** involve (i) a phenolic hydroxy group which binds neutral amines to form a salt complex, (ii) a strong electron-withdrawing group attached to the *para* position of the OH group, facilitating binding with amines and (iii) phenyl groups introduced to the right position of the macrocyclic framework as chiral barriers. Since we anticipated that the ring size of (*S*,*S*)-**1** would be too small for binding a secondary amine, we designed larger macrocycle (*S*,*S*)-**3** and

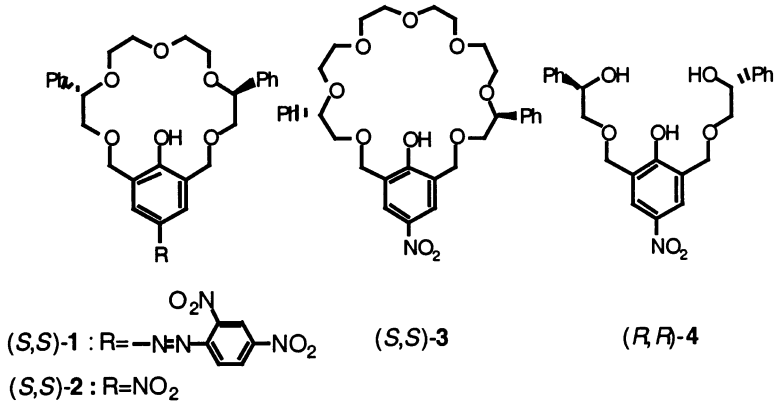

Figure 1. The structures of hosts (*S*,*S*)-**1**–**3** and (*R*,*R*)-**4**.

Keywords: chiral recognition; secondary amine; crown ether; podand.

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† This paper is dedicated to Emeritus Professor Soichi Misumi on the occasion of his 77th birthday.

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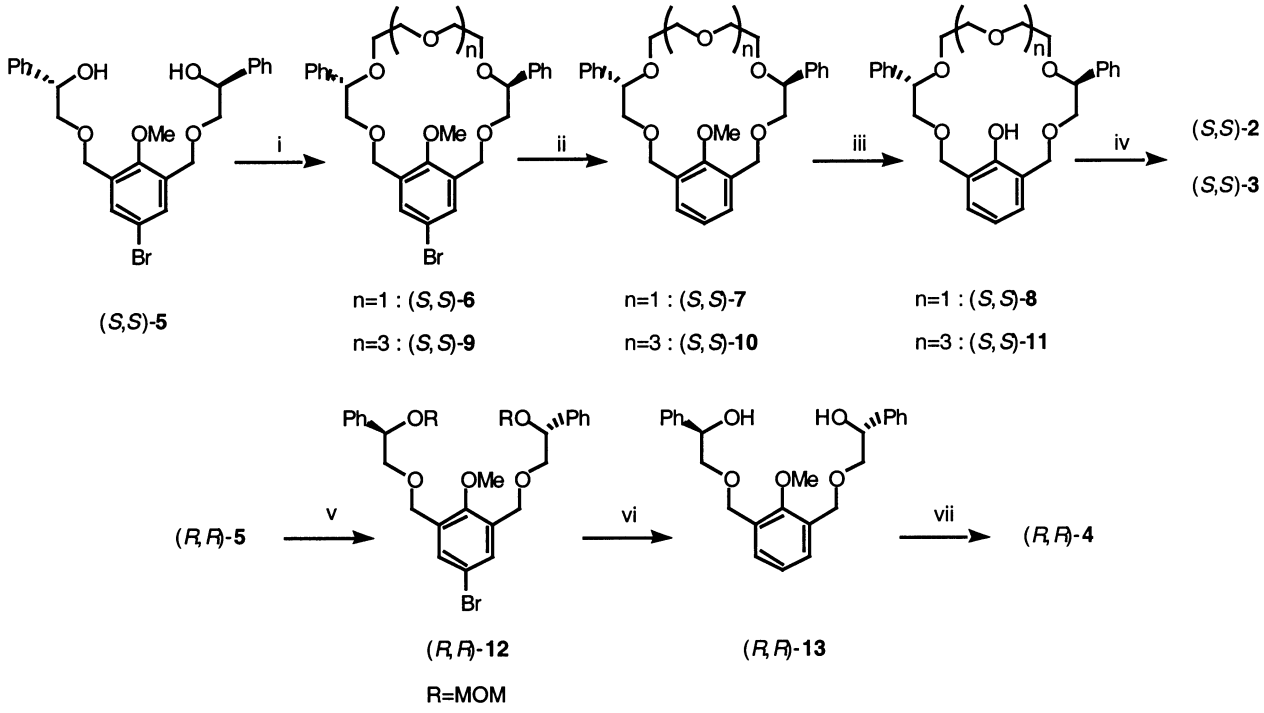
acyclic host (*R*,*R*)-**4**. In the case of a podand type host, however, introduction of a 2,4-dinitrophenylazo group at the *para* position of the OH group resulted in the product which existed as both azophenol and its tautomeric hydrazone forms.[6] Therefore, a nitro group is used instead since its electron-withdrawing property is same as that of a 2,4-dinitrophenylazo group.[7] Pseudo-18-crown-6 (*S*,*S*)-**2** possessing the same ring size as that of (*S*,*S*)-**1** was prepared for comparison. The ring size of pseudo-24-crown-8 (*S*,*S*)-**3** is assumed to be almost the same as that of dibenzo-24-crown-8 which is reported to form a stable complex with a dibenzylammonium ion.[8] Podand (*R*,*R*)-**4** should have a larger binding site than that of (*S*,*S*)-**3** (Fig. 1).

The preparation of (*S*,*S*)-**2**, (*S*,*S*)-**3** and (*R*,*R*)-**4** was carried out using diol **5** as a common intermediate as shown in Scheme 1. Ring closure of (*S*,*S*)-**5**[9] with diethylene glycol ditosylate under high dilution condition gave (*S*,*S*)-**6**. Reductive removal of the bromo group of (*S*,*S*)-**6** gave (*S*,*S*)-**7**, and its demethylation afforded (*S*,*S*)-**8**. Nitration at the *para* position of the OH group of (*S*,*S*)-**8** gave (*S*,*S*)-**2**,[11] pseudo-24-crown-8 (*S*,*S*)-**3**[12] (through (*S*,*S*)-**9**, (*S*,*S*)-**10** and (*S*,*S*)-**11**) and podand (*R*,*R*)-**4**[13] were prepared by essentially the same procedure as that for the preparation of (*S*,*S*)-**2**, except that *R*,*R* isomer of **5** was used as the starting material for (*R*,*R*)-**4** and the two OH groups of (*R*,*R*)-**5** was first protected by MOM groups to give (*R*,*R*)-**12**. Reduction and deprotection gave (*R*,*R*)-**13**, which was subjected to demethylation and nitration to furnish (*R*,*R*)-**4**.

In order to examine the binding ability of (*S*,*S*)-**2**, (*S*,*S*)-**3** and (*R*,*R*)-**4** with secondary amines, *N*-methylbenzylamine (**14**) was selected as a guest. The enantiomer selective complexation of (*S*,*S*)-**3** and (*R*,*R*)-**4** was studied with *R* and *S* enantiomers of *N*,α-dimethylbenzylamine (**15**) which has a methyl group at α-position of **14** and propranolol (**16**) having a chiral center at β-position of an amino group. The binding constants for complexes of (*S*,*S*)-**2** and (*S*,*S*)-**3** with the amines were determined by the non-linear least-squares curve fitting method on the basis of the ^{1}H NMR titration in $CDCl_3$ at 15°C. Because of the limited solubility of (*R*,*R*)-**4** in $CDCl_3$, the binding constants for complexes of (*R*,*R*)-**4** with the amines were determined by the Rose–Drago method on the basis of the UV–vis titration in $CHCl_3$ at 15°C.[14] The binding constants of the hosts with **14**, **15** and **16** and enantiomer selectivities of the hosts toward **15** and **16** which are the ratio of binding constants (K_S/K_R), are summarized in Table 1. As shown in Table 1, the binding constant of pseudo-24-crown-8 (*S*,*S*)-**3** with **14** is three times as large as that of pseudo-18-crown-6 (*S*,*S*)-**2**. Similarly, the binding constant of podand (*R*,*R*)-**4** is eight times larger than that of (*S*,*S*)-**2**. These results clearly exhibit that the cavity of pseudo-18-crown-6 (*S*,*S*)-**2** is too small for a secondary amine, while pseudo-24-crown-8 (*S*,*S*)-**3** and podand (*R*,*R*)-**4** possess large binding sites enough to include a secondary amine.[15] Next, we investigated chiral recognition abilities of the hosts toward amine **15**. Since (*S*,*S*)-**2** did not bind *S* and *R* enantiomers of **15** (K<1 M^{-1}), we could not estimate the selectivity. Thus introduction of a methyl group in the guest amine



Scheme 1. *Reagents and conditions*: (i) diethylene glycol ditosylate, NaH, 53% (n=1), tetraethylene glycol ditosylate, NaH, 36% (n=3); (ii) 1. *n*-BuLi, then H_2O, 62% (n=1), 62% (n=3); (iii) EtSNa, 91% (n=1), 86% (n=3); (iv) HNO_3, $NaNO_2$, 58% (n=1), 34% (n=3); (v) $(CH_3O)_2CH_2$, LiBr, TsOH, 45%; (vi) 1. *n*-BuLi, then H_2O, 2. 6N HCl, 53%; (vii) 1. EtSNa, 2. HNO_3, $NaNO_2$, 19%.

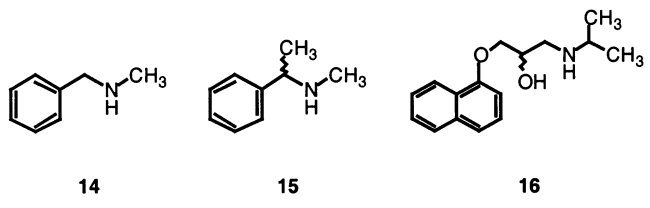
Table 1. Binding constants and enantioselectivities in complexations of (*S*,*S*)-**2**, (*S*,*S*)-**3** and (R,R)-**4** with **14**, **15** and **16**

		(*S*,*S*)-**2**[a]	(*S*,*S*)-**3**[a]	(*R*,*R*)-**4**[b]
14		$(1.4\pm0.2)\times10$	$(4.6\pm0.1)\times10$	$(1.0\pm0.1)\times10^2$
15	K_S	<1	$(1.8\pm0.1)\times10$	$(1.0\pm0.1)\times10^2$
15	K_R	<1	8.8 ± 0.7	$(7.2\pm0.7)\times10$
15	K_S/K_R	–	2.0	1.4
16	K_S	–	$(5.3\pm0.1)\times10$	$(2.3\pm0.1)\times10^2$
16	K_R	–	$(3.1\pm0.2)\times10$	$(3.7\pm0.5)\times10^2$
16	K_S/K_R	–	1.7	0.6

[a] Measured by ^{1}H NMR spectroscopy (270 MHz) in $CDCl_3$ at 15°C.
[b] Measured by UV–vis spectroscopy in $CHCl_3$ at 15°C.

reduce the binding ability of (*S*,*S*)-**2** dramatically, suggesting a severe steric repulsion between the α-methyl group of **15** and the host. With (*S*,*S*)-**3**, however, the binding constants with *S* and *R* enantiomers of **15** were 18 and 8.8 M^{-1}, respectively. As we expected, considerable enantiomer selectivity was observed ($K_S/K_R=2.0$). The binding constants of (*S*,*S*)-**3** with *S* and *R* enantiomers of **15** decreased considerably compared with that with **14**. In the case of (*R*,*R*)-**4**, binding constants with *S* and *R* enantiomers of **15** were 100 and 72 M^{-1}, respectively. The enantiomer selectivity (1.4) is smaller than that of (*S*,*S*)-**3**, indicating the role of macrocyclic ring in molecular recognition. In contrast to the case of (*S*,*S*)-**2** and (*S*,*S*)-**3**, the binding constants of (*R*,*R*)-**4** with **15** scarcely decreased from that with achiral amine **14**, a result consistent with the relatively low enantiomer selectivity of (*R*,*R*)-**4**. Chiral recognition abilities toward **16** were investigated by using (*S*,*S*)-**3** and (*R*,*R*)-**4** which showed high binding abilities toward chiral secondary amine **15**. Amine **16** is one of the bioactive aminoalcohols possessing a hydroxy group on a chiral center at β-position of an amino group. In the case of (*S*,*S*)-**3**, the binding constants with *S* and *R* enantiomers of **16** were 53 and 31 M^{-1}, respectively. The binding constants with both enantiomers of **16** considerably increased compared with those of **15** and good enantiomer selectivity (1.7) was observed. Similarly, the binding constants of (*R*,*R*)-**4** with both enantiomers of **16** were 2 to 5 times larger than those in the case of **15**. The binding constants with *S* and *R* enantiomers of **16** were 230 and 370 M^{-1}, respectively. In this case, considerable enantiomer selectivity (0.6) was also observed (Fig. 2).

In conclusion, we prepared chiral pseudo-24-crown-8 (*S*,*S*)-**3** and podand (*R*,*R*)-**4** which exhibited stronger binding ability than pseudo-18-crown-6 (*S*,*S*)-**2** toward an achiral secondary amine and good enantiomer selectivity toward chiral secondary amines which have a chiral center at α or β position. The enantiomer selectivity of (*S*,*S*)-**3** and (*R*,*R*)-**4** toward other chiral secondary amines and further modification of the host structure are currently under investigation.



14 **15** **16**

Figure 2. The structures of the amines **14**, **15** and **16**.

Acknowledgements

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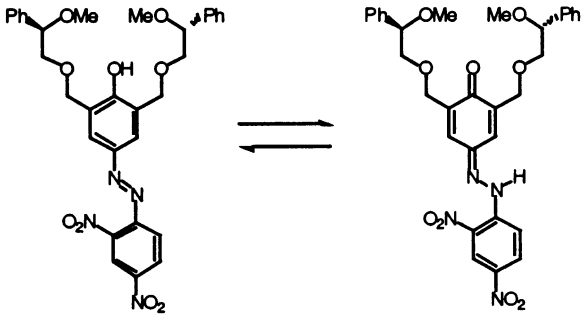
6. For example, the azophenol podand (i) exists in equilibrium with its hydrazone form (ii) in a ratio of 5:1 in $CDCl_3$ at 30°C.



i **ii**

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9. Diol (*S*,*S*)-**5** was prepared by the same procedure as that of -1,3-bis[(4*S*)-4-hydroxy-4-phenyl-2-oxabutyl]-2,5-dimethoxybenzene[10] from 5-bromo-1,3-bis(bromomethyl)-2-methoxybenzene.

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11. Spectral data for (*S*,*S*)-**2**: mp 52–54°C; $[\alpha]_D^{25}$ +97.2 (*c* 0.61, $CHCl_3$); IR (KBr) 3319, 2871, 1600, 1520, 1452, 1339, 1091, 749, 703 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, ppm) δ 3.54–3.78 (m, 12H, -OCH_2-), 4.66 (dd, $J=3.7$, 7.2 Hz, 2H, C*H*), 4.83 (s, 4H, benzyl CH_2), 7.30–7.38 (m, 10H, C_6H_5), 8.10 (s, 2H, phenol moiety C*H*), 9.20 (s, 1H, O*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$, ppm) δ 69.0, 70.0, 70.6, 75.2, 76.5, 125.1, 125.2, 126.8, 128.1, 128.5, 138.0, 139.9, 161.2; MS (FAB) *m*/*z* 510 $(M+H)^+$, 532 $(M+Na)^+$; HRMS (FAB) calcd for $C_{28}H_{32}NO_8$ $(M+H)^+$: 510.2128, Found: 510.2102.
12. Spectral data for (*S*,*S*)-**3**: $[\alpha]_D^{25}$ +53.3 (*c* 1.06, $CHCl_3$); IR (neat) 3277, 2867, 1596, 1521, 1452, 1339, 1097, 751, 702 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, ppm) δ 3.45–3.87 (m, 20H, -OCH_2-), 4.70 (dd, $J=5.8$, 5.8 Hz, 2H, C*H*), 4.81, 4.85 (AB, $J=12.9$ $\Delta\nu=17.9$ Hz, 4H, benzyl CH_2), 7.26–7.40 (m, 10H, C_6H_5), 8.08 (s, 2H, phenol moiety C*H*), 9.13 (1H, s, O*H*); ^{13}C NMR (67.8 MHz, $CDCl_3$, ppm) δ 68.8, 69.9, 69.9, 70.7, 70.9, 75.5, 81.7, 123.6, 125.3, 126.8, 128.1, 128.5, 138.2, 140.2, 159.6; MS (FAB) *m*/*z* 598 $(M+H)^+$, 620 $(M+Na)^+$; HRMS (FAB) calcd for $C_{32}H_{40}NO_{10}$ $(M+H)^+$: 598.2652, Found: 598.2671.
13. Spectral data for (*R*,*R*)-**4**: mp 52–53°C; $[\alpha]_D^{26}$ −29.3 (*c* 1.01, $CHCl_3$); IR (KBr) 3306, 2868, 1597, 1520, 1454, 1338, 1274, 1198, 1099, 909, 750, 701 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$, ppm) δ 2.74 (s, 2H, O*H*), 3.65 (dd, $J=8.6$, 10.1, 2H, -O-CH(Ph)-CH_2), 3.78 (dd, $J=3.2$, 10.1, 2H, -O-CH(Ph)-CH_2), 4.77 (s, 4H, benzyl CH_2), 5.00 (dd, $J=3.2$, 8.6, 2H, -O-C*H*(Ph)-CH_2), 7.25–7.40 (m, 10H, C_6H_5), 8.09 (s, 2H, phenol moiety C*H*), 8.93 (s, 1H, phenol O*H*); MS (FAB) *m*/*z* 440 $(M+H)^+$, 462 $(M+Na)^+$. The high-resolution mass spectrum could not be recorded because of the weak molecular ion peak.
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15. Regarding the binding ability toward a primary amine, we also measured and compared the binding constants of (*S*,*S*)-**2**, (*S*,*S*)-**3** and (*R*,*R*)-**4** with ethanolamine. The binding constants of (*S*,*S*)-**2**, (*S*,*S*)-**3** and (*R*,*R*)-**4** with ethanolamine were 8800, 360 and 35 M^{-1}, respectively. The binding constant of pseudo-18-crown-6 (*S*,*S*)-**2** is 25 and 250 times as large as those of pseudo-24-crown-8 (*S*,*S*)-**3** and podand (*R*,*R*)-**4**, respectively, indicating that (*S*,*S*)-**2** is a better binder for a primary amine than (*S*,*S*)-**3** and (*R*,*R*)-**4**.